The Accuracy of Memorial Sloan-Kettering Cancer Center Nomogram in Anatolian Breast Cancer Patients

Memorial Sloan-Kettering Cancer Center Nomogramının Anadolu'da Yaşayan Meme Kanseri Hastalarındaki Doğruluğu

Osman Erdoğan[1], Ulvi Murat Yüksel[1], Uğur Berberoğlu[1], Kaptan Gülben[1], Bülent Aksel[1], Osman Uyar[1], Müjdat Turan[1]

[1]Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Ankara, Türkiye

Dergiye Ulaşma Tarihi:23/02/2016 Dergiye Kabul Tarihi: 08/05/2016 Doi: 10.5505/aot.2016.04127

ÖZET

Amaç: Bir çok meme kanseri hastasında sentinel lenf nodundan başka metastatik lenf nodu olmadığı halde gereksiz yere aksiller diseksiyon uygulanmaktadır. Bu çalışmanın amacı Memorial Sloan-Kettering Cancer Center (MSKCC) nomogramının Anadolu'da yaşayan meme kanseri hastalarındaki doğruluğunu araştırmaktır.
Gereç ve yöntem: Sentinel lenf nodu (SLN) biyopsisi pozitif olduğu için aksiller lenf nodu diseksiyonu yapılan 120 meme kanserli hastanın hasta ve tümör özellikleri irdelendi. Bu hastaların her birisinin non-SLN tutulum riski MSKCC nomogramı kullanılarak hesaplandı.
Bulgular: Negatif SLN sayısı, pozitif SLN sayısı, SLN ekstrakapsüler yayılımı, pozitif SLN sayısının toplam SLN sayısına oranı (pozitif SLN oranı), lenfovasküler invazyon varlığı, tumor çapı, human epidermal growth factor receptor-2 durumu tek değişkenli analizde non-SLN metastazı ile istatistiksel olarak ilişkili bulunan faktörlerdi. Çok değişkenli analizde ise tümör çapı ≥ 5cm ($p<0.036$) ve pozitif SLN oranı ($p<0.005$) non-SLN metastazı ile ilişkili bulunan parametrelerdi. Nomogramın sonucuna göre ROC eğrisi çizildi ve eğri altı alan 0,779 ($p<0.001$) olarak bulundu.
Sonuç: SLN pozitif meme kanserli hastalarda non-SLN metastaz riskini belirlemede MSKCC nomogramı bizim hasta populasyonumuz için iyi bir ayıraç olmuştur.
Anahtar kelimeler: Meme kanseri, nomogramlar, lenf nod diseksiyonu

ABSTRACT

Background and Aim: Many breast cancer patients undergo to unnecessary axillary dissection as additional nodal metastasis is not detected other than sentinel lymph node in most of the patients. This study is conducted to establish the accuracy of Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram in Anatolian patients.
Materials and Methods: One hundred and twenty sentinel lymph node (SLN) biopsy positive breast cancer patients who received completion axillary lymph node dissection were reviewed according to patient and tumour characteristics. The likelihood of having positive non-SLN metastasis based on the factors and the performance of the diagnostic value of MSKCC nomogram were evaluated.
Results: The number of negative SLNs, the number of positive SLNs, SLN extracapsular extention, proportion of positive SLNs to total SLNs (positive SLN ratio), lymphovascular invasion, tumor size, human epidermal growth factor receptor-2 status were found statistically significant on non-SLN metastasis in univariate analysis. Tumor size ≥ 5cm ($p<0.036$) and positive SLN ratio ($p<0.005$) were found to be correlated with non-SLN metastasis in multivariate analysis. Receiver operating characteristic (ROC) curve was formed according to the nomogram and areas under curve (AUC) was found as 0,779 ($p<0.001$).
Conclusions: The MSKCC nomogram was good discriminator of non-SLN metastasis in SLN positive breast cancer patients for our patient population.
Key Words: breast cancer, nomograms, lymph node dissection

Adress for correspondence: Ulvi Murat Yüksel, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Ankara, Türkiye
e-mail: iv_murat@hotmail.com
Available at www.actaoncologicaturcica.com

Introduction:

Breast cancer is the most common cancer type among women in the world and 1.67 million new cases diagnosed each year [1]. The identification of clinical, pathological and biological factors such as tumour size, axillary lymph node status, hormonal receptor and human epidermal growth factor receptor-2 (HER-2) status have a role in risk stratification and affect treatment modality in breast cancer [2]. Axillary lymph node metastasis is the most important prognostic factor in breast cancer and therefore to determine the axillary lymph node status is the principle together with the resection of primary tumour [3]. If there is sentinel lymph node (SLN) metastasis, axillary lymph node dissection (ALND) is still the standard procedure for breast cancer patients; however, additional nodal metastasis is detected in the rest of axilla in only about 40%-70% of these patients [4]. Therefore, many patients undergo to unnecessary axillary dissection. The importance of sentinel lymph node biopsy (SLNB) is because of the complications like seroma, lymphedema, nerve injury and frozen shoulder in the patients those who receive ALND. To identify the possible risk of non-SLN metastasis, Memorial Sloan-Kettering Cancer Center (MSKCC) developed a nomogram in 2003.

We conducted this study to establish the accuracy of the nomogram in Anatolian patients those who were referred to a single tertiary centre.

Materials and Methods:

Totally 120 breast cancer patients who lived in Anatolia and ALND applied because of positive SLNB between December 2011 and May 2013 were included in this study. The study protocol was approved by the Ethics Committee of Ankara Oncology Training and Research Hospital. Patients who had clinically axillary lymph node positivity, received neoadjuvant therapy or received axillary surgical manuplation before and those who failed in successfully locating SLN were excluded. Both lymphosintigraphy and metilen blue technique was used to locate SLN. SLNB was applied either through the same insicion with mastectomy or through another minimal incision. Gama probe was used for the identification of sentinel lymph node/nodes and frozen section was carried out on the biopsy material. Simultaneous ALND applied in all the patients those whom SLNB result reported as micrometastasis or macrometastasis. SLNB material was also analyzed by immunohistochemistry post-operatively. Patient's age, tumour size and histology, nuclear grade, presence of lymphovascular invasion (LVI), SLN extracapsular extention and multifocality of the tumor, the number of removed SLNs, the number of positive and negative SLNs, the method of detection of SLNs [frozensection (FS), routine haematoxylin & eosin, serial section haematoxylin & eosin and immunohistochemistry (IHC)], estrogen receptor, progesterone receptor, HER2 receptor and KI67 status were recorded. The likelihood of non-SLN metastasis based on the factors were evaluated by using chi square test, student t-test and Mann Whitney U test. Logistic regression analysis was used on the multivariate method.

The areas under curve (AUC), the receiver operating characteristic curve (ROC) were used to describe the performance of the diagnostic value of MSKCC. www.mskcc.org/applications/nomograms/breast/BreastAdditionalNonSLNMetastasesPage.aspx is the web site address for MSKCC Nomogram. SPSS 15 program was used for evaluating the risk factors in axillary metastasis.

Results:

There were total 120 patients all women with mean age 49.48 (±11.21). There were 53 patients (44%) in Group-1 with positive non-SLN and 67 patients (55.8%) with negative non-SLN in Group-2. Groups were similar according to age, tumour type, multifocality, nuclear grade, ER and PR status. Patients and tumour characteristics are shown in table-1.

Frozen section was the method used for the pathological verification of non-SLN in 53 patients (100%) in Group-1 and 63 patients (94%) in Group-2. IHC was used for pathological verification of non-SLN in 4 patients (6%) in Group 2. The method used for the pathological verification of non-SLN did not differ significantly between the groups

Adress for correspondence: Ulvi Murat Yüksel, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Ankara, Türkiye
e-mail: iv_murat@hotmail.com
Available at www.actaoncologicaturcica.com

Table 1: Patient and tumour characteristics

		Group 1 (n%)	Group 2 (n%)	p
Age	0-50	32(%60.4)	39(%58.2)	0.479
	≥ 51	21(%39.6)	28(%41.8)	
Tumour Size	T1-T2	44(%83)	65(%97)	0.010
	T3	9(%17)	2(%3)	
Tumour Type	IDK	50(%94.3)	60(%89.6)	0.275
	ILK	3(%5.7)	7(%10.4)	
Nuclear Grade	1-2	23(%43.4)	35(%52.2)	0.218
	3	30(%56.6)	32(%47.8)	
LVI	+	25(%47.2)	11(%16.4)	0.001
	-	28(%52.8)	25(%83.6)	
HER-2	+	27(%50.9)	12(%17.9)	0.001
	-	26(%49.1)	55(%82.1)	
Metastatic SLN Ratio	Ratio=1	35(%66)	20(%29,9)	0.001
	Ratio≤1	18(%34)	47(%29.9)	
SLN Extracapsuler Extention	+	30(%56.6)	20(%29.9)	0.003
	-	23(%43.4)	47(%79.1)	

LVI: Lenfovascular Invasion, HER-2 : Human Epidermal Growth Factor Receptor-2

Adress for correspondence: Ulvi Murat Yüksel, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Ankara, Türkiye
e-mail: iv_murat@hotmail.com
Available at www.actaoncologicaturcica.com

Table 2: The significant factors identified in univariate analysis

Variables	P Value
Tumour Size	0,002
Tumour Size ≥ 5cm	0,01
LVI	0,001
Metastatic SLN Ratio	0,001
The number of positive SLN	0,001
The number of negative SLN	0,001
HER-2	0,001
Extracapsular Extension	0,003

LVI: Lenfovascular Invasion,
SLN: Sentinel Lymph Node,
HER-2: Human Epidermal Growth Factor Receptor-2

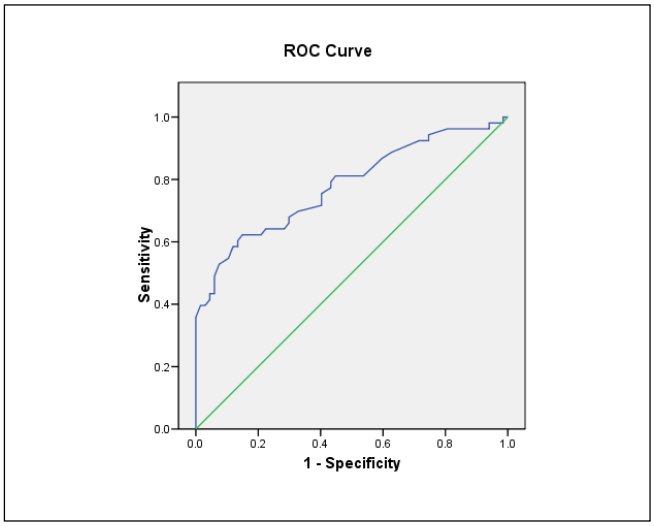


Figure 1: ROC Curve; Sensitivity and 1-Specificity Graphic.

Table 3: Multivariate Analysis Results

	Odds Ratio	P Value	95% Confidential
Tumour Size ≥5cm	6.928	0.036	1.130-42.474
Extracapsular Extension	0.591	0.252	0.240-1.454
HER-2	0.404	0.07	0.152-1.077
LVI	0.445	0.12	0.160-1.235
Positive SLN Ratio	3.626	0.005	1.479-8.890

LVI: Lenfovascular Invasion, SLN : Sentinel Lymph Node, HER-2 : Human Epidermal Growth Factor Receptor-2

Adress for correspondence: Ulvi Murat Yüksel, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Ankara, Türkiye
e-mail: iv_murat@hotmail.com
Available at www.actaoncologicaturcica.com

(p=0.93). In group 1, mean tumour size was 36.21 mm (± 12.9) and it was 28.96 mm (±11.60) in group 2 (p=0.002). There was no statistically significance in KI67 status among the groups, however HER2 was significantly positive in Group1 (p=0.001). The mean number of metastatic SLN showed statistically significance between the groups; it was 1,83 in Group-1 and 1,29 in Group-2 (p=0.001). The significant factors identified according to the univariate analysis are shown in table-2.

Thereafter stepwise multiple logistic regression analysis was performed for the factors those which showed significance in univariate analysis. Tumour size over 5 cm and the parameter positive SLN ratio (metastatic SLN/total SLN = 1) were the independent factors affecting non-SLN metastasis. The results of logistic regression analyse are shown in table-3. Group-1 presented the value 64,32 and Group-2 presented the value 45,86 according to MSKCC nomogram scoring system. It was statistically significant (p=0.001). The receiver operating characteristic curve (ROC) were used to describe the performance of the diagnostic value of MSKCC nomogram in non-SLN positivity (Figure-1). The area under the curve was calculated as 0.779 and showed significance (p<0.001).

Discussion:

Axillary lymph node metastasis is known as the most significant prognostic factor in early stage breast cancer patients. Both the treatment and survival differs according to the presence of axillary lymph node metastasis [3]. For this reason, presence and abundance of axillary lymph node metastasis is important for determining adjuvant chemotherapy depending on correct staging. Because of the complications of ALND such as seroma, lymphedema, shoulder dysfunction and arm paresthesia, surgeons targeted on limited surgery on axilla instead of complete ALND [5-7]. In accordance with the previous studies, in 40-70 % of the patients SLN is the only metastatic lymph node; so there is no additional metastatic lymph node in the rest of the axilla [8-10]. As a result of these studies, determining the axillary status with non-invasive methods after diagnosing positive SLN provided matter for discussion.

In the year 2003, Van Zee et al. presented a nomogram by using retrospective analyse method throughout Memorial Sloan-Kettering Cancer Center records. This nomogram was tested prospectively and AUC was found as 0,76 in ROC curve. Therefore, this is the first nomogram estimating the non-SLN metastasis risk [11]. In breast cancer diagnosed patients, clinicopathological characteristics such as age, ER, PR, HER2 status may vary according to race or socia-economic status. For example, African–American breast cancer patients are more likely to have a triple-negative (ER-/PR-/HER2-) subtype than Asian women [12]. For this reason, the validity of MSKCC nomogram is tested on patients who belong to various ethnic groups or socia-economic status by various centres and the results differ from one centre to another [13-17]. There are some other developed nomograms in literature to predict non-SLN status in patients with breast cancer with SLN metastasis as well; these include the nomogram developed by Degnim et al [Mayo nomogram], the nomogram developed by Pal et al [Cambridge nomogram], and the nomogram developed by Kohrt et al [Stanford nomogram] [18-20]. Nomograms may be useful tools to avoid complete axillary dissection in non-SLN negative patients. However, before being incorporated into routine clinical practice, such nomograms must be validated in independent patient populations. Among these nomograms, MSKCC nomogram is the first nomogram in literature and various validation studies have been performed to evaluate the accuracy of this nomogram in different populations, so comparable data occured in literature. For this reason, we prefered to test the validity of MSKCC nomogram in Anatolian breast cancer patients and to determine the useful parameters in estimating axillary metastasis. Anatolia is the greater part of Turkey in which people from various cultures, various ethnic groups and socio-economic status are settled. Vast of the previous studies are performed on alike people.

In breast cancer patients, non-SLN metastasis risk is due to the clinical and

Adress for correspondence: Ulvi Murat Yüksel, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Ankara, Türkiye
e-mail: iv_murat@hotmail.com
Available at www.actaoncologicaturcica.com

pathological characteristics of both the primary tumour and the SLN metastasis. Van Zee et al., found tumour size, LVI, the method of detection of SLNs, the number of positive and negative SLNs as the the related parameters with non-SLN metastasis; multifocality had borderline effect on non-SLN metastasis where tumour type, nuclear grade, ER status did not show significant effect on non-SLN metastasis [11].

Tumour size is also reported as a related factor with non-SLN metastasis in some other various studies [21-23]. In our study, there was significance between the non-SLN positive and negative groups according to mean tumour size (p=0.002) and in multivariate analysis tumour size over 5 cm. was found as an independent factor increasing non-SLN metastasis risk (p=0.04). This result stated the aggravated risk corolated with tumour size. In the present study; LVI, the number of positive SLNs, extracapsular extension and the positive SLN ratio (proportion of positive SLN to total SLN) were the other factors affecting non-SLN metastasis risk in univariate analysis compatible with literature [22-24]. However, only the positive SLN ratio showed significance in multivariate analysis (p=0.005). In previous studies on the topic, there was no relationship between non-SLN metastasis and ER, PR and HER2 status[17,20-23]. In the present study, hormonal receptor status (ER, PR) did not affect the non-SLN metastasis risk however HER2 showed significance in univariate analysis. There are both contradicting and sustaining studies in literature about multifocality, nuclear grade and the number of negative SLNs [11,17,20,23,25,26]. In this study, mean number of negative SLNs was another factor affecting non-SLN positivity in univariate analysis but multifocality and nuclear grade were not related with non-SLN metastasis. We did not find the tumour type as a related factor with non-SLN metastasis similar to previous studies either [11,17].

Van Zee et al., found AUC as 0.76 in their retrospective study and 0.77 in their prospective study [11]. In our study AUC was found as 0.78. Our results checked the validation of MSKCC nomogram. Tumor size $\geq$ 5cm and positive SLN ratio were found to be independent factors which affect non-SLN metastasis risk in our study. The MSKCC nomogram was good discriminator of non-SLN metastasis in SLN positive Anatolian breast cancer patients. In the various validation studies of MSKCC nomogram for different nations AUC was found between 0.58 - 0.82 [27]. As can be seen, this wide range of AUC is due to different breast cancer subtypes which may vary according to race or socia-economic status.

In a more recent study, SLNB alone resulted in similar survival compared to ALND [28], thereby there is a further increase in the importance of nomograms. We recommend that nomograms can be used in routine clinical practice after validation for the related patient population.

Conflict of interest: None

References:

1. International Agency for Research on Cancer. GLOBOCAN 2012: estimated incidence, mortality and prevalence worldwide in 2012. http:// globocan. iarc. fr/Pages/fact_sheets_cancer.aspx [Accessed July 25, 2014].
2. Patani N, Martin LA, Dowsett M. Biomarkers for the clinical management of breast cancer: international perspective. Int J Cancer. 2013; 133: 1-13.
3. Chen JJ, Wu J. Management strategy of early-stage breast cancer patients with a positive sentinel lymph node with or without axillary lymph node dissection. Crit Rev Oncol Hematol. 2011; 79: 293-301.
4. Cady B. Case against axillary lymphadenectomy for most patients with infiltrating breast cancer. J Surg Oncol. 1997; 66: 7-10.
5. Schrenk P, Rieger R, Shamiyeh A, Wayand W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. Cancer. 2000; 88: 608-14.
6. Velanovich V, Szymanski W. Quality of life breast cancer patients with lymphedema. Am J Surg. 1999; 177: 184-7

Adress for correspondence: Ulvi Murat Yüksel, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Ankara, Türkiye
e-mail: iv_murat@hotmail.com
Available at www.actaoncologicaturcica.com

7. Krag DN. Minimal access surgery for staging regional lymph nodes: The sentinel node concept. Curr Probl Surg. 1998; 35: 951-1016.
8. Yu JC, Hsu GC, Hsieh CB, Sheu LF, Chao TY. Prediction of metastases to nonsentinel nodes by sentinel node status and primary tumor characteristics in primary breast cancer in Taiwan. World J Surg. 2005; 29: 813-8
9. Guenther JM, Hansen NM, DiFronzon LA, et al. Axillary dissection is not required for all patients with breast cancer and pozitive sentinel nodes. Arch Surg. 2003; 138: 52-6.
10. Sachdev U, Murphy K, Derzie A, Jaffer S, Bleiweiss U, Brower S. Prediction of nonsentinel Lymph node metastases in breast cancer patients. Am J Surg. 2002; 183: 213-7.
11. Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A Nomogram for Predicting the Likelihood of Additional Nodal Metastases in Breast Cancer Patients With a Positive Sentinel Node Biopsy. Ann Surg Oncol. 2003; 10: 1140-51.
12. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007; 109: 1721-8.
13. Viale G, Maiorano E, Pruneri G, et al. Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy. Ann Surg. 2005; 241: 319-25.
14. Alran S, De Rycke Y, Fourchotte V, et al. Validation and limitations of use of a breast cancer nomogram predicting the likelihood of non–sentinel node involvement after positive sentinel node biopsy. Ann Surg Oncol. 2007; 14: 2195-201
15. Smidt ML, Kuster DM, Van der Wilt GJ, Thunnissen FB, Van Zee KJ, Strobbe LJ. Can the Memorial Sloan-Kettering Cancer Center nomogram predict the likelihood of nonsentinel lymph node metastases in breast cancer patients in the Netherlands. Ann Surg Oncol. 2005; 12: 1066-72.
16. Van la Parra RF, Ernst MF, Bevilacqua JL, et al. Validation of a nomogram to predict the risk of nonsentinel lymph node metastases in breast cancer patients with a positive sentinel node biopsy: Validation of the MSKCC Breast Nomogram. Ann Surg Oncol. 2009; 16: 1128-35
17. Unal B, Gur AS, Kayiran O, et al. Models for predicting non-sentinel lymph node positivity in sentinel node positive breast cancer: the importance of scoring system. Int J Clin Pract. 2008; 62: 1785-91
18. Degnim AC, Reynolds C, Pantvaidya G, et al: Nonsentinel node metastasis in breast cancer patients: Assessment of an existing and a new predictive nomogram. Am J Surg 2005; 190: 543-550.
19. Pal A, Provenzano E, Duffy SW, et al: A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. Br J Surg 2008; 95: 302-309.
20. Kohrt HE, Olshen RA, Bermas HR, et al. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. BMC Cancer. 2008; 4;8:66.
21. Chagpar AB, Scoggins CR, Martin RC , et al. Prediction of sentinel lymph node-only disease in women with invasive breast cancer; University of Louisville Breast Sentinel Lymph Node Study. Am J Surg. 2006; 192: 882-7
22. Cho J, Han W, Lee JW, et al. A scoring system to predict nonsentinel lymph node status in breast cancer patients with metastatic sentinel lymph nodes: a comparison with other scoring systems. Ann Surg Oncol. 2008; 15: 2278-86.
23. Koca B, Kuru B, Ozen N, Yoruker S, Bek Y. A breast cancer nomogram for prediction of non-sentinel node metastasis - validation of fourteen existing models. Asian Pac J Cancer Prev. 2014; 15: 1481-8.
24. A.S. Gur, B. Unal, Ozbek U, et al. Turkish Federation of BreastDisease Associations Protocol MF08-01 investigators. Validation of breast cancer nomograms for predicting the non-sentinel lymph node metastases after a positive sentinel lymph node biopsy in a multi-center study. Eur J Surg Oncol. 2010; 36: 30-5.
25. Derici S, Sevinc A, Harmancioglu O, et al. Validation of three breast cancer nomograms and a new formula for predicting non-sentinel lymph node status. Asian Pac J Cancer Prev. 2012; 13: 6181-5.
26. Kuo YL, Chen WC, Yao WJ, et al. Validation of Memorial Sloan-Kettering Cancer Center nomogram for prediction of non-sentinel lymph node metastasis in sentinel lymph node positive breast cancer patients an international comparison. Int J Surg. 2013;11:538-43.
27. Klar M, Jochmann A, Foeldi M, et al. The MSKCC nomogram for prediction the likelihood of non-sentinel node involvement in a German breast cancer population. Breast Can Res Treat 2008; 112: 523-31
28. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 9; 305: 569-75.

Adress for correspondence: Ulvi Murat Yüksel, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Ankara, Türkiye
e-mail: iv_murat@hotmail.com
Available at www.actaoncologicaturcica.com

Malignancy Rates in Bethesda Category AUS/FLUS: Single Center Experience

Bethesda Kategori ÖBA/ÖBFL için Malignite Oranları: Tek Merkez Deneyimi

Nuray Can[1], Semra Aytürk[2], Ebru Taştekin[1], Yavuz Atakan Sezer[3], Mehmet Çelik[2], Fulya Öz Puyan[1], Ufuk Usta[1], Sibel Güldiken[2], Funda Üstün[4], Buket Yılmaz Bülbül[2], Tülin Deniz Yalta[1], Nurtaç Sarıkaş[1]

[1]Trakya Üniversitesi Tıp Fakültesi Tıbbi Patoloji ABD, Edirne, Türkiye
[2]Trakya Üniversitesi Tıp Fakültesi Endokrinoloji Ve Metabolizma Hastalıkları BD, Edirne, Türkiye
[3]Trakya Üniversitesi Tıp Fakültesi Genel Cerrahi ABD, Edirne, Türkiye
[4]Trakya Üniversitesi Tıp Fakültesi Nükleer Tıp ABD, Edirne, Türkiye

Dergiye Ulaşma Tarihi: 11/05/2016 Dergiye Kabul Tarihi: 28/08/2016 Doi: 10.5505/aot.2016.98704

ÖZET

Amaç: Tiroid nodüllerinin prevelansı yüksek olmasına rağmen, bu nodüller için malignite oranları düşüktür. Bu nedenle, cerrahi yaklaşım gerektiren malign nodülleri, benign nodüllerden ayırmak çok önemlidir. Ultrasonografi, ultrasonografi eşliğinde ince iğne aspirasyonu ve ayrıca Tiroid Sitopatolojisi için Bethesda Raporlama Sistemi tiroid nodüllerinin değerlendirilmesinde fayda sağlamaktadır. Ancak, bu sistem 'Önemi Belirsiz Atipi/ Önemi Belirsiz Foliküler Lezyon (ÖBA/ÖBFL)' olarak adlandırılan problemli bir kategori içermektedir. Bu kategori için son zamanlarda bildirilen malignite yüzdeleri %5 ile %96,7 arasında değişmektedir. Bu çalışmada merkezimizde incelenen ilk ince iğne aspirasyon tanısı ÖBA/ÖBFL olan tiroid nodüllerindeki malignite oranlarının sunulması amaçlanmaktadır.

Yöntem: Yedi yıl süresince, Trakya Üniversitesi Tıp Fakültesi Patoloji Anabilimdalı'nda (Edirne, Türkiye) incelenen hastaların tanıları (ince iğne aspirasyon ve tiroidektomi) geriye dönük olarak değerlendirildi.

Bulgular: İnce iğne aspirasyon sitolojisinde ÖBA/ÖBFL tanısı alan 153 hastadan 68'inde (%44,4) histopatolojik tanı papiller tiroid karsinomu, 1'inde (%7) foliküler karsinom ve 1'inde (%7) de medüller karsinom idi.

Tartışma ve Sonuç: Tiroid Sitopatolojisi için Bethesda Raporlama Sistemi bazı tanı kategorilerinde standardizasyon sağlamışsa da, ÖBA/ÖBFL kategorisi hala subjektif sitolojik kriterleri barındırmakta ve farklı çalışmalarda oldukça değişken histolojik malignite oranları bildirilmektedir. Bu nedenle, immünositokimya ve özellikle moleküler testler gibi yardımcı yöntemlerin kullanılması tiroid nodüllerinin preoperatif tanısında faydalı olabilir.

Anahtar Kelimeler: Tiroid Karsinomu, Sitoloji, Önemi Belirsiz Atipi/ Önemi Belirsiz Foliküler Lezyon

ABSTRACT

Introduction: Although the prevelance of thyroid nodules is high, the rate of malignancy in these nodules is low. Thus, the distinction between the malignant nodules requiring surgical approach and the benign ones is very important. Ultrasound, ultrasound guided fine needle aspiration and also The Bethesda Reporting System for Thyroid Cytopathology are useful tools for interpretation of thyroid nodules. However, this system includes a problematic category titled as 'Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance (AUS/FLUS)'. The reported percentages of malignancy in these nodules range between 5-96,7%, recently. We aimed to present the rate of malignancy in thyroid nodules with initial fine needle aspiration diagnosis as AUS/FLUS.

Methods: The final diagnosis (fine needle aspiration and thyroidectomy) of patients who presented at the Department of Pathology of the Trakya University Medical Faculty (Edirne, Turkey) were reviewed for seven years.

Results: Histological diagnosis was papillary thyroid carcinoma in 68 (44,4%), follicular carcinoma in 1 (0.7%) and medullary carcinoma in 1 (0.7%) of the 153 patients with prior fine needle aspiration diagnosis as AUS/FLUS.

Discussion and Conclusion: Although, The Bethesda Reporting System for Thyroid Cytopathology have provided standardisation in some of categories, the category of AUS/FLUS remains to be including subjective cytological criteria and subsequent malignancy rates are highly variable in different reports. So, ancillary tools

Adress for correspondence: Dr. Nuray Can Trakya Üniversitesi, Balkan Kampüsü, Tıp Fakültesi, Tıbbi Patoloji Abd Edirne - Türkiye
e-mail: nuraycan@ymail.com
Available at www.actaoncologicaturcica.com

such as immunocytochemistry and particularly molecular tests may be appropriate in preoperative diagnosis of thyroid nodules.
Keywords: Thyroid Carcinoma, Cytology, Atypia of Undetermined Significance/Follicular Lession of Undetermined Significance

Introduction:

Although the prevalence of thyroid nodules is high, the rate of malignancy in these nodules is low. Thus, the distinction between the malignant nodules requiring surgical approach and the benign ones is very important. Ultrasound (US), ultrasound guided fine needle aspiration (USGFNA) and also The Bethesda Reporting System for Thyroid Cytopathology (BRSTC) are useful tools for interpretation of thyroid nodules. The system includes six categories; nondiagnostic as category 1, benign as category 2, atypia of undetermined significance and follicular lesion of undetermined significance (AUS/FLUS) as category 3, suspicious for follicular neoplasia and follicular neoplasia (FNS/FN) as category 4, suspicious for malignancy (SFM) as category 5 and finally, malignant as category 6 (1). The system informs the rates of malignancy and also requires the type of management for each category (2). However, this system includes a problematic category titled as 'Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance (AUS/FLUS)' (2). BRSTC declares the rate of malignancy for category AUS/FLUS as 5-15% (1,2), but the reported percentages of malignancy in these nodules range between 6% (3) and 96,7 (4), recently.

The present study aims to present the experience of single center which is located in the northwest part of Turkey aboutthe rates of malignancy in thyroid nodules with prior FNA diagnosis as AUS/FLUS.

Methods:

The final diagnoses of FNA materials of patients who presented at Department of Pathology of Trakya University Medical Faculty (Edirne, Turkey) were reviewed for seven years (March 2007- March 2014). The patients with preoperative initial FNA diagnosis as Bethesda Category 3, namely AUS /FLUS and subsequent thyroid surgery (lobectomy/thyroidectomy) were included in the study group. Cytological examination of FNA materials were performed by liquid based preparings and conventional smears. The diagnosis of FNA materials were grouped according to BRSTC (Table 1) (1,2). Histopathological examination was performed by obtaining at least 4 samples, mean 8 samples per lobe. If there was any gross pathological mass or lesion, these areas were demonstrated totally for microscopic evaluation. The lesions containing suspicious (but not diagnostic) nuclear features for papillary carcinoma in conventional Hematoxylin-eosin (H&E) stained slides, otherwise immunohistochemistry was performed by using antibodies such as HBME-1, Galectin-3 and cytokeratin 19. Encapsulated nodules were interpreted carefully for capsular or vascular invasion.

Prior FNA diagnosis and postoperative histopathological diagnosis of the patients were documented. The results were presented as numbers and percentages.

Results:

Out of 6290 patients who had been performed USGFNA, 410 (6,5%) patients had been diagnosed as Bethesda Category 3, namely AUS /FLUS. In this group, 153 patients had undergone thyroid surgery. 124 (81%) of the patients were female, 29 (19%) of the group included male patients.

Malignant tumors were present in 70 (45,8%) of the patients. Histological diagnosis was papillary thyroid carcinoma (PTC) in 67 (43.7%) of the patients. One of the patients had been diagnosed as well differentiated tumor with unknown malignant potential. The histopathological reevaluation converted this diagnosis into follicular variant of papillary carcinoma. The final percentage of PTC was

Adress for correspondence: Dr. Nuray Can Trakya Üniversitesi, Balkan Kampüsü, Tıp Fakültesi, Tıbbi Patoloji Abd Edirne - Türkiye
e-mail: nuraycan@ymail.com
Available at www.actaoncologicaturcica.com

Table 1: The Bethesda System forreporting thyroid cytopathology: recommended diagnostic categories, implied risk of malignancy, and recommended clinical management (1, 2).

Diagnostic category	***Risk of malignancy (%)***	***Management*** [a]
(I) Nondiagnostic or unsatisfactory (ND/UNS) *Cyst fluid only* *Virtually acellular specimen* *Other (obscuring blood, clotting artifact, etc.)*		Repeat FNA with ultrasoundguidance
(II) Benign *Consistent with a benign follicular nodule (includes ,colloid nodule etc.)* *Consistent with lymphocytic (Hashimoto) thyroiditis in theproperclinical context* *Consistentwithgranulomatous (subacute) thyroiditis* *Other*	0-3	Clinicalfollow-up
(III) Atypia of undetermined significance or follicularlesion of undetermined significance (AUS/FLUS)	5–15[b]	Repeat FNA
(IV) Follicular neoplasm or suspicious for follicular neoplasm (FN/SFN) *-specifyifHurthle cell (oncocytic) type*	15–30	Surgical lobectomy
(V) Suspicious for malignancy (SFM) *Suspicious for papillary carcinoma* *Suspicious for medullary carcinoma* *Suspicious for metastatic carcinoma* *Suspicious for lymphoma* *Other*	60–75	Near-total thyroidectomy or surgical lobectomy [c]
(VI)Malignant *Papillarythyroidcarcinoma* *Poorlydifferentiatedcarcinoma* *Medullarythyroidcarcinoma* *Undifferentiated (anaplastic) carcinoma* *Squamouscellcarcinoma* *Carcinomawithmixedfeatures (specify)* *Metastaticcarcinoma* *Non-Hodgkinlymphoma* *Other*	97–99	Near-total thyroidectomy [c]

[a]Actual management may depend on other factors (e.g.,clinical and sonographic) besides the FNA interpretation.
[b]Estimate extrapolated from histopathologic data from patients with “repeated atypicals” .
[c]In the case of “suspicious for metastatic tumor” or a “malignant” interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

Adress for correspondence: Dr. Nuray Can Trakya Üniversitesi, Balkan Kampüsü, Tıp Fakültesi, Tıbbi Patoloji Abd Edirne - Türkiye
e-mail: nuraycan@ymail.com
Available at www.actaoncologicaturcica.com

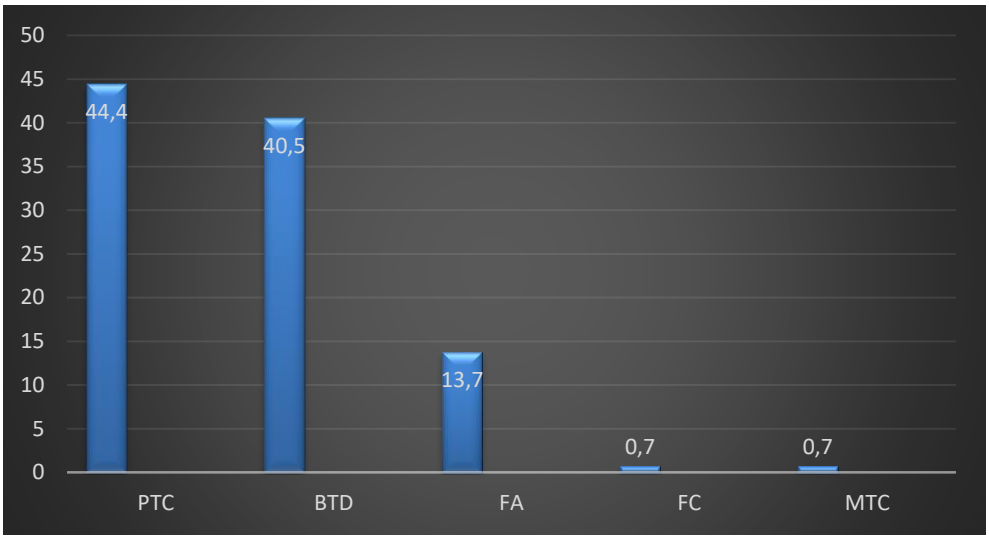


Figure 1: Histopathological diagnosis of the patients with prior cytological diagnosis as AUS/FLUS
PTC: Papillarythyroidcarcinoma, BTD: Benignthyroiddisease, FA: Follicular adenoma, FC: Follicularcarcinoma, MTC: Medullarythyroidcarcinoma

44,4% (68/153) (Fig 1). Histological variant was conventional PTC in 21 (30,9%) of the cases diagnosed as PTC and follicular variant PTC in 46 (67,6 %) of the patients in PTC group. One of the patients (1,4%) had clear cell variant PTC (Fig 2). The tumor size was ≤ 10mm in 40 (58,8%) of the patients. Histopathological diagnosis was follicular carcinoma in 1 (0.7%) of the patients and medullary carcinoma in 1 (0.7%) of the patients with prior FNA diagnosis as AUS/FLUS.

The only benign tumor of the follicular epithelial cells, namely follicular adenoma was present in 21 (13,7%) of the cases. Benign nonneoplastic thyroid diseases including lymphocytic thyroiditis and follicular nodular disease were present in 11(7,2%) and 51(33,3%) of the patients, respectively.

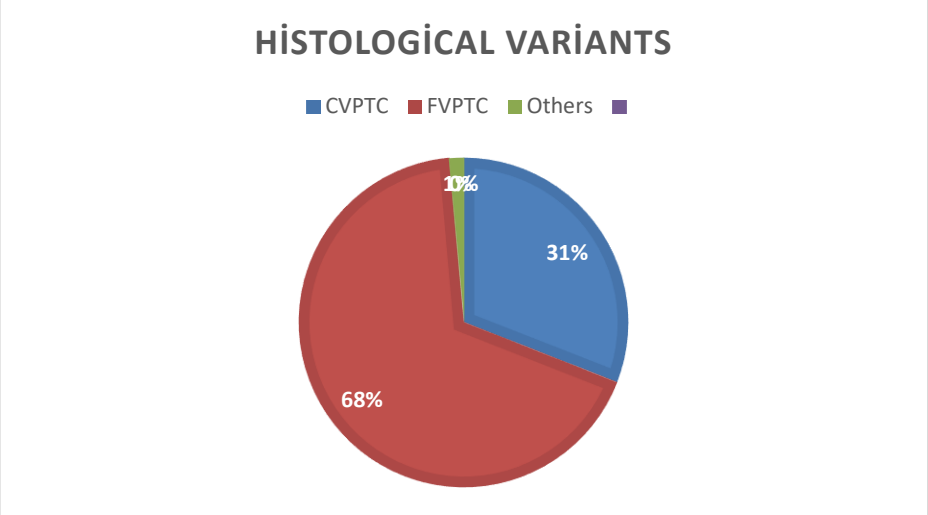


Figure 2: Histological variants in papillary thyroid carcinoma.
CVPTC: Conventional variant papillary carcinoma
FVPTC: Follicular variant papillary carcinoma

Adress for correspondence: Dr. Nuray Can Trakya Üniversitesi, Balkan Kampüsü, Tıp Fakültesi, Tıbbi Patoloji Abd Edirne - Türkiye
e-mail: nuraycan@ymail.com
Available at www.actaoncologicaturcica.com

Discussion:

Bethesda Reporting System for Thyroid Cytopathology predicts the risk of malignancy as 5-15% in Category 3; AUS/FLUS (1,2). However, the published reports after the widespread use of BRSTC informed highly variable risk of malignancy ranging between 6 %-96,7% in this group (3-8). The malignancy rate in AUS/FLUS category of our center was 45,8% and is placed centrally in previosly reported wide risk spectrum (3-8).

The percentage of AUS/FLUS for FNA materials is reported as 7% in BRSTC. The rate of this category in our center was close to the recommended rates by BRSTC. Although, BRSTC have standardized the cytopathological diagnosis in FNA of thyroid gland, there are surviving problems in Categories 3, 4 and 5 due to the subjective cytological evaluation and interobserver variability (1,2,9,10). But the main problem emerges in category 3; AUS/FLUS, since the management of other two categories somehow contains surgery. BRSTC suggests repeat FNA for the initial diagnosis of Category 3 in the absence of any other risk such as suspicious or malignant radiological images (1,2). Probable cause of these percentages of category 3 may be the numerical expression of endocrine atypia. As the thyroid gland is an endocrine organ, follicular epithelial cells also have endocrine atypia in their nature. Besides, some of the benign thyroid diseases or some of the therapies for benign diseases may result worrisome endocrine atypia. So, clinical information should be considered in the interpretation of FNA of thyroid nodules in addition to the cytological evaluation.

In our study, higher rates of malignancy in histopathology may be explained by triage of the patients for surgery as it was reported by some authors previously (11). In our center, nearly all of the thyroid nodules diagnosed as AUS/FLUS are discussed in multidisciplinary conferences and if there is no unsettling radiological feature in US imaging of the nodule, the management goes on by repeating FNA as it is recommended by BRSTC (2). So, indication for surgery is defined by eliminating false-positive results in cytology by following USFNA in the background of clinical and radiological data. The most common malignancy was PTC with the percentage of 44,4% and most of the tumors were microcarcinomas and follicular variant in the study group. It is well documented that FVPTC does not express the conventional nuclear features of PTC and may localize the cytological diagnosis in subcategories. This may be one of the causes resulting the higher malignancy rates in histology as reported in several reports (12, 13).

The widespread use of liquid-based preparations have generated ancillary tools in the cytological interpretation via availability of cell blocks. These tools contain immuno-cytochemistry and molecular analysis. Immunocytochemical studies including HBME-1 and Galectin 3 may have value in specimens diagnosed as AUS/FLUS, especially in the means of conventional variant of PTC. Molecular analyses can be descriptive and exclusive in differentiating malignancy and benign diseases. Molecular alterations of several genes such as point mutations of *BRAF, K/NRAS, TERT, TSHR* genes and fusions in *THADA, PPRG* and *NTRK3* genes may reveal the malignant potential of the nodule (rule-in tests) (14). On the other side, gene expression classifier tests may exclude the malignant potential (rule-out tests) (15).

Conclusion:

Although, The Bethesda Reporting System for Thyroid Cytopathology have provided standardization in some of categories, the category of AUS/FLUS remains to be including subjective cytological criteria and subsequent malignancy rates are highly variable in different reports. So, ancillary tools such as immunocytochemistry and particularly molecular tests may be appropriate in preoperative diagnosis of thyroid nodules.

Conflict of Interest: None

Adress for correspondence: Dr. Nuray Can Trakya Üniversitesi, Balkan Kampüsü, Tıp Fakültesi, Tıbbi Patoloji Abd Edirne - Türkiye
e-mail: nuraycan@ymail.com
Available at www.actaoncologicaturcica.com

References:

1. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Am J Clin Pathol. 2009; 132: 658–65
2. Ali ZS, Cibas ES. The Bethesda System for Reporting Thyroid Cytopathology. New York,Springer, 2010
3. Nayar R, Ivanovic M. The indeterminate thyroid fine-needle aspiration: experience from an academic center using terminology similar to that proposed in the 2007 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. Cancer Cytopathol. 2009; 117: 195–202
4. Kim SK, Hwang TS, Yoo YB et al. Surgical results of thyroid nodules according to amanagement guideline based on the BRAFV600E mutation status. J Clin Endocrinol Metab. 2011; 96: 658–64
5. VanderLaan PA, Marqusee E, Krane JF. Clinical outcome for atypia of undetermined significance in thyroid fine-needle aspirations:should repeated FNA be the preferred initial approach? Am J Clin Pathol. 2011; 135: 770–5
6. VanderLaan PA, Krane JF, Cibas ES. The frequencyof 'atypia of undetermined significance interpretations for thyroid fine-needleaspirations is negatively correlated with histologically proven malignant outcomes. Acta Cytol. 2011; 55: 512–7
7. Dincer N, Balci S, Yazgan A, Guney G, ErsoyR, Cakir B, Guler G. Follow-up of atypia andfollicular lesions of undetermined significancein thyroid fine needle aspiration cytology.Cytopathology. 2013; 24: 385–90.
8. Olson MT, Clark DP, Erozan YS, Ali SZ. Spectrum of risk of malignancy in subcategories of atypia of undetermined significance. Acta Cytol.2011; 55: 518–25
9. Kholov I, Ludvıkov_M. Thyroid atypia of undetermined significance or follicular lesion of undetermined significance: an indispensable Bethesda 2010 diagnostic category or waste garbage? Acta Cytol. 2014; 58:319–29.
10. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda system for reporting thyroid cytopathology: a metaanalysis. Acta Cytol.2012;56:333–9
11. Kuru B, Atmaca A, Tarim IA et al. Risk factors associated with malignancy and with triage to surgery in thyroid nodules classified as Bethesda category III (AUS/FLUS). EurJ Surg Oncol. 2016; 42: 87-93
12. Liu X, Medici M, Kwong Net al. Bethesda Categorization of Thyroid Nodule Cytology and Prediction of Thyroid Cancer Type and Prognosis. Thyroid. 2016; 26: 256-61
13. Fazeli R, VandenBussche C.J, Bishop J.A, Ali S.Z.Cytological Diagnosis of Follicular Variant of Papillary Thyroid Carcinoma before and after the Bethesda System for Reporting Thyroid Cytopathology. Acta Cytologica.2016; 60:14-8
14. Nikiforov YE, Carty SE, Chiosea SI et al. Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. Cancer. 2014; 120: 3627-34
15. Ali SZ, Fish SA, Lanman RB, Randolph GW, Sosa JA. Use of the Afirma® Gene Expression Classifier for Preoperative Identification of Benign Thyroid Nodules with Indeterminate Fine Needle Aspiration Cytopathology. PLOS Currents Evidence on Genomic Tests. 2013 doi: 10.1371/ currents. eogt. e557cbb5c7e4f66568ce582a373057e7.

Adress for correspondence: Dr. Nuray Can Trakya Üniversitesi, Balkan Kampüsü, Tıp Fakültesi, Tıbbi Patoloji Abd Edirne - Türkiye
e-mail: nuraycan@ymail.com
Available at www.actaoncologicaturcica.com

The Effects of Radical Nephrectomy and Nephron Sparing Surgery on Glomerular Filtration Rate for the Patients who Underwent Surgery for Localized Renal Mass

Lokalize Renal Kitle Nedeniyle Cerrahi Uygulanan Hastalarda Radikal Nefrektomi ile Nefron Koruyucu Cerrahinin Glomerüler Filtrasyon Oranı Üzerine Etkileri

Ahmet Güdeloğlu[1], Bülent Akdoğan[2],Haluk Özen[2]

[1]Memorial Ankara Hastanesi, Ankara, Türkiye
[2]Hacettepe Üniversitesi Tıp Fakültesi, Üroloji Anabilim Dalı, Ankara, Türkiye

Dergiye Ulaşma Tarihi: 17.10.2016 Dergiye Kabul Tarihi: 23.10.2016 Doi: 10.5505/aot.2016.93063

ÖZET

Amaç: Bu çalışmada, radikal nefrektomi (RN) ile nefron koruyucu cerrahinin (NKC) uzun dönem böbrek fonksiyonları üzerine etkisini ortaya koymak amaçlanmıştır.

Hastalar veYöntem: Hacettepe Üniversitesi Tıp Fakültesi Üroloji Anabilim Dalı'nda Ocak 1990 - Nisan 2011 tarihleri arasında renal kitle nedeniyle ameliyat edilen 1016 hastaya ait veriler, retrospektif olarak incelenmiştir. Tanı anında metastatik olduğu bilinen 78 olgu çalışma dışı tutulmuştur.

Bulgular: Çalışmaya alınan olguların 579'u (%61,7) erkek ve 359'u (%38,3) kadındır. 624 olguya RN, 314 olguya NKC yapılmıştır. Hastaların ortalama takip süresi RN yapılan grupta 46.7 ay iken, NKC uygulanan grupta 39.9 aydır. Ortalama radyolojik tümör boyutu sırasıyla 75±33,5 mm ve 37,8±26 mm'dir ($p<0.001$). Ortalama ameliyat süresi RN ve NKC grupları için sırasıyla 137.6 ve 139.5 dakikadır. NKC uygulanan grupta ortalama sıcak iskemi süresi 18,9±6,8 (3-36) dakikadır. Uzun dönem takip sonunda RN yapılan gruptaki kreatinin değerindeki ortalama 0,51 mg/dl artış, NKC uygulanan gruptaki 0,39 mg/dl artıştan anlamlı şekilde daha fazladır ($p<0.001$). Uzun dönem takipte preoperatif GFR'ı ≥60 olan hastaların halen GFR değerinin ≥60 olarak devam etme oranları, RN ve NKC yapılan gruplarda sırasıyla %47.6 ve %74.8 olarak tespit edilmiştir ($p<0.001$).

Sonuç: Çalışmamızda GFR'de azalma oranının uzun dönemde RN yapılan hastalarda NKC yapılanlara göre daha fazla olduğu bulunmuştur. T1 renal tümörü olan birçok olguda RN ile bütün böbreği çıkarmak fazladan tedavidir. T1 renal tümörü olan hastalarda teknik olarak mümkün oldukça parsiyel nefrektomi tercih edilmelidir.

Anahtar kelimeler: Renal Hücreli Karsinom, Radikal Nefrektomi, Nefron Koruyucu Cerrahi, Glomerüler Filtrasyon Oranı

ABSTRACT

Objectives: The goal of this study was to demonstrate the long-term effects of radical nephrectomy (RN) and nephron sparing surgery (NSS) on kidney functions.

Patients and Methods: The medical records of 1016 patients who underwent kidney surgery from January 1990 to April 2011 at Hacettepe University School of Medicine, Department of Urology were retrospectively collected and analyzed. Metastatic 78 patients at presentation were excluded.

Results: Radical nephrectomy and nephron sparing surgery was performed in 624 and 314 cases, respectively. Male to female ratio was 579/314. The mean follow up was 46.7 and 39.9 months for RN and NSS, respectively. The mean radiological tumor size was 75±33,5 mm for RN and 37,8±26 mm for NSS ($p<0.001$). The mean duration of surgery for RN and NSS was 137 and 139 minutes, respectively. The mean warm ischemia time for NSS was 18.9 minutes. Serum creatinin level was increased 0.51mg/dl and 0.39mg/dl for RN and NSS after long-term follow up, respectively ($p<0.001$). Glomerular filtration rate (GFR) was ≥ 60 ml/min/m^2 in 47.6% and 74.8% of RN and NSS patients in long-term follow up, respectively ($p<0.001$).

Conclusion: Decrease in GFR was more prominent in RN compared to NSS patients in long term. Therefore, removing the whole kidney for especially T1 renal tumours is over treatment in most cases. Partial nephrectomy should be preferred for all T1 renal tumours whenever technically feasible.

Adressforcorrespondence: Uzm. Dr. Ahmet Güdeloğlu, Memorial Ankara Hastanesi, Mevlana Bulvarı 1422. Sok No:4 Balgat Çankaya Ankara Türkiye
e-mail: a_gudeloglu@yahoo.com
Available at www.actaoncologicaturcica.com

Key Words: Renal Cell Carcinoma, Radical Nephrectomy, Nephron Sparing Surgery, Glomerular Filtration Rate

Giriş

Konunun devamındaki paragraf ikinci sütuna geçtiğinde başlık ile aynı hizada olacak (diğer paragraf ile değil)Böbrekte yer işgal eden en yaygın solid lezyon renal hücreli karsinomdur (RHK) ve tüm böbrek tümörlerinin yaklaşık %90'ını oluşturur (1). Yetişkinlerdeki tüm kanserlerin yaklaşık %3'ünü oluşturan RHK, ürogenital sistemin en agresif tümörlerindendir ve prostat ile mesane kanserinden sonra 3. sıklıkta görülür (2). Amerika Birleşik Devletleri verilerine göre tahminen her 75 kişiden biri hayatı boyunca RHK geliştirecektir ve bununla birlikte RHK erkeklerde kanserden ölümde 7. sırada iken kadınlarda 8. sıradadır (3). Sonuçta RHK toplum sağlığını azımsanmayacak ölçüde tehdit eden önemli kanserlerden biridir.

Geçmişte RHK hastaları sıklıkla hastalığa ait "klasik triad" olarak bilinen; hematüri, yan ağrısı ve ele gelen kitle gibi belirti ve bulgularla doktora başvururlardı ve bu hastalara uygulanan tek küratif tedavi radikal nefrektomiydi (4). Günümüzde olguların %70'den fazlasını nonspesifik abdominal şikâyetlere sahip hastalara rutin olarak uygulanan görüntüleme tetkikleri sonucu tesadüfen saptanan olgular oluşturmaktadır. Özellikle son 20 yılda gelişen bu değişiklik, hastalığın evresinde ileri evreden erken evreye kaymaya sebep olmuştur.

Eskiden semptomatik RHK hastaları sıklıkla metastatik evrede yakalanırken ve kür olma şansını yitirirken günümüzde olguların çoğu hastalık henüz böbreğe lokalize halde iken tanı almakta ve uygulanan çeşitli nefron koruyucu cerrahi (NKC) yöntemlerle yüz güldürücü sonuçlar elde edilebilmektedir (5). Görüntüleme tekniklerindeki gelişme sadece tesadüfen saptanan renal kitle insidansını artırmakla kalmamış, aynı zamanda renal kitleler daha küçük boyutta yakalandıkları için, geçmiş dönemlere nazaran daha sık nefron koruyucu cerrahi yapılır hale gelmiştir.

Kronik böbrek hastalığı (KBH) glomerüler filtrasyon oranının (GFR) <60 ml/dk/1,73m^2 olması şeklinde tanımlanır. Renal kortikal tümörlü hastalarda RN, KBH gelişimi için önemli bir risk faktörüdür (6). KBH'nın kardiyovasküler hastalık için bağımsız bir risk faktörü olduğu ortaya konulmuştur (7). Bununla birlikte KBH olan hastalarda kardiyovasküler mortalite, KBH olmayanlara göre daha fazladır (32/1.000'e karşı 16/1.000)(8). Genç (<65 yaş) ve küçük renal kitleli (<4 cm) hastalarda RN ile NKC karşılaştırıldığında, RN'nin daha kısa genel sağkalım ile ilişkili olduğu gösterilmiştir (9). Görüntüleme ve ameliyat tekniklerindeki bu gelişmeler sonucunda günümüzde RHK hastalarında onkolojik başarı artık tek başına başarı olarak kabul edilemez. Asıl başarı kansere özgü sağkalım yanında; ameliyattan sonra korunan iyi bir renal rezerv ile genel sağkalımın da kanser dışı sebeplerle olumsuz etkilenmesini engellemektir.

Bu çalışmada, Hacettepe Üniversitesi Tıp Fakültesi Üroloji Anabilim Dalı'nda, 1990 yılından 2011 yılına kadar lokalize renal kitle nedeniyle cerrahi girişim yapılmış olan hastaların tüm verileri retrospektif olarak incelenerek, radikal nefrektominin ve NKC'nin böbrek fonksiyonunun en önemli göstergesi olan GFR üzerine etkilerini ortaya koymak hedeflenmiştir.

Hastalar ve Yöntem

Ocak 1990 ile Nisan 2011 tarihleri arasında böbrekte yer işgal eden lezyon nedeniyle laparoskopik veya açık yöntemle RN veya NKC yapılan 1016 hastanın klinik ve demografik verileri retrospektif olarak incelenmiştir. Hastaların ameliyat öncesi, ameliyat sonrası erken dönem ve uzun dönem sonundaki GFR değerleri hesaplanarak, RN ve NKC'nin GFR değerleri üzerine olan etkileri ve bu cerrahilerden sonra kalan renal rezerv ile sağkalım ilişkisi ortaya konulmaya çalışılmıştır.

Tanı anındaki ve son kontrole geldikleri tarihteki üre, kreatinin değerleriyle *Modification of Diet in Renal Disease* (MDRD) çalışması formülüne göre hesaplanmış GFR değerleri incelenmiştir (10). MDRD çalışmasına göre GFR "GFR=175 x

Adressforcorrespondence: Uzm. Dr. Ahmet Güdeloğlu, Memorial Ankara Hastanesi, Mevlana Bulvarı 1422. Sok No:4 Balgat Çankaya Ankara Türkiye
e-mail: a_gudeloglu@yahoo.com
Available at www.actaoncologicaturcica.com

(serum kreatinin)$^{-1.154}$ x (yaş)$^{-0.203}$ x 0.742 (eğer birey kadınsa)" formülü ile hesaplanmıştır.
Temel istatistiksel kavramlar ile hastaların özellikleri özetlenmiştir. Sayısal parametrelerin özetlenmesinde ortalama, standart sapma, ortanca, minimum ve maksimum değerleri gerekli durumlarda %95 güven aralıkları; kategorik değişkenler ise sayı ve yüzde değerleri kullanılmıştır. İstatistik anlamlılık sınırı (p) 0.05 olarak belirlenmiştir. İstatistiksel analizler SPSS ver 16.0 programı ile yapılmıştır.

Bulgular

Hacettepe Üniversitesi Tıp Fakültesi Üroloji Anabilim Dalı'nda Ocak 1990 - Nisan 2011 tarihleri arasında renal kitle nedeniyle ameliyat edilen 1016 hastaya ait veriler retrospektif olarak toplanmıştır. Tanı anında metastatik olduğu bilinen 78 olgu çalışma dışı tutulup, 938 hastanın verileri incelenmiştir.

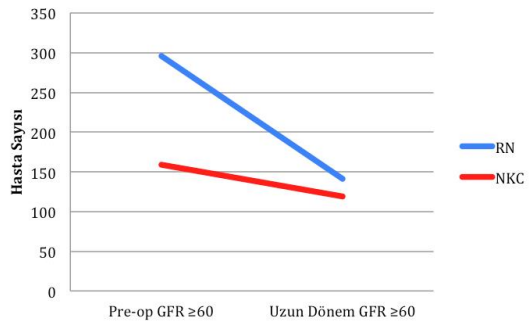
Çalışmaya alınan olguların 579 (%61,7)'u erkek ve 359 (%38,3)'u kadındır. 624 olguya (%66,5) RN, 314 olguya (%33,5) NKC yapılmıştır. Hastaların ortalama takip süresi 44.3±50.5 aydır. RN veya NKC yapılan hastaların yaş ortalaması sırasıyla 56,07±12,21 yıl ve 51,87±12,25 yıl olarak bulunmuştur (p<0,001). Cerrahi uygulanan renal kitlelerin ortalama radyolojik boyutu RN yapılan grupta 75±33,5 mm (4-250) iken, NKC yapılan grupta 37,8±26 mm (10-240) olarak hesaplanmıştır (p<0.001). Ortalama ameliyat süresi RN için 137,6±59,3 (45-500) dakika iken NKC için 139,5±51,6 (45-360) dakikadır. NKC uygulanan grupta ortalama sıcak iskemi süresi 18,9±6,8 (3-36) dakikadır. Patolojik incelemede RN yapılan grubun %10,2'si benign iken NKC uygulanan grubun %29'u benigndir (p<0.001). Hastaların uzun dönem takiplerinde hastalıksız sağkalım RN yapılan grupta %83,66 iken NKC uygulanan grupta %97,23'tür (p<0.001).
Preoperatif kreatinin ortalaması RN ve NKC uygulanan grupta sırasıyla 0,98±0,74 mg/dl (0,2-11,85) ve 0,89±0,28 mg/dl (0,39-2,41)'dir (p=0,135). Hastaların uzun dönem takip sonunda RN'de ve NKC'de kreatinin ortalamaları sırasıyla; 1,49±1,54 mg/dl ve 1,28±1,61 mg/dl'dir (p<0.001). RN yapılan gruptaki ortalama 0,51 mg/dl artış, NKC uygulanan gruptaki 0,39 mg/dl artıştan anlamlı şekilde daha fazladır (p<0.001).
Hastaların preoperatif GFR değerlerine bakılmaksızın uzun dönem takip sonunda GFR değerleri incelendiğinde; RN yapılan hastalardan son kontrol bilgilerine ulaşabildiğimiz toplam 351 hastanın 145 (%41.3)'inin GFR değeri ≥60 iken, NKC uygulanan grupta ise 178 hastanın 124 (%69.7)'ünün GFR değeri ≥60'dır (p<0.001) (Tablo 1).

Tablo 1. Ameliyat öncesi ve uzun dönem kontrolde GFR değerleri dağılımı

Preop GFR	**Uzun Dönem Kontrol GFR**	
	<60	**≥60**
RN		
<60 n=55	51 (92,7)	4 (7,3)
≥60 n=296	155 (52,4)	141 (47,6)
NKC		
<60 n=19	14 (73,7)	5 (26,3)
≥60 n=159	40 (25,2)	119 (74,8)
p	<0,001	<0,001

Ameliyat öncesi GFR değeri ≥60 olan hastaların ameliyat sonrası da ≥60 kalma oranları RN (n:296) ve NKC (n:159) hastalarında sırasıyla %47.6 ve %74.8 olarak bulunmuştur (p<0.001),(Şekil 1). Ameliyat öncesi GFR değeri < 60 olan hastaların ameliyat sonrası da <60 kalma oranları RN ve NKC için sırasıyla %92.7 ve %73.7'dir. Uzun dönemde RN yapılan hastalar NKC uygulanan hastalara göre daha fazla oranda GFR <60 olma durumunu sürdürmektedir (p<0.001).

Adressforcorrespondence: Uzm. Dr. Ahmet Güdeloğlu, Memorial Ankara Hastanesi, Mevlana Bulvarı 1422. Sok No:4 Balgat Çankaya Ankara Türkiye
e-mail: a_gudeloglu@yahoo.com
Available at www.actaoncologicaturcica.com



Şekil 1. Ameliyat öncesi GFR Değeri ≥60 mg/dk/m^2 olan hastaların uzun dönem GFR değerlerinin 60'ın üstünde kalma oranları

Tartışma

Renal hücreli karsinom insidansının artmasına, insidental erken tanı ile lokalize evreye doğru evre kaymasına, ameliyat tekniklerindeki gelişmelere ve daha fazla RN ve NKC uygulanmasına rağmen, RHK mortalitesi halen artmaktadır. Yaklaşık 34.500 hastanın incelendiği bir kohort çalışmasında yaşa uyarlanmış insidans 1983'den 2002 yılına kadar 100.000'de 7,1'den 10,8'e yükselmiştir. Bu artışın da büyük bir kısmından ≤4 cm tümörler sorumludur. Boyutu <2 cm ve 2-4 cm tümörlerin insidansı sırasıyla 100.000'de 2'den 3'e ve 1'den 3.3'e yükselmiştir. Bununla birlikte her tümör boyutuna ait kategoride böbrek cerrahisi, insidanstaki artışa paralel olarak artmıştır. Aynı çalışmada böbrek kanserine özgü ve genel mortalite oranları sırasıyla 100.000'de 1,2'den 3,2'ye ve 1,5'den 6,5'e yükselmiştir. Özellikle küçük tümörlerde daha fazla olmakla birlikte böbrek kanseri insidansı artmasına ve buna paralel olarak böbrek kanseri cerrahisi daha sık yapılmasına rağmen, en azından küçük tümörlerde bile mortalite oranları artmaya devam etmiştir (11). Böbrek kanseri tedavisindeki bu güncel paradoks tüm küçük renal kitleli hastalara uygulanan cerrahi girişimlerin uygunluğunu sorgulatmaktadır.

Geçmişten beri süregelen yanlış düşüncelerden birisi de normal kontralateral böbreği olan hastalarda tümör tarafından tutulmamış normal renal parankimin, RN ile feda edilmesine bağlı serum kreatinindeki kalıcı yüksekliğin, uzun dönemde ciddi yan etkiye neden olmayacağıdır. Bu düşüncenin oluşmasındaki en önemli sebep 20 yıldan fazla takip edilen donör nefrektomi yapılan hastalarda normal popülasyona kıyasla daha fazla oranda herhangi bir ciddi hastalık, diyaliz ihtiyacı gerektirecek böbrek yetmezliği ve ölüm görülmediğinin bildirilmiş olması gerçeğidir (12). Böbrek donörleri ile böbrek tümörlü hastalar arasında dikkat edilmesi gereken önemli bir nüans, donörler pek çok komorbidite açısından taranmış, dikkatle seçilmiş sağlıklı ve sıklıkla genç (<40 yaş) insanlar iken, böbrek tümörlü hastalar bu durumun tam tersi olarak, genellikle daha yaşlı ve sıklıkla metabolik sendrom, hipertansiyon, koroner arter hastalığı, obezite ve diyabet gibi böbrek fonksiyonunu da etkileyebilecek çok çeşitli komorbiditelerden bir veya birkaçına sahiptirler.

Kronik böbrek hastalığı (KBH) insidansı ve prevalansı gün geçtikçe artan büyük bir sağlık problemidir. GFR değerinin <60 ml/dk/1,73m^2 olması şeklinde tanımlanan KBH'nin risk faktörleri; 60 yaşından büyük olma, hipertansiyon, diyabet, kardiyovasküler hastalık ve böbrek hastalığı aile öyküsüdür. Amerika'da günümüzde erken evre KBH'ye sahip 19 milyon yetişkinin olduğu ve 2030 yılında 2 milyonunun kronik diyalize veya renal transplantasyona gereksinim duyacağı tahmin edilmektedir (15).

Toplum tabanlı büyük bir çalışmada tahmini GFR azaldıkça, ölüm, kardiyovasküler olay ve hastanede yatış riskinin arttığı gösterilmiştir (17). RN, KBY gelişimi için önemli bir risk faktörüdür. Küçük renalkortikal tümörlerin yaklaşık %20'sinin benign patolojiye sahip olduğu için, RN'nin artık altın standart yöntem olarak görülmemesi gerektiği kabul edilmiş bir gerçektir (6, 18).

Mayo klinik ekibinin 2000 yılında tek taraflı RHK, diğer böbreği ve kreatinin değeri normal olan hastalarda RN ile NKC'yi karşılaştırdığı bir çalışmada kreatinin değerinin >2 mg/dl olması şeklinde tanımlandığı kronik renal yetmezlik, 10 yıllık takip sonunda RN grubunda %22,4 iken NKC grubunda %11,6 olarak bulunmuştur. Bununla birlikte RN grubunda daha fazla oranda protenüri olduğu da gösterilmiştir (%55,2'ye karşı %34,5). RN'nin daha fazla kronik böbrek yetmezliği ve proteinüri riski taşıdığı ve NKC ile onkolojik sonuçlar açısından fark olmadığı 15 yıl önce Mayo klinikten bildirilmiştir. Bu nedenle

Adressforcorrespondence: Uzm. Dr. Ahmet Güdeloğlu, Memorial Ankara Hastanesi, Mevlana Bulvarı 1422. Sok No:4 Balgat Çankaya Ankara Türkiye
e-mail: a_gudeloglu@yahoo.com
Available at www.actaoncologicaturcica.com

normal kontralateral böbrekli ve tek taraflı RHK olan hastalarda NKC uygulanması gerekliliğini savunmuşlardır (21). Bundan 2 yıl sonra Memorial Sloan - Kettering Cancer Center'den bildirilen çalışmada, RN ve NKC yapılan hastaların ortanca 25 ay takip sonunda kreatinin değerinin 1,5 mg/dl ve 1,0 mg/dl olduğu bildirilmiştir (p<0.001)(22). Bizim verilerimizde de preoperatif kreatinin değerlerinde farklılık yok iken uzun dönem takipte kreatinin değeri ortalaması RN grubunda NKC grubundan daha fazladır.

Lokalize renal kitle nedeniyle 1995 ile 2005 yılları arasında opere edilen 1.500 hastanın 10 yıldan fazla takip sonuçlarının incelendiği bir başka çalışmada ameliyat öncesi GFR, vücut kitle indeksi (VKİ) ve komorbidite ile hastalıksız sağkalım arasında ilişki gösterilememiştir. Bununla birlikte hafif azalmış GFR (45-60 ml/dk/1,73m^2) ve ciddi derecede azalmış GFR (<45 ml/dk/1,73m^2) ile genel sağkalım arasında anlamlı ilişki gösterilmiştir (23). Küçük renal kitlelerde RN ile NKC'yi karşılaştıran bir başka çalışmada tüm yaş gruplarında genel sağkalımı benzer bulunmuş, hâlbuki 65 yaş altındaki 327 hastada NKC daha iyi sağkalıma sebep olmuştur (p=0.002) (9). Yaklaşık 2550 RN ve 550 NKC yapılan hastanın kardiyovasküler olay açısından karşılaştırıldığı bir çalışmada da RN yapılan grupta hem daha fazla oranda genel mortalite (%32,1' e karşı %19,8) hem de 1,4 kat artmış ilk kardiyovasküler olay riski olduğu gösterilmiştir (24).

Hacettepe verilerine göre ortalama kreatinin değerindeki artış uzun dönemde RN hastalarında NKC uygulananlardan daha fazladır (p<0.001). Preoperatif GFR'si≥60 olan hastalarda, bunun ameliyat sonrası uzun dönemde 60'ın altına düşme oranı da RN yapılan grupta NKC uygulanan gruba göre daha fazladır (p<0.001). GFR değerlerindeki bu anlamlı değişiklik bile yukarıdaki literatürde bahsedilen, KBH, kardiyovasküler olay ve ölüm üçgeninde bizim elektif NKC yapma doğrultusunda duruşumuzu daha da sağlamlaştırmaktadır. İlerleyen yıllarda uzayan takip süreleri ile bu fark çok daha hissedilir düzeye ulaşacaktır. Onkolojik sonuçlardan ödün vermeden tedavi kararını belirlerken dikkat edilmesi gereken en önemli husus, böbrek fonksiyonlarının korunmasıdır. Bu bağlamda böbreğe lokalize RHK'nin güncel tedavisi; mükemmel sağkalım ve yüz güldürücü onkolojik sonucu nedeniyle NKC'dir(19). Avrupa ve Amerika Üroloji Dernekleri'nin kılavuzlarında T1 böbrek tümörü tedavisinde artık NKC altın standart yöntem olmuş ve komorbiditesi nedeniyle cerrahisi riskli olan hastalarda ablatif yöntemler ve izlem kendine yer bulmuştur (1, 20).

Sonuç

Tüm bu bilgiler ışığında çalışma sonuçları özetlenecek olursa; günümüzde insidental olarak saptanan renal kitlelerin özellikle de lokalize olanların insidansı artmıştır. Buna paralel olarak NKC yapılma oranı da artmaktadır. Geçmişten beri süregelen RN deneyimi bize soliter böbrekte tümörü olan hastalarının daha fazla oranda KBH sürecine girdiğini göstermiştir. KBH sürecindeki hastalarda da daha fazla oranda kardiyovasküler olay ve buna bağlı ölüm görüldüğü literatür verileriyle ispatlanmış bir gerçektir. Lokalize böbrek tümörü nedeniyle RN ile NKC yapılan hastalar karşılaştırıldığında da kansere özgü sağkalımda fark yokken genel sağkalımın RN yapılan grupta daha düşük olmasının en rasyonel sebebinin bu hastalarda uzun dönem takipte gelişen KBH olması muhtemeldir.

Bizim verilerimize göre de RN yapılan hastalarda NKC uygulananlara göre GFR, uzun dönemde daha fazla oranda azalmaktadır. Bunun yanı sıra lokalize renal kitleler için NKC hala yeteri kadar sıklıkta yapılmamaktadır. Hastayı RN ile tümörden tamamıyla kurtardıkları için kendilerini kahraman olarak gören cerrahlar, uzun dönemde RN ameliyatının çok da masum bir işlem olmadığını hesaba katmalı ve teknik olarak çıkarılması mümkün olan her renal kitleye artık günümüzde lokalize böbrek tümörünün standart tedavisi haline gelmiş olan NKC işlemini uygulamalıdırlar.

Çıkar Çatışması: Yok

Adressforcorrespondence: Uzm. Dr. Ahmet Güdeloğlu, Memorial Ankara Hastanesi, Mevlana Bulvarı 1422. Sok No:4 Balgat Çankaya Ankara Türkiye
e-mail: a_gudeloglu@yahoo.com
Available at www.actaoncologicaturcica.com

Referanslar

1. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. EAU guidelines on renal cell carcinoma: the 2010 update. European urology. 2010;58(3):398-406. Epub 2010/07/17.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer Journal international du cancer. 2010;127(12):2893-917. Epub 2011/02/26.
3. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59(4):225-49.
4. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. The Journal of urology. 1969;101(3):297-301. Epub 1969/03/01.
5. Chen DY, Uzzo RG. Evaluation and management of the renal mass. Med Clin North Am. 2011;95(1):179-89. Epub 2010/11/26.
6. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. The lancet oncology. 2006;7(9):735-40. Epub 2006/09/02.
7. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation. 2003;108(17):2154-69.
8. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA. 2005;293(14):1737-45. Epub 2005/04/14.
9. Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Cheville JC, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. The Journal of urology. 2008;179(2):468-71; discussion 72-3. Epub 2007/12/14.
10. Tamura MK, Anand S, Li S, Chen S-C, Whaley-Connell AT, Stevens LA, et al. Comparison of CKD awareness in a screening population using the Modification of Diet in Renal Disease (MDRD) study and CKD Epidemiology Collaboration (CKD-EPI) equations. Am J Kidney Dis. 2011;57(3):S17-S23.
11. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst. 2006;98(18):1331-4. Epub 2006/09/21.
12. Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living kidney donors. Lancet. 1992;340(8823):807-10. Epub 1992/10/03.
13. Kaplan C, Pasternack B, Shah H, Gallo G. Age-related incidence of sclerotic glomeruli in human kidneys. Am J Pathol. 1975;80(2):227-34. Epub 1975/08/01.
14. Bijol V, Mendez GP, Hurwitz S, Rennke HG, Nose V. Evaluation of the nonneoplastic pathology in tumor nephrectomy specimens: predicting the risk of progressive renal failure. Am J Surg Pathol. 2006;30(5):575-84. Epub 2006/05/16.
15. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298(17):2038-47. Epub 2007/11/08.
16. Suleymanlar G, Utas C, Arinsoy T, Ates K, Altun B, Altiparmak MR, et al. A population-based survey of Chronic REnal Disease In Turkey--the CREDIT study. Nephrol Dial Transplant. 2011;26(6):1862-71. Epub 2010/11/06.
17. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305. Epub 2004/09/24.
18. Remzi M, Ozsoy M, Klingler HC, Susani M, Waldert M, Seitz C, et al. Are small renal tumors harmless? Analysis of histopathological features according to tumors 4 cm or less in diameter. The Journal of urology. 2006;176(3):896-9. Epub 2006/08/08.
19. Van Poppel H, Becker F, Cadeddu JA, Gill IS, Janetschek G, Jewett MA, et al. Treatment of localised renal cell carcinoma. European urology. 2011;60(4):662-72. Epub 2011/07/06.
20. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for management of the clinical T1 renal mass. The Journal of urology. 2009;182(4):1271-9. Epub 2009/08/18.
21. Leibovich BC, Blute M, Cheville JC, Lohse CM, Weaver AL, Zincke H. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. The Journal of urology. 2004;171(3):1066-70. Epub 2004/02/10.
22. McKiernan J, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. Urology. 2002;59(6):816-20. Epub 2002/05/29.
23. Pettus JA, Jang TL, Thompson RH, Yossepowitch O, Kagiwada M, Russo P. Effect of baseline glomerular filtration rate on survival in patients undergoing partial or radical nephrectomy for renal cortical tumors. Mayo Clin Proc. 2008;83(10):1101-6. Epub 2008/10/03.
24. Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? The Journal of urology. 2009;181(1):55-61; discussion -2. Epub 2008/11/18.

Adressforcorrespondence: Uzm. Dr. Ahmet Güdeloğlu, Memorial Ankara Hastanesi, Mevlana Bulvarı 1422. Sok No:4 Balgat Çankaya Ankara Türkiye
e-mail: a_gudeloglu@yahoo.com
Available at www.actaoncologicaturcica.com

Clinical, Radiological and Surgical Pitfalls in Fibular Tumors

Fibula Yerleşimli Tümörlerde Klinik, Radyolojik ve Cerrahi Tuzaklar

Hasan Göçer[1], Alper Çıraklı[2], Halil Atmaca[3], Nevzat Dabak[1]

[1]Department of Orthopedic and Traumatology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey
[2]Orthopedic and Traumatology Clinic, Kayseri Research and Training Hospital, Kayseri, Turkey
[3]Department of Orthopedic and Traumatology, Faculty of Medicine, Akdeniz University, Antalya, Turkey

Dergiye Ulaşma Tarihi: 02/06/2016 Dergiye Kabul Tarihi: 21/07/2016 Doi: 10.5505/aot.2016.50251

ÖZET

Giriş ve Amaç: Fibula kaynaklı tümörler daha az sıklıkla görülmekle birlikte çoğunun lokal agresif ve malign olmasından dolayı önem arz etmektedir. Fibula kaynaklı tümör nedeniyle tedavi edilen hastalar incelenerek, tanı ve tedavideki tuzak noktalara dikkat çekilmesi amaçlandı.
Yöntem ve Gereçler: Mayıs 2007 ile Haziran 2015 tarihleri arasında fibula yerleşimli tümör nedeniyle tanı ve tedavi edilmiş 36 hasta retrospektif olarak incelendi. Hastaların yaşı, cinsiyeti ve lezyonların lokalizasyonu belirlendi. Tümörün radyolojik özellikleri, histolojik tipi, uygulanan rezeksiyon tipi ve komplikasyonlar incelendi.
Bulgular: Hastaların 20' si kadın, 16' sı erkek olup yaş ortalaması 31.5 (6-74) yıl bulundu. Fibula 1/3 proksimal bölge 26, 1/3 orta bölge 6, 1/3 distal bölge 4 hastada tespit edildi. Histolojik olarak tümörlerin 23' ü bening, 9' u malign ve 4' ü metastatik tümördü. Hastaların 19'una intralezyonel küretaj, 15' ine geniş rezeksiyon ve 2' sine amputasyon uygulandı.
Tartışma ve Sonuç: Fibula diz eklemi ve ayak bileği stabilitesine katkısı ve proksimalde nörovasküler yapılara yakın komşuluğu nedeniyle birtakım cerrahi zorluklar içermektedir. Radyolojik olarak tümörün sınırları ve ne kadar kemiğin feda edilebileceği iyi planlanmalıdır. İyi bir planlama ve dikkatli bir cerrahi tedavi ile tümörün komplikasyonsuz bir şekilde uzaklaştırılabileceği kanaatindeyiz.
Anahtar Kelimeler: Fibula tümörü, Geniş rezeksiyon, Cerrahi sınır

ABSTRACT

Introduction: Although fibula based tumors are less common, they are important since a great number of them are local aggressive and malign. The purpose of this study is to evaluate the patients with fibula based tumors and to focus on pitfalls in diagnosis and treatment.
Methods: 36 patients who had been diagnosed with and treated for tumor involving fibula between May 2007 and June 2015 were examined retrospectively. The patients' ages, genders and localizations were specified. Tumor's radiologic features and histological type, type of resection and complications were analyzed.
Results: 20 of the patients were women, while 16 were men and the average age of the patients was 31.5 (6-74) years of age. Tumor was found in fibula 1/3 proximal zone of 26 patients, in fibula 1/3 middle zone of 6 patients and in fibula 1/3 distal zone of 4 patients. Histological, 23 were benign, 9 were malign and 4 were metastatic tumors. Intralesional curettage was performed on 19 patients, wide resection was performed on 15 patients and amputation was performed on 2.
Discussion and Conclusion: Fibula involves some surgical difficulties because of its contribution to knee joint and ankle stability and its close adjacency to neurovascular structures in proximal. Radiologically, tumor borders and how much bone can be sacrificed should be planned well. With a good planning and a careful surgical treatment, tumor can be removed without complications.
Keywords: Fibula tumor, Wide resection, Surgical margins

Adress for correspondence: Alper Çıraklı, Orthopedic and Traumatology Clinic, Kayseri Research and Training Hospital, Kayseri, Turkey
e-mail:alperomu@gmail.com
Available at www.actaoncologicaturcica.com

Introduction

Fibular tumors make up 2.4% of all extremity tumors and most of these are in proximal 1/3. Wide resection is preferred since they are generally composed of local aggressive or malign tumors. However, due to fibula's contribution to joint stability and its close adjacency to important neurovascular structures, it makes surgical interventions more complicated (1). On the other hand, the goal is making sure that the remaining part is functional and creates least morbidity while completely removing the part where the tumor is.

Different resection types are recommended for proximal fibula and the integrity of lateral collateral ligament should be maintained (2). In distal fibula, ligament reconstruction or arthrodesis methods are applied to increase ankle stability (3, 4). However, since fibula tumors are rare and since it is not possible to get ideal resection all the time, it may cause some complications such as instability in joints and local relapse in tumor. Although the reason for local relapse is generally the tumor's not being removed completely, there are no studies about the radiological borders of fibula tumors and surgical border (5, 6)

In this study, we analyzed the fibular tumors we came across in clinic and discussed the clinical difficulties, radiological features and surgical pitfalls with the literature.

Methods:

After local ethical board permissions were taken, patients recorded in two central tumor archives were scanned between May 2007 and June 2015. Age, gender, and anatomic locations were found. The sizes of tumors were calculated with radiological images such as X-Ray, computerized tomography (CT), magnetic resonance imaging (MRI), whole body bone scintigraphy and thorax CT and later they were compared with the sizes of the removed resection bone. Histopathological type, amount of the resection and complications were found. Patients who did not have files and radiological data, those whose histological types were not known and those who did not receive surgery were not included in the study.

Results:

36 patients were included in the study. 20 of the patients were women, while 16 were men and the average age of the patients was 31.5 (6-74) years of age. Tumor was found in fibula 1/3 proximal zone of 26 patients, in fibula 1/3 middle zone of 6 patients and in fibula 1/3 distal zone of 4 patients. The patients were divided in two groups as benign and malign (Table 1).

The surgical excision of cases according to fibula localization has been shown in Table 2. Type I excision defined by Malawer et al. (7) was performed on 4 patients while type II excision was performed on 2 patients, modified excision defined by Mootha et al. (8) was performed on 4 patients and above-knee amputation was performed on one patient in wide resection. Wide excision was performed on 3 diaphysis located ewing sarcoma cases and 2 metastasis (Figure 1). Biopsy was made on one lymphoma patient for diagnosis. In patients with fibula distal involvement, osteochondroma excision was performed in 2, intralesional curettage was performed in one and below-knee amputation was performed in one patient due to relapse of tumor who had previously total distal fibula excision and ankle arthrodesis (Figure 2) (Table 2).

In primary fibula malign tumors, such as especially ewing sarcoma, osteosarcoma and chondrosarcoma, it was found that the tumor continued in 6 of 8 patients within first resection borders when compared with the preoperative

Adress for correspondence: Alper Çıraklı, Orthopedic and Traumatology Clinic, Kayseri Research and Training Hospital, Kayseri, Turkey
e-mail:alperomu@gmail.com
Available at www.actaoncologicaturcica.com

tumor sizes. Tumor sizes were measured by radiologicaly before and after operation in Table 3. Radiologically and surgical resection sizes were measured in Table 3. In one of the patients who were operated, fibula proximal zone was sacrificed, since peroneal nerve and tibialis anterior artery continued in tumor. 4 patients were found to have drop foot, while three of these patients recovered in follow-up period, drop foot has continued in one patient whose fibular nerve was resected. In 2 of the 6 patients who underwent fibula proximal type I and type II excision, knee instability developed. One of these patients was performed lateral collateral ligament (LCL) reconstruction, the other one was followed with above knee bracing. Both patients however, they were amputated due to relapse, which included neurovascular structures.

Discussion:

With the developments in orthopedic oncology, adjuvant, neoadjuvant chemotherapy and radiotherapy, 5 yearlong patient survival rises from 10% to 70% (9). With this increase in survival, it is a must to gain the most functional extremity in the remaining anatomy as well as removing the tumor. Most of the fibula tumors are located proximal section of the bone (10). The benign tumors in this area can be removed without causing too much morbidity. However, since local aggressive and malign tumors need to be removed with wider borders, they may cause knee instability and neurovascular complications. Thus, the anatomy of the area should also be considered while determining the surgical excision. Ligament repair after excision becomes more important (11).

Different resection types have been recommended in fibula proximal zone (7, 11). According to Malewer (7) type I resection is performed for benign aggressive, low-grade malignant tumors and metastatic. Type II resection is performed for high-grade malignant tumors, Erler et al. (11) modified Malawer classification by adding two more detailed types of resection. Dieckman et al. (4) claimed that previous classification systems were dependent on the tumour differentiation but not on the tumour size or extension (12). Thus, they reported new classification system. They used this new classification system independent of the surgical margins. Authors stated that, there has to be a proximal area of more than 3-4 cm. of healthy bone in order to preserve the LCL in malignant tumors. If there is less than 3-4 cm. of healthy bone an intraarticular resection of the proximal fibula with the LCL must be cut.

Clinical problems, fibula related pathologies may be neglected in outpatients and give priority to adjacent anatomic structures. Knee joints come to mind first and inside the knee are evaluated (13, 14). Tumors, which affect fibular nerve, are evaluated as pitfall neuropathy (15). In cururis middle zone pathologies, tibia is generally evaluated in the foreground and fibular pathologies are neglected. Although distal fibula tumors are less common, lateral malleolus is relatively taken into consideration more while evaluating ankle (16). Thus, we think that distal fibula (lateral malleolus) pathologies are luckier in terms of clinical doubt and diagnosis.

Regarding to radiologic diffucuities on evaluation, when pathology about the cururis area comes to mind, images of all anatomical structures should be taken. In plain radiograph, pathologies in fibula proximal zone should not be overlooked while focusing on pathologies inside the joint. Fibula cortical continuity should be followed and its super position with tibia proximal zone should be taken into consideration. MRI helps the measurement of tumor sizes and measurement of intramedullary extension and soft tissue sizes (17). In tumors which extend the cortex, fibular nerve and the

Adress for correspondence: Alper Çıraklı, Orthopedic and Traumatology Clinic, Kayseri Research and Training Hospital, Kayseri, Turkey
e-mail:alperomu@gmail.com
Available at www.actaoncologicaturcica.com

anterior tibial artery in its medial should be assessed and its association with the tumor should be revealed. In their study on 316 patients with tumor, Panicek et al. (18) reported that MRI was not better than CT. There are also studies which show that MRI is better than PET CT (17). Grimmer et al. (9) reported that insufficient marginal excision was higher in fibular osteosarcomas. In these study, resection which passed from 2 cm. away from the sizes measured according to radiological images were performed in 8 patients due to primary malign fibula tumor. In our malign fibula tumor cases, preoperative radiological measurements were not found to be parallel to our intraoperative frozen section. The reason for this may be the fact that fibula has narrower and more spiral medulla when compared with femur and tibia. In bones with a narrow medulla such as fibula, medulla extended tumors such as ewing sarcoma and osteosarcoma should be given more attention. Frozen section should be performed from surgical margins and resection should be made from wider margins when necessary. Surgical margin check should be made in patients who had curettage, resection and excision due to benign or local aggressive fibula tumor.

Surgical difficulties on treatment, proximal zone is less experienced since it is less common in orthopedic oncology when compared with other bones. In fibula proximal local aggressive and malign tumors, type II resection is recommended; however, this surgery should be performed very carefully (7). An especially deep branch of peroneal nerve has motor functions and it should be protected to the utmost. However, it can be sacrificed in cases if the nerve is surrounded in malign tumors (19). In the unplanned and careless surgeries of this area, peroneal nerve injury, artery-vein injury and knee instability may develop (10). Peroneal nerve injury was seen in 4 of the 26 patients with fibula proximal zone tumor. One of these patients developed permanent drop foot since peroneal nerve was not protected due to tumor, the other three patients had complete recovery. Modified resection technique has been defined in fibula proximal zone osteochondroma in order to protect LCL (8). LCL reconstruction should be performed to prevent knee instability. In two of the patients who extended to fibula proximal, knee instability developed. Two was treated with LCL reconstruction, while the other was treated with above knee bracing. Since artery is more resistant to invasion and more important than vein, it may be protected more (20). In case of need, the association between vascular structure-tumor should be examined in lumen invasion or thrombus with advanced techniques such as CT angio (21). While chemotherapy and radiotherapy can decrease with efficient use, amputation may be a treatment option in malign tumors with posterior tibial artery and tibial nerve invasion (22). Amputation was performed on our two patients who had undergone surgery due to giant cell tumor and chondrosarcoma after a relapse which surrounded neurovascular structures was found.

In fibula 1/3 middle diaphysis involved tumor excision, knee and ankle stability is not much affected (23). Morbidity of excision in this area is less and more reliable surgical excision can be made. There is medial arterial collateral sirculation in the medial of fibula diaphysis area. This collateral circulation should be protected if vascular invasion is not. In diaphysis located tumors, the narrowness of medulla and the insufficiency of images should be taken into consideration and frozen should be performed and in case of positive margin, the margins of the resection should be extended to safer borders.

Distal fibula tumors are rare and when compared with the proximal zone, its

Adress for correspondence: Alper Çıraklı, Orthopedic and Traumatology Clinic, Kayseri Research and Training Hospital, Kayseri, Turkey
e-mail:alperomu@gmail.com
Available at www.actaoncologicaturcica.com

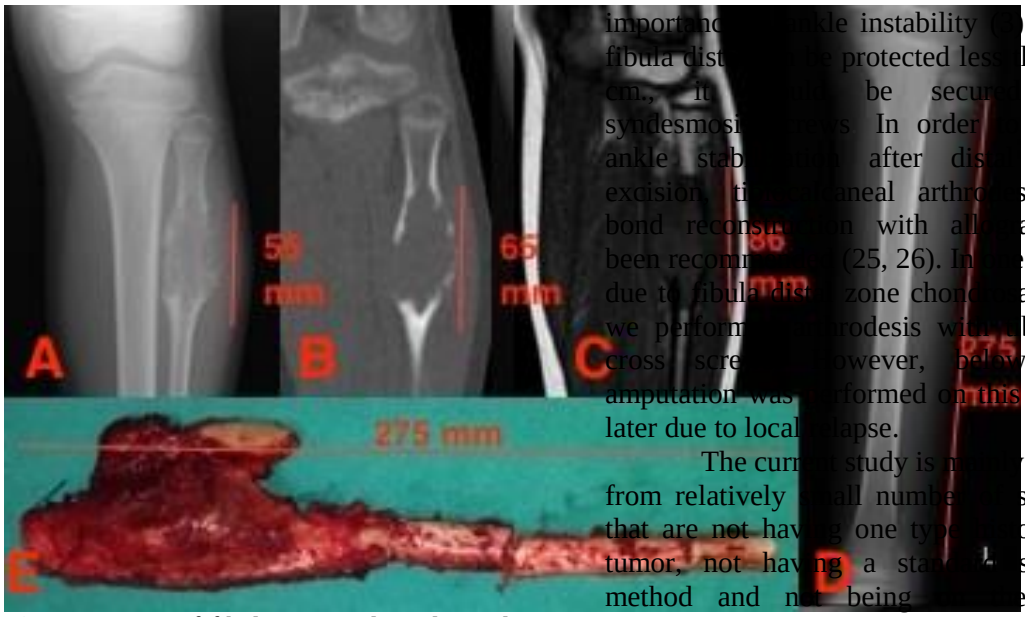


Figure 1: Size of fibula proximal 1/3 located Osteosarcoma. Preoperative imaging A. X-ray, B. CT, C. MRI, Postoperative imaging D. X-ray, E. intraoperative view.

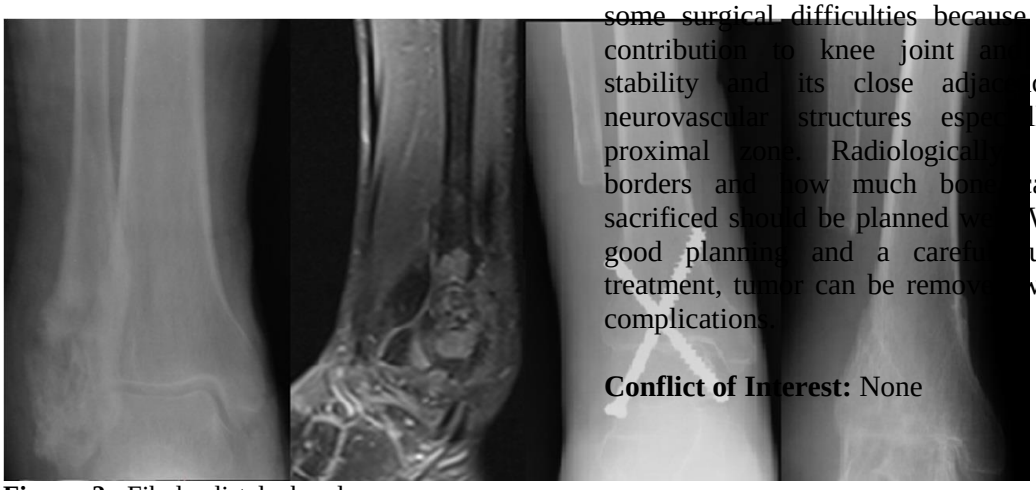


Figure 2: Fibula distal chondrosarcoma was excision and ankle arthrodesis.

surgical resection is easier and its prognosis is better due to its being far from neurovascular structures (24). However, it should be protected due to its importance in ankle instability (27). If the fibula distal can be protected less than 3-5 cm., it should be secured with syndesmosis screws. In order to secure ankle stability after distal fibula excision, tibiocalcaneal arthrodesis and bond reconstruction with allograft has been recommended (25, 26). In the patient, due to fibula distal zone chondrosarcoma, we performed arthrodesis with biotalar cross screw. However, below knee amputation was performed on this patient later due to local relapse.

The current study is major suffers from relatively small number of subjects that are not having one type of biological tumor, not having a standard surgical method and not being in the same anatomical region. Nonetheless, the present study includes information that might be a reference for the future studies, which will perform dynamic, prospective, case control studies on knee and ankle biomechanics.

As a conclusion, Fibula involves some surgical difficulties because of its contribution to knee joint and ankle stability and its close adjacency to neurovascular structures especially in proximal zone. Radiological tumor borders and how much bone can be sacrificed should be planned well. With a good planning and a careful surgical treatment, tumor can be removed without complications.

Conflict of Interest: None

Adress for correspondence: Alper Çıraklı, Orthopedic and Traumatology Clinic, Kayseri Research and Training Hospital, Kayseri, Turkey
e-mail:alperomu@gmail.com
Available at www.actaoncologicaturcica.com

Table 1: Histopathological types of cases.

	Tumor	Case number
Benign bone tumor (23)	Osteochondroma	8
	Aneurismal bone cyst	6
	Giant cell tumor	3
	Simple bone cyst	2
	Enchondroma	2
	Osteoid osteoma	2
Malign bone tumor (13)	Ewing sarcoma	3
	Osteosarcoma	3
	Chondrosarcoma	2
	Lymphoma	1
	Metastatic bone tumor	4

Table 2: The surgical excision of cases according to fibula localization.

	Proximal 1/3	Middle 1/3	Distal 1/3
Excision (Intralesional curettage)	15	1	3
Wide resection	10	5	-
Amputation	1	-	1
Total	**26**	**6**	**4**

Table 3: Comparison of radiologically measured tumor sizes and tumor sizes with negative resected borders.

OS: Osteosarcoma, EW: Ewing sarcoma, CS: Chondrosarcoma, G: Gender.

Case	Age Year	Histology	G	Side	Localization	X-ray (mm)	CT (mm)	MRI (mm)	Excision (mm)
1	10	OS	M	Left	1/3 proximal	60	105	115	250
2	13	EW	F	Left	1/3 middle	90	125	170	270
3	17	OS	M	Right	1/3 proximal	70	120	145	240
4	52	CS	M	Left	1/3 distal	60	68	73	103
5	9	EW	M	left	1/3 middle	80	84	96	175
6	12	EW	F	Right	1/3 middle	65	69	76	145

References:

Adress for correspondence: Alper Çıraklı, Orthopedic and Traumatology Clinic, Kayseri Research and Training Hospital, Kayseri, Turkey
e-mail:alperomu@gmail.com
Available at www.actaoncologicaturcica.com

1. Zhao SC, Zhang CQ, Zhang CL. Reconstruction of lateral knee joint stability following resection of proximal fibula tumors. Exp Ther Med. 2014;7(2):405-10
2. Patil RS, Saindane K, Surwade AP, Chinchole SS. Giant Cell Tumor of Proximal Fibula Treated With En Block Resection: A Case Report. IJHSR. 2015;5(1):398-401
3. Perisano C, Marzetti E, Spinelli MS, Graci C, Fabbriciani C, Maffulli N, et al. Clinical management and surgical treatment of distal fibular tumours: a case series and review of the literature. Int Orthop. 2012;36(9):1907-13
4. Dieckmann R, Ahrens H, Streitbürger A, Budny TB, Henrichs MP, Vieth V, et al. Reconstruction after wide resection of the entire distal fibula in malignant bone tumours. Int Orthop. 2011;35(1):87-92
5. Leichtle C, Leichtle U, Gärtner V, Schimmel H, Hartmann J, Rudert M. Multiple skeletal metastases from a giant cell tumour of the distal fibula with fatal outcome. J Bone Joint Surg Br. 2006;88(3):396-9
6. Gikas P, Keller S, Boyle R, Stalley P. Principles of the surgical management of bone tumours. Orthopaedics and Trauma. 2015;29(3):160-2
7. Malawer MM. Surgical management of aggressive and malignant tumors of the proximal fibula. Clin Orthop Relat Res. 1984;186:172-81
8. Mootha A, Saini R, Dhillon M, Bali K, Dhatt S, Kumar V. Modified resection technique for proximal fibular osteochondromas. Orthop Traumatol Surg Res. 2011;97(5):569-73
9. Grimer R, Taminiau A, Cannon S. Surgical outcomes in osteosarcoma. J Bone Joint Surg Br. 2002;84(3):395-400
10. Abdel MP, Papagelopoulos PJ, Morrey ME, Wenger DE, Rose PS, Sim FH. Surgical management of 121 benign proximal fibula tumors. Clin Orthop Relat Res. 2010;468(11):3056-62
11. Erler K, Demiralp B, Ozdemir MT, Basbozkurt M. Treatment of proximal fibular tumors with en bloc resection. The Knee. 2004;11(6):489-96
12. Dieckmann R, Gebert C, Streitbürger A, Henrichs M-P, Dirksen U, Rödl R, et al. Proximal fibula resection in the treatment of bone tumours. Intl Orthop. 2011;35(11):1689-94
13. Kwon JH, Han JH, Almeida VR, Kim SH, Park HJ, Nha K-W. Localized Pigmented Villonodular Synovitis of the Proximal Tibiofibular Joint. KSRR. 2014;26(4):249-52.
14. Mhuircheartaigh JN, Lin YC, Wu JS. Bone tumor mimickers: A pictorial essay. Indian J Radiol Imaging. 2014;24(3):225-36
15. Paprottka FJ, Machens HG, Lohmeyer JA. Partially irreversible paresis of the deep peroneal nerve caused by osteocartilaginous exostosis of the fibula without affecting the tibialis anterior muscle. J Plast Reconstr Aesthet Surg. 2012;65(8):223-5
16. Papagelopoulos PJ, Savvidou OD, Mavrogenis AF, Galanis EC, Shaughnessy WJ, Unni KK, et al. Lateral malleolus en bloc resection and ankle reconstruction for malignant tumors. Clin Orthop Relat Res. 2005(437):209-18
17. Schmidt GP, Schoenberg SO, Schmid R, Stahl R, Tiling R, Becker CR, et al. Screening for bone metastases: whole-body MRI using a 32-channel system versus dual-modality PET-CT. Eur Radiol. 2007;17(4):939-49
18. Panicek DM, Gatsonis C, Rosenthal DI, Seeger LL, Huvos AG, Moore SG, et al. CT and MR imaging in the local staging of primary malignant musculoskeletal neoplasms: Report of the Radiology Diagnostic Oncology Group. Radiology. 1997;202(1):237-46
19. Takahashi S, Ogose A, Tajino T, Osanai T, Okada K. Osteosarcoma of the proximal fibula. An analysis of 13 cases in the northern Japan. Ups J Med Sci. 2007;112(3):366-72
20. Holzapfel K, Regler J, Baum T, Rechl H, Specht K, Haller B, et al. Local Staging of Soft-Tissue Sarcoma: Emphasis on Assessment of Neurovascular Encasement-Value of MR Imaging in 174 Confirmed Cases. Radiology. 2015;275(2):501-9
21. Feydy A. Multidetector CT angiography for vascular invasion of musculoskeletal tumors-Response. Radiological Soc North America 820 Jorie BLVD, Oak Brook, IL 60523 USA; 2007. p. 634
22. Saglik Y, Yildiz Y, Atalar H, Basarir K. Primary angiosarcoma of the fibula: a case report. Acta Orthop Belg. 2007;73(6):799-803
23. Bozkurt M, Yavuzer G, Tönük E, Kentel B. Dynamic function of the fibula. Gait analysis evaluation of three different parts of the shank after fibulectomy: proximal, middle and distal. Arch Orthop Traum Su. 2005;125(10):713-20
24. Lee S, Kim H-S, Park Y-B, Rhie T-Y, Lee H. Prosthetic reconstruction for tumours of the distal tibia and fibula. J Bone Joint Surg Br. 1999;81(5):803-7
25. Sharma S, Wani IH, Gupta N, Mahajan N, Salaria AQ. Giant cell tumor of talus: a case report. Cases J. 2009;2(1):74
26. Gupte CM, DasGupta R, Beverly MC. The transfibular approach for distal tibial osteochondroma: an alternative technique for excision. J Foot Ankle Surg. 2003;42(2):95-8

Adress for correspondence: Alper Çıraklı, Orthopedic and Traumatology Clinic, Kayseri Research and Training Hospital, Kayseri, Turkey
e-mail:alperomu@gmail.com
Available at www.actaoncologicaturcica.com

Our Experience in Osteoid Osteoma Patients Treated with Computed Tomography Guided Percutaneous Radiofrequency Ablation

Osteoid Osteoma Olgularımızın Bilgisayarlı Tomografi Rehberliğinde Radyofrekans Ablasyon ile Tedavisi

Namık Kemal Altınbaş[1], Cemil Yağcı[1], Kerem Başarır[2]

[1]Ankara Üniversitesi Tıp Fakültesi, Radyoloji Ana Bilim Dalı, Ankara
[2]Ankara Üniversitesi Tıp Fakültesi, Ortopedi ve Travmatoloji Ana Bilim Dalı, Ankara

Dergiye Ulaşma Tarihi 07.04.2016: Dergiye Kabul Tarihi:18.04.2016 DOI: 10.5505/aot.2016.08108

ÖZET

Amaç: Günümüzde osteoid osteoma olgularında bilgisayarlı tomografi (BT) rehberliğinde perkütan radyofrekans (RF) ablasyon tedavisi popular bir yöntem olarak uygulanmaktadır. Bu çalışmanın amacı işlemin komplikasyonlarını ve etkinliğini değerlendirmektir.

Yöntem: Ağustos 2012 ile Kasım 2015 tarihleri arasında işlem yapılan ardışık 35 hasta çalışmaya dâhil edildi. Hastalara BT ünitesinde, sedasyon anestezisi altında RF jeneratörüne bağlanan elektrot ile ablasyon uygulaması yapıldı. Arşiv görüntüler ve dosya kaydı retrospektif olarak incelendi. Lezyonların yerleşim yeri, nidus genişliği ve etkilenen bölge (kortikal, kortikal-intramedüller, medüller) not edildi. İşlem sonrası ağrının kaybolması başarı kriteri olarak kabul edildi. Hastalar rutin olarak işlem sonrası bir gün yatırılarak takip edildi.

Bulgular: Çalışma dâhilinde 25 erkek, 10 kız hasta mevcuttu. Hastaların yaş ortalaması ve nidus ortalama çapı sırasıyla 16±5.59 ve 5.64±2.5 mm idi. Nidusların 24'ü kortikal, 7'si kortikal-intramedüller, 4'ü medüller bölgede idi. Lezyonlar femur (n=19), tibia (n=9), asetabulum (n=3), fibula (n=1), kalkaneus (n=1), skapula (n=1) ve iliak kemik (n=1) yerleşimli idi. İşlemi takiben bir hasta hariç tüm hastalarda ağrının kaybolduğu gözlendi. Bu hastaya 3 hafta sonra re-ablasyon yapıldı. Bir hastada işlem sonrası 1 saat süren peroneal nöropraksi, bir hastada 5-6 gün süren karıncalanma hissi gelişti. Bir hastada 15. ayda yeniden başlayan ağrı (rekürrens) saptandı ve RF ablasyon önerildi. Üç hastada işleme bağlı yanık (üçüncü derece) gelişti.

Sonuç: Osteoid osteomaya yönelik RF ablasyon uygulamalarının tedavi başarısı yüksektir. İşlem başarısızlığı ve rekürrens oranı düşüktür. Tedavi sonrası ağrıda dramatik düzelme, erken taburculuk ve gündelik yaşama kısa sürede dönüş beklenir. Uygun lokalizasyonlardaki lezyonlarda RF ablasyon cerrahi tedavinin önüne geçmiştir. İşleme bağlı komplikasyon oranı düşüktür. Ancak işlem sırasında gelişebilen yanık ciddi bir sorun teşkil etmektedir.

Anahtar Kelimeler: BT, Osteoid osteoma, RF ablasyon

ABSTRACT

Objective: Percutaneous radiofrequency (RF) ablation via computed tomography (CT) guidance has been currently performed in treatment of osteoid osteoma as a popular method. The purpose of this study was to evaluate the complications and efficacy of the procedure.

Methods: A total of thirty-five consecutive patients from August 2012 to November 2015, were included in the study. The ablation procedure was performed under conscious sedation with a RF electrode in tomography unit. Archive images and file records were retrospectively evaluated. Lesions' locations, nidus diameters, and affected areas (cortical, cortical-intramedullary, medullary) were noted. Relief of pain after the procedure was accepted as success criteria. The patients were routinely hospitalized a day after the procedure.

Results: Twenty-five male and ten female patients were included. The mean age and nidus size were 16±5.59 and 5.64±2.5 mm, respectively. Niduses were located in cortical (n=24), cortical-intramedullary (n=7), and medullary (n=4) regions. Lesions were located in femur (n=19), tibia (n=9), acetabulum (n=3), fibula (n=1), calcaneus (n=1), scapula (n=1) and iliac bone (n=1). All of the patients except one achieved pain relief after the procedure. The patient, who had pain after ablation, had been re-ablated 3 weeks later. Two patients had peroneal neuropraxia lasting in an hour (n=1) and tingling sensation lasting in 5-6 days (n=1) after ablation. Recurrence was recorded in one patient 15 months after the procedure, and re-ablation was offered. Third degree burn associated with ablation procedure was observed in three patients.

Conclusion: RF ablation technique in the treatment of osteoid osteoma has a high success rate. Procedure failure and recurrence rates are lower. Dramatic pain relief, early discharge and return to daily life in a short time are expected. RF ablation is the first-line therapy in appropriate lesion locations. Complication rate is low. However, burn complication, which can occur during the procedure, seems to be a serious problem.

Keywords: CT, Osteoid osteoma, RF ablation

Adress for correspondence: Namık Kemal Altınbaş, Ankara Üniversitesi Tıp Fakültesi İbni Sina Hastanesi Radyoloji Anabilim Dalı, Samanpazarı Altındağ, Türkiye
e-mail: namikaltin@gmail.com
Available at www.actaoncologicaturcica.com

Giriş

Benign kemik tümörleri, ürettikleri matriks veya maddelere bağlı olarak sınıflandırılabilirler. Osteoid osteoma ve osteoblastoma, benign kemik oluşturan tümörlerdir. Osteoid osteoma, tipik olarak çocuklarda özellikle de adölesanlarda görülür. Görülme yaş aralığı 10-35 yaş düzeyidir (1). Küçük nidus yapısına sahiptir(2). Klasik olarak geceleri belirginleşen ağrılara neden olur ve bu ağrıları salisilat analjeziye cevap verir (3). Tüm benign kemik lezyonlarının yaklaşık %10'unu oluşturur ve erkeklerde 2-4 kat daha sıktır (1).

Osteoid osteomaların tanısı anamnez, muayene ve radyolojik yöntemler ile yapılabilir. Lezyonun yerleşim yerine göre ek problemler gelişebilir. Bunlara örnek olarak skolyoz, ekstremiteler arasında uzunluk farklılığı, eklem efüzyonu, inflamatuar artropati ya da sinovit verilebilir (1,4,5). En sık etkilenen bölge alt ekstremite olup proksimal femur en sık görüldüğü yerdir. Ancak her kemikte görülebilir. Tibia, femurun geri kalan kesimleri ve omurga diğer sık görülen bölgeleri oluşturur. Tibiada orta diyafizde, vertebralarda lomber bölgede ve ağırlıklı olarak posterior elemanlarda daha sıktır. Osteoid osteomalar genellikle kortikal lezyonlardır ancak medüller, subperiosteal ya da intrakapsüler alanlar gibi kemik içinde herhangi bir yerde ortaya çıkabilirler (1,6,7).

Radyolojik değerlendirmede tipik olarak ovoid şekilli olan, genellikle 2 cm'den küçük olan nidus yapısı ve sklerotik marjin aranır (1). Direkt grafi, bilgisayarlı tomografi (BT), manyetik rezonans görüntüleme, sintigrafi, uygun lezyonlarda ultrasonografi ve Doppler ultrasonografi inceleme yöntemlerini oluşturur.

Osteoid osteoma tedavisi semptom varlığına bağlıdır. Tolere edilebilen lezyona sahip hastalar ya da non-steroid antienflamatuar ajanlarla kontrol edilebilen lezyonlar takip edilebilir. Bu lezyonlar zamanla spontan regresyon gösterebilmektedirler (8,9). Semptomatik lezyonlarda tedavi en-blok cerrahi rezeksiyon, açık nidus küretajı ya da BT rehberliğinde radyofrekans ablasyon ile yapılabilir (10-12).

Çalışmamızda, osteoid osteoma olgularında BT rehberliğinde gerçekleştirilen radyofrekans (RF) ablasyon tedavisi, işlem komplikasyonları ve sonuçlarının tartışılması amaçlandı.

Gereç ve Yöntem

Hasta Seçimi

Ağustos 2012 ile Kasım 2015 tarihleri arasında BT rehberliğinde RF ablasyon uygulaması yapılan ardışık 35 hasta çalışmaya dâhil edildi. Hastalara BT ünitesinde, sedasyon anestezisi altında RF jeneratörüne bağlanan elektrot ile ablasyon uygulaması yapıldı. İşlem öncesi tüm hastalar işlem ve olası komplikasyonları hakkında bilgilendirilerek onam formu alındı. RF ablasyon uygulaması yapılan hastalara ait arşiv görüntüler ve dosya kaydı retrospektif olarak incelendi. Çalışmamız için kurumumuzdan etik kurul onayı alındı.

Lezyonların yerleşim yeri, nidus genişliği ve etkilenen bölge (kortikal, kortikal-intramedüller, medüller) not edildi. İşlem sonrası ağrının kaybolması başarı kriteri olarak kabul edildi.

BT Rehberliğinde RF Ablasyon Tedavisi

İşlemler girişimsel radyolog ya da ortopedist tarafından gerçekleştirildi. Hasta uygun pozisyonda BT masasına yatırıldı. BT görüntüsü alınarak lezyonun yeri konfirme edildi. Topraklama pedi, işlem yapılacak lezyon bölgesi göz önüne alınarak sıkı ve doğru bir biçimde hastanın cildine işlem süresince yerleştirildi. Yerleşim yerine göre lezyona en uygun yaklaşım şekli belirlendi. Lezyona dik açı ile yaklaşıma olanak veren en kısa ulaşım mesafesi arandı. Trokarın kaymasını engellemek için dik açı ile yaklaşım tercih edildi. RF ablasyon tedavisi, BT ünitesinde sedasyon anestezisi altında, aseptik koşullar sağlanarak gerçekleştirildi. Giriş yeri işaretlendi ve küçük bir cilt insizyonu açılarak künt diseksiyon yapıldı. Çevre önemli anatomik yapılara zarar vermemek için gerektiğinde karşı normal korteksten giriş yapılarak lezyona ulaşıldı. Trokar ve kanül lezyona ilerletildi. Spot BT görüntüsü alınarak uygun pozisyonda olunup olunmadığı kontrol edildi. Trokarın nidus içinde olduğu görülünce trokar çıkarılıp kanülün içinden elektrot (UniBlade, AngioDynamics, Inc., USA) ilerletildi. Kanülün RF ablasyon elektrotunun yalıtımsız aktif ucu ile temasından korunmak için kanül elektrotun aktif ucunu kaplamayacak şekilde 1 cm' den daha güvenli

Adress for correspondence: Namık Kemal Altınbaş, Ankara Üniversitesi Tıp Fakültesi İbni Sina Hastanesi Radyoloji Anabilim Dalı, Samanpazarı Altındağ, Türkiye
e-mail: namikaltin@gmail.com
Available at www.actaoncologicaturcica.com

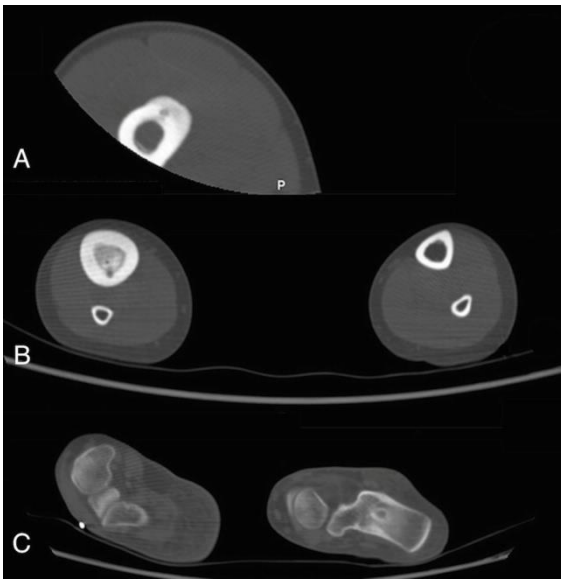
mesafeye geri çekildi. Elektrot RF jeneratörüne (RITA 1500X, AngioDynamics, Inc., USA) bağlandı. Isı 2-3 dakikada 77 dereceden 90 dereceye çıkarıldı. 90 derecede RF elektrotu ile 4-6 dakika süreyle termal ablasyon uygulandı. İşlem sonrası elektrot ve kanül çıkarılarak yara yeri steril spanç ile kapatıldı. Tüm hastalar rutin olarak işlem sonrası bir gün yatırılarak takip edildi.

İstatistik

İstatistiksel değerlendirme amacı ile hasta yaşını, cinsiyetini içeren temel veriler ile lezyonun yerleşim yeri, nidus boyutu ve etkilenen bölge bilgisi kullanıldı. Tanımlayıcı istatistik verileri oluşturuldu. İstatistiksel analizler Microsoft Excel ve SPSS yazılımı ile değerlendirildi.

Sonuçlar

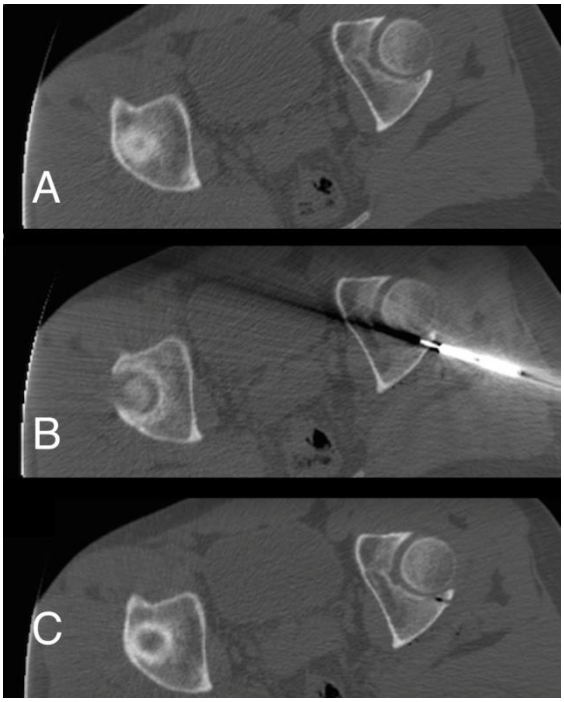
Çalışma dâhilinde 25 erkek, 10 kız hasta mevcuttu. Hastaların yaş ortalaması ve nidus ortalama çapı sırasıyla 16±5.59 ve 5.64±2.5 mm (minimum-maksimum: 1.6-12.3 mm) idi (**Tablo 1**). Nidusların 24'ü kortikal **(Resim 1a)**, 7'si kortikal-intramedüller **(Resim 1b)**, 4'ü medüller **(Resim 1c)** bölgede idi. Lezyonlar femur (n=19), tibia (n=9), asetabulum (n=3), fibula (n=1), kalkaneus (n=1) **(Resim 1c)**, skapula (n=1) ve iliak kemik (n=1) yerleşimli idi. Hastaların ortalama takip süresi 16.14 ± 10.56 ay (minimum-maksimum: 1-40 ay) idi.



Resim 1: Femurda kortikal **(a)**, sağ tibiada kortikal-intramedüller **(b)** ve sol kalkaneusta medüller **(c)** bölgede yerleşimli osteoid osteoma nidusları izlenmektedir

İşlemi takiben bir hasta hariç tüm hastalarda ağrının kaybolduğu gözlendi. Ağrısı kaybolmayan bu hastaya 3 hafta sonra yapılan re-ablasyonu takiben ağrı şikâyetinin kaybolduğu görüldü. Asetabulum yerleşimli osteoid osteomalı bir hastada işlem sonrası 1 saat sürüp kaybolan peroneal nöropraksi gelişti **(Resim 2a-c)**.

Bir hastada (femur boyun yerleşimli) işlem sonrası 5-6 gün süren karıncalanma hissi gelişti. Bir hastada 15. ayda yeniden başlayan ağrı (rekürrens) saptandı ve RF ablasyon önerildi. Üç hastada işleme bağlı cilt yanığı (üçüncü derece) gelişti. Bir hastaya debritman ve primer sütürasyon, bir hastaya debritman ve cilt grefti, bir hastaya ise iki kez flep çevirme ve cilt grefti ameliyatı uygulanarak tedavi edildi.



Resim 2: Sol asetabulum arka duvarında yerleşimli osteoid osteoma lezyonu**(a)**, RF ablasyon işlemi **(b)** ve işlem sonrası kontrol BT görüntüsü **(c)** izlenmektedir. Bu hastada işlem sonrası 1 saat sürüp kaybolan peroneal nöropraksi gelişti.

Lezyonların 30'una lezyon tarafındaki korteksten, 5'ine karşı korteksten medulla geçilerek ulaşıldı **(Resim 3a-c)**.

Adress for correspondence: Namık Kemal Altınbaş, Ankara Üniversitesi Tıp Fakültesi İbni Sina Hastanesi Radyoloji Anabilim Dalı, Samanpazarı Altındağ, Türkiye
e-mail: namikaltin@gmail.com
Available at www.actaoncologicaturcica.com

Tablo 1. RF Ablasyon tedavisi uygulanan hastalara ait cinsiyet, yaş, lezyon tarafı, yerleşim yeri ve bölgesi ile nidus çapları gösterilmektedir.

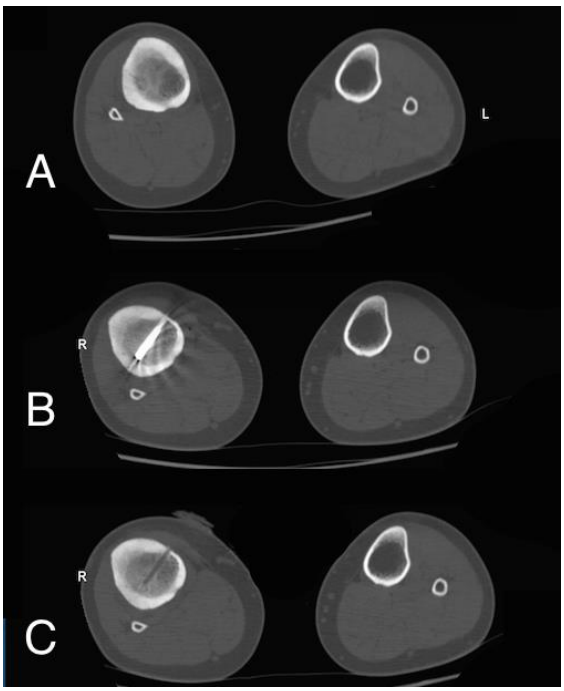
Cinsiyet	*Yaş*	*Taraf*	*Lezyon Yeri*	*Nidus Bölgesi*	*Nidus Çapı*
E	19	Sağ	Femur Orta Diafiz	Kortikal	3,8
K	13	Sağ	İliak Kemik	Kortikal	6,9
E	18	Sol	FemurTrokanter Minör	Kortikal+İntramedüller	10
E	17	Sağ	FemurProksimalDiafiz	Kortikal	3,5
E	15	Sağ	TibiaProksimalMetafiz	Kortikal+İntramedüller	7,9
K	7	Sağ	Femur Orta Diafiz	Kortikal	4,6
K	8	Sağ	Femur Boyun	Kortikal	7,9
E	14	Sol	FemurProksimalDiafiz	Kortikal	5
E	14	Sağ	TibiaProksimalDiafiz	İntramedüller	9,2
E	12	Sağ	TibiaProksimalDiafiz	Kortikal+İntramedüller	6,9
K	16	Sağ	FibulaDistalDiafiz	Kortikal	1,6
E	13	Sağ	Tibia Orta Diafiz	Kortikal	5,9
E	10	Sağ	Femur Boyun	Kortikal	4,5
K	15	Sol	Kalkaneus	İntramedüller	5,8
E	14	Sağ	Femur Boyun	Kortikal	4,4
E	22	Sol	Skapula	Kortikal+İntramedüller	12,3
E	14	Sağ	TibiaMetafizodiafizer	Kortikal	4,6
E	23	Sol	Femur Boyun	Kortikal	4,5
E	29	Sol	FemurProksimalDiafiz	Kortikal	3,8
K	13	Sol	FemurTrokanter	Kortikal	6,8
E	15	Sağ	FemurSubtrokanterik	Kortikal	5,5
K	6	Sağ	Femur Boyun	Kortikal+İntramedüller	5,8
E	23	Sağ	FemurProksimalDiafiz	Kortikal	3,8
E	19	Sağ	FemurProksimalDiafiz	Kortikal	4
E	18	Sol	TibiaDistalDiafiz	Kortikal	3,6
E	11	Sağ	Tibia Orta Diafiz	Kortikal+İntramedüller	5,7
E	18	Sol	TibiaDistalDiafiz	Kortikal	3,6
E	31	Sol	Asetabulum	Kortikal	5,4
K	25	Sağ	Femur Orta Diafiz	Kortikal	4,4
K	10	Sağ	Asetabulum	Kortikal+İntramedüller	10,4
E	16	Sol	Tibia Orta Diafiz	Kortikal	2,6
E	14	Sağ	Femur Orta Diafiz	İntramedüller	4,4
E	15	Sol	FemurSubtrokanterik	Kortikal	3,2
E	19	Sağ	FemurProksimalDiafiz	Kortikal	4,1
K	14	Sağ	Asetabulum	İntramedüller	11

Tartışma

Günümüzde gelişen teknoloji sonucunda osteoid osteomalı hastaların tedavisinde cerrahi tedavi yerine hastanede kalış süresini azaltan, daha az komplikasyon oranına sahip RF ablasyon gibi girişimsel yöntemler gelişmeye ve kullanılmaya

Adress for correspondence: Namık Kemal Altınbaş, Ankara Üniversitesi Tıp Fakültesi İbni Sina Hastanesi Radyoloji Anabilim Dalı, Samanpazarı Altındağ, Türkiye
e-mail: namikaltin@gmail.com
Available at www.actaoncologicaturcica.com

başlamıştır. Osteoid osteoma da BT rehberliğinde uygulanabilen RF ablasyon tedavisinin gelişimi ile ilk olarak tanımlandığı 1989 (13) yılından bu yana girişimsel olarak tedavi edilebilen, cerrahiye alternatif yöntem bulunabilmiş lezyonlardan birisidir (14). Bu çalışmada, BT rehberliğinde gerçekleştirdiğimiz RF ablasyon tedavisinin etkinliğinin yüksek olduğunu, gündelik yaşama kısa sürede dönüşe olanak verdiğini ancak işleme bağlı gelişebilen cilt yanığının ciddi bir komplikasyon olduğunu gördük.



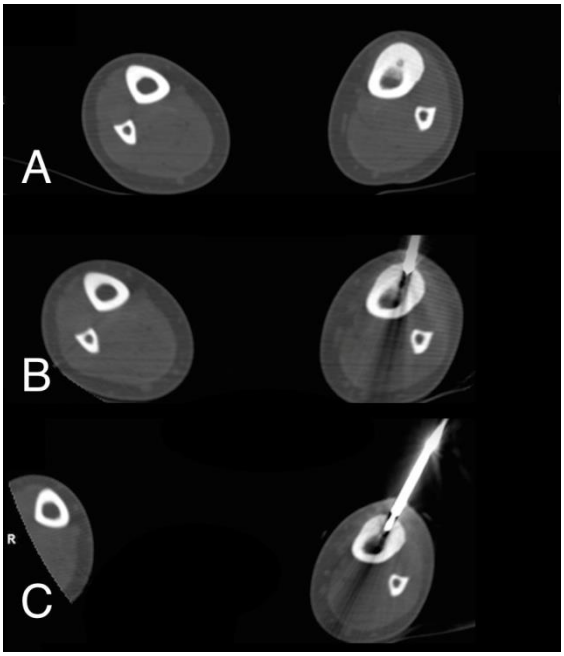
Resim 3: Sağ tibiada yerleşimli osteoid osteoma lezyonu **(a),** karşı medial korteksten ilerletilen RF ablasyon elektrotu **(b)** ve işlem sonrası kontrol BT görüntüsü **(c)** izlenmektedir.

Osteoid osteomalar genellikle kortikal bölgede bulunan lezyonlardır. Ancak kemikte medulla, subperiosteal ve intrakapsüler alanlar gibi herhangi bir yerde de ortaya çıkabilirler. Ayrıca nidusu çevreleyen sklerozun da reaktif olduğu ve lezyonun kendisini yansıtmadığı unutulmamalıdır (1). Çalışmamızda lezyonlar nidusunun bulunduğu bölgeye göre değerlendirildiğinde 35 lezyonun 24'ünün kortikal, 7'sinin kortikal-intramedüller ve 4'ünün medüller bölgelerde olduğu görüldü.

Osteoid osteomalar vücutta her kemikte bulunabilmekle birlikte en sık proksimal femurda saptanırlar. Tibia tutulumu var ise orta diyafizde, vertebra tutulumu var ise lomber bölgede ve ağırlıklı olarak posterior elemanlarda daha sıktır(7). Hasta grubumuzda da lezyonların çoğunun femur yerleşimli olduğu (n=19) görülmüştür. Ayrıca tibia (n=9), asetabulum (n=3), fibula (n=1), kalkaneus (n=1), skapula (n=1) ve iliak kemik (n=1) yerleşimli lezyonlarda da RF ablasyon tedavisi yapılmıştır.

BT rehberliğinde RF ablasyon işlemini lokal anestezi altında (14), derin sedasyon eşliğinde (15), spinal anestezi (11)ve genel anestezi altında (özellikle çocuk hastalarda) (15,16) yaptığını belirten yazarlar bulunmaktadır. Çalışma grubumuzdaki tüm hastalarda RF ablasyon uygulaması derin sedasyon anestezisi altındabaşarı ile gerçekleştirilmiştir.

Osteoid osteomada RF ablasyon tedavisinin başarı oranı yüksektirve dünya genelinde popularitesi artmıştır (11). Sadece bir hastamızda işlemi takiben ağrının kaybolmadığı görüldü. Bu hastaya 3 hafta sonra yapılan re-ablasyonu takiben ağrı şikâyeti kayboldu **(Resim 4a-c)**. Bu hastada ilk ablasyon uygulaması sırasında nidusun tedavi edilememe nedeni, korteksin kalınlaşmış olması ve bu nedenle elektrotun nidusun hafif uzağında kalmış olması şeklinde değerlendirildi. Kalın korteks nedeni ile nidusa ulaşımın zor olduğu olgularda ablasyon öncesi korteks drillenerek nidusa daha kolay ulaşım için yol açılabilir.



Resim 4: Sol tibia anterior kortekste belirgin kalınlaşmaya neden olan osteoid osteoma lezyonu **(a)** izlenmektedir. İlk RF ablasyon uygulaması **(b)**

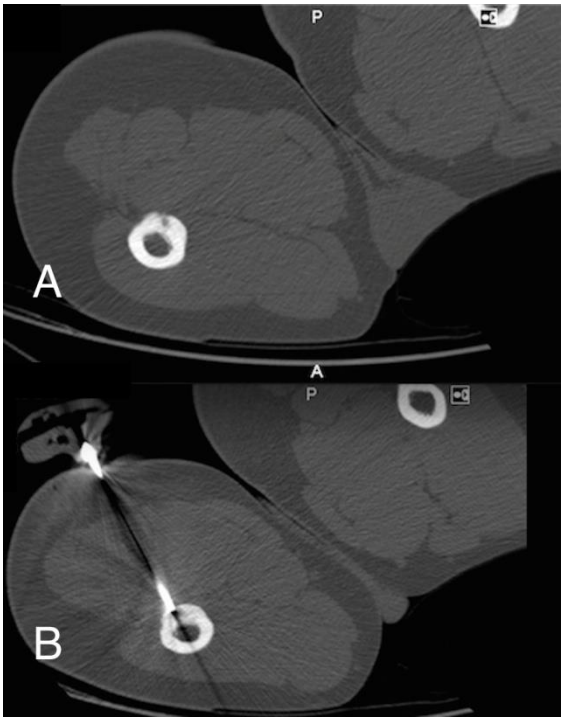
Adress for correspondence: Namık Kemal Altınbaş, Ankara Üniversitesi Tıp Fakültesi İbni Sina Hastanesi Radyoloji Anabilim Dalı, Samanpazarı Altındağ, Türkiye
e-mail: namikaltin@gmail.com
Available at www.actaoncologicaturcica.com

sonrası ağrısı kaybolmayan bu hastaya 3 hafta sonra yapılan re-ablasyon işlemini **(c)** takiben ağrı şikâyeti kayboldu.

Osteoid osteomada rekürrens en-blok rezeksiyon sonrası nadirdir. Küretaj ile tedavi edilenlerde rezeksiyona kıyasla hafif yüksektir (17). Rekürrensin özellikle birden fazla nidusa sahip lezyonlarda inkomplet rezeksiyona bağlı olduğu düşünülmektedir (18,19). Son zamanlarda BT rehberliğinde RF ablasyon tedavisi güvenilir ve efektif, minimal invaziv bir yöntem olarak ve birçok klinik merkezde osteoid osteomada ilk tedavi yöntemi olarak tercih edilmektedir. RF ablasyon tedavisinin klinikbaşarı oranı %76-100 aralığındadır (10). Osteoid osteomada rekürrensler re-eksizyon ya da ablasyon ile başarıyla tedavi edilebilir. Rezidü semptomatik tümör varlığında re-ablasyon daha başarılı iken, ağrısız interval sonrası nüks geliştiğinde ablasyon daha az başarılıdır (20). Çalışma grubumuzdaki bir hastada 15. ayda yeniden başlayan ağrı (rekürrens) saptandı ve RF ablasyon ile tedavi önerildi.

Osteoid osteomada RF ablasyon tedavisinin komplikasyon oranı düşüktür. Önceki çalışmalarda cilt yanığı, fraktür, osteomyelit, vazomotor instabilite, tendinit ve muskuler hematom komplikasyonları bildirilmiştir (12, 14-16, 21). Hasta grubumuzda işleme bağlı olarak gelişen komplikasyonları şöyle sıralayabiliriz: Asetabulum yerleşimli osteoid osteomalı bir hastada işlem sonrası 1 saat sürüp kaybolan peroneal nöropraksi gelişti. Femur boynu yerleşimli lezyona sahip bir hastada işlem sonrası 5-6 gün süren karıncalanma hissi gelişti. Üç hastada ise üçüncü derece yanık geliştiği görüldü.

RF ablasyon tedavisi sırasında gelişen işlem bölgesindeki cilt yanıklarının elektrotun yalıtımındaki defektten kaynaklandığı düşünülmektedir. Kanülün RF ablasyon elektrotunun yalıtımsız aktif ucu ile temasından korunmak için kanülün elektrotun aktif ucunu kaplamayacak şekilde 1 cm den daha güvenli mesafeye geri çekilmesi önemlidir. Biyopsi kanülünün geri çekilmesi sırasında elektrotun yalıtımına zarar verme olasılığı da mevcuttur. Elektrotun metal kanüle teması ısınmaya ve işlem bölgesinde üçüncü derece cilt ve yumuşak doku yanığına neden olmaktadır(22). Hastanın uyluk veya bacak bölgelerine bağlanan topraklama pedi bölgesinde, kılavuz kenar ya da ped köşesindeki cilt yanıkları ise pedin cilt ile zayıf teması, kablo devresindeki kırıklar ve ped dizaynı ile ilgili problemler yüzündendir (23). Ancak literatürde herhangi bir neden gösterilememiş olgu sunumları da mevcuttur (21). Çalışmamızda üç hastada işleme bağlı yanık (üçüncü derece) gelişti. Bunlardan ikisi iğne giriş bölgesi üzerindeydi **(Resim 5a-b)** ve biri debridman ve primer sütürasyon ile, diğeri iki kez flep çevirme ve cilt grefti ameliyatı uygulanarak tedavi edildi. Üçüncü hastada yanık, topraklama pedi hemen proksimalinde kaydedildi **(Resim 6a-b)**. Bu hastanın tedavisi debritman ve cilt grefti ile yapıldı. Yapılan değerlendirmelerde bu üç yanık olgusu için de işlemlerin uygun şekilde yapılmış olduğu görüldü. Yanığa sebep olan gerçek neden bulunamadı.

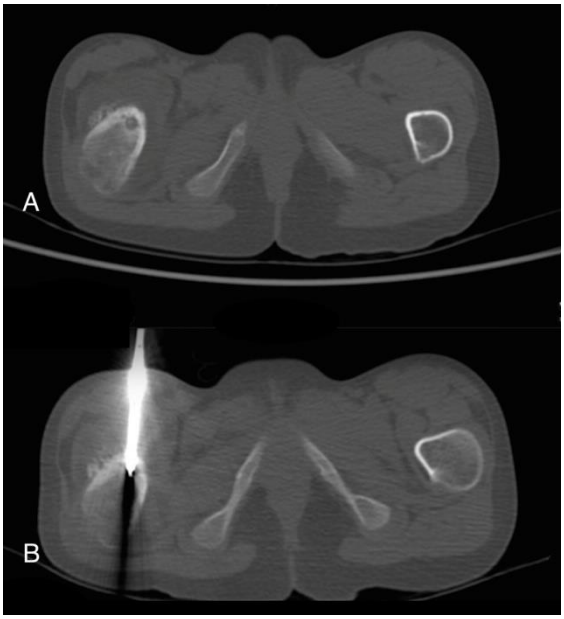


Resim 5: Sağ femurda osteoid osteoma lezyonu **(a)** ve RF ablasyon işlemine ait BT görüntüsü **(b)** izlenmektedir. Bu hastada iğne giriş bölgesi üzerinde üçüncü derece yanık gelişti.

Literatür ışığında değerlendirildiğinde mevcut topraklayıcı ped teknolojisi ve dizaynının RF gücünü daha fazla artırmak için sınırlayıcı bir faktör olduğu görülmektedir. Monopolar sistemler RF döngüsünü tamamlamak için topraklama pedi kullanırlar. Aynı miktarda enerji cilt pedinde olduğu gibi elektrotun

Adress for correspondence: Namık Kemal Altınbaş, Ankara Üniversitesi Tıp Fakültesi İbni Sina Hastanesi Radyoloji Anabilim Dalı, Samanpazarı Altındağ, Türkiye
e-mail: namikaltin@gmail.com
Available at www.actaoncologicaturcica.com

ucunda toplanır. Kılavuz kenar maksimum güç konsantrasyonu alanıdır. Topraklama pedi bölgesindeki termal hasar güncel ve daha güçlü sistemlerde artan sıklıkla rapor edilmektedir. Cilt ısınmasını azaltmak için önerilen yöntemler mevcuttur. Topraklayıcı pedin yüzey alanını genişletmek, pedlerin sayısını artırmak, cilt altındaki sıcaklığı ölçebi-



Resim 6a,b: Sağ proksimal femurda yerleşimli osteoid osteoma lezyonu **(a)** ve RF ablasyon işlemine ait BT görüntüsü **(b)** izlenmektedir. İşlem sonrasında, bu hastada krural bölgeye yerleştirilen topraklama pedinin proksimalinde, sağ diz altı düzeyde abrazyon ve renk değişikliği saptandı.

len elektrot kullanmak ve pedlerde sekansiyel aktivasyon kullanmak şeklindeki uygulamalar ile iyi sonuçlar rapor edilmiştir (21, 24, 25). Ayrıca anterior tibia gibi özellikle ciltaltı yumuşak doku kalınlığının az olduğu bölgelerde olmak üzere işlem sırasında profilaktik olarak kanül giriş bölgesi çevresine soğuk uygulaması da yapılabilir (22,15,26). Alternatif ve daha güvenli bir yöntem olarak navigasyonel bipolar RF ablasyon sistemi de, ped gerektirmemesi, lezyon periferinde ısıtakibiyle güvenli ve daha kısa sürede ablasyona olanak vermesi ve navigasyonla daha geniş alanda tek girişle ablasyon sağlayabilmesinedeniyle tercih edilebilir (27).

Osteoid osteomada radyofrekans ablasyon dışındaki perkütan ablasyon teknikleralkol enjeksiyonunu (28,29) ve interstisyel lazer fotokoagülasyonu (30) içermektedir. Alkol enjeksiyonunun dezavantajı doku üzerine non-selektif etki göstermesi ve ekstravaze olan alkolün çevre normal dokuyu etkilemesi olarak tanımlanmıştır. Lazer fotokoagülasyon oldukça pahalıdır ve gerekli vakalarda simultane biyopsi yapılamamaktadır(16).

Karaciğer tümörlerinin tedavisinde de birçok merkezde uygun lezyonlarda primer ablasyon yöntemi olarak RF ablasyon uygulanmaktadır (31). RF ablasyon ile osteoid osteoma olgularında olduğu gibi hepatosellüler karsinom (HCC) lezyonlarında da tedavi başarısı yüksektir. HCC lezyonlarında RF ablasyonla, Livraghi ve arkadaşlarının serisinde %90.4 ve Shiratove arkadaşlarının serisinde %93.3 tam yanıt görülmüştür (32, 33). Osteoid osteomada RF ablasyon tedavisinin klinik başarı oranı %76-100 aralığındadır (10).

Sonuç olarak, osteoid osteomaya yönelik RF ablasyon uygulamalarının tedavi başarısı yüksektir. İşlem başarısızlığı ve rekürrens oranı düşüktür. Tedavi sonrası ağrıda dramatik düzelme, erken taburculuk ve gündelik yaşama ağrısız olarak kısa sürede geri dönebilme beklenir. Osteoid osteoma tedavisinde uygun lokalizasyonlardaki lezyonlarda RF ablasyon cerrahi tedavinin önüne geçmiştir. İşleme bağlı komplikasyon oranı düşüktür. Ancak işlem sırasında işleme bağlı olarak gelişebilen yanık ciddi bir sorun teşkil etmektedir**.**

Çıkar Çatışması: Yok

Kaynaklar

1. Greenspan A, Jundt G, Remagen W. Bone-Forming (Osteogenic) Lesions. In: Greenspan A, Jundt G, Remagen W, eds. Differential Diagnosis in Orthopaedic Oncology (2nd ed). Philadelphia; Lippincott Williams & Wilkins; 2007:2;59-74
2. Springfield DS, Gebhardt MC. Bone and soft tissue tumors. In: Morrissy RT, Weinstein SL, eds. Lovell and Winter's Pediatric Orthopaedics (6th ed). Philadelphia; Lippincott Williams & Wilkins; 2006:493
3. Papathanassiou ZG, Megas P, Petsas T, et al. Osteoid osteoma: diagnosis and treatment. Orthopedics. 2008;31:1118
4. Kaweblum M, Lehman WB, Bash J, et al. Diagnosis of osteoid osteoma in the child. Orthop Rev 1993;22:1305
5. Schlesinger AE, Hernandez RJ. Intracapsular osteoid osteoma of the proximal femur: findings on plain film and CT. AJR Am J Roentgeno. 1990;154:1241-4

Adress for correspondence: Namık Kemal Altınbaş, Ankara Üniversitesi Tıp Fakültesi İbni Sina Hastanesi Radyoloji Anabilim Dalı, Samanpazarı Altındağ, Türkiye
e-mail: namikaltin@gmail.com
Available at www.actaoncologicaturcica.com

6. Horvai A, Klein M. Osteoid osteoma. In: Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F, eds. WHO Classification of Tumours of Soft Tissue and Bone (4th ed). Lyons; International Agency for Research on Cancer; 2013:277
7. Unni KK, Inwards CY. Dahlin's bone tumors, general aspects and data on 10,165 cases (6th ed). Philadelphia; Lippincott Williams & Wilkins; 2009:9;102-12
8. Feletar M, Hall S. Osteoid osteoma: a case for conservative management. Rheumatology 2002;41:585-6
9. Kneisl JS, Simon MA. Medical management compared with operative treatment for osteoid-osteoma. J Bone Joint Surg Am 1992;74:179
10. Cantwell CP, Obyrne J, Eustace S. Current trends in treatment of osteoid osteoma with an emphasis on radiofrequency ablation. Eur Radiol 2004;14:607-617
11. Cioni R, Armillotta N, Bargellini I, et al. CT-guided radiofrequency ablation of osteoid osteoma: long term results. Eur Radiol 2004;14:1203-8
12. Earhart J, Wellman D, Donaldson J, et al. Radiofrequency ablation in the treatment of osteoid osteoma: results and complications. Pediatr Radiol 2013;43:814
13. Tillotson CL, Rosenberg AE, Rosenthal DI. Controlled thermal injury of bone. Report of a percutaneous technique using radiofrequency electrode and generator. Invest Radiol 1989;24:888-92
14. Çakar M, Esenyel CZ, Seyran M, et al. Osteoid osteoma treated with radiofrequency ablation. Adv Orthop 2015; 2015:807274. DOI: 10.1155/2015/807274
15. Hoffmann RT, Jacobs TF, Kubisch CH, Trumm CG, Weber C, Duerr HR, Helmberger TK, Reiser MF. Radiofrequency ablation in the treatment of osteoid osteoma-5-year experience. Eur J Radiol 2010;73:374-9
16. Yip PS, Lam YL, Chan MK, Shu JS, Lai KC, So YC. Computed tomography-guided percutaneous radiofrequency ablation of osteoid osteoma: local experience. Hong Kong Med J 2006;12:305-9
17. Sluga M, Windhager R, PfeifferM, DominkusM, Kotz R. Peripheral osteoid osteoma. Is there still a place for traditional surgery? J Bone Joint Surg (Br) 2002;84:249-51
18. Allieu Y, Lussiez B, Benichou M, Cenac P. A double nidus osteoid osteoma in a finger. J Hand Surg 1989;14:538-41
19. Sampath SC, Sampath SC, Rosenthal DI. Serially recurrent osteoid osteoma. Skeletal Radiol 2015;44:875-81
20. Motamedi D, Learch TJ, Ishimitsu DN, et al. Thermal Ablation of Osteoid Osteoma: Overview and Step-by-Step Guide. RadioGraphics 2009;29:2127-41)
21. Huffman SD, Huffman NP, Lewandowski RJ, Brown DB. Radiofrequency ablation complicated by skin burn. Semin Intervent Radiol 2011;28:179-82
22. Widmann G, Jaschke W, Bale R. Case report: Third-degree skin and soft tissue burn after radiofrequency ablation of an osteoid osteoma guided through a triple-crown biopsy cannula. Skeletal Radiol 2012;41:1627-30
23. Steinke K, Gananadha S, King J, Zhao J, Morris DL. Dispersive pad site burns with modern radiofrequency ablation equipment. Surg Laparosc Endosc Percutan Tech. 2003;13:366–71
24. Schutt DJ, Swindle MM, Bastarrika GA, Haemmerich D. Sequential activation of ground pads reduces skin heating during radiofrequency ablation: initial in vivo porcine results. Conf Proc IEEE Eng Med Biol Soc. 2009;2009: 4287-90
25. Thiagalingam A, Pouliopoulos JM, Barry MA, et al. A thermochromic dispersive electrode can measure the underlying skin temperature and prevent burns during radiofrequency ablation. J Cardiovasc Electrophysiol. 2005;16:781-88
26. Pinto CH, Taminiau AH, Vanderschueren GM, Hogendoorn PC, Bloem JL, Obermann WR. Technical considerations in CT-guided radiofrequency thermal ablation of osteoid osteoma: tricks of the trade. AJR. 2002;179:1633-42
27. Wallace AN, Tomasian A, Chang RO, Jennings JW. Treatment of Osteoid Osteomas Using a Navigational Bipolar Radiofrequency Ablation System. Cardivasc Intervent Radiol 2016;39:768-772)
28. Adam G, Keulers P, Vorwerk D, Heller KD, Fuzesi L, Guenther RW. The percutaneous CT-guided treatment of osteoid osteoma: a combined procedure with a biopsy drill and subsequent ethanol injection [in German]. Rofo. 1995;162:232-5
29. Sanhaji L, Gharbaoui IS, Hassani RE, Chakir N, Jiddane M, Boukhrissi N. A new treatment of osteoid osteoma: percutaneous sclerosis with ethanol under scanner guidance [in French]. J Radiol 1996;77:37-40
30. Witt JD, Hall-Craggs MA, Ripley P, Cobb JP, Bown SG. Interstitial laser photocoagulation for the treatment of osteoid osteoma. J Bone Joint Surg Br. 2000;82:1125-8
31. Arıbaş BK. Karaciğer malign tümörlerinde perkütan radyofrekans (RF) ablasyon. Güncel Gastroenteroloji 2009;13:81-88)
32. Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: Treatment with radio-frequency ablation versus ethanol injection. Radiology 1999;210:655-61
33. Shirato K, Morimoto M, Tomita N, et al. Small hepatocellular carcinoma: Therapeutic effectiveness of percutaneous radiofrequency ablation therapy with a LeVeen needle electrode. J Ultrasound Med 2002;21:67-76)

Adress for correspondence: Namık Kemal Altınbaş, Ankara Üniversitesi Tıp Fakültesi İbni Sina Hastanesi Radyoloji Anabilim Dalı, Samanpazarı Altındağ, Türkiye
e-mail: namikaltin@gmail.com
Available at www.actaoncologicaturcica.com

AOT ACTA ONCOLOGICA TURCICA Original Article

Evaluating Depression, Anxiety, Sexuality and Quality of Life in Metastatic Lung Cancer Patients

Metastatik Akciğer Kanseri Hastalarında Depresyon, Anksiyete, Cinsellik ve Yaşam Kalitesinin Değerlendirilmesi

Yelda Varol[1], Umut Varol[2], Mustafa Değirmenci[3], Gönül Pişkin[3], Nuri Aşık[2], Murat Akyol[4], Tarık Salman[2], Utku Oflazoğlu[2], Yüksel Küçükzeybek[2], Ahmet Alacacıoğlu[2], Mustafa Oktay Tarhan[5]

[1]Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Chest Diseases, Izmir, Turkey
[2]Katip Celebi University Ataturk Training and Research Hospital, Department of Medical Oncology, Izmir, Turkey
[3]Tepecik Training and Research Hospital, Department of Medical Oncology, Izmir, Turkey
[4]Manisa Government Hospital, Medical Oncology Clinic, Manisa, Turkey
[5]Institute of Oncology, Dokuz Eylul University, Izmir, Turkey

Dergiye Ulaşma Tarihi: Dergiye Kabul Tarihi: DOI: 10.5505/aot.2016.27122

ÖZET

Amaç: Akciğer kanseri kısa yaşam beklentisi ve agresif tedavi seçenekleri nedeniyle hastaların hem yaşam kalitesini hem de psikoseksüel durumlarını etkilemektedir. Bu çalışmanın amacı akciğer kanseri hastalarında anksiyete, depresyon, cinsel doyum durumu ve yaşam kalitesinin değerlendirilmesidir.
Yöntemler: Birinci veya ikinci sıra kemoterapi alan metastatik akciğer kanseri hastalarıyla yüz yüze anketler yapılarak bilgiler toplanmıştır. Kullanılan anketler sosyodemografik karakteristikleri, Beck Depresyon Anketini (BDI), Golombok-Rust Cinsel Doyum Anketini (GRISS) and European Organization for Research on Treatment of Cancer Questionnaires-C30 Yaşam Kalitesi Anketini (EORTC-QoL-C30) içermektedir.
Bulgular: Bu çalışma 44 hastanın anket verilerini içermektedir. Hastaların anksiyete ve depresyon durumu için toplam Beck skoru çok yüksek çıkmıştır (sırasıyla; 15.60 ± 12.30 ve 16.02 ± 11.39). Metastatik akciğer kanseri hastalarımızın GRISS skorları anksiyete ve depresyon durumlarına göre değerlendirildiğinde herhangi bir istatistiksel anlamlılık bulunamamıştır. Hastalarımızdan anksiyete ve depresyon skorları yüksek olanlarda EORTC-QLQ-C30'un fiziksel, bilişsel, duygusal ve sosyal fonksiyonları istatistiksel olarak anlamlı şekilde düşük bulunmuştur. Rol fonksiyonu açısından sadece yüksek anksiyete skorlu hastalarda istatistiksel anlamlılık saptanmıştır.
Sonuç: Metastatik akciğer kanserli hastalarda yüksek anksiyete ve depresyon durumu, azalmış cinsel doyum ve bozulmuş yaşam kalitesi izlenmiştir.
Anahtar Kelimeler: Metastatik akciğer kanseri, depresyon, anksiyete, cinsellik, yaşam kalitesi

ABSTRACT

Introduction: Lung cancer (LC) affects psychosexual outcome and quality of life (QoL) of the patients because of short survival period and aggressive treatment modalities. The aim of our study was to investigate anxiety, depression, QoL and sexual satisfaction levels of LC patients.
Methods: The data for metastatic LC patients treated with first or second-line chemotherapy were collected by using four forms completed during face-to-face interviews. The forms consist of socio-demographic characteristics, the Beck Depression Inventory (BDI), Golombok-Rust Inventory of Sexual Satisfaction (GRISS) and European Organization for Research on Treatment of Cancer Questionnaires Quality of Life-C30 (EORTC-QoL-C30).
Results: Forty-four LC patients were participated in this study. The total Beck scores of patients for anxiety and depression were very high (15.60 ± 12.30 and 16.02 ± 11.39; respectively). When we evaluated GRISS scores of our metastatic LC patients with respect to their anxiety or depression levels, we could not find any statistical significance. In the metastatic LC patients whose anxiety and depression scores were high, physical, cognitive, emotional and social functioning of EORTC-QLQ-C30 was found statistically significantly low. Statistical significance in terms of role functioning was only found in the patients with high anxiety scores.
Conclusion: Metastatic LC patients had high anxiety and depression levels, decreased sexual satisfaction and impaired QoL.
Keywords: Metastatic lung cancer, depression, anxiety, sexuality, quality of life

Adress for correspondence: Umut Varol, İzmir Katip Çelebi Üniversitesi Atatürk Eğitim Ve Araştırma Hastanesi, İzmir, Türkiye
e-mail: varolumut@yahoo.com
Available at www.actaoncologicaturcica.com

Introduction

Lung cancer (LC) is the most common cancer in the worldwide. Patients with lung tumors have a poor prognosis with 41% of patients surviving 1 year and only 15% surviving 5 years (1). The mechanisms through which lung cancer and its treatments affect patients' performance status and sexual desire are likely multifactorial; including physical, biological and psychological factors (2). Beyond the direct impact of lung cancer on patients, treatment itself may cause disstress, depression, anxiety and fear contributing to poor health outcomes. As a whole, because of the negative effects of cancer or its treatment, increasing quality of life (QoL) and emotional intimacy of these patients are very important (3).

Due to the decreased survival of LC patients, very few studies focused especially on sexual functioning during their treatment period (4,5). So, little is known about the effects of lung cancer or chemotherapeutics on intimate and sexual relationships. Additionally, chemotherapy can cause several physical sexual problems, such as erectile dysfunction and ejaculatory failure, and emotional changes that affect lives of LC patients (6,7). Alterations in physical appearance may also play an important role in sexuality of the patients with lung cancer receiving chemotherapy and influence their sexual identities. The impact of treatment with chemotherapy on appearance, self-esteem, and sexuality has been associated with decreased QoL and mental distress (8). Therefore, it is important to recognize the consequences of chemotherapy on sexual desire and counsel LC patients about their sexual activities are important aspects in providing comprehensive care.

Most of the lung cancer patients treated with chemotherapy have deterioration in QoL which is defined within five dimensions; physical well-being, material well-being, social well-being, emotional well-being, and, development and activity (9). However, physicians may sometimes ignore the importance of sexuality and social relationships for quality of life in LC patients. In this study, we aimed to examine anxiety, depression, changes in sexual functioning and QoL of the LC patients during their treatment period.

Patients and Methods

Patient Selection

Forty-four male metastatic LC patients with Eastern Cooperative Oncology Group performance status 0-1 and who was having treatment for first or second-line chemotherapy in medical oncology clinics of Izmir Tepecik Training and Research Hospital, Izmir Katip Celebi University Atatürk Research and Training Hospital and Manisa Government Hospital between January 2015 and February 2016 were included in this study. Patients with poor performance status (ECOG≥2), old age (>70) or receiving chemotherapy in the adjuvant stetting were excluded.A series of forms completed during face-to-face interviews by trained interviewers for determination of the sexual satisfaction, psychological status and quality of life of the patients were used. All of the participants were informed about the study and informed written consent was applied.

Forms Completed

In our study, there were four forms which were completed by the participants. In the first form, questions about the demographic characteristics of the patients were present.

Beck Depression Inventory (BDI) was the second form. It is composed of questions developed to measure the intensity, severity, and depth of depression in patients with psychiatric disorders. BDI included 21 questions or items, each with 4 possible responses. In order to indicate the severity of the symptom, each response is assigned a score ranging from zero to three. The questions of BDI assess mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, body image, work difficulties, insomnia, fatigue, appetite, weight loss, bodily preoccupation, and loss of libido. BDI was translated into Turkish and its reliability was recalculated by Tegin and Hisli (10,11). Items 1 to 13 assess symptoms that are psychological in nature, while items 14 to 21 assess more physical symptoms (12).

The third form was the *Golombok-Rust Inventory of Sexual Satisfaction* (GRISS). The

Adress for correspondence: Umut Varol, İzmir Katip Çelebi Üniversitesi Atatürk Eğitim Ve Araştırma Hastanesi, İzmir, Türkiye
e-mail: varolumut@yahoo.com
Available at www.actaoncologicaturcica.com

GRISS is composed of 28-item questionnaire used to assess the presence and extent of sexual problems (13). It includes 12 subscales evaluating impotence, premature ejaculation, orgasmic disorder, vaginismus, lack of communication, avoidance in males and females, nonsensuality, insensitivity and dissatisfaction. In any category, a score of 5 points or higher indicates sexual dysfunction. A validation and reliability study of the GRISS in Turkish population was performed by Tugrul et al (14).

The fourth form was *European Organization for Research on Treatment of Cancer Questionnaires Quality of Life-C30* (EORTC-QoL-C30). In this form, there are 30 items divided into three major domains that measure the quality of life of cancer patients: functional scales, global health/quality of life and symptom scales (15). Functional scales consist of physical (five items), social (two items), emotional (four items), role (two items) and cognitive (two items) items. Quality of life scale consists of two items. There are also nine symptom scales which were not included in our analysis (16).

Statistical Analysis

The data was analyzed by using SPSS for Windows version 20.0. A value of $p<0.05$ was considered as significant. Descriptive statistics summarized frequencies and percentages for categorical variables, mean and standard deviation for continuous variables. For independent samples, T-tests were used to compare categorical variables.

Results

The median age of metastatic lung cancer survivors was 53.9 (range: 36-66). Thirty of 44 had received chemotherapy in the first-line while the rest had in the second-line treatment. About 6.8% of the LC patients had university educations. Thirty % of the lung cancer patients had members with cancer in their family before. Most of the patients (86.4%) were smoker. Nearly almost all of the patients were married (95.5%). Demographic variables of the patients were shown in *Table 1*.

In the validation study of BDI in Turkey, the cut off value of anxiety is defined as ≥8 and the cut off value of depression is defined as 10. The total Beck scores of lung cancer patients for anxiety were 15.60 ± 12.30 and for depression were 16.02 ± 11.39. In our study, the depression rate of LC patients was 68.2% (n:32) and anxiety rate was 75% (n:34) respectively.

When the patients' GRISS scores were evaluated with respect to their anxiety or depression levels, we could not find any statistical significance in our metastatic lung cancer patients. The mean GRISS scores of lung cancer patients were shown in *Table 2*. The mean GRISS scores of our patients according to their anxiety and depression levels were shown in *Table 3*.

Table 1: Socio-demographic variables of the patients

Socio-demographic Characteristics	**Patients (n=44)**
Age (mean±SS) (min-max)	53.9 ± 7.56(36-66)
Education	
Primary Education	5 (11.4%)
High School	36 (81.8%)
University	3 (6.8%)
Marital status	
Married	42 (95.5%)
Single	2 (4.5%)
Cancer History of Family	
Yes	13 (29.5%)
No	31 (70.5%)
Smoking History	
Yes	38 (86.4%)
No	6 (13.6%)
Alcohol History	
Yes	30 (68.2%)
No	14 (31.8%)
Lung Cancer Surgery	
Yes	17 (38.6%)
No	27 (61.4%)

In the metastatic lung cancer patients whose anxiety scores were high, physical, role, cognitive, emotional and social functioning subscores of EORTC-QLQ-C30 was found statistically significantly low. In the metastatic lung cancer patients whose depression scores were high, physical, cognitive, emotional and social functioning subscores of EORTC-QLQ-C30 were found statistically significantly low. There was not any significant difference in terms of global quality of life scores. The mean

Adress for correspondence: Umut Varol, İzmir Katip Çelebi Üniversitesi Atatürk Eğitim Ve Araştırma Hastanesi, İzmir, Türkiye
e-mail: varolumut@yahoo.com
Available at www.actaoncologicaturcica.com

EORTC-QLQ-C30 scores of our patients were shown in *Table 4*. The mean EORTC-QLQ-C30 scores of our patients according to their anxiety and depression levels were shown in *Table 5*.

Discussion

In our study, the depression and anxiety rates of our metastatic patients were very high (68.2%, 75%; respectively) and most of the patients had high psychological distress as expected. They were affected in terms of anxiety and depression mostly because of the short life-expentancy (17). Cataldo et al also found high anxiety, depression and symptom severity in metastatic lung cancer patients (18). In another study conducted by Haun, not only lung cancer patients but also their partners are prone to high levels of depression and anxiety or severe distress related to the poor prognosis of the illness (19). In advanced lung cancer patients, the changes of the severity of psychological distress was also investigated and moderate to severe depressive symptoms were found almost three times more common in the final 3 months of life (20). In addition to the chemotherapy duration, the place where cancer patients recieve chemotherapy may also be important. Delibegovic et al reported that when they treated the lung cancer patients at the Palliative Care Centre, they found that their high levels of anxiety and depression scores were significantly reduced and they represented a better way of treatment than treatment at home (3).

Table 2: The mean scores of Glombock-Rust Sexual Satisfaction of the patients

	Patient score
Frequency	5.08 ± 1.78
Communication	4.47 ± 2.30
Satisfaction	3.70 ± 1.91
Avoidance	5.65 ± 1.03
Touch	3.77 ± 2.27
Premature Ejaculation	5.02 ± 1.67
Erectile Dysfunction	6.0 ± 1.12

When we evaluated our patients' sexuality in terms of their depression and anxiety scores, we could not find any significant relation between the patients with low and high depression and anxiety scores. However, their GRISS scores were very high which means sexual dysfunction. This may be due to the psychological factors other than their mood disorders which may play an important role in sexuality of LC patients as well as their toxic treatments. Limited number of the studies was focused on sexual functioning during the treatment of patients with metastatic lung cancer. Because this was a cancer in which the mortality was too high. Besides, patients with lung cancer receiving chemotherapy can be affected by changes in appearance, self-esteem, and sexuality, and therefore may need sexual counseling (6). Lindau et al evaluated the communication about intimacy and sexual relationships for couples affected by lung cancer. They found that couples described negative effects which were driven by cancer or its treatment, including physical and psychological effects, and positive effects included an increase in non-coital physical closeness and appreciation of the spouse (4). Reese et al assessed the sexual concerns in patients with lung cancer and concluded that sexual concerns were common and stable, with 52% of patients reporting at least mild sexual concerns which were basically related to physical and emotional symptoms. They also found an association between age, gender and distress causing sexual symptoms in this population (5). In another study, researchers investigated changes in sexual functioning for lung cancer patients having treatment and determined baseline sexual function below-normal which was also worsened over time (7). According to this analysis, age was found to be a significant factor affecting sexual function.

Quality of life is usually associated with physical, phycological, sexual and social factors of cancer patients (21). We found that the presence of anxiety and depression in metastatic lung cancer patients deteriorated nearly all of these QoL functional scales

Adress for correspondence: Umut Varol, İzmir Katip Çelebi Üniversitesi Atatürk Eğitim Ve Araştırma Hastanesi, İzmir, Türkiye
e-mail: varolumut@yahoo.com
Available at www.actaoncologicaturcica.com

except the global quality of life. For this reason, we have to consider rehabilitation of lung cancer patients in every stage of their disease. In a prospective study examining patients with advanced stage LC, depression and anxiety which was present in one-third of the cohort were associated with decreased QoL scales, and depression was independently associated with treatment adherence and with poor prognosis (2). Chen et al analyzed the effects of the walking exercise programme on anxiety, depression and cancer-related symptoms in patients with lung cancer and found that it is an effective intervention method for managing anxiety and depression in lung cancer (22).Similar to this study, Quist et al showed that a 6-week hospital-based supervised and structured exercise program, patients with advanced-stage lung cancer improved their physical capacity, functional capacity, anxiety level, and emotional well-being (23).In advanced lung cancer patients, poor performance status and psychological distress was found to be related with fatigue (24). So, by decreasing fatigue with exercise, both functional and psychological functions of the patients can be improved.

Table 3. The mean GRISS scores according to anxiety and depression levels of the patients

	Patient score	P		Patient score	P
Frequency			**Frequency**		
Anxiety ≥ 8	5.87 ± 1.80	0.734	Depression ≥ 10	6.01 ± 1.76	0.126
Anxiety < 8	5.66 ± 1.77		Depression < 10	5.21 ± 1.71	
Communication			**Communication**		
Anxiety ≥ 8	4.53 ± 2.27	0.803	Depression ≥ 10	4.56 ± 2.11	0.711
Anxiety < 8	4.33 ± 2.49		Depression < 10	4.28 ± 2.75	
Satisfaction			**Satisfaction**		
Anxiety ≥ 8	3.93 ± 2.06	0.190	Depression ≥ 10	3.96 ± 1.97	0.186
Anxiety < 8	3.08 ± 1.31		Depression < 10	3.14 ± 1.70	
Avoidance			**Avoidance**		
Anxiety ≥ 8	5.71 ± 1.17	0.398	Depression ≥ 10	5.76 ± 1.16	0.318
Anxiety < 8	5.50 ± 0.52		Depression < 10	5.42 ± 0.64	
Touch			**Touch**		
Anxiety ≥ 8	3.96 ± 2.30	0.356	Depression ≥ 10	3.76 ± 2.20	0.980
Anxiety < 8	3.25 ± 2.17		Depression < 10	3.78 ± 2.48	
Premature Ejaculation			**Premature Ejaculation**		
Anxiety ≥ 8	5.31 ± 1.59	0.060	Depression ≥ 10	5.33 ± 1.68	0.072
Anxiety < 8	4.25 ± 1.71		Depression < 10	4.35 ± 1.49	
Erectile Dysfunction			**Erectile Dysfunction**		
Anxiety ≥ 8	6.09 ± 1.14	0.371	Depression ≥ 10	6.13 ± 1.13	0.253
Anxiety < 8	5.75 ± 1.05		Depression < 10	5.71 ± 1.06	

GRISS: Golombok-Rust Inventory of Sexual Satisfaction

Table 4. The mean scores of EORTC-QLQ-C30 function scales of the patients

	Patient score
Physical functioning	57.9 ± 24.54
Role functioning	71.09 ± 31.2
Cognitive functioning	77.5 ± 25.3
Emotional functioning	68.47 ± 27.33
Social functioning	68.81 ± 25.11

Adress for correspondence: Umut Varol, İzmir Katip Çelebi Üniversitesi Atatürk Eğitim Ve Araştırma Hastanesi, İzmir, Türkiye
e-mail: varolumut@yahoo.com
Available at www.actaoncologicaturcica.com

Global quality of life	53.93 ± 29.54

Table 5. The mean EORTC-QLQ-C30 scores according to anxiety and depression levels of the patients

	Patient score	P		Patient score	P
Physical functioning			**Physical functioning**		
Anxiety ≥ 8	49.31 ± 21.04	**0.000**	Depression ≥ 10	53.23 ± 22.16	**0.064**
Anxiety < 8	80.83 ± 17.82		Depression < 10	67.92 ± 27.15	
Role functioning			**Role functioning**		
Anxiety ≥ 8	62.81 ± 31.85	**0.000**	Depression ≥ 10	65.86 ± 30.17	0.105
Anxiety < 8	93.16 ± 14.92		Depression < 10	82.20 ± 31.59	
Cognitive functioning			**Cognitive functioning**		
Anxiety ≥ 8	70.06 ± 25.87	**0.000**	Depression ≥ 10	71.30 ± 26.90	**0.005**
Anxiety < 8	97.33 ± 6.22		Depression < 10	90.64 ± 15.51	
Emotional functioning			**Emotional functioning**		
Anxiety ≥ 8	61.81 ± 27.79	**0.001**	Depression ≥ 10	58.93 ± 26.92	**0.000**
Anxiety < 8	86.25 ± 16.38		Depression < 10	88.92 ± 13.89	
Social functioning			**Social functioning**		
Anxiety ≥ 8	61.75 ± 24.41	**0.001**	Depression ≥ 10	61.93 ± 24.36	**0.006**
Anxiety < 8	87.66 ± 15.91		Depression < 10	83.57 ± 20.46	
Global quality of life			**Global quality of life**		
Anxiety ≥ 8	55.09 ± 28.10	0.675	Depression ≥ 10	53.79 ± 29.32	0.966
Anxiety < 8	50.83 ± 34.20		Depression < 10	54.21 ± 31.11	

Our study, although conducted in a limited number of patients, emphasized that depression and anxiety rates of metastatic LC patients were very high. Symptoms of depression and anxiety are frequently seen after the diagnosis of LC and may deteriorate both health-related QoL and survival (25,26). Additionally, diagnosis of this type of mostly incurable cancer increases their psychological distress including sexual dysfunction. Therefore, we have to deal with all problems of metastatic lung cancer patients while treating them with chemotherapeutics. Their state of anxiety, depression and sexual satisfaction needs to be assessed as frequently as possible. When there was significant depression or anxiety, we have to refer them for psychosocial treatment in order to improve their quality of life.

Conflict of Interest: None

References

1. Sarna L, Brown JK, Cooley ME, et al. Quality of life and meaning of illness of women with lung cancer. Oncol Nurs Forum 2005;32:E9-19
2. Arrieta O, Angulo LP, Núñez-Valencia C, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Ann Surg Oncol 2013;20:1941-8
3. Delibegovic A, Sinanovic O. The influence of palliative care on the level of anxiety and depression in lung cancer patients. Med Arch 2013;67:263-5
4. Lindau ST, Surawska H, Paice J, Baron SR. Communication about sexuality and intimacy in couples affected by lung cancer and their clinical-care providers. Psychooncology 2011;20:179-85
5. Reese JB, Shelby RA, Abernethy AP. Sexual concerns in lung cancer patients: an examination of predictors and moderating effects of age and gender. Support Care Cancer 2011;19:161-5
6. Schwartz S, Plawecki HM. Consequences of chemotherapy on the sexuality of patients with lung cancer. Clin J Oncol Nurs 2002;6:212-6
7. Shell JA, Carolan M, Zhang Y, Meneses KD. The longitudinal effects of cancer treatment on sexuality in

individuals with lung cancer. Oncol Nurs Forum 2008;35:73-9
8. Ilonen IK, Räsänen JV, Knuuttila A, et al. Quality of life following lobectomy or bilobectomy for non-smallcell lung cancer, a two-year prospective follow-up study. Lung Cancer 2010;70:347-51
9. Dancey J, Shepherd FA, Gralla RJ, Kim YS. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-celllung cancer previously treated with platinum-based chemo-herapy: results of a prospective, randomized phase III trial.Lung Cancer 2004;43:183-94
10. Tegin B. Cognitive disorders in depression: A review according to Beck Model. Ankara 1980. Psychol J 1987;6:116-23 (in Turkish)
11. Hisli N. A study on the validity of the Beck Depression Inventory. Psychol J 1988;22:118-26 (in Turkish).
12. Beck AT, Guthy D, Steer RA, Ball R. Interna con-l sistencies of the original and revised Beck Depression Inventory. J Clin Psychol 1984;40:1365-7
13. Rust J, Golombok S. The GRISS: a psychometric instrument for the assessment of sexual dysfunction. Arch Sex Behav 1986;15:157-165
14. Tuğrul C, Öztan N, Kabakçı E. Golombok - Rust Cinsel Doyum Ölçeği'nin standardizasyon çalışması. Türk Psikiyatri Dergisi 1993; 4:83-8
15. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-c30: a quality of life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76
16. Fayers P, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A (2001). EORTC QLQ-C30 Scoring Manual, In third edition ed 2001
17. Kramer JA. Use of the Hospital Anxiety and Depression Scale (HADS) in the assessment of depression in patients with inoperable lung cancer. Palliat Med 1999;13:353-4
18. Cataldo JK, Brodsky JL. Lung cancer stigma, anxiety, depression and symptom severity. Oncology 2013;85:33-40
19. Haun MW, Sklenarova H, Villalobos M, et al. Depression, anxiety and disease-related distress in couples affected by advanced lung cancer. Lung Cancer 2014;86:274-80
20. Lo C, Zimmermann C, Rydall A, et al. Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. J Clin Oncol. 2010;28:3084-9
21. Nipp RD, Greer JA, El-Jawahri A, et al. Age and Gender Moderate the Impact of Early Palliative Care in Metastatic Non-Small Cell Lung Cancer. Oncologist. 2016;21:119-26
22. Chen HM, Tsai CM, Wu YC, Lin KC, Lin CC. Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. Br J Cancer 2015;112:438-45
23. Quist M, Adamsen L, Rørth M, Laursen JH , Christensen KB, Langer SW. The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. Integr Cancer Ther 2015;14:341-9
24. Brown DJ, McMillan DC, Milroy R. The correlation between fatigue, physical function, the systemic inflammatory response, and psychological distress in patients with advanced lung cancer. Cancer 2005;103:377-82
25. Songür N, Erenci G, Özdilekcan C, Karşıgil H, Akkoç Z. Depression Rates Before Diagnosis and After Treatment in Patients With Advanced Lung Cancer. Turkish Respiratory Journal 2004;5:073-081
26. Suna N, Yalcın B, Ekinci AS, et al. İkinci basamak kemoterapi alan veya almayan ileri evre küçük hücreli dışı akciğer kanserli hastalarda yaşam kalitesi değerlendirilmesi. Acta Oncol Tur 2015;48:53-62

Giant lipomas of the upper extremity

Üst ekstremite yerleşimli dev lipomlar

Hasan Göçer[1], Nevzat Dabak[1], Alper Çıraklı[2]

[1]Department of Orthopedic and Traumatology, Ondokuz Mayıs University, Samsun
[2]Orthopedic and Traumatology Clinic, Kayseri Research and Training Hospital, Kayseri

Dergiye Ulaşma Tarihi: 27.02.2016 Dergiye Kabul Tarihi: 11.04.2016 Doi: 10.5505/aot.2016.37450

ÖZET

GİRİŞ ve AMAÇ: Lipomlar en sık görülen yumuşak doku tümörleri olup özellikle omuz, sırt ve alt ekstremitede görülmektedir. Nadir görülmekle birlikte 5 cm' in üzerinde olanlar ise dev lipom şeklinde tanımlanmaktadır. Yazımızda tanıda ve tedavide sıkıntılara yol açabilecek üst ekstremite yerleşimli dev lipom nedeniyle cerrahi tedavi edilen olgular literatür eşliğinde sunulmuştur.
YÖNTEM ve GEREÇLER: Mart 2009 ile Aralık 2014 tarihleri arasında üst ekstremite yerleşimli dev lipom nedeniyle cerrahi total eksizyon uygulanmış ve son kontrolleri yapılan 17 olgu çalışmaya dahil edildi. Hastalar yaş, cinsiyet, lokalizasyon, cerrahi yaklaşım, histopatolojik özellik ve nüks açısından değerlendirildi. Veriler SPSS sistemine yüklendikten sonra normal dağılıma uyup uymadığı Shapiro-Wilk testi ile değerlendirildi.
BULGULAR: Olguların 7'si kadın, 10'u erkek ve ortalama yaşı 44 (8-81) idi. Lezyon olguların 4'ünde el, 4'ünde önkol, 3'ünde kol ve 6'sında omuz bölgesinde, sağ/sol yerleşimi ise 12/5 şeklinde idi. Olguların ortalama takip süresi 42 ay (9-84) idi. Takiplerinde el yerleşimli bir olgumuzda 22. ayda nüks geliştiği gözlendi ve kitleye cerrahi olarak re-eksizyon uygulandı.
TARTIŞMA ve SONUÇ: Sonuç: Lipomların kesin tedavisi cerrahi olarak total eksizyondur. Bunun için özellikle üst ekstremite yerleşimli lipomlarda tüm sınırlara ulaşmak ve komşu nörovasküler yapıları korumak için yeterince geniş insizyon kullanılmalıdır.
Anahtar Kelimeler: Lipom, Dev lipom, Üst ekstremite, Total eksizyon

ABSTRACT

INTRODUCTION: Lipomas are the most frequently seen soft tissue tumors and are seen particularly in the shoulder, back and lower extremity. Although rarely seen, lipomas of >5 cm are known as giant lipomas. In this paper, cases treated surgically due to giant lipoma located in the upper extremity, which can lead to problems in diagnosis and treatment, are presented in the light of current literature.
METHODS: The study included 17 cases that underwent surgical total excision for giant lipoma located in the upper extremity and underwent final follow-up examination between March 2009 and December 2014. Patients were evaluated in point of age, gender, localization, surgical approach, histopathological characteristics and recurrence. Data were evaluated to confirm normal distribution using the Shapiro-Wilk test.
RESULTS: The patients were 7 females and 10 males with a mean age of 44 years (ranging from 8 to 81 years). The lesions were in the hand in 4 cases, in the arm in 3 cases and the shoulder region in 6 cases, with right/left location in 12/5 cases. The mean follow-up period was 42 months (ranging from 9 to 84 months). In one case, recurrence was seen at 22nd month and surgical re-excision of the mass was applied.
DISCUSSION and CONCLUSION: The definitive treatment for lipomas is surgical total excision. To achieve this, particularly in lipomas located in the upper extremity, a sufficient wide incision must be used to reach all the nerves and protect the neurovascular structures.
Keywords: Lipoma, Giant lipoma, Upper extremity, Total excision

Introduction

Lipomas are the most frequently seen soft tissue tumors and originate from the mesenchymal tissue (1). Generally, they have regular borders and are separated from the surrounding soft tissue with a connective tissue capsule. Location is often in the back and shoulder region, and may be subcutaneous (superficial) or between the muscle tissues (deep) (2, 3). Although the etiology is not fully known, it has been suggested that trauma, obesity and female gender trigger formation or growth of the mass (4). Lipomas are slow

Adress for correspondence: Uzm. Dr. Alper Çıraklı. Kayseri Eğitim ve Araştırma Hastanesi Kayseri - Türkiye
e-mail: alperomu@gmail.com
Available at www.actaoncologicaturcica.com

growing and some of them that is over 5 cm in size known as giant lipomas although they are rarely seen (5).
Masses are generally painless and asymptomatic but when they are close to the skin or create pressure on neighboring anatomic structures, symptoms might be seen. Although many studies have been conducted on lipomas, there are very few which have examined giant lipomas in the upper extremity (6, 7). In this paper, cases treated surgically due to giant lipomas located in the upper extremity that can lead to problems in diagnosis and treatment, are presented in the light of current literature.

Material and Method

The study comprised of 17 patients, surgically treated for a lipoma >5 cm in size located in the upper extremity, which was confirmed histopathologically between March 2009 and December 2014. All patients attended a final follow-up examination. Evaluation of the patients was made in respect of age, gender, localization, surgical approach, histopathological features and recurrence. According to the clinical complaints, direct radiography (X-ray), ultrasonography (USG) and/or magnetic resonance imaging (MRI) were applied. To be able to better evaluate lesions with a deep location adjacent to bone and with a heterogeneous appearance on MRI, computed tomography (CT) was applied. In addition, electromyographical (EMG) records also evaluated for monitorisation in some cases. In the postoperative follow-up USG or MRI was used.
In statistical analysis, Shapiro-Wilk test was used to determine normality. Data stated as mean ± standard deviation and median (min-max) with normal and non normal distribution respectively.

Results

The patients were 7 females and 10 males with a mean age of 44 years (ranging from, 8 to 81 years). The lesions were in the hand in 4 cases, in the arm in 3 cases and the shoulder region in 6 cases, with right/left location in 12/5 cases (Table 1). No biopsy was made of lesions, which were radiologically confirmed as lipoma. Tru-cut biopsy was applied to only 2 patients because of the heterogeneous appearance and septal thickness of the lesion (Figure 1). In patients with involvement of two compartments in the forearm, a volar and dorsal double incision was used (Figure 2). In 2 patients, localization was in the axillary region (Figure 3). The mean follow-up period was 42 months (ranging from 9 to 84 months). In one case with location in the hand, recurrence was seen to have developed in the 22nd month and surgical re-excision of the mass was applied.

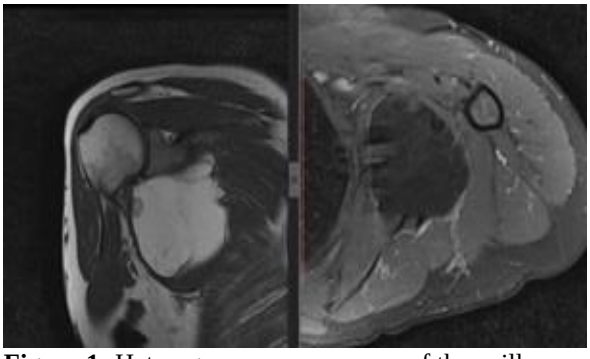


Figure 1: Heterogeneous appearance of the axillary area on MRI.

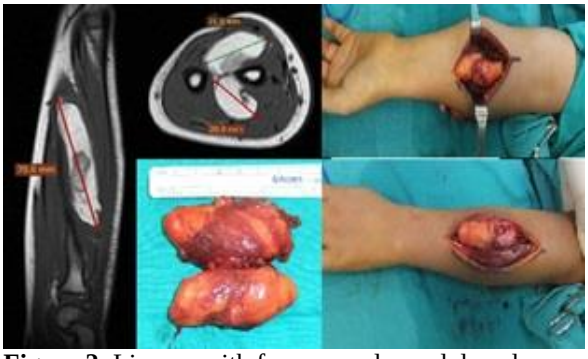


Figure 2: Lipoma with forearm volar and dorsal compartment localization.

Adress for correspondence: Uzm. Dr. Alper Çıraklı. Kayseri Eğitim ve Araştırma Hastanesi Kayseri - Türkiye
e-mail: alperomu@gmail.com
Available at www.actaoncologicaturcica.com

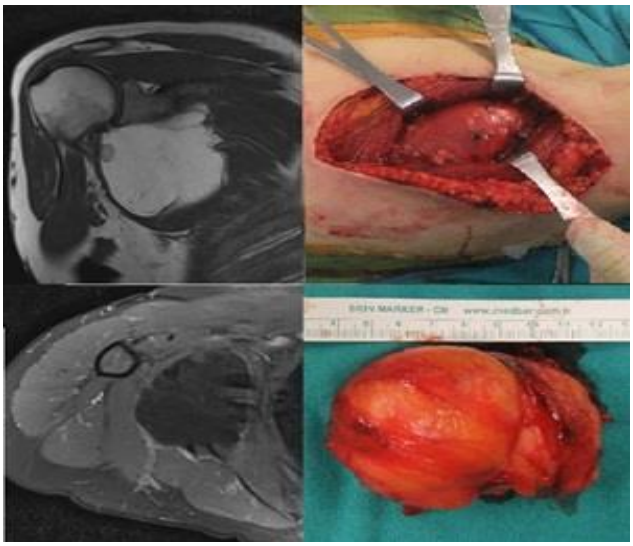


Figure 3: Lipoma with axillary region localization.

Table 1: Features of patients.

Case number	Age (years)	Gender	Affected side	Location
1	29	Female	Left	Forearm
2	81	Female	Right	Hand
3	60	Male	Right	Shoulder
4	30	Female	Right	Hand
5	31	Female	Right	Forearm
6	80	Male	Right	Hand
7	38	Male	Right	Shoulder
8	44	Female	Right	Shoulder
9	40	Female	Right	Shoulder
10	52	Male	Right	Shoulder
11	8	Male	Left	Forearm
12	51	Male	Right	Forearm
13	44	Male	Right	Arm
14	53	Male	Left	Shoulder
15	52	Male	Right	Arm
16	36	Female	Left	Hand
17	46	Male	Right	Arm

Discussion

Lipoma is the most frequently seen soft tissue tumor and is seen especially in the shoulder, back and on the posterior surface of the lower extremity. Most reports are related to lower extremity location and studies regarding upper extremity located lipomas are involved in single case reports with the lack of comprehensive evaluation (7-9).

Generally, lipomas are <2-3 cm in size and are rarely bigger than this. When the size is >5 cm, they are accepted as giant lipomas and may be confused clinically and radiologically with atypical lipomatosis tumor or well-differentiated liposarcoma (5, 10). In cases where giant lipomas are not removed together with the capsule, it can be seen either increased risk of local recurrence and difficulty of re-excision (11). In the current series, all the masses were >5 cm in size unless observation of malignant transformation.

Liposarcoma is the most frequently seen malignant soft tissue tumor that can be encountered mostly in between the 4th-6th decades of life (12). The risk of malignant lipoma increases when there is deep location, onset of pain in a previously painless mass >5 cm in size and a heterogeneous appearance on MRI (12, 13). In the current study, there was a

Adress for correspondence: Uzm. Dr. Alper Çıraklı. Kayseri Eğitim ve Araştırma Hastanesi Kayseri - Türkiye
e-mail: alperomu@gmail.com
Available at www.actaoncologicaturcica.com

palpable swelling in 10 patients, including 2 with complaints of pain. In other 7 patients (with arm, forearm and axillary region location), although there was a deep feeling of swelling and fullness, they had no any complains since the lack of palpable swelling evident which resulted in delay in diagnosis and treatment.

Although the etiology of lipomas has not been clarified, trauma and obesity have been thought to create a risk (14, 15). In the current cases, because of location on the volar surface and proximity to the muscles providing the flexion-adduction movement, the mass can be considered to have occurred with friction or the interaction of the fascia and the continuously contracting muscle rather than directly from an external trauma.

Lipomas are seen more in females than males (5). However, in the current cases there were seen to be more males. As the location of the mass was in the upper extremity, the formation of the mass may have been triggered by the use of the arm in work undertaken by males, which requires more strength, or exposure to trauma.

Although lipomas are generally seen alone, there may occasionally be several and may accompany lipomatosis or syndromes such as Gardner (16, 17).

Lipomas are generally painless due to slow growth and the absence of spread to surrounding tissues. Depending on the mechanical pressure in the anatomical location, nerve entrapment and impingement syndrome may lead to symptoms (18-21). In particular, when there is proximity to the nerve, neurological symptoms such as numbness, burning, tingling and weakness may be noticed early. Clinical symptoms are expected in lipoma, which develops in close proximity to neurovascular structures, especially in the upper extremity. In the current study, only one case had neurological symptoms in the preoperative period. However, evaluation was made with EMG for monitorisation in some cases of the current study. With the exception of the one patient with pre-operative neurological symptoms, no postoperative neurological deficit was seen in any patient and this information has not been seen in literature. Despite both pre-operative and intra-operative trauma to the nerves adjacent to giant lipoma, that no neurological deficit developed can be interpreted as the nerve having developed resistance to these slow-growing types of masses and thus the nerve communication and feeding is not disrupted. A neurological deficit may develop during surgical fixation following bone fractures due to nerve damage even if the condition of slight tension.

Although the most common complaint in cases of lipoma is palpable swelling, as this swelling is generally occur in between deep tissues, it is generally noticed late (8). In 6 patients of the current study with forearm and axillary location, despite feelings of tenseness, fullness and swelling for long time, there was no evident pain and any imaging methods additional to x-ray were examined which lead to late diagnosis. Although direct radiography is the imaging method used first by orthopedic surgeons, it rarely gives sufficient information for diagnosis in cases of lipoma. The first test required in cases of palpable soft tissue swellings is USG, which can be applied easily as it is cheap, simple and non-invasive. MRI is the most valuable imaging method in the diagnosis of lipoma and should be the first imaging method used after USG in patients having swelling and feeling of tension (12). MRI shows the tissue content, dimensions and relationship with surrounding soft tissues and is useful in planning surgical treatment.

Lipomas must be removed totally (4, 22). Careful surgical exploration is required as the compartments of the upper extremity are relatively smaller and because of neurovascular proximity. In 2 cases with forearm volar and dorsal location in the current study, a double incision was preferred to protect the neurovascular tissues and to remove the mass entirely with the capsule.

Even though there many morphological variants of lipoma have been described according to the presence of additional mesenchymal components such as angiolipoma, myxolipoma and fibrolipoma, classification is of separate prognostic importance. Especially in lipoma with a deep location, it is important that differentiation can be made from atypical lipomatosis tumor and well-differentiated liposarcoma, which closely resemble lipoma. Especially in tumors of large diameter, with irregular contours and heterogeneous and sclerotic appearance, the pathologist must be informed in respect of the

Adress for correspondence: Uzm. Dr. Alper Çıraklı. Kayseri Eğitim ve Araştırma Hastanesi Kayseri - Türkiye
e-mail: alperomu@gmail.com
Available at www.actaoncologicaturcica.com

radiological and clinical characteristics (23, 24).

In conclusion, the definitive treatment for lipomas is surgical total excision. Particularly in lipoma located in the upper extremity, a sufficiently wide incision must be used to reach all the nerves and protect the neurovascular structures. In cases of large, deeply located masses with heterogeneous appearance on MRI, the pathologist must be informed in detail.

Conflict of interests: The authors declare that they have no competing interests.

References

1. Murphey MD, Carroll JF, Flemming DJ, Pope TL, Gannon FH, Kransdorf MJ. From the archives of the AFIP: benign musculoskeletal lipomatous lesions. Radiographics. 2004; 24: 1433-66
2. Erwteman AS, Balach T. Clinical evaluation and management of benign soft tissue tumors of the extremities. Cancer Treat Res. 2014; 162: 171-202
3. McTighe S, Chernev I. Intramuscular lipoma: a review of the literature. Orthop Rev (Pavia). 2014; 6: 5618
4. Gogi AM, Ramanujam R. Clinicopathological study and management of peripheral soft tissue tumours. J Clin Diagn Res. 2013; 7: 2524-6
5. Cribb GL, Cool WP, Ford DJ, Mangham DC. Giant lipomatous tumours of the hand and forearm. J Hand Surg Br. 2005; 30: 509-12
6. Carbone S, Candela V, Passaretti D, et al. Subdeltoid lipomas: a consecutive series of 13 cases. Musculoskelet Surg. 2012; 96: 53-6
7. Elbardouni A, Kharmaz M, Salah Berrada M, Mahfoud M, Elyaacoubi M. Well-circumscribed deep-seated lipomas of the upper extremity. A report of 13 cases. Orthop Traumatol Surg Res. 2011; 97: 152-8
8. Allen B, Rader C, Babigian A. Giant lipomas of the upper extremity. Can J Plast Surg. 2007; 15: 141-4.
9. Grimaldi L, Cuomo R, Castagna A, et al. Giant lipoma of the back. Indian J Plast Surg. 52015; 48: 220-1
10. Celik C, Karakousis CP, Moore R, Holyoke ED. Liposarcomas: prognosis and management. J Surg Oncol. 1980; 14: 245-9
11. Nakamura Y, Teramoto Y, Sato S, et al. Axillary giant lipoma: a report of two cases and published work review. J Dermatol. 2014; 41: 841-4
12. Nagano S, Yokouchi M, Setoguchi T, et al. Differentiation of lipoma and atypical lipomatous tumor by a scoring system: implication of increased vascularity on pathogenesis of liposarcoma. BMC Musculoskelet Disord. 2015; 16: 36
13. Han HH, Choi JY, Seo BF, et al. Treatment for intramuscular lipoma frequently confused with sarcoma: a 6-year restrospective study and literature review. Biomed Res Int. 2014: 867689
14. Nigri G, Dente M, Valabrega S, et al. Giant inframuscular lipoma disclosed 14 years after a blunt trauma: a case report. J Med Case Rep. 2008; 2: 318
15. Terzioglu A, Tuncali D, Yuksel A, Bingul F, Aslan G. Giant lipomas: a series of 12 consecutive cases and a giant liposarcoma of the thigh. Dermatol Surg. 2004; 30: 463-7
16. Ardeleanu V, Chicos S, Georgescu C, Tutunaru D. Multiple benign symmetric lipomatosis--a differential diagnosis of obesity. Chirurgia (Bucur). 2013; 108: 580-3
17. Park KH, Hong YH, Choi SJ, Sung JJ, Lee KW. Multiple Symmetric Lipomatosis Presenting with Bilateral Brachial Plexopathy. J Clin Neurol. 2015; 11: 400-1
18. Ferrari L, Haynes P, Mack J, DiFelice GS. Intramuscular lipoma of the supraspinatus causing impingement syndrome. Orthopedics. 2009; 32(8)
19. Pagonis T, Givissis P, Christodoulou A. Complications arising from a misdiagnosed giant lipoma of the hand and palm: a case report. J Med Case Rep. 2011; 5: 552
20. Sergeant G, Gheysens O, Seynaeve P, Van Cauwelaert J, Ceuppens H. Neurovascular compression by a subpectoral lipoma. A case report of a rare cause of thoracic outlet syndrome. Acta Chir Belg. 2003;103(5):528-31
21. Yoon S, Jung SN. Lipoma of the finger presenting as restricted motion. Indian J Plast Surg. 2008; 41: 237-8
22. Fisher SB, Baxter KJ, Staley CA, et al. The General Surgeon's quandary: atypical lipomatous tumor vs lipoma, who needs a surgical oncologist? J Am Coll Surg. 2013; 217: 881-8
23. Patel J, Deb R, Speake W, Macculloch TA. Primary small bowel liposarcoma (atypical lipomatous tumour) with myogenic differentiation. Sarcoma. 2010;2010
24. Parakh RS, Zawar MP, Gadgil PA, Kaujalagi NS. Dedifferentiated liposarcoma of the retro-peritoneum: histologically low-grade type. Indian J Pathol Microbiol. 2010; 53: 353-5.

Adress for correspondence: Uzm. Dr. Alper Çıraklı. Kayseri Eğitim ve Araştırma Hastanesi Kayseri - Türkiye
e-mail: alperomu@gmail.com
Available at www.actaoncologicaturcica.com

Pulmonary Metastasectomy For 29 Patients With Colorectal Carcinoma: A Single Center Experience

Yirmidokuz Kolon Kanserli Hastada Akciğer Metastezektomi: Tek Merkez Deneyimi

Mehmet Serdar Cengizhan[1], İlhan Öztop[2], Tarık Salman[3], Aydın Şanlı[4], Olçun Ümit Ünal[5]

[1]Dokuz eylül üniversitesi Tıp Fakültesi İç Hastalıkları Ana Bilim Dalı, İzmir, Türkiye
[2]Dokuz eylül üniversitesi Onkoloji Enstitüsü Tıbbi Onkoloji Bilim Dalı, İzmir, Türkiye
[3]İzmir Katip Çelebi üniversitesi Tıp Fakültesi Tıbbi Onkoloji Bilim Dalı, İzmir, Türkiye
[4]Dokuz eylül üniversitesi Tıp Fakültesi Göğüs Cerrahisi Ana Bilim Dalı, İzmir, Türkiye
[5]Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye

Dergiye Ulaşma Tarihi: 7.5.2016 Dergiye Kabul Tarihi: 5.10.2016 Doi: 10.5505/aot.2016.80299

ÖZET

Amaç: Kolorektal kanserli hastaların yaklaşık olarak %50-60'ında senkron veya metakron uzak metastazlar izlenmektedir. Kolorektal kanserlerin hepatik ve pulmoner metastazlarının cerrahi rezeksiyonu hastalıksız sağkalım (DFS) ve genel sağkalımı (OS) anlamlı düzeyde uzatmakta ve böylece son yıllarda yaygın olarak uygulanmaktadır.

Yöntem: Bu araştırmada, Dokuz Eylül Üniversitesi Tıp Fakültesi Hastanesi'nde tedavi gören ve kolorektal kanserlere bağlı akciğer metastazları nedeniyle metastazektomi uygulanan 29 hasta değerlendirildi. Hastalara ait bilgiler retrospektif olarak elde edildi.

Bulgular: Hastaların 24'ü (%82.8) izole akciğer metastazı, gerikalan 5'i (%17.2) ise hem akciğer hem karaciğer metastazına sahipti. Çalışmaya alınan hastaların tümüne akciğer metastazına yönelik rezeksiyon uygulanırken, 5 (%17.2) hastaya ise akciğer+karaciğer metastazektomisi uygulanmıştı. Tüm hasta grubunda ortanca OSx 57 ay (SD± 4 ay), 1, 3 ve 5 yıllık sağkalım oranları sırasıyla %96, %92 ve %49 olarak tespit edildi. Metastazektomi operasyonu sonrası izlenen lezyonu olmayan hastalarda ortanca DFS 31 ay (SD± 3 ay), 1, 3 ve 5 yıllık DFS oranları sırasıyla %86, %42 ve %1 olarak saptandı. Metastazektominin şekline göre OS değerlendirildiğinde wedge rezeksiyon yapılanlarda ortanca OS 58 ay (SD± 5 ay), lobektomi yapılanlarda ise 50 ay (SD± 2 ay) olarak bulundu. Rezeksiyon türüne göre OS değerlendirildiğinde R0 rezeksiyon yapılanlarda ortanca OS 66 ay (SD± 5 ay), R1 rezeksiyon yapılanlarda ise ortanca OS 47 (SD± 7 ay) ay olarak bulundu.

Sonuç: Sonuçlarımız kolorektal kanser akciğer metastazlarının cerrahi rezeksiyonunun, özellikle R0 rezeksiyonun OS süresinin uzamasına katkı sağladığını göstermektedir.

Anahtar Kelimeler: Kolorektal kanser; Akciğer metastazektomi, Sağkalım

ABSTRACT

Aim: Synchronous or metachoronous distant metastasis develops in approximately 50-60% of patients with colorectal cancer during the clinical course. Surgical resection of the hepatic and/or pulmonary metastasis of colorectal cancers significantly extends disease-free survival (DFS) and overall survival (OS) rates, and thus has been applied more broadly in recent years.

Methods: In this study, 29 patients who were treated at the Dokuz Eylül University Medical Faculty Hospital and who had received a metastasectomy due to a lung metastasis related to colorectal cancer were evaluated. Information on the patients was obtained retrospectively.

Results: Twenty-four (82.8%) patients had an isolated lung metastasis and 5 (17.2%) had both lung and liver metastasis. Resection was performed on all patients for lung metastasis, and a lung+liver metastasectomy was performed on 5 (17.2%). For the entire patient group, the median OS was 57 months (SD± 4 months), and 1, 3, and 5 year survival rates were 96%, 92% and 49%, respectively. In patients who received follow-up treatment after undergoing the metastasectomy operation and who did not have lesions, the median DFS was 31 months (SD± 3 months), and 1, 3, and 5 year DFS rates were 86.3%, 42% and 1%, respectively. In patients who received wedge resection treatment, the median OS was 58 months (SD± 5 months), and for the patients who received lobectomy treatment, the median OS was 50 months (SD± 2 months). In the evaluations made according to the resection type, median OS was 66 months (SD± 5 months) in patients who had R0 resection and 47 months (SD± 7 months) in patients who had R1 resection.

Adress for correspondence: Olçun Ümit Ünal, Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye
e-mail: drolcun@hotmail.com
Available at www.actaoncologicaturcica.com

Conclusion: Our results show that surgical resection, particularly an R0 resection of lung metastasis in colorectal cancer patients contributes to extended patient OS time.
Keywords: Colorectal cancer; Pulmonary metastasectomy, Survival

Introduction

Colorectal cancer is one of most common type of cancer (1). Metastasis is the primary cause of death in these patients, with the most common metastasis areas being the liver, lung and peritoneum. Distant metastasis is present in approximately 20-25% of patients with colorectal cancer at the time of diagnosis (2). Metachronous metastasis develops during the course of disease in approximately 40-50% of patients who received a resection and adjuvant therapies (3).

When patients with metastatic colorectal cancer are not treated, the prognosis is poor, with a median survival rate of approximately 5-9 months (4). The primary treatment for metastatic colorectal cancer is systemic; however, when metastasis is present in only the liver or the lung, a metastasectomy can also be performed. In systemic treatments, combinations of chemotherapeutic agents, such as 5-fluorouracil (5-FU), oxaliplatin, and irinotecan, are typically used. With the recent addition of targeted agents that have been used, the level of efficiency has increased and due to their high response rates, they have become the agents of choice in induction treatments (5).

Among the colorectal cancer metastases, lung and liver metastases are particularly important, especially in terms of determining the treatment approach. In these patients, local ablative approaches are also commonly performed, in addition to systemic treatments. In liver metastases related to colorectal cancer, hepatic resection is the only curative treatment option, and 5-year survival rates are reported to have a ratio of 25-40%. Today, hepatic resection serves as the gold standard of treatment types (6, 7).

Patients with lung metastasis only are believed to have a more suitable biology in terms of local or systemic treatment options as compared to patients with multi-organ metastasis. In an autopsy study performed on patients who had died of metastatic lung disease, it was observed that the lungs were the single metastasis area in 20% of the patients. This lends strength to the idea that surgical resection of lung metastases can extend survival time. Among all metastases, patients who are able to receive complete resection have a longer survival rate as compared to patients who unable to receive resection. It has been shown that time of survival of over 5 years can be obtained in about 20 to 40% of patients who have resectable lung metastasis (8). It has also been reported that synchronous or sequential resection of liver and lung metastases can extend survival (9).

In this study, the objective is to evaluate the effects on survival and prognosis of patients with colorectal-cancer-related lung metastasis who have undergone a metastasectomy.

Methods

Patient Characteristics

Evaluations were conducted on colorectal cancer patients who had received a metastasectomy due to lung metastasis and who were receiving follow-up treatment at Dokuz Eylül University Medical Faculty, Department of Internal Diseases, Medical Oncology between January 2001 and May 2013. The files of the patients, including information on their metastasectomy operation, the efficiency and toxicity of the treatments performed, as well as their demographical data, were retrospectively evaluated. The staging of the patients involved in the study was performed according to the American Joint Committee on Cancer's (AJCC) Cancer Staging, 6th edition, 2002 TNM staging system.

Treatment Characteristics

In patients who had previously had stage II colon cancer or who have any of the high risk factors, the De Gramont regimen (Folinic acid 400 mg/m² + 5-FU 400 mg/m² bolus + 5-FU 2400 mg/m² 46-h infusion, fortnightly) was performed as the adjuvant chemotherapy, and for stage III patients, the mFOLFOX-4 (Folinic acid 400 mg/m² + 5-FU 400 mg/m² bolus + 5-FU 2400 mg/m² 46-h infusion+ Oxaliplatin 85 mg/m², fortnightly) regimens were performed. For patients who had rectal cancer and were

Adress for correspondence: Olçun Ümit Ünal, Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye
e-mail: drolcun@hotmail.com
Available at www.actaoncologicaturcica.com

undergoing chemoradiotherapy (CRT), radiotherapy was delivered 45 Gy in 25 fractions, at a dose of 1.8 Gy fraction a day, and 5-FU 225 mg/m²/day was administered in a continuous infusion. Chemotherapy regimens applied due to metastatic diseases were also grouped.

Efficiency Evaluation

For patients receiving systemic treatment, a response evaluation was conducted once every 6 courses of treatments. The response evaluation was carried out according to the tumor response evaluation criteria of the World Health Organization (WHO). Complete disappearance of tumor and confirmation of this result in four weeks was considered a complete response (CR); a regression of 50% or above in the target lesion and a maximum progression of 25% in any lesion and confirmation of this result in four weeks was considered a partial response (PR); no change in the target lesion was considered a stable disease (SD); and a progression of 25% or above in the target lesion or determination of a new lesion was considered a progressive disease (PD). The sum of CR and PR was regarded as an objective response rate (ORR).

Patients' pre-metastasectomy evaluations were carried out with thoracic, lower and upper abdominal computed tomography; PET-CT and colonoscopy were performed in the required cases. The lung metastasectomy process was grouped into wedge resection, segmentectomy, and lobectomy. The resection type was classified as R0, R1 or R2 resection.

Survival Analysis

For patients who received follow-up after the metastasectomy operation and who did not have any lesions, the time between operation and recurrence was regarded as disease-free survival (DFS), and the time until death was considered as overall survival (OS).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS), Windows Version 15.0 was used to conduct statistical analysis of the data; the Chi-Square test and Fisher exact test were used for the comparison between the independent group rates of two groups. For DFS and OS analyses, the Kaplan-Meier Method was used, and for the comparison of two survival curves, the Log rank Test was used. Statistical significance was set at $p<0.05$.

Results

Patient Characteristics

Twenty-nine patients who were treated and received follow-up after being diagnosed with metastatic colorectal cancer and who had had a lung metastasectomy were involved in the study. A majority of the patients were female, and in a large portion of the female patients, the primary tumor was located in the colon. The tumor histology was adenocarcinoma in all patients. Six (20.7%) were metastatic at the time of diagnosis, while 23 (79.3%) became metastatic at a later period. Three of the 17 patients with a primary tumor location in the colon were metastatic at the time of diagnosis, and none of the 12 patients with a primary tumor location in the rectum were metastatic at the time of diagnosis. All the patients that were not metastatic at the time of diagnosis had a previous adjuvant history. Twenty-four (82.8%) patients had an isolated lung metastasis, and 5 (17.2%) had both lung and liver metastasis. Lung metastases were located mostly in the left lung's upper lobe and right lung's lower lobe. Wedge resection and R0 resection were the most commonly performed metastasectomy types. Resection was performed on all patients for lung metastasis, while additional liver metastasectomy was performed on 5 (17.2%). Patients' characteristics are shown in detail in Table 1. There were no operation related deaths.

Treatment regimens

Neoadjuvant treatment was given to 18 (62.1%) patients before they had received a lung metastasectomy; on the remaining 11 (37.9%) patients, a lung metastasectomy was performed directly. Adjuvant treatment was performed on all patients after metastasectomy, with the most common treatment being the Folfiri- bevacizumab regimen. The chemotherapy characteristics of patients are shown in detail in Table 2.

Adress for correspondence: Olçun Ümit Ünal, Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye
e-mail: drolcun@hotmail.com
Available at www.actaoncologicaturcica.com

Table 1. Patient and tumor characteristics

Variable	n (%)
Gender	
Male	16 (55.2%)
Female	13 (44.8%)
Primary Tumor localization	
Colon	17 (58.6%)
Rectum	12 (41.4%)
Location of tumor metastases during lung metastasectomy	
Isolated lung	24 (82.8%)
Lung+liver	5 (17.2%)
Metastasis location	
Left lung's upper lobe	8 (27.5%)
Right lung's lower lobe	6 (20.6%)
Left lung's lower lobe	5 (17.2%)
Right lung's upper lobe	3 (10.2%)
Right lung's upper + left lung's lower lobe	2 (6.8%)
Right lung's upper and lower lobe	2 (6.8%)
Right lung's lower + left lung's upper lobe	1 (3.4%)
Left lung's upper and lower lobe	1 (3.4%)
Right lung's lower + left lung's lower lobe	1 (3.4%)
Operation type	
Solitary Lung metastasectomy	24 (82.8%)
Lung + liver metastasectomy	5 (17.2%)
Type of Lung Metastasectomy	
Wedge resection	24 (82.8%)
Lobectomy	5 (17.2%)
Type of Resection in Lung Metastasectomy	
R0	17 (58.6%)
R1	12 (41.4%)

Adress for correspondence: Olçun Ümit Ünal, Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye
e-mail: drolcun@hotmail.com
Available at www.actaoncologicaturcica.com

Table 2. Chemotherapy characteristics and diagrams of patient	
Neoadjuvant chemotherapy	
Performed	18 (62.1%)
Non-performed	11 (37.9%)
Adjuvant chemotherapy type	
Folfiri+bevacizumab	10 (34.5%)
Folfiri + cetuximab	4 (13.7%)
Folfox6	3 (10.3%)
Folfox4	3 (10.3%)
Folfiri	3 (10.3%)
Folfox + Bevacizumab	2 (6.9%)
Folfox7	1 (3.4%)
Raltitrexed + oxaliplatin	1 (3.4%)

Table 3. Recurrence pattern following metastasectomy	
Recurrence organ	**n (%)**
Isolated lung	12 (41.3%)
Lung + liver	1 (3.4%)
Liver + peritoneum	2 (6.9%)
Lung + brain	4 (13.8%)
Spleen	1 (3.4%)
Rectum	1 (3.4%)
No recurrence	8 (27.6%)

Survival

In the entire patient group, the median OS was 57 months (SD±4 months), and 1, 3, and 5 year survival rates were 96%, 92%, and 49%, respectively (Figure 1). In patients who received follow-up after undergoing the metastasectomy operation and who did not have lesions, the median DFS was 31 months (SD±3 months), and 1, 3, and 5 year DFS rates were 86.3%, 42%, and 1%, respectively (Figure 2). In patients who had received treatment at a prior time under the diagnosis of early stage colorectal cancer and then became metastatic, the median time between diagnosis and metastasis was 23 months. When the survival is evaluated according to the resection type, median OS was determined as 66 months (SD±5 months) in patients who had R0 resection and 47 months (SD±7 months) in patients who had R1 resection (Figure 3). When survival was evaluated according to the type of metastasectomy, the median OS was 58 months (SD±5 months) and 50 months (SD± 2 months) in patients that had wedge resection and lobectomy, respectively (Figure 4). When survival analyses were assessed according to the primary tumor location, the median OS was 45 months for those whose tumor was in the colon and 63 months for those whose tumor was in the rectum (Figure 5). In the patients that received chemotherapy as adjuvant treatment after metastasectomy, there was no significant difference in terms of survival according to CT regimen.

Recurrence pattern after metastasectomy and treatment characteristics

Recurrence occurred in 21 (72.4%) patients after receiving a lung metastasectomy. Metastasis was present in a single organ in 14 of these patients and 7 had metastasis in two organs. Location and distribution of recurrences are shown in Table 3. A lung metastasectomy was repeated in 4 (19%) of the patients who had a recurrence; in 3 (15%) patients, a lung metastasectomy was performed after neoadjuvant chemotherapy; and palliative chemotherapy was performed on 14 (66%) patients. Of the 7 patients who had a second lung metastasectomy as a result of the recurrence, 6 were rectum derived and 1 colon derived.

Conclusions

Colorectal cancers rank second among cancer related deaths. Lung metastasis occurs in 10-20% of colorectal cancers, whereas colorectal cancer metastasis accounts for only 2-4% of the lung metastases (10, 11, 12). The primary treatment for metastatic colorectal cancers is systemic treatment; however, additional metastasectomy treatment contributes to long-term survival in liver and lung metastases (9,13).

In our study, survival time following a lung metastasectomy in patients with a primary tumor location in the rectum was found to be longer than that in patients with a primary tumor location in the colon. In the literature, it is emphasized that survival time is typically

Adress for correspondence: Olçun Ümit Ünal, Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye
e-mail: drolcun@hotmail.com
Available at www.actaoncologicaturcica.com

shorter for patients with a primary tumor in the rectum, and that this might be the result, to a large extent, of the rectum's lack of peritoneal protection (mean 5-year survival rate for colon and rectum is 35-65% and 30-53%, respectively) (12,14,-18). However, certain publications have suggested that the primary tumor's localization is not very effective in measuring mean survival rate (12). In the analysis performed on our patients, although there was no statistically significant difference between colon cancer and rectum cancer metastases in terms of survival after metastasectomy, the 5-year survival expectancy was 66% and 76%, respectively. The mean survival time was 45 months (SD±6 months) in patients with primary colon cancer and 63 months (SD±4 months) in patients with primary rectum cancer. We believe that the reason behind obtaining completely opposite results from the above mentioned study (14-18) can be attributed to the small number of patients with tumor location in rectum and the fact that most of the primary colon cancer cases were metastatic at the time of diagnosis.

Although chemotherapy is suitable in metastatic colon cancers that are unresectable and that show a systemic distribution, median OS time in these non-operable patients is 20-22 months, whereas the 5-year OS expectancy is only 5%. On the other hand, the mean 5-year OS time of colorectal cancer patients who had lung metastasectomy is reported to be 48% (varying between 41%-56%) (12). In our study, the median OS was 57 months (SD±4 months), and the 1, 3, and 5 year OS rates were 96%, 92%, and 49%, respectively, in the entire group. Published literature results are also similar to the results of the study conducted at our health center.

The report on disease free survival (DFS) published by the International Registry of Lung Metastases (IRLM) in 1997 suggested that a period of more than 36 months had a positive effect on prognosis; Pfannschmidt et al, however, reviewed many studies and stated that the DFS interval was effective on prognosis, independent of other factors, in only two of 20 case series (12,14, 17,19,20). Many of the publications with opposing views involve only predictions for lung metastases of colorectal cancers. The mean survival time in patients with <36 months of DFS was reported as 43.3 months, whereas the mean OS in patients with >36 months of DFS was reported as 47.3 months (14). Similar to the studies seen in the literature, in our study, statistically significant data on the effect of median DFS time on mean OS time were not determined.

It has been reported that synchronous lung and liver metastases were found in approximately 5-10% of patients with primary colorectal cancer. Some studies suggest that systemic chemotherapy will provide better results than radical resection in primary colorectal cancers with synchronous lung and liver metastases (21,22), while some researchers indicate that complete resection of pulmonary metastasis and liver metastasis would have almost the same survival outcomes. Therefore, the performance of a complete resection on solitary liver and lung metastases in selected patients could lead to lasting palliation and encouraging results (14). In three other interesting studies found in the literature, the mean 5-year survival rate was reported as 31% in colorectal cancer diagnosed patients who had both a lung and a liver resection (23-25). Five of our patients had liver metastasis. While the mean 5-year OS was not measured in our study (because there were only 5 patients), the mean survival time for colorectal cancer diagnosed patients who had both a lung and a liver resection was 40 months. Moreover, the survival values of our patients were observed to be consistent with other studies, and the multiple metastases partially reduced mean survival time. However, it is difficult to assert more definite claims given that there are only a limited number of patients with primary colorectal cancer and multiple diagnoses..

In many multi-centered studies, the effects on mean survival of colorectal cancer patients who received R0 and R1/R2 metastasectomy resections for lung metastases were compared (12). Even though the results of these studies were not very clear, a significant effect on survival was not found for R0 and R1/R2 resections, but it was concluded that an R0 resection provided a partially better prognosis in comparison to an R1 resection. In our study, the mean OS time was 66 months (SD±5 months) and 47 months (SD±7 months) in patients that had R0 resection (n:17) and R1 resection (n:12), respectively; given these results, our study supports the view in the

Adress for correspondence: Olçun Ümit Ünal, Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye
e-mail: drolcun@hotmail.com
Available at www.actaoncologicaturcica.com

literature that an R0 resection offers a better prognosis as compared to an R1 resection (12).

In most of the studies found in the literature, a wedge resection or segmentectomy (60-65%) was performed. A lobectomy was preferred in 35-40% of patients, while a pneumonectomy was performed in only 1-2% of patients (12). In a study conducted by Vogelsang et al, a wedge resection was performed on 52 patients and better results were obtained in terms of 5-year life expectancy as compared to an anatomic lung resection performed on 23 patients (5-year survival wedge resection: 39%, anatomic lung resection: 25%) (26). In other large studies conducted, it was found that resection type did not have a prognostic significance on life expectancy (11,24,27-29). In our study, a wedge resection was performed on 24 patients and a lobectomy on 5 patients. Mean OS following the wedge resection and lobectomy surgeries were 58 months (SD±5 months) and 50 months (SD±2 months), respectively. Similar to many of the studies published in the literature, the results of our study support the view that the type of resection does not have a significant effect on prognosis.

Neoadjuvant treatment was given to 18 (62.1%) colorectal cancer patients who had a lung metastasectomy, while the remaining 11 (37.9%) had a direct lung metastasectomy operation; all patients received adjuvant chemotherapy following the operation. As the neoadjuvant chemotherapy and adjuvant chemotherapy types given in studies published in the literature are very different, it is quite difficult to examine the effect of chemotherapy on expected survival time (12). Adjuvant chemotherapy, however, was given after lung resection in 4 different studies, and no effect was reported on the prognosis or the expected survival time (26,27, 29, 30).

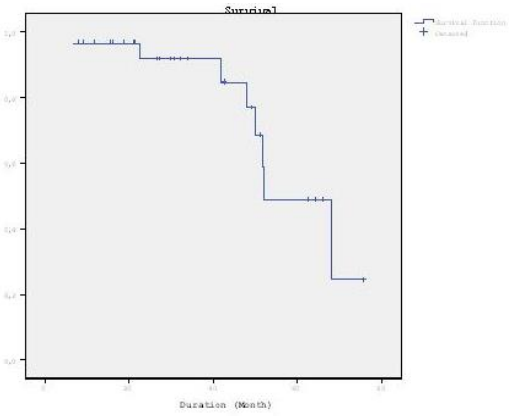


Figure 1

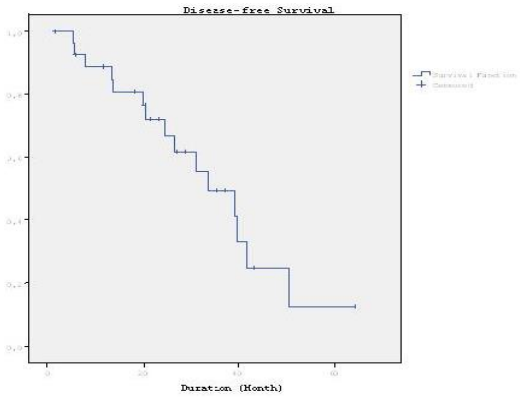


Figure 2

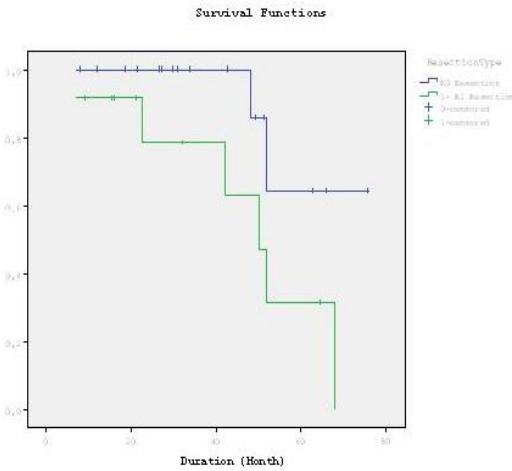


Figure 3

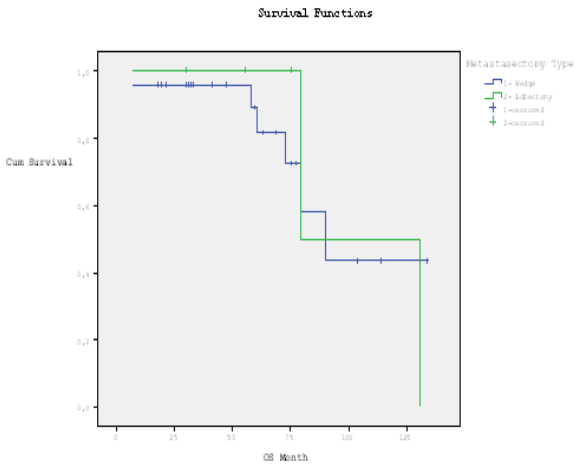


Figure 4

Adress for correspondence: Olçun Ümit Ünal, Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye
e-mail: drolcun@hotmail.com
Available at www.actaoncologicaturcica.com

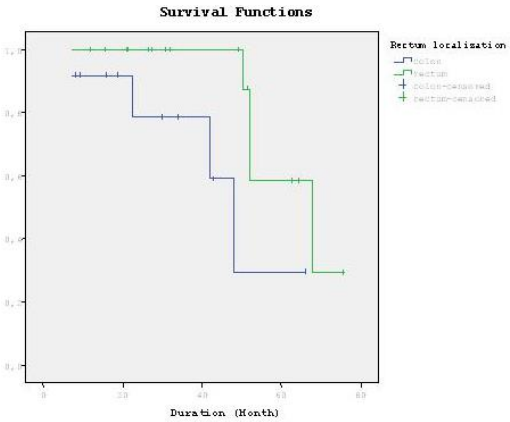


Figure 5

The mean value for isolated lung recurrence of coloreactal cancers with lung metastasis following the lung resection was reported to be 36% (12) in the literature. In our study, recurrence was seen in a total of 21 patients, 12 of which (41%) had isolated lung recurrence, data similar to those seen in the published studies.

As a result of this study being performed on a limited number of patients with colorectal cancer, metastasectomy approaches on isolated metastases involving the lung generally provided results similar to those seen in the literature. It is quite clear that the multidisciplinary approach in metastatic colorectal tumors, early diagnosis, newly developed and efficient chemotherapeutic agents and effective lung metastasectomies have reached quite significant and promising levels in terms of life expectancy compared to previous years. Complete resections (R0) performed following efficient neoadjuvant treatment, especially in metastases that emerge after a long disease-free survival period, provide significant improvements in the results of patients. Serial follow-up of patients is also very important, and serial metastasectomies performed in the event of recurrences contribute to survival. Therefore, a multidisciplinary approach plays a very important role in the follow-up of patients with colorectal cancer, just as it does in other cancer types.

Conflict of interest: None

References

1.Duran AO, Karaca H, Besiroglu M, Bayoglu IV, Menekse S, Yapici HS, Yazilitas D, Bahceci A, Uysal M, Sevinc A, Hacibekiroglu I, Aksoy A, Tanriverdi O, Arpaci E, Inanc M, Dane F, Ozkan M.. XELOX plus bevacizumab vs. FOLFIRI plus bevacizumab treatment for first-line chemotherapy in metastatic colon cancer: a retrospective study of the Anatolian Society of Medical Oncology. Asian Pac J Cancer Prev 2014;15:10375-9

2.Cokmert S, Ellidokuz H, Demir L, Fuzun M, Astarcioglu I, Aslan D, Yilmaz U, Oztop I. Survival outcomes of liver metastasectomy in colorectal cancer cases: a single-center analysis in Turkey. Asian Pac J Cancer Prev 2014;15: 5195-200

3.Eker B, Ozaslan E, Karaca H, Berk V, Bozkurt O, Inanc M, Duran AO, Ozkan M. Factors affecting prognosis in metastatic colorectal cancer patients. Asian Pac J Cancer Prev 2015;16:3015-21

4. Gunel N, Yamaç D, Akçalı Z, Taneri F, Oguz M. The clinico-pathologic characteristics of colorectal cancer under 50 years of age; experience of an oncology center. Tumori 2001;87:74-7

5.Zhu LM, Zhao YZ, Ju HX, Liu LY, Chen L, Liu BX, Xu Q, Luo C, Ying JE, Yang YS,Zhong HJ.. Efficacy and safety of bevacizumab in Chinese patients with metastatic colorectal cancer. Asian Pac J Cancer Prev 2014;15: 6559-64

6.Van Cutsem E, Nordlinger B, Adam R,Köhne CH, Pozzo C, Poston G, Ychou M,Rougier P; European Colorectal Metastases Treatment Group. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer2006;42:2212-21

7. Fong Y. Surgical therapy of hepatic colorectal metastasis. CA Cancer J Clin 1999;49:231-55

8. Inoue M, Ohta M, Iuchi K, Matsumura A, Ideguchi K, Yasumitsu T, Nakagawa K, Fukuhara K, Maeda H, Takeda S, Minami M, Ohno Y, Matsuda H; Thoracic Surgery Study Group of Osaka University. Benefits of Surgery for Patients With Pulmonary Metastases From Colorectal Carcinoma. Ann Thorac Surg 2004;78:238-44

9. Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF. Liver resection for colorectal metastases. J Clin Oncol 1997;15:938-46

10. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43-66

11. Rena O, Casadio C, Viano F, Cristofori R, Ruffini E, Filosso PL, Maggi G. Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. Europen Journal of Cardio-thoracic Surgery 2002;21:906-12

12.Pfannschmidt J, Dienemann H, Hoffmann H. Surgical Resection of Pulmonary Metastases From Colorectal Cancer: A Systematic Review of Published Series. Ann Thorac Surg 2007;84:324-38

Adress for correspondence: Olçun Ümit Ünal, Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye
e-mail: drolcun@hotmail.com
Available at www.actaoncologicaturcica.com

13.Kaba E, Toker A. Who Actually Profits from Pulmonary Metastasectomy Operation? Retrospective Analysis of 12 Years. Eurasian J Pulmonol 2014;16:208-9
14.Pfannschmidt J, Muley T, Hoffman H, Dienemann H. Prognostic factors and survival after complete resection of pulmonary metastases from colorectal carcinoma: Experiences in 167 patients. J Thorac Cardiovasc Surg 2003;126:732-9
15.Saito Y, Omiya H, Kohno K, Kobayashi T, Itoi K, Teramachi M, Sasaki M, Suzuki H, Takao H, Nakade M.. Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment. J Thorac Cardiovasc Surg 2002;124:1007-13
16.Higashiyama M, Kodama K, Higaki N, Takami K, Murata K, Kameyama M, Yokouchi H. Surgery for pulmonary metastases from colorectal cancer: the importance of prethoracotomy serum carcinoembryonic antigen as an indicator of prognosis. Jpn J Thorac Cardiovasc Surg 2003;51:289-96
17.Lee WS, Yun SH, Chun HK, Lee WY, Yun HR, Kim J, Kim K, Shim YM. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. Int J Colorectal Dis 2007;22:699-704
18.Iizasa T, Suzuki M, Yoshida S, Motohashi S, Yasufuku K, Iyoda A, Shibuya K, Hiroshima K, Nakatani Y, Fujisawa T. Prediction of prognosis and surgical indications for pulmonary metastasectomy from colorectal cancer. Ann Thorac Surg 2006;82:254-60
19.Yedibela S, Klein P, Feuchter K, Hoffmann M, Meyer T, Papadopoulos T, Göhl J, Hohenberger W. Surgical management of pulmonary metastases from colorectal cancer in 153 patients. Ann Surg Oncol 2006;13:1538-44
20.Rotolo N, De Monte L, Imperatori A, Dominioni L, et al. Pulmonary resections of single metastases from colorectal cancer. Surg Oncol 2007; 16 Suppl 1:141-4
21. Ike H, Shimada H, Ohki S, Togo S, Yamaguchi S, Ichikawa Y. Results of aggressive resection of lung metastases from colorectal carcinoma detected by intensive follow-up. Dis Colon Rectum 2002;45:468-73
22.McCormack PM, Martini N. The changing role of surgery for pulmonary metastases. Ann Thorac Surg 1997;28:139-45
23.DeMatteo RM, Minnard EA, Kemeney N. Surgical resection of both hepatic and pulmonary metastases inpatients with colorectal cancer. Proceedings of ASCO ,1999,abstract 958
24.Headrick JR, Miller DL, Nagorney DM, Allen MS, Deschamps C, Trastek VF,Pairolero PC. Surgical treatment of hepatic and pulmonary metastases from colon cancer. Ann Thorac Surg 2002;71:975-9
25.Kobayashi K, Kawamura M, Ishihara T. Surgical treatment for both pulmonary and hepatic metastases from colorectal cancer. J Thorac Cardiovasc Surg 1999;118:1090-6
26.Vogelsang H, Haas S, Hierholzer C, Berger U, Siewert JR, Präuer H. Factors influencing survival after resection of pulmonary metastases from colorectal cancer. Br J Surg 2004;91:1066-71
27.Kanemitsu Y, Kato T, Hirai T, Yasuki K. Preoperative probability model for predicting overall survival after resection of pulmonary metastases from colorectal cancer. Br J Surg, 2004;91:112-20
28. Melloni G, Doglioni C, Bandiera A, Carretta A, Ciriaco P, Arrigoni G, Zannini P. Prognostic factors and analysis of microsatellite instability in resected pulmonary metastases from colorectal carcinoma. Ann Thorac Surg 2006;81:2008-13
29.Welter S, Jacobs J, Krbek T, Poettgen C, Stamatis G. Prognostic impact of lymph node involvement in pulmonary metastases from colorectal cancer. Eur J Cardiothorac Surg 2007;31:167-72
30.Moore KH, McCaughan BC. Surgical resection for pulmonary metastases from colorectal cancer. ANZ J Surg 2001;71:143-6

Adress for correspondence: Olçun Ümit Ünal, Izmir Bozyaka Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Bölümü, İzmir, Türkiye
e-mail: drolcun@hotmail.com
Available at www.actaoncologicaturcica.com

Current Advances in the Treatment of Basal Cell Carcinoma

Bazal Hücreli Karsinomun Tedavisinde Güncel Gelişmeler

Mert Çalış, Hakan Uzun

Hacettepe Üniversitesi Tıp Fakültesi, Plastik, Rekonstrüktif ve Estetik Cerrahi AD, Ankara, Türkiye

Dergiye Ulaşma Tarihi: 27.04.2016 Dergiye Kabul Tarihi: 13.05.2016 DOI:10.5505/aot.2016.69188

ÖZET

Bazal hücreli karsinom, derinin en sık görülen malign tümörü olup insidansı giderek artmaktadır. Predispozan faktörler arasında en önemlisi güneş ışınlarına maruz kalmaktır. Bununla birlikte genetik hastalıklar, organ nakilleri ve immünsupresyon da bazal hücreli karsinom gelişimini tetiklemektedir. Oldukça nadir metastaz yapmasına rağmen lokal agresif seyreder. Ana tedavi şekli cerrahi olup cerrahiye aday olmayan hastalarda radyoterapi, kriyoterapi, kemoterapi ve hedgehog yolak inhibitörleri kullanılabilir. Bu derlemede bazal hücreli karsinomun tedavisi konusunda güncel gelişmeler tartışılmıştır.

Anahtar Kelimeler: bazal hücreli karsinom, cerrahi, vismodegib

ABSTRACT

Basal cell carcinoma is the most commonly seen malignant tumor of the skin and its incidence is gradually increasing. Sun exposure is the single most important predisposing factor. In addition, genetic disorders, organ transplantations and immunesupression may trigger the development of basal cell carcinoma. Although it metastasizes rarely, its clinical course is local aggressive. The main treatment modality is surgery. In patients who are not candidates for surgery; radiotherapy, cryotherapy, chemotherapy and hedgehog pathway modulators can be used. In this review, current advances in the treatment of basal cell carcinoma is discussed.

Keywords: basal cell carcinoma, surgery, vismodegib

Giriş

Melanom dışı deri kanserleri dünyadaki en sık kanser tipi olup her yıl 2 milyon insanda ortaya çıkmaktadır[1]. Bu nedenle, deri kanserleri için plastik, rekonstrüktif ve estetik cerrahi uzmanları tarafından yılda 4 milyondan fazla eksizyon yapılmaktadır. Düşük morbidite ve mortalite ile seyretmesi nedeniyle genellikle ihmal edilen bir sağlık problemi olan melanom dışı deri kanserlerinin ne yazık ki insidansı giderek artmaktadır[2]. Melanom dışı deri kanserlerinin dünyadaki insidansını değerlendiren sistematik bir çalışmada, dünyada en yüksek insidansın Avustralya'da olduğu ortaya konmuştur[3].

Bazal hücreli karsinom (BHK) ilk olarak 1827 yılında Arthur Jacob tarafından tariflenmiştir. BHK'nın etiyolojisinde en önemli faktör solar ultraviyole (UV) radyasyona (özellikle 290-320 nm. dalga boyundaki UVB) aralıklı olarak fazla maruz kalınmasıdır. Bu nedenle vücudun en fazla güneşe maruz kalan baş, boyun ve ekstremite bölgelerinde BHK'ya daha fazla rastlanır. Tüm olguların %85'i baş boyun bölgesinde lokalizedir. UV radyasyonun tetiklediği BHK karsinogenezi, temel olarak UV radyasyonun tetiklediği DNA hasarının onarımındaki bir defekt ile ilişkilidir. Hedgehog sinyal yolaklarındaki mutasyonlar BHK gelişmesine neden olurlar[4].

BHK, epidermisin bazal hücrelerinden köken alır. Tipik olarak 4. dekattan sonra ortaya çıkar, ancak özellikle Gorlin sendromu, xeroderma pigmentosum, Rasmussen sendromu gibi genadodermatozlarda istisnalar görülebilir[5]. Güneş ışınlarına maruziyet BHK gelişmesinde en önemli risk faktörü olduğu için, Fitzpatrick tip 1 ve 2 cilt yapsısına sahip açık tenli, mavi gözlü, kızıl saçlı ve çilli insanlar ve açık havada ve güneş altında çalışan insanlar daha fazla risk altındadır. Diğer risk faktörleri arasında immünsupresyon, arseniğe, kömür tozuna ve radyasyona maruz kalmak yer alır. BHK, ayrıca, yassı hücreli karsinoma gibi, kronik skar, sinüs ve yanık zemininde gelişebilir[6].

Klinik olarak telanjiyektatik damarlara sahip pembe veya et renginde bir papül olarak ortaya çıkar. Giderek büyüdüğünde üzerinde kurutlanma, kepeklenme, kanama ve ülserasyon görülebilir. BHK'nın histolojik

Adress for correspondence: Hakan Uzun, Hacettepe Üniversitesi Tıp Fakültesi, Plastik, Rekonstrüktif ve Estetik Cerrahi AD, Ankara, Türkiye
e-mail: shakanuzuns@gmail.com
Available at www.actaoncologicaturcica.com

alttipleri, nodüler, yüzeyel yayılan, pigmente, mikronodüler, infiltratif, metatipik (bazos-kuamoz karsinom) ve sklerozan morfeaform tipleridir. Nodüler BHK, tüm olguların %75'i ile %80'ni oluşturur. Nodüler BHK'nın da %90'ı baş-boyun bölgesinde lokalizedir. Yüksek oranda melanin içeren bu tümörleri klinik olarak melanomdan ayırmak neredeyse imkansızdır[7]. Yüzeyel BHK, ikinci en sık alttip olup özellikle gövdede ve ekstremitelerde yerleşim gösterir[8]. Bazoskuamoz karsinom ise nadir görülen bir alttip olup morfolojik olarak BHK'ya benzemesine rağmen, BHK'ya kıyasla daha agresif seyirli ve metastaz yapmaya daha fazla eğilimlidir[9].

BHK, yavaş büyüme ve nadir metastaz yapması ile karakterize olmasına rağmen, yetersiz sınırla eksizyon yapılması veya gecikmiş tanı konulması, daha fazla sağlıklı dokunun feda edilmesine neden olur[10].

BHK Tedavi Seçenekleri ve Güncel Yaklaşımlar

BHK tedavisinde başlıca tedavi hedef - leri; lezyonun total olarakuzaklaştırılması, sağlıklı dokunun korunması, fonksiyonun korunması, nüksün olmaması ve estetik olarak kabul edilebilir sonuçların elde edilmesi olarak sıralanabilir[11]. Klinik davranış itibariyle BHK nadiren uzak organ metastazına yol açması nedeniyle genellikle klinik ortamda değer-lendirilirken ihmal edilme veya yetersiz tedavi ile iyileştirme durumları ile karşı karşıya kalınabilmektedir[12].

BHK yönetiminde hastaya uygulanacak tedavinin seçiminde hasta yaşı, lezyon sayısı ve boyutları, tümörün morfolojik görünümü ve histopatolojik tipi, tümörün primer veya rekürren olması ve anatomik yerleşimi dikkate alınmalıdır. BHK yönetiminde tedavi seçenekleri temelde cerrahi ve cerrahi dışı seçenekler olarak iki başlık altında değer-lendirilebilir.

Cerrahi tedavi seçenekleri;

1. Elektrodisseksiyon ve küretaj,
2. Kriyoterapi,
3. Cerrahi eksizyon,
4. Mohs mikrografik cerrahisi, olarak sıralanabilir.

Elektrodisseksiyon ve küretaj, cerrahi seçenekler arasında birinci basamak olarak tanımlanabilir. Her ne kadar deneyim sonucunda küretaj ile sağlıklı dokuya ulaşıldığı hissedilebildiği sıklıkla dile getirilse bile, bu subjektif bir tespit olup, eksizyon sonrasında sınır güvenliği açısından patoloji tarafından değerlendirmenin mümkün olmadığı da değerlendirilmeli ve lezyon genişliği dikkate alınarak seçilmiş olgularda kullanılmalıdır[13]. 2 mm.ye kadar olan küçük ve erken tanı almış lezyonlarda %100 tedavi sağlayan bir cerrahi seçenektir. 2-5 mm. arasındaki lezyon boyutlarında bu seçenek %85 kadar tedavi edici olarak bulunmuştur. Daha büyük lezyonlarda ise rekürrens olasılığı dikkate alınarak elektrodisseksiyon ve küretaj seçeneği tercih edilmemelidir[14].

Kriyoterapi 2 cm.ye kadar olan lezyonların tedavisinde %97e kadar tedavi edici olarak raporlamıştır[15,16]. Kriyoterapi seçeneğinin uygun koşullarda uygulanması çok önemlidir. Bu tedavi seçeneği, sıvı nitrogen spreyler veya kriyoprob yoluyla uygulan-maktadır[17]. Sıvı nitrojene daldırılan pamuktu çubuklar veya pamuk diskler yoluyla uygulanması uygun olmayıp, yüzeyel BHK lezyonlarında bile tedavi edici değildir. Bu tedavinin en belirgin yan etkileri uzamış ödem, hipopigmentasyon, atrofik veya hipertrofik skar gelişimi ve nöropraksi olup, en önemli dezavantajı uygulama sonucunda patolojik tanının konfirmasyonu ve cerrahi sınır hakkında bilgi verebilecek herhangi bir patolojik spesimen elde edilmemesidir[6].

Cerrahi eksizyon BHK tedavisinde uzak ara en sık uygulanan yöntemdir[18,19]. Standart eksizyon 5 yıllık rekürrens oranlarının %2- 10 arasında değiştiği bütün primer BHK olgularda etkili tedavi seçeneğidir[20-22]. Genel kabul gören güvenli cerrahi sınır 3-5 mm. arasında değişmekte iken[8] 10 mm.den büyük, rekürren ve infiltratif BHK olgularında en az 5 mm.lik güvenli cerrahi sınır ile eksizyonun gerçekleştirilmesi planlanmalıdır. 2 cm.den büyük lezyonlarda geniş subklinik uzanım görülebileceğinden 10 mm.ye kadar güvenli cerrahi sınır planlanabilir[23].

10 mm.den küçük lezyonlarda, gövde veya sırt gibi düşük riskli anatomik alanlarda ve reeksizyonun zor olmayacağı lezyonlarda, frozen kesitlerin değerlendirilmesi gerekme-mektedir ve nihayi patoloji raporu beklenebilir. Gerekmesi halinde reeksizyon planlanması hastalık seyrini olumsuz etkilemeyecektir. Ancak yüksek riskli, rekürren, morfeoform gibi agresif histolopatolojik tiplerde ve 2

Adress for correspondence: Hakan Uzun, Hacettepe Üniversitesi Tıp Fakültesi, Plastik, Rekonstrüktif ve Estetik Cerrahi AD, Ankara, Türkiye
e-mail: shakanuzuns@gmail.com
Available at www.actaoncologicaturcica.com

cm.den büyük lezyonlarda eksizyonu takiben intraoperatif frozen kesitlerin değerlendirilmesi gerekmektedir[6].

Mohs mikrografik cerrahisi, Frederich Mohs tarafından tanımlanmış olup, eş zamanlı olarak taze spesimenden histopatolojik değerlendirmeyi içermektedir[24]. Sadece vertikal planda lezyonun derinliği değil, aynı zamanda horizontal planda lezyonun tabanı da değerlendirilmektedir. Primer BHK tedavisinde basit eksizyonla kıyaslandığında maliyet 3 kat kadar fazla olarak bulunmuştur[25]. Primer lezyonda, 5 yıllık kür oranları %94 ile %99 arasında değişmektedir[26-28]. Mohs cerrahisinin başlıca endikasyonları 2 cm.den büyük, rekürren, yüksek risk içeren alanlarda BHK bulunması, periorbital, paranazal gibi geniş sınırlarla eksizyonun zor olduğu alanlarda BHK bulunması yer almaktadır[6].

BHK tedavisinde başlıca cerrahi dışı seçenekler[29]:

1. Radyoterapi
2. Fotodinamik terapi
3. Farmakolojik terapi olarak sıralanabilir.

BHK radyosensitif bir tümör olup, cerrahinin yüksek riskli olduğu, yaşlı, komorbiditelerin olduğu seçilmiş olgularda tercih edilebilir[30,31]. Tedavide radyoterapinin tercih edildiği primer BHK hastalarında beş yıllık rekürrens oranları %8-15 arasında değişmektedir[32]. Radyoterapi uygulanan hastalarda sık karşılaşılan komplikasyonlar uygulanan alana bağlı olarak göz kuruluğu, xerostomi, alopesi, hiperpigmentasyon ve cilt nekrozu olarak sıralanabilir[33-36].

Fotodinamik terapi yaklaşık olarak 20 yıldan beri uygulanmakta olup, terapötik etkisi belirli dalgaboyunda ışık uygulandığında neoplastik hücreler tarafından absorbe edilmiş olan porfirinlerle reaksiyona girip, oluşan enerji ve açığa çıkan serbest oksijen radikaller vasıtasıyla hasar oluşturmasına dayanmaktadır[37]. Bu amaçla sıklıkla 5-aminolevülinik asit kullanılmakta olup, küratif değil palyatif amaçlar için öncelikli olarak tercih edilmelidir[38].

BHK tedavisinde kullanılan farmakolojik ajanların başında 5-florourasil gelmektedir. Nükleik asitlerin metilasyonunun ve timidilat sentetaz enzimlerinin inhibisyonu ile hücre proliferasyonu inhibe olmaktadır[39]. %5lik 5-FU krem şeklinde sadece düşük risk taşıyan alanlardaki, küçük ve yüzeyel BHK lezyonlarına uygulanmaktadır. Günde iki defa ve en az 6 ay boyunca uygulanmaktadır. Çok küçük lezyonlarda tedavi edici olabildiği doğru hasta seçimi çok önemli olup, yakın takip gerekmektedir. BHK tedavisindekullanılabilen bir başka farmakolojik ajan immün sistem üzerinde sitokin salınımını uyararak interferonlar üzerinde etkisi ortaya çıkartan imiquimod olup, yine %5lik krem formunda uygulanmaktadır. Amerikan İlaç ve Gıda Dairesi'nin de onayını almış olan bu ilaç yüz dışındaki alanlarda yüzeyel lezyonlara uygulanabilmektedir[40]. Yine yüzeyel, küçük lezyonlarda uygulanabilen bir başka farmakolojik ajan reseptör selektif bir retinoid olan tazarotendir. Cilt kanseri hücrelerinde apoptoz indüklenerek ve hücre çoğalması baskılanarak etkili olmaktadır. Cilt irritasyonu yaratması ve uzun kullanım süreleri gerektirmesi ilacın kullanımında en önemli dezavantajlardır[41].

Mevcut cerrahi dışı seçeneklerin kullanımı sadece yüzeyel ve küçük lezyonlarla kısıtlı iken, güncel geliştirilen ve hedgehog sinyal yolağı üzerinde etkisini gösteren vismodegib, metastatik ve lokal ileri evre BHK hastaların tedavisinde yeni bir tedavi seçeneği olarak gözükmektedir.

Hedgehog Sinyal Yolağı

PTCH1 geninin mutasyonları ilk olarak Gorlin sendromunda, daha sonra da sporadik BHK'da tanımlanmıştır[42,43]. Sonic hedgehog (SHH) yolağının bir üyesi olan PTCH1 geni, *smoothened* (SMO) adı verilenbirtrans- membranproteine bağlanan ve onu inaktive eden başka bir transmembran proteini kodlar. SHH yolağı, hücresel proliferasyonda görev alması nedeniyle embriyonik hayatta kritik bir öneme sahiptir[44]. İlginç olarak, Gorlin sendromunda görülen BHK'da ve diğer tümörlerde PTCH1 geninde mutasyonlar saptanmış, aynı zamanda sporadk BHK olgularında da PTCH1 geni mutasyonu ve SMO mutasyonları tespit edilmiştir[45]. UV-ilişkili PTCH1 mutasyonları xeroderma pigmentosumlu hastalarda da görülür[46].

Vismodegib

Vismodegib (GDC-0449), bir SMOinhibitörü-dür. Aynı gen yolağına sahip medulloblastoma allogreftlerinde etkinliği gösterilmiştir[47]. Faz-1 çalışması 68 ileri evre kanserli hastada ve 33 ileri evre BHK (15 lokal ileri ve 18 metastatik) hastasında

Adress for correspondence: Hakan Uzun, Hacettepe Üniversitesi Tıp Fakültesi, Plastik, Rekonstrüktif ve Estetik Cerrahi AD, Ankara, Türkiye
e-mail: shakanuzuns@gmail.com
Available at www.actaoncologicaturcica.com

tamamlanmıştır. Yaygın görülen yan etkileri arasında kas spazmları, tat almada bozukluk, yorgunluk, saç dökülmesi ve bulantı yer almaktadır. Metastatik BHK hastalarının yanıt oranı %50, lokal ileri BHK hastalarının yanıt oranı %60 olarak bulunmuştur[48,49]. Faz-2 çalışmasına tüm BHK hastalarına günlük 150 mg Vismodegib uygulanmıştır. Çalışmaya dahil edilen 104 hastanın 96'sından (63 lokal agresif, 33 metastatik) sonuçlar elde edilmiş ve metastatik BHK için %30, lokal ileri BHK için %43 yanıt alınmıştır. Lokal ileri BHK grubunda, 13 hastada komplet yanıt (patolojik incelemede BHK'nın gösterilememesi) alınmıştır[50]. Bu fazda en sık görülen yan etkiler, kas spazmları, alopesi, tat bozuklukları, kilo kaybı, yorgunluk, bulantı, anoreksi ve ishal olmuştur. Alopesi ve tat bozukluklarının sebebi olarak kıl foliküllerinde ve tat tomurcuklarında SMO inhibitörü ile inaktive edilen Hedgehog yolağının bulunması gösterilmiştir. Bu faz-2 çalışması ile 2012 yılında lokal ileri, *unrezektabl* ve metastatik BHK için Amerikan Gıda ve İlaç Dairesi (FDA) tarafından onaylanmıştır50.

Şu anda vismodegibin neoadjuvan veya adjuvan tedavide kullanılmasını destekleyen randomize kontrollü bir çalışma yoktur. Vismodegibin operabl (rezektabl) BHK'da Mohs mikrografik cerrahi sonrasında kullanımını araştıran bir Faz-II çalışması mevcuttur ancak henüz sonuçları bilinmemektedir *(NCT01201915).* Yakın dönemde 11 primer BHK hastasında yapılan küçük bir çalışmada cerrahi defektin %27 oranında azaldığı gösterilmiştir[51].

Vismodegib tedavisi alan hastalarda yassı hücreli karsinom geliştiğine dair yayınlar mevcuttur. Henüz kesin bir kanıt olmamakla birlikte hedgehog sinyalinin azalması YHK karsinogenezisini artırıyor olabilir[52].

Sonuç

BHK tedavisinde cerrahi ve cerrahi dışı birçok tedavi seçeneği olmasına rağmen tümör rekürrens oranları ve maliyet-kazanç oranları da dikkate alındığında en sık başvurulan seçenek olan cerrahi eksizyon, tedavide ilk basamak olarak gözükmektedir. Cerrahi dışı mevcut diğer seçenekler küçük, yüzeyel lezyonlarda etkili olmasına rağmen güncel tedavi seçeneklerinden olan hedgehog sinyal yolak inhibitörleri cerrahi eksizyonun mümkün olmadığı, ileri rekürren veya metastatik BHK olgularında sistemik tedavi olanağı sağlayarak gelecek vaadetmektedir. Cerrahi eksizyonun zor veya mümkün olmadığı rekürren, metastatik veya rekürrens yüksek riskli olgularda hedgehog sinyal yolak inhibitörlerinin tedavide yeri olabileceği akılda tutulmalıdır.

Çıkar Çatışması: Yok

Kaynaklar

1. Jemal A, Saraiya M, Patel P, et al. Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006. J Am Acad Dermatol 2011;65:S17-25 e1-3
2. Geller AC, Annas GD. Epidemiology of melanoma and nonmelanoma skin cancer. Semin Oncol Nurs 2003;19:2-11
3. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012;166:1069-80
4. Goppner D, Leverkus M. Basal cell carcinoma: from the molecular understanding of the pathogenesis to targeted therapy of progressive disease. J Skin Cancer 2011;2011:650258
5. Goldberg LH. Basal cell carcinoma. Lancet 1996;347:663-7
6. Netscher DT, Leong M, Orengo I, Yang D, Berg C, Krishnan B. Cutaneous malignancies: melanoma and nonmelanoma types. Plast Reconstr Surg 2011;127:37e-56e
7. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 2002;147:41-7
8. Gulleth Y, Goldberg N, Silverman RP, Gastman BR. What is the best surgical margin for a Basal cell carcinoma: a meta-analysis of the literature. Plast Reconstr Surg 2010;126:1222-31
9. Shanoff LB, Spira M, Hardy SB. Basal cell carcinoma: a statistical approach to rational management. Plast Reconstr Surg 1967;39:619-24
10. Kimyai-Asadi A, Alam M, Goldberg LH, Peterson SR, Silapunt S, Jih MH. Efficacy of narrow-margin excision of well-demarcated primary facial basal cell carcinomas. J Am Acad Dermatol 2005;53:464-8
11. Goldberg L, Stal S, Spira M. Recognition and treatment of recurrent basal cell carcinoma. Ann Plast Surg 1983;11:313-8
12. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. J Am Acad Dermatol 1984;10:1043-60
13. Dubin N, Kopf AW. Multivariate risk score for recurrence of cutaneous basal cell carcinomas. Arch Dermatol 1983;119:373-7
14. Suhge d'Aubermont PC, Bennett RG. Failure of curettage and electrodesiccation for removal of basal cell carcinoma. Arch Dermatol 1984;120:1456-60

Adress for correspondence: Hakan Uzun, Hacettepe Üniversitesi Tıp Fakültesi, Plastik, Rekonstrüktif ve Estetik Cerrahi AD, Ankara, Türkiye
e-mail: shakanuzuns@gmail.com
Available at www.actaoncologicaturcica.com

15. Zacarian SA. Cryosurgery in the management of cutaneous disorders and malignant tumors of the skin. Compr Ther 1994;20:379-401
16. Zacarian SA. Cryosurgery of cutaneous carcinomas. An 18-year study of 3,022 patients with 4,228 carcinomas. J Am Acad Dermatol 1983;9:947-56
17. Knox JM, Freeman RG, Duncan WC, Heaton CL. Treatment of skin cancer. South Med J 1967;60:241-6
18. Vallejo-Torres L, Morris S, Kinge JM, Poirier V, Verne J. Measuring current and future cost of skin cancer in England. J Public Health (Oxf) 2014;36:140-8
19. Flohil SC, Proby CM, Forrest AD, et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. Br J Dermatol 2012;167 Suppl 2:22-8
20. Chren MM, Linos E, Torres JS, Stuart SE, Parvataneni R, Boscardin WJ. Tumor recurrence 5 years after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. J Invest Dermatol 2013;133:1188-96
21. Hausauer AK, Maurer T, Leslie KS, Parvataneni R, Stuart SE, Chren MM. Recurrence after treatment of cutaneous basal cell and squamous cell carcinomas in patients infected with human immunodeficiency virus. JAMA Dermatol 2013;149:239-41
22. Chren MM, Torres JS, Stuart SE, Bertenthal D, Labrador RJ, Boscardin WJ. Recurrence after treatment of nonmelanoma skin cancer: a prospective cohort study. Arch Dermatol 2011;147:540-6
23. Hoorens I, Vossaert K, Ongenae K, Brochez L. Is early detection of basal cell carcinoma worthwhile? Systematic review based on the WHO criteria for screening. Br J Dermatol 2016
24. Flohil SC, van Dorst AM, Nijsten T, Martino Neumann HA, Munte K. Mohs micrographic surgery for basal cell carcinomas: appropriateness of 'Rotterdam' criteria and predictive factors for three or more stages. J Eur Acad Dermatol Venereol 2013;27:1228-35
25. Essers BA, Dirksen CD, Nieman FH, et al. Cost-effectiveness of Mohs Micrographic Surgery vs Surgical Excision for Basal Cell Carcinoma of the Face. Arch Dermatol 2006;142:187-94
26. Do D. Mohs micrographic surgery for Basal cell carcinoma of the face. Arch Dermatol 2009;145:1428-30
27. Mosterd K, Krekels GA, Nieman FH, et al. Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomised controlled trial with 5-years' follow-up. Lancet Oncol 2008;9:1149-56
28. Smeets NW, Kuijpers DI, Nelemans P, et al. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face--results of a retrospective study and review of the literature. Br J Dermatol 2004;151:141-7
29. Limmer BL, Clark D. Nonsurgical management of primary skin malignancies. Otolaryngol Clin North Am 1993;26:167-83
30. Knox JM. Treatment of skin cancer. J Am Acad Dermatol 1985;12:589
31. Handa Y, Miwa S, Yamada M, Ono H, Suzuki T, Tomita Y. Multiple pigmented basal cell carcinomas arising in the normal-appearing skin after radiotherapy for carcinoma of the cervix. Dermatol Surg 2003;29:1233-5
32. Zagrodnik B, Kempf W, Seifert B, et al. Superficial radiotherapy for patients with basal cell carcinoma: recurrence rates, histologic subtypes, and expression of p53 and Bcl-2. Cancer 2003;98:2708-14
33. Avril MF, Auperin A, Margulis A, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. Br J Cancer 1997;76:100-6
34. Smith SP, Grande DJ. Basal cell carcinoma recurring after radiotherapy: a unique, difficult treatment subclass of recurrent basal cell carcinoma. J Dermatol Surg Oncol 1991;17:26-30
35. Orton CI. The treatment of basal cell carcinoma by radiotherapy. Clin Oncol 1978;4:317-22
36. Cobb GM, Thompson GA, Allt WE. Treatment of Basal Cell Carcinoma of the Eyelids by Radiotherapy. Can Med Assoc J 1964;91:743-8
37. Morton CA, Brown SB, Collins S, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. Br J Dermatol 2002;146:552-67
38. Puccioni M, Santoro N, Giansanti F, et al. Photodynamic therapy using methyl aminolevulinate acid in eyelid basal cell carcinoma: a 5-year follow-up study. Ophthal Plast Reconstr Surg 2009;25:115-8
39. Miller BH, Shavin JS, Cognetta A, et al. Nonsurgical treatment of basal cell carcinomas with intralesional 5-fluorouracil/epinephrine injectable gel. J Am Acad Dermatol 1997;36:72-7
40. Marks R, Gebauer K, Shumack S, et al. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicenter 6-week dose-response trial. J Am Acad Dermatol 2001;44:807-13
41. Bianchi L, Orlandi A, Campione E, et al. Topical treatment of basal cell carcinoma with tazarotene: a clinicopathological study on a large series of cases. Br J Dermatol 2004;151:148-56
42. Hahn H, Wicking C, Zaphiropoulous PG, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell 1996;85:841–851
43. Johnson RL, Rothman AL, Xie J, et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. Science 1996;272: 1668–1671
44. Lin TL, Matsui W. Hedgehog pathway as a drug target: smoothened inhibitors in development. OncoTargets Ther 2012;5: 47–58
45. Xie J, Murone M, Luoh SM, et al. Activating smoothened mutations in sporadic basal-cell carcinoma. Nature 1998;391(6662):90–92
46. Daya-Grosjean L, Sarasin A. UV-specific mutations of the human patched gene in basal cell carcinomas from normal individuals and xeroderma pigmentosum patients. Mutation Res 2000;450:193–199
47. Robarge KD, Brunton SA, Castanedo GM, et al. GDC-0449-a potent inhibitor of the hedgehog pathway. Bioorg Med Chem Lett 2009;19: 5576–5581
48. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. N Engl J Med 2009;361:1164–1172
49. LoRusso PM, Rudin CM, Reddy JC, et al. Phase I trial of hedgehog pathway inhibitor vismodegib

Adress for correspondence: Hakan Uzun, Hacettepe Üniversitesi Tıp Fakültesi, Plastik, Rekonstrüktif ve Estetik Cerrahi AD, Ankara, Türkiye
e-mail: shakanuzuns@gmail.com
Available at www.actaoncologicaturcica.com

(GDC-0449) in patients with refrac- tory, locally advanced or metastatic solid tumors. Clin Cancer Res 2011;17:2502–2511

50. Sekulic A, Migden MR, Basset-Seguin N, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update (30-month) of the pivotal ERIVANCE BCC study [abstract]. J Clin Oncol 2014;32:5s(Suppl; abstr 9013)
51. Ally MS, Aasi S, Wysong A, et al. An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. J Am Acad Dermatol 2014;71(5):904–911. e1. Epub June 11, 2014
52. Wakabayashi Y, Mao JH, Brown K, Girardi M, Balmain A. Promotion of Hras-induced squamous carcinomas by a polymorphic variant of the patched gene in FVB mice. Nature 2007;445(7129):761–765.

Adress for correspondence: Hakan Uzun, Hacettepe Üniversitesi Tıp Fakültesi, Plastik, Rekonstrüktif ve Estetik Cerrahi AD, Ankara, Türkiye
e-mail: shakanuzuns@gmail.com
Available at www.actaoncologicaturcica.com

Thyroiditis During Pegylated Interferon Therapy and HbsAg Seroconvertion after the Treatment

Pegile İnterferon Alfa Tedavisi Sırasında Gelişen Tiroidit ve sonrasında HBsAg Serokonversiyonu

Sabahat Çeken[1], Gülşen İskender[1], Mustafa Cihat Oğan[1], Fazilet Duygu[1], Mustafa Ertek[1]

[1]Dr. A.Y. Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Enfeksiyon Hastalıkları Kliniği

Dergiye Ulaşma Tarihi: 19.9.2015 Dergiye Kabul Tarihi: 24.8.2016 Doi: 10.5505/aot.2016.89421

ÖZET

Giriş: Kronik hepatit B tedavisinde pegile interferon grubu ilaçlar, HBs Ag kaybının oral antivirallerden daha sık gelişmesi, direnç olmaması ve tedavi süresinin sınırlı olması nedeniyle özellikle genç hastalarda tercih edilmektedir. Grip benzeri sendrom, asteni, nöropati, anksiyete, depresyon, hepatotoksisite, nötropeni, trombositopeni ve tiroid fonksiyon bozukluğu gibi yan etkiler tedaviye uyumu zorlaştırmaktadır. Bu yazıda pegile interferon alfa (Peg-IFNα) tedavisi sırasında tiroidit gelişen bir kronik hepatit B hastası sunuldu.

Olgu: Yirmidokuz yaşındaki kadın hasta, tedavi öncesi bakılan tiroid fonksiyon testleri normalken, tedavinin 4. ayında saç dökülmesi ve kilo kaybı şikayetleri ile başvurdu. Yapılan tetkiklerde HBV DNA düzeyi negatif, karaciğer fonksiyon testleri normal, tiroid stimülan hormon (TSH) düzeyi düşük ve serbest T3 ve T4 değerleri yüksekti. Hastaya yapılan ileri tetkiklerde Anti tiroid peroksidaz (TPO) antikoru, Anti tiroglobulin (TG) antikoru ve TSH reseptör antikoru pozitif bulundu. Tiroid USG ve radyoaktif iyot uptake testi troidit ile uyumlu idi. Hipertiroidi için tedavi verilmeyen hastanın Peg-IFNα tedavisine devam edildi. Tedavinin 8. ayında TSH yükselince subklinik hipotiroidi nedeniyle levotiroksin sodyum başlandı. PegIFN-α tedavisi 48 haftaya tamamlanan hastanın tedavi sonunda ve daha sonraki takiplerinde tiroid fonksiyonları normal devam etti. Takibin 4. yılında HBs Ag'nin negatifleştiği, anti HBs düzeyinin 250mU/mL olduğu görüldü.

Sonuç: Peg-IFNα tedavisi alan hastalar klinik ve laboratuar olarak tiroid fonksiyonları açısından takip edilmeli ve tiroidit gelişme ihtimali akılda tutulmalıdır. Yan etki yönetiminde bu tedavinin uygun sürede verilmesinin kronik hepatit B tedavisinde Hbs Ag serokonversiyonu ihtimalini arttıracağı unutulmamalıdır.

Anahtar Kelimeler: Hepatit B; Pegile interferon; Tiroidit

ABSTRACT

Introduction: Interferon alfa is preferred in treatment of hepatitis B, especially for young patients, because of the greater chance of HBs Ag loss, the absence of resistance and the finite duration of treatment. But its side effects like flu like symptoms, asthenia, neuropathy, anxiety, depression, hepatotoxicity, neutropenia, thrombositopenia and throid disfunction causes poor tolerance to treatment. We described a chronic hepatitis B patient who had thyroid dysfunction during Peg-IFNα therapy.

Case: A twenty-nine year old woman admitted to hospital with hair and weight loss on fourth month of Peg-IFNα therapy while her TSH level was normal at the beginning of the treatment. AST and ALT levels were within normal limits and HBV DNA was negative, TSH was low and T3 and T4 levels were high. Anti thyroid peroxidase antibody, anti thyroglobulin antibody and TSH receptor antibody were positive. Tiroid US and radioactive iodine uptake tests were compatible with troiditis. Peg-INFα was continued and the patient was not treated for hyperthyroidism. At the eight month of Peg-INFα therapy, levothyroxine was initiated for subclinical hypothyroidism. Hepatitis B treatment ended in the 48th week. Thyroid functions were normal at the end of HBV treatment and follow-up. At the fourth year of the therapy the patient had HBs Ag seroconvertion, with Anti HBs level of 250mU/mL.

Conclusion: The patients who have Peg-IFNα treatment should be evaluated for thyroid dysfunction and probability of thyroiditis should be kept in mind. As optimal treatment duration is important for achievement of Hbs Ag seroconvertion, appropriate management of side effects is essential in these patients.

Keywords: Hepatitis B; Pegylated interferon; Thyroiditis

Adress for correspondence: Sabahat Çeken, Dr A.Y. Onkoloji Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları Kliniği, Yenimahalle, Ankara, Türkiye
e-mail: sabahatceken@yahoo.com
Available at www.actaoncologicaturcica.com

Giriş

Dünya nüfusunun üçte biri hepatit B virüsü (HBV) ile karşılaşmıştır ve 350-400 milyon kişi Hbs Ag pozitiftir (1). Hepatit B açısından orta derecede endemik bölgede olan ülkemizde 3 milyon kişinin HBV ile enfekte olduğu tahmin edilmektedir. (2)

Kronik HBV enfeksiyonununun tedavisinde rekombinan veya pegile interferon alfa (Peg IFN-α) veya nukleozid analogları kullanılmaktadır (1). PegIFN-α nukleozid analogları ile karşılaştırıldığında; direnç gelişmemesi, tedavi süresinin 48 hafta ile sınırlı olması ve birinci yılın sonunda tedavi alan hastaların %3-7'sinde HBs Ag kaybının olması açısından avantajlı bir ilaçtır (1,3).

Dezavantajları ise antiviral etkisinin oral ajanlara göre düşük olması ve tedaviye uyumu zorlaştıran yan etkileridir (4). İnterferon alfa tedavisinde akut dönemde grip benzeri bulgular (ateş, titreme, baş ağrısı, kas ve eklem ağrıları) sık görülürken uzun dönemde nöropsikiyatrik, iskemik, hematolojik, enfeksiyöz ve otoimmün hastalıklar ortaya çıkabilir veya var olan hastalıklar alevlenebilir (5). İnterferon alfa tedavisi sırasında otoimmün tiroidit, sistemik lupus eritematosus, romatoid artrit, polimiyozit, tip 1 diabetes mellitus ve immün trombositopenik purpura gibi çeşitli otoimmün hastalıklar görülebilir (5,6).

Bu yazıda Peg-IFNα tedavisi sırasında otoimmün tiroidit gelişen bir kronik hepatit B hastası sunulmuştur.

Olgu sunumu

Yirmi dokuz yaşında kadın hastaya kronik hepatit B tanısıyla Peg-IFNα 2a 180 µg haftada bir başlandı. Tedavi öncesi yapılan tetkiklerde HBs Ag (+), HBe Ag (-), Anti HBe (+), HBV DNA: 10^5 IU/mL, ALT:59 U/L (0-55U/L), AST: 45 U/L (5-34 U/L), TSH:0,91 uIU/mL (0.34-5.60 uIU/mL), sT3: 2.5 pg/mL (2.5-3.9 pg/mL), sT4:0,6 ng/mL (0.61-1.48 ng/mL), ANA, ASMA ve LKM1 negatif idi.

Tedavinin 4. ayında, saç dökülmesi ve kilo kaybı şikâyetleri olan hasta, tedaviye 3 hafta ara vermiş olarak başvurdu. Yapılan tetkiklerde HBV DNA düzeyi negatif, ALT: 47 U/L, AST: 29 U/L, bulundu. Hastaya yapılan ileri tetkiklerde TSH: 0.01 uIU/mL, sT3:6.12 pg/mL, sT4: 3.1 ng/mL, Anti TPO antikor: >910 IU/mL (0-9 IU/mL), Anti TG antikor: 99.5 IU/mL (0-4 IU/mL), TSH reseptör antikor: 15.9 IU/L (0-14 IU/L) tiroid USG troidit ile uyumlu, radyoaktif iyot uptake testi: % 0.5-0.4 (normalden düşük, tiroidit ile uyumlu) bulundu.

Endokrinoloji kliniğine danışılan hastaya tedavi önerilmedi. Hasta Peg-IFNα tedavisine iyi yanıt vermiş olduğu ve hipertiroidi ile ilgili semptomları tolere edebildiği için tedaviye devam edildi.

Tedavinin 8. ayında hastanın TSH düzeyi 10.5 uIU/mL, sT3 değeri 0.5 pg/mL, sT4 3.1 ng/mL olunca levotiroksin sodyum başlandı. Takip sırasında hafif nötropeni ve trombositopenisi olmakla beraber doz azaltmaya neden olacak başka bir yan etki gözlenmedi. Peg-IFNα tedavisi 48 haftaya tamamlandı.

Tedavi sonunda HBV DNA düzeyi 54 IU/mL, ALT: 26 U/L, AST: 34 U/L, TSH: 3.7 uIU/mL sT3:3.0 pg/mL, sT4: 1.4 ng/mL idi. Daha sonraki takiplerinde tiroid fonksiyonlarıyla ilgili bir problem tespit edilmedi. Takiplerinde HBV DNA negatif, karaciğer enzimleri normal olarak seyretti. Takibin 4. yılda HBs Ag serokonversiyonu gelişti ve Anti HBs pozitifleşti (Anti HBs: 250mU/mL).

Tartışma

Pegile interferon kullanan kronik hepatit B hastalarında tiroidit gibi otoimmün yan etkiler ortaya çıkabilir. Ancak, yan etkilerin doğru yönetilmesi, tedaviye uygun sürede devam edilmesi, tedavi başarısını artırarak, kronik HBV tedavisinde asıl hedef olan HBs Ag serokonversiyonuna neden olabilir. Bu yazıda kronik hepatit B nedeniyle aldığı Peg-IFNα tedavisi sırasında otoimmün tiroidit gelişen, fakat tedaviyi uygun sürede alan ve daha sonaki takiplerinde HBs Ag negatifleşen bir hasta sunuldu.

Interferon tedavisinin tiroid hastalıkları ile ilişkisi ilk defa 1985'te meme kanseri nedeniyle interferon tedavisi alan hastalarda rapor edilmiştir (7). O zamandan beri hepatit B ve C hastalarında interferon tedavisi sırasında gelişen tiroiditler ve tiroid fonksiyon bozukluklarını araştıran pek çok çalışma yayınlanmıştır (8,9).

Interferon alfanın tiroid disfonksiyonununa yol açma mekanizması net olarak bilinmemekle beraber otoimmün mekanizmanın önemli rol oynadığı bildirilmiştir (10). Interferon alfanın major

Adress for correspondence: Sabahat Çeken, Dr A.Y. Onkoloji Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları Kliniği, Yenimahalle, Ankara, Türkiye
e-mail: sabahatceken@yahoo.com
Available at www.actaoncologicaturcica.com

histocompatibility complex (MHC) Class 1 antijenlerinin yüzey ekspresyonunu arttırdığı, bunun da sitotoksik T hücrelerinin fonksiyonunu aktifleştirdiği bildirilmiştir. Interferon alfa otoimmün tiroid hastalığı olan kişilerde tiroid hücrelerindeki MHC Class 2 antijenleri de indükler. Ayrıca interferon alfa tarafından indüklenen TNF alfa ve IL-1 beta gibi sitokinler immünomodulatör etkiyle direkt veya dolaylı yoldan tiroid fonksiyonlarını bozabilir (11).

Peg-IFNα ile tedavi edilen hastalarda tiroid antikorlarının indüklenebileceği ve bunun hipotiroidi veya tirotoksikozla sonuçlanabileceği bildirilmiştir (9). Bizim hastamızda tiroidite bağlı önce hipertiroidi, daha sonra hipotiroidi gelişti. Ayrıca saç dökülmesi ve kilo kaybı da mevcuttu.

PegIFN-α ve ribavirin tedavisi verilen 59 hepatit C hastasının tiroid fonksiyonları açısından incelendiği bir çalışmada, 7 hastada (%12) tiroid fonksiyon bozukluğu saptanmış. Bir hastada bizim hastamızda olduğu gibi hipertiroidiyi izleyen hipotiroidi gelişmiş ve hasta tedavi kesilmeden T4 replasmanı ile takip edilmiş. Graves nedeniyle tedaviyi bırakan bir hasta dışında diğer hastalar asemptomatik olup tiroid disfonksiyonuyla ilgili bir tedavi almaları gerekmemiştir (12). Bizim hastamızda da hipertiroidi döneminde kısa süre tedaviye ara verilmiş olmakla beraber antitiroid tedavi gereksinimi olmadı ve hasta hepatit tedavisini tamamladı.

İnterferon alfa tedavisi alan hepatit B ve C hastalarında otoimmün tiroid hastalığının araştırıldığı başka bir çalışmada tedavi sonunda kronik hepatit C (KHC) hastalarında tiroid disfonksiyonu oranı %12, kronik hepatit B (KHB) hastalarında %5 olarak bildirilmiştir. Bu çalışmada tiroid disfonksiyonu açısından kadın cinsiyet, ortalama sT3 değerinin düşük olması ve anti TPO antikorun pozitif olması, tiroid disfonksiyonu açısından anlamlı bulunmuştur (13)

Ülkemizden yapılan bir çalışmada, tiroid difonksiyonu olan hastaların %80'inin kadın olduğu, KHC'de %15.2, KHB'de % 6.7 oranında tiroid disfonksiyonu geliştiği bildirilmiştir (8).

Peg-IFNα 2a ile tedavi edilen 106 KHB'li hastada yapılan bir çalışmada; tiroid disfonksiyonu, 80 erkek hastanın 1'inde (%1.25) görülürken, 26 kadın hastanın 6'sında (%23) görülmüştür. Bu hastaların hiçbirinde doz ayarlaması veya interferon tedavisini kesme gereksinimi olmamıştır. Hastaların 6'sı tiroid disfonksiyonu için tedavi almıştır (4). Bizim hastamızda da Peg-IFNα tedavisini kesmemizi gerektirecek kadar şiddetli semptom veya bulgu görülmedi, hipotiroidi için levotiroksin sodyum tedavisi verildi.

Türkiye'den yapılan bir çalışmada KHB'li hastalarda tiroid disfonksiyonunun ortalama 4. ayda, başka bir çalışmada 22-24. Haftalar arasında ortaya çıktığı bildirilmiştir (4,8). Bizim hastamızda semptomlar tedavinin 4. ayında başladı, levotiroksin sodyum tedavisine 8. ayda hipotiroidi nedeniyle başlandı.

Literatürde interferon tedavisinden önce otoantikor pozitifliklerinin saptanması önerilmektedir (6). Fakat KHB'li hastalarda otoimmün troidit sık görülmediğinden, özellikle aile hikâyesi olmayan hastalarda, interferon tedavisi öncesi antitiroid antikorların rutin olarak bakılması önerilmemektedir (4). Ancak tiroid fonksiyonlarının takibi subklinik hipotiroidi veya hipertiroidinin tespiti açısından önemlidir (6, 13).

Kronik hepatit B hastalarında interferon tedavisinin uzun dönem sonuçlarının incelendiği çalışmalara bakıldığında, HBe Ag pozitif hastalarda, %11 Hbs Ag kaybı görülmüş, yanıtsız hastaların hiçbirinde Hbs Ag kaybı olmamış (14). HBeAg negatif hastaların uzun süreli tedavi yanıtlarının araştırıldığı bir çalışmada ise tedavi sonrası 3. yılda hastaların %8.7'sinde HBs Ag kaybı olduğu bildirilmiş, tedavi sonunda HBV DNA düzeyi negatif olan hastalarda bu oranın % 44'e yükseldiği görülmüştür (15). Bizim hastamızda da kalıcı viral yanıt elde edildi ve tedavinin 4. yılında HBs Ag'i negatifleşti.

Sonuç olarak tiroid disfonksiyonu, KHB'li hastalarda KHC'den daha nadir olmakla beraber özellikle kadın hastalarda karşımıza çıkmaktadır. İnterferon tedavisi sırasında TSH düzeyinin takip edilmesi ve gerektiğinde bir Endokrinoloji uzmanı ile işbirliği yapılmasının önemli olduğunu düşünüyoruz. Yan etkileri nedeniyle tedaviyi kesmeden önce, hastanın tedavinin uzun dönem etkilerinden yararlanamayacağı gerçeği göz önünde bulundurularak hasta ile birlikte karar verilmelidir.

Conflict of interest: No

Adress for correspondence: Sabahat Çeken, Dr A.Y. Onkoloji Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları Kliniği, Yenimahalle, Ankara, Türkiye
e-mail: sabahatceken@yahoo.com
Available at www.actaoncologicaturcica.com

Referanslar

1. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus Infection. Journal of Hepatology 2012;57:167-85
2. Mıstık R, Balık İ. Türkiye'de viral hepatitlerin epidemiyolojik analizi. Kılıçturgay K, BadurS. Viral Hepatit 2001. İstanbul: Viral Hepatitle Savaşım Derneği, 2001:10-55
3. Lok AS, McMahon BJ. Chronic Hepatitis B: Update 2009, AASLD Practice Guidelines, Hepatology. 2009;50:661-2
4. Kozielewicz D, Zaleśna A, Dybowska D. Can pegylated interferon α 2a cause development of thyroid disorders in patients with chronic hepatitis B? Expert Opin Drug Saf. 2014;13:1009-14
5. Sünbül M, Kahraman H, Eroğlu C, Leblebicioğlu H, Çınar T. İnterferon Tedavisi Sırasında Subakut Tiroidit Gelişen Kronik Hepatit C Olgusu. O.M.Ü. Tıp Dergisi 1999;16:62-66
6. Mine Durusu Tanrıöver, Tümay Sözen. İnterferon alfa Tedavisi ve Otoimmünite. Hacettepe Tıp Dergisi 2007
7. Fentiman IS, Thomas BS, Balkwill FR, Rubens RD, Hayward JL. Primary hypothyroidism associated with interferon therapy of breast cancer. Lancet 1985;1: 1166
8. Sünbül M, Şahbat E, Akkuş M, Esen Ş. İnterferon-Alfa Tedavisi Alan Kronik Viral Hepatitli Hastalarda Tiroid Fonksiyonlarının Değerlendirilmesi VHSD 2004;9:67-71
9. Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology. 2006;43:661-7
10. El Shafie O, Hussein S, El Awady w, Woodhouse N. Graves' Disease following Interferon Therapy for Chronic Hepatitis C Infection Sultan Qaboos Univ Med J. 2008;8:75-7
11. Koizumi S, Mashio Y, Mizuo H, Matsuda A, Matsuay K, Mizumoto H, et al. Grave's Hyperthyroidism Following Transient Thyrotoxicosis during Interferon Therapy for Chronic Hepatitis Type C. Intern Med.1995;34:58-60
12. Friedrich-Rust M, Theobald J, Zeuzem S, Bojunga J. Thyroid function and changes in ultrasound morphology during antiviral therapy with pegylated interferon and ribavirin in patients with chronic hepatitis C. J Viral Hepat. 2009;16:168-77
13. Fernandez-Soto L, Gonzalez A, Escobar-Jimenez F, Vazquez R, Ocete E, Olea N, Salmeron JIncreased risk of autoimmune thyroid disease in hepatitis C vs hepatitis B before, during, and after discontinuing interferon therapy. Arch Intern Med. 1998;158:1445-8
14. Buster EH, Flink HJ, Cakaloglu Y, et al. Sustained HBeAg and HBsAg loss after long-term follow-up of HBeAg-positive patients treated with peginterferon alpha-2b. Gastroenterology 2008;135:459-67
15. Marcellin P, Bonino F, Lau GK, et al. Sustained response of hepatitis B e antigen-negative patients 3 years after treatment with peginterferon alpha-2a. Gastroenterology 2009;136:2169-79

Adress for correspondence: Sabahat Çeken, Dr A.Y. Onkoloji Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları Kliniği, Yenimahalle, Ankara, Türkiye
e-mail: sabahatceken@yahoo.com
Available at www.actaoncologicaturcica.com

Coexistence of Primary Myelodysplastic Syndrome and Multiple Myeloma

Primer Myelodisplastik Sendrom ve Multipl Myelom Birlikteliği

Sinem Namdaroğlu[1], Emre Tekgündüz[1], Sinem Bozdağ[2], Ali Hakan Kaya[1], Fevzi Altuntaş[1]

[1]Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Hematolji ve Kemik İliği Nakil Ünitesi, Ankara, Türkiye
[2]Ankara Üniversitesi Tıp Fakültesi, Hematoloji Ana Bilim Dalı, Ankara, Türkiye

Dergiye Ulaşma Tarihi:21/06/2015 Dergiye Kabul Tarihi:06/01/2016 Doi: 10.5505/aot.2016.35220

ÖZET

Multipl miyelom (MM) ve myelodisplasik sendrom (MDS) birlikteliğine nadir rastlanmaktadır. MM tedavisinde kullanılan alkilleyici ajanların bir komplikasyonu olarak MDS gelişimi olabileceği bilinmektedir. Bu yazımızda öncesinde herhangi bir alkilleyici ajan tedavisi ve radyoterapi maruziyeti olmaksızın eşzamanlı MDS ve MM gelişen bir olgumuzu tartıştık. 63 yaşında kadın hasta, ateş ve halsizlik şikâyeti ile kliniğimize başvurdu. Laboratuvar incelemelerinde lökosit: 1.51x 109 / L, hemoglobin: 8 g/l, MCV 85.4 fl., trombosit: 71,000/mm^3,total protein: 10.2 g/dl (normal değerler: 6-8,5), albumin: 4 g/dl (normal değerler: 3,5-5)saptandı. Periferik yaymada makrositer- normokrom eritrositler, anizopoikilositoz ve target hücreler izlendi. Hastanın yapılan serum immünfiksasyonunda IG G Lambda monoklonal protein saptandı. Kemik iliği aspirasyon ve biyopsisinde;% 70 atipik plazma hücre infiltrasyonu ve immünhistokimyasal incelemede bu plazma hücrelerinde IG G ve lambda ile pozitif boyanma saptandı.Kemik iliği aspirasyonunda her üç seriye ait öncül hücrelerde displastik değişiklikler ve 14% miyeloblast izlendi. Bu bulgularla hastamıza MM IG G Lambda ve MDS RAEB II tanısı koyduk. Hastaya VCD (Bortezomib, Siklofosfamid ve Deksametazon) kemoterapisi başlandı. MDS ve MM gibi farklı hücrelerden köken aldığı bilinen hastalıkların birlikteliği literatürde de görüldüğü üzere nadir değildir ve pluripotent kök hücre kökenli olduğu fikrini desteklemektedir. Bu olguyu paylaşmamızın nedeni hem literatürün bu görüşünü desteklemek hem de yeni tanı multipl myelom hastalarında görülen sitopenilerde eşlik edebilecek diğer myeloid neoplazilerinde akla getirilmesine dikkat çekmektir.
Anahtar Kelimeler: multipl miyelom, myelodisplasik sendrom, birlikteliği

ABSTRACT

Coexistence of multiple myeloma (MM) and myelodysplastic syndrome (MDS) are rare. It has been known that coexistence of MM and MDS may occur as a complication of treatment. Due to treatment with alkylating agents myelodysplastic syndrome (MDS) may occur in multiple myeloma patients. Here we report a case of coexistent MM and MDS in a patient without history of treatment with any cytotoxic drugs or radiation therapy. A 63-years-old female was presented to our clinic with fever and weakness. Her blood counts were- WBC: 1.51x 109/l – HGB: 8g/dL– MCV 85.4 fl. - PLT: 71,000/mm3. Her serum total protein elevated at 10.2 g/dl albumin 4 g/dl. The peripheral blood smear showed macrocytic and normochromic cells, anisopoikilocytosis and target cells. Bone marrow biopsy specimen showed 70 % monoclonal growth of lambda-positive plasma cells infiltration and was tri-lineage cellular dysplastic features, which included multinucleated erythroblasts and dysplastic megakaryocytes with hypolobulated nucleus. 14 % myeloblasts were seen. Serum immunofixation studies showed a monoclonal IgG lambda. These findings were characteristic for Primary MDS RAEB II and MM. We started treatment for her multiple myeloma with VCD (bortezomib, cyclophosphamide and dexamethasone). Presence the coexistence of both diseases originating from different cell lines may not be rare as they known. There have been some reports of coexistence of MDS and myeloma; supporting the idea of pluripotent stem cell origin of the disease. We suggest that MM patients administrating with cytopenie should be evaluated for coexistent myeloid neoplasms.
Keywords: multıple myeloma, myelodysplastic syndrome, coexistence

Adress for correspondence: Sinem Namdaroğlu, Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Hematolji ve Kemik İliği Nakil Ünitesi, Ankara, Türkiye
e-mail: drsinemnamdaroglu@gmail.com
Available at www.actaoncologicaturcica.com

Introduction:

Myelodysplastic syndrome (MDS) is a colonal disorder of the hematopoietic system characterized by dysplasia, presence of ineffective hematopoiesis, peripheral cytopenias and an increased risk of transformation to acute myeloid leukemia (AML) (1). Multiple myeloma (MM) is a plasma cell malignancy that affect B-cells maturations, producer of immunoglobulines and bone marrow (BM) infiltration (2). The coexistence of both diseases are rare. It has been known that coexistence of multiple myeloma (MM) and myelodysplastic syndrome (MDS) may occur as a complication of treatment. Due to treatment with alkylating agents in multiple myeloma patients, myelodysplastic syndrome (MDS) can be occur.

Chemotherapy induced MDS (secondary MDS) is more resistant to therapy and have a poor prognosis (3).

Here we report a case of coexistent MM and MDS in a patient without history of treatment with any cytotoxic drugs or radiation therapy.

Case Report:

A 63-years-old female was presented to our clinic with fever and weakness. Her blood counts were- WBC: 1.51x 109/l – HGB: 8g/dL– MCV 85.4 fl.- PLT: 71,000/mm3. Her serum total protein elevated at 10.2 g/dl, albumin 4 g/dl. Serum iron levels were normal and serum ferritin was elevated at 539 ng /ml. The peripheral blood smear showed normochromic erythrocytes, anisopoikilocytosis and target cells. Bone marrow biopsy specimen showed 70 % monoclonal growth of lambda-positive plasma cells infiltration and were tri-lineage cellular dysplastic features, which included multinucleated erythroblasts, dysplastic megakaryocytes with hypolobulated nucleus and 14% myeloblasts were seen. Serum immunoglobulins showed an elevated IgG (37.6 g/l) with increase in lambda free light chains (4.68 g/l), serum protein electrophoresis and serum immunofixation studies showed a monoclonal IgG lambda. Urine protein electrophoresis and immunofixation studies showed a monoclonal lambda light chain.

Her radiologic full body-bone survey showed no lytic lesions. These findings were charasteristic for MDS RAEB II and MM. Karyotype was normal: 46, XX. FISH analysis did not find any chromosomal abnormality.

Our patient was diagnosed with coexistence MM IgG Lambda and Primary MDS-RAEB II. We started treatment for her multiple myeloma with VCD (bortezomib, cyclophosphamide and dexamethasone). After receive 4 cycles of with VCD regimen then patient achieve Complete response (CR).

Discussion:

Our patient was diagnosed with coexistence MM and MDS. Multiple myeloma (MM) is a plasma cell malignancy, representing 1% of all cancers and 10% of hematologic neoplasms. Incidence increases with age, the median age at diagnosis is 70 years. (4)

The myelodysplastic syndrom (MDS) is a clonal disorder of the hematopoietic system and occur in older adults with a median age of 70 years. The overall annual incidence of MDS is 3-20 per 100,000 (5).

Myelodysplastic syndrome (MDS) is a hematological malignancy characterized by dysplasia and ineffective hematopoiesis. The lineage affected in this pathology is the myeloid one. Plasma cells disorders (PCD) affect B-cells, producer of immunoglobulines. Despite the different pathogenesis of these hematologic diseases, but there have been some reports of coexistenceof MDS and myeloma supporting the idea of pluripotent stem cell origin of the disease. Therapy-related MDS following chemotherapy for MM is well recognized but the coexistence of both diseases are rare.

Coppelstone et al. proposed that both multiple myeloma and MDS can produce growth factors which affect the other cell line (6). This hypothes was sustained by Sefer at al. who established elevated IL-6 levels in both disorders (7).

Adress for correspondence: Sinem Namdaroğlu, Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Hematolji ve Kemik İliği Nakil Ünitesi, Ankara, Türkiye
e-mail: drsinemnamdaroglu@gmail.com
Available at www.actaoncologicaturcica.com

Mufti et. al. showed in MM patients some unstable haematopoietic clones, they can transformed into myeloid neoplasms so that simultaneous de novo diseases both myeloid and lymphoid lineages can occur (8).

Nilsson et al have demonstrated that a 5q deletion-which is well known specific clonal alteration of MDS – may occur in hematopoietic stem cells (HSCs) with a combined lympho-myeloid potential (9). The coexistence of MM and MDS arising from different cell lines can be explained by this data.

In addition; contrary to Mufti, Tsiara et. al. suggested that malignant transformation of a single precursor cell has ability to transformate either lymphoid and myeloid neoplasms as possible etiology of coexistence of both diseases orginating from different cell lines (10). Both in MM and MDS, some cytogenetic abnormalities are common as deletion of chromosome 13, this data is compatible with their theory.

Dewald et al. have shown some specific chromosome alterations for MDS which present in MM patients, who had leucopenia and had the poor prognosis. (11).

Várkonyi et al showed that the hemochromatosis gene mutations (C282Y and H63D) found with higher rate in MM patients who have low WBC at presentation. They also showed that 49% of MDS patients positive for either HFE variant which could be tested for another indirect approach to make MDS diagnosis more probable (12,13).

Conclusion:

In this case we reported a patient diagnosed with coexistence both MM and Primary MDS. Presence the coexistence of both diseases originating from different cell lines may not be rare as they known. Despite the different cell origin of these hematologic diseases, published reports of coexistence of MDS and myeloma supporting the idea of pluripotent stem cell origin of the disease. We suggest that MM patients administrating with cytopenie should be evaluated for coexistent myeloid neoplasm. In literature there are some similar reports, support this.

Conflict of interest: None

References:

1. Abdel-Wahab O, and Figueroa ME. Interpreting new molecular genetics in myelodysplastic syndromes. ASH Education Program Book2012.1 (2012): 56-64.
2. Palumbo A, Cavallo F. Have drug combinations supplanted stem cell transplantation in myeloma? Blood: the journal of hematology (Washington, DC: American Society of Hematology), Vol. 120, No. 24 (2012), p. 4692-4698
3. Mehendale S, Patel P, Lindgren V, Rondelli D,Gaitonde S. Coexistent systemic amyloidosis, multiple myeloma, and refractory anemia with ringed sideroblasts in a previously untreated patient. International Journal of Case Reports and Images 2011; 2:1-4.
4. Altekruse SF, Kosary C, Krapcho M, Neyman N, Aminou R, Waldron W. SEER Cancer Statistics Review, 1975–2007. Bethesda, MD: National Cancer Institute; 2010. [7 September 2010].
5. Aul C, Gattermann N, Schneider W. Age related incidence and other epidemiologic aspects of myelodysplastic syndromes. Br J Haematol 1992; 82:358-367.
6. Coppelstone JA, Manoharan A, Catovsky D, et al: Simultaneous or spontaneous occurrence of lympho- and myeloproliferative disorders: A report of four cases. Br J Haematol. 1981;48:111–116.
7. Sefer D, Marisavljevic D, Bogdanovic A, at al: Circulating Interleukin-6 (IL-6) in patients with myelodysplastic syndromes. Leukemia Res; 1999, 23, 78
8. Mufti GJ, Hamblin TJ, Clein GP, Race C.Coexistent myelodysplasia and plasma cell neoplasia. Br J Haematol 1983; 54:91-96
9. Nilsson L, Astrand-Grundstörm I, Arvidsson I, et al. Isolation and characterization of hematopoietic progenitor stem cells in 5q deleted myelodysplastic syndromes: evidence for involvement at the hematopoietic stem cell level. Blood, 2000; 96:2012–2021.
10.Tsiara S, Economou G, Panteli A, Isaakidis P, Kapsali E and Bourantas KL. Coexistence of myelodysplastic syndrome and multiple myeloma. J Exp Clin Cancer Res 1999; 18:565-566.
11.Dewald GW, Kyle RA, Hicks GA, Greipp PR.The clinical significance of cytogenetic studies in 100 patients with multiple myeloma, plasma cell leukemia, or amyloidosis. Blood, 1985; 66:380–390.
12.Várkonyi J, Demeter J, Tordai A, Andrikovics H. The significance of the Hemochromatosis genetic variants in multiple myeloma in comparison to that of myelodysplastic syndrome. Ann.Hematol. 2006; 85: 869–871

Adress for correspondence: Sinem Namdaroğlu, Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Hematolji ve Kemik İliği Nakil Ünitesi, Ankara, Türkiye
e-mail: drsinemnamdaroglu@gmail.com
Available at www.actaoncologicaturcica.com

13. Várkonyi J, Tarkovács G, Karádi I, at al. High incidence of hemochromatosis gene mutations in the myelodysplastic syndrome: The Budapest study on 50 patients. Acta Haematol. 2003; 109: 64–67.

Adress for correspondence: Sinem Namdaroğlu, Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Hematolji ve Kemik İliği Nakil Ünitesi, Ankara, Türkiye
e-mail: drsinemnamdaroglu@gmail.com
Available at www.actaoncologicaturcica.com

Lymphadenopathy of A Newborn: Langerhans Cell Histiocytosis

Yenidoğanda Lenfadenopati: Langerhans Hücreli Histiositozis

Ayşenur Bahadır[1], Erol Erduran[1]

[1]Karadeniz Teknik Üniversitesi, Pediatrik Hematoloji-Onkoloji Bilim Dalı, Trabzon, Türkiye

Dergiye Ulaşma Tarihi: 06/11/2015 Dergiye Kabul Tarihi: 23/12/2015 Doi: 10.5505/aot.2016.04909

ÖZET

Langerhans hücreli histiositozis (LHH) etyolojisi tam bilinmeyen, myeloid dentritik hücrelerin nadir bir bozukluğudur. Lokalize kemik ve cilt lezyonları yapabileceği gibi multi organ yetmezliğine neden olabilecek kadar yaygın tutulum da yapabilir. Yenidoğan döneminde LHH'li hastalar sıklıkla cilt bulgusu ile tanı almaktadır. Hastaların ilk başvuru da lenfadenopati ile başvurması sık görülmemektedir.

Boyunda kitle? lenadenopati(LAP)? ön tanıları ile 35 günlük erkek hasta hastanemize başvurdu. Hastanın şikâyetleri 10 günlükken başlamıştı ve almış olduğu tedavilere rağmen boyundaki şişlik geçmemişti. Boyun ultrasonografisinde lenfadenit?, lenfoma? olarak değerlendirildi. Hastanın LAP'den alınan biyopsi sonucu LHH olarak raporlandı.

Bu yaş grubunda deri bulgusu eşlik etmeden, ilk başvuru şikâyeti LAP olup LHH tanısı koyulan literatürdeki nadir vakalardandır. Yenidoğan dönemindeki LAP'lerin çok iyi değerlendirilmesi, klinik ve ultrason görüntüsü ile LHH'un enfeksiyon ve malignite ile karışabileceği akılda tutulmalıdır.

Anahtar kelimeler: Langerhans Hücreli Histiyositozis, lenfadenopati, yenidoğan.

ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disorder of myeloid dendritic cells with an unknown etiology. It may cause localized bone and skin lesions also may be so widespread that the involvement can lead to multiple organ failure. In the neonatal period, patients with LCH is often diagnosed by skin lesions. In the first application of the patient, lymphadenopathy is not an expected finding.

A 35 day old male patient was admitted to our hospital with a presumptive diagnosis of mass in the neck? lymphadenopathy (LAP). His complaints had begun when he was 10 days old and despite the taken treatment, swelling in the neck was ongoing. It was evaluated as lymphadenitis? lymphoma? with cervical ultrasonography. LCH was reported as a result of the biopsy taken from LAP.

In this age group without accompanying cutaneous manifestations, the first complaint as LAP in patients diagnosed with LCH is rare in the literature. During the neonatal period, a good evaluation of the LAP must be done and it should be kept in mind that clinical and ultrasound images of LCH may interfere with infection and malignancy.

Key words: Langerhans Cell Histiocytosis, lymphadenopathy, newborn

Giriş:

Langerhans hücreli histiositozis (LHH) myeloid dentritik hücrelerin nadir bir bozukluğudur. Halen etyolojisi tam olarak aydınlatılamamıştır. Bununla beraber patogenezde immun sistem disregülasyonu, infeksiyon ajanlarının reaksiyonuna bağlı

Adress for correspondence: Ayşenur Bahadır, Karadeniz Teknik Üniversitesi, Pediatrik Hematoloji-Onkoloji Bilim Dalı, Trabzon, Türkiye
e-mail:aysenurkbr@yahoo.com
Available at www.actaoncologicaturcica.com

olduğu düşünülmektedir (1). LHH lokalize kemik lezyonları yapabileceği gibi multi organ yetmezliğine neden olabilecek kadar yaygın tutulum da yapabilir. Özelikle karaciğer, dalak, kemik iliği gibi riskli organ tutulumları olduğunda mortalitesi artmaktadır. LHH'li hastalar sıklıkla ekzama veya seboreik dermatit gibi cilt lezyonları ya da skalp tutulumu ile başvurmaktadır (1,2,3).

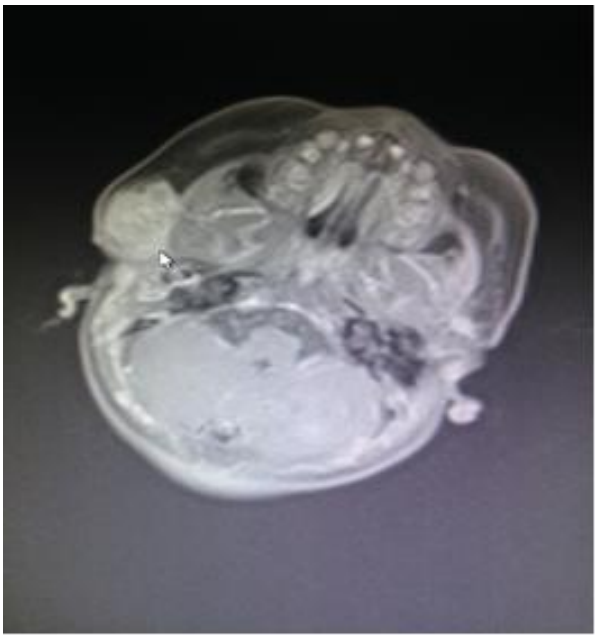
Hastaların ilk başvuru da lenfadenopati (LAP) ile başvurması sık görülmemektedir (4). Özellikle yenidoğan döneminde LHH'li hastalar sıklıkla cilt bulgusu ile tanı almaktadır (3). Yenidoğan döneminde şikâyetleri başlayan, 35 günlük iken boyunda LAP ile kliniğimize başvuran hastaya LHH tanısı koyduk. Bu yaş grubunda deri bulgusu eşlik etmeden, ilk başvuru şikâyeti LAP olup LHH tanısı koyulan nadir vakalardan biri olması nedeni ile rapor ettik.

Olgu:

32 yaşındaki annenin birinci gebeliğinden 39 haftalık spinal sezeryan ile doğan 35 günlük erkek hasta boyunda şişlik şikâyeti ile hastanemiz pediatri acil polikliniğine başvurdu. Doğumdan sonra yaklaşık olarak 10.günde **kulak önünden boyuna yayılan** bir şişlik ortaya çıkmış. Dış merkezde ayrı zamanlarda iki kez antibiyotik tedavisi verilen hastanın şikâyetlerinin gerilememesi nedeni ile hastanemize gönderilmiş.

Lenfadenit?, lenfadenopati? ön tanılarıyla pediatri hematolojiye konsulte edilen hasta, tetkik edilmek üzere hemotoloji servisine yatırıldı. Hastanın yapılan değerlendirilmesinde Hb: 10.9 mg/dL Lökosit: 19.000 u/L sedimentasyon: 79 mmsaat, CRP:9.59 mg/dL LDH:278 U/L GGT: 292 U/L AFP: 249.31 ng/mL. Fizik muayenesinde sağ submandibular bölgede büyüğü yaklaşık 3 x 4 cm büyüklüğünde çok sayıda LAP mevcuttu. Karaciğer kot altında 3 cm palpable, diğer sistem muayeneleri doğaldı.

Boyun ultrasonografisinde (USG); sağ submandibular bölgeden retroaurikular alana kadar uzanan 23x17mm ve 32x24 mm boyutunda **izoekoik LAP pakesi** izlendi. Tanımlanan LAP'ler miks kanlanma paterni göstermekte olup ekojen hilusları seçilememekte, radyolojik görünüm **malign tutulum (lenfoma)** veya **atipik enfeksiyon** tutulumunu düşündürmekte olarak raporlandı. Nazofareks magnetik rezonans (MR) da; sağ submandibular, jugulodigastrik, posterior servikal bölgeye uzanım gösteren çok sayıda büyüğü 20x15 mm boyutunda konglemarat oluşturan T1 ve T2 A'da izointens çok sayıda LAP'ler izlendi (Resim 1). Akciğer grafisinde timüs gölgesi izlendi. Batın USG'de; karaciğer 90 mm olup hasta yaşına oranla normalin üst sınırında, karaciğer parankim ekosu homojen olup kitle izlenmemişti.



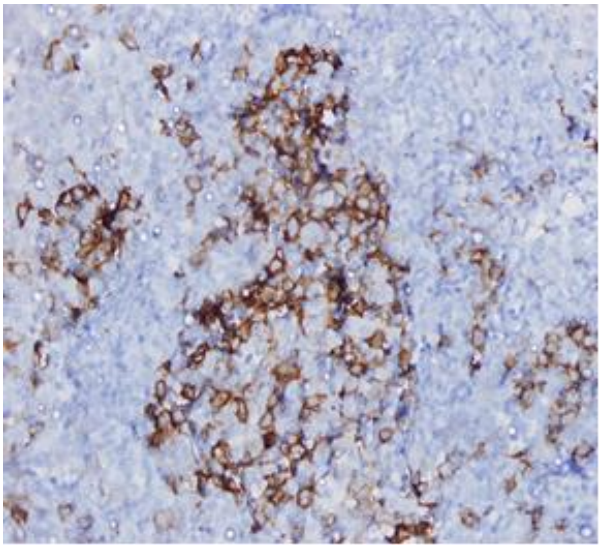
Resim 1: Nazofarenks MR'da T1'de sağ submandibular üst juguler bölgeye uzanım gösteren çok sayıda lenfadenopati.

Hastanın kulak önündeki LAP'den, eksizyonel lenf nodu biyopsisi yapıldı. Biyopsi sonucu; CD1a(+), S100 protein zayıf (+), LCA

Adress for correspondence: Ayşenur Bahadır, Karadeniz Teknik Üniversitesi, Pediatrik Hematoloji-Onkoloji Bilim Dalı, Trabzon, Türkiye
e-mail:aysenurkbr@yahoo.com
Available at www.actaoncologicaturcica.com

(-), pansitokeratin (-), PLAP (-), CD30 (-), CD (-), CD20 (-), Langerhans hücreli histiyositoz olarak rapor edildi (Resim 2). Hastanın LHH açısından muhtemel tutulum yerleri olan kemik, akciğer, karaciğer taraması yapıldı. Toraks bilgisayarlı tomografisinde (BT) akciğer parankimi, içerisinde hareket artefaktı nedeniyle net değerlendirilemedi. Sağ akciğer üst lob posterior segmentte buzlu cam dansiteleri içerisinde langerhans hücreli histiostoz açısından şüpheli kistik görünümler izlendi. Abdominal BT; karaciğer vertikal uzunluğu 94 mm olup normalden büyük, kontürü düzgün, parankim dansitesi normal, dalak vertikal uzunluğu 77 mm olup normalden büyüktü. Kraniel MR normaldi. Kemik iliği aspirasyonu normaldi. Kemik sintigrafisinde tutulum izlenmedi.

Hastaya langerhans hücreli histiositozis tedavi protokolü (vinblastin 6mg/m^2 ve prednizolon 40mg/m^2) başlandı. Komple tam remisyonda olan hasta 2,5 yaşında olup kliniğimizde takip edilmeye devam edilmektedir.



Resim 2: CD1a boyalı Langerhans hücreleri.

Tartışma:

Çocuklarda boyundaki kitleler genellikle gelişimsel, inflamatuar, neoplastik olmak üzere üç kısımda incelenir. Konjenital gelişimsel boyun kitleleri tiroglassal kist, brankial yarık kisti, dermoid kist, vasküler malformasyon ve hemanjiomlardır; İnflamatuvar boyun kitleleri reaktif LAP, infeksiyöz lenfadenit; benign neoplastik lezyonlar pilomatriksoma, lipom, fibrom, nörofibrom, tükrük bezi tümörleri; malign lezyonlar lenfoma, rabdomyosarkom, tiroid karsinomu ve metazlardır. Beş yaşından küçük çocuklarda en yaygın kitle nedeni LAP'lerdir. Kitle nedeninin aydınlatılmasında en önemli tetkiklerden biri USG'dir ve invaziv olmaması kolay yapılabilmesi en önemli avantajıdır. Ayrıca USG ile kitlenin solit, kistik ayırımı yapılabilmekte bize yol gösterici olmaktadır. Malignensi şüphesi olan durumlarda, kesin tanı için LAP'den biyopsi yapılması gerekmektedir (5).

Bizim hastamızın şikâyeti 10 günlük iken kulak önünde ve boyunda ele gelen şişlik şeklinde başlamıştı, dış merkezde lenfadenit olarak düşünülüp antibiyotik tedavisi almıştı ve tedaviye rağmen gerileme olmayınca tarafımıza başvurmuştu. Enfeksiyon açısından gönderilen EBV, CMV, toksoplazma sonuçları negatifti, ayrıca almış olduğu antibiyotik tedavisine rağmen LAP boyutunda küçülme olmamıştı. Hastamızın çekilen USG'de lenfoma şüphesi olması, tanısının netleştirilebilmesi için boyundaki LAP'den biyopsi yapıldı. Hastamızın LAP'den alınan biyopsi sonucu LHH olarak raporlandı. LHH açısından muhtemel tutulum yerleri olan kemik, karaciğer, akciğer, kemik iliği tarandı. Hastanın akciğer bulgusu olması, karaciğer tutulumu olması nedeni ile multisistemik LHH olarak kabul edildi ve sistemik kemoterapi başlandı. Kemik ve deri tutulumu yoktu.

LHH her yıl yaklaşık 2-10 milyon çocukta görülmektedir. Özellikle karaciğer, dalak, kemik iliği gibi riskli organ tutulumu

Adress for correspondence: Ayşenur Bahadır, Karadeniz Teknik Üniversitesi, Pediatrik Hematoloji-Onkoloji Bilim Dalı, Trabzon, Türkiye
e-mail:aysenurkbr@yahoo.com
Available at www.actaoncologicaturcica.com

olduğunda mortalitesi yüksektir. Hastalara verilen tedavi tekli organ tutulumu olması ya da çoklu organ tutulumu olmasına bağlı olarak belirlenmektedir (2).

LHH da lenf nodu tutulumu sık görülmeyip, genellikle sistemik tutulumu olan olgularda görülmektedir. LHH'lu 15 gün-18 yaş arasındaki (ortalama 5 yaş) 133 hastanın ilk tutulum yerlerinin değerlendirildiği bir çalışmada; 114 hastada kemik, 34 hastada kulak, 30 hastada deri, 18 hastada karaciğer, 14 hastada akciğer, 14 hastada lenf nodu, 12 hastada dalak, 9 hastada diabetes insiputus, 2 hastada kemik iliği tutulumu saptanmıştır (4). Kwon ve arkadaşlarının (6) yapmış olduğu retrospektif çalışmada 30 vaka taranmış ve LAP ile başvuran vaka sayısı %3.3 olarak bulunmuştur. Ayrıca bu çalışmada en sık başvuru şikâyetinin deri ve kemik tutulumu olduğu gözlenmiştir. Özellikle yenidoğan döneminde tanı alan LHH vakaları genellikle deri bulguları ile başvurmaktadır (3,6). Bizim vakamızın deri bulgusu yoktu ve boyunda LAP ile başvurmuştu. Bununla beraber hastanın tanısı netleştirildikten sonra yapılan taramasında akciğer ve karaciğer tutulumu da tespit edildi.

LHH özellikle infant döneminde en sık başvuru şikâyeti cilt lezyonları olmakla beraber, nadir de olsa boyunda LAP ile başvurabilir. Yenidoğan dönemindeki LAP'ler yakın takip edilmeli, klinik ve USG görüntü olarak enfeksiyon ve malignite ile LHH'un karışabileceği akılda tutulmalıdır. Hastanın şikâyetleri gerilemediğinde en kısa sürede doku biyopsisi yapılıp hastalığın tanısının netleştirilmesi gerekir. Ayrıca LHH'da LAP tutulumuna sistemik organ tutulumunun da eşlik edebileceği unutulmamalı ve tedavinin planlanabilmesi için hasta ayrıntılı taranmalıdır.

Çıkar Çatışması: Yok

Kaynaklar:

1. Ribeiro KB, DDS, Degar B, Gianotti Antoneli CB, Rollins B, Rodriguez-Galindo C. Ethnicity, Race, and Socioeconomic Status Influence Incidence of Langerhans Cell Histiocytosis. Pediatr Blood Cancer, 2015; 62: 982–987.
2. Simko JS, Garmezy B, Abhyankar H, Lupo JP, Chakraborty R, Phaik Har Lim K, Shih A, Hicks J, Wright TS, Levy LM, McClain KL, Allen CE. Differentiating Skin-Limited and Multisystem Langerhans Cell Histiocytosis. J Pediatr 2014;165:990-6.
3. Tan Q, Gan Q, Wang H. Congenital self-healing Langerhans cell histiocytosis in a male neonate. 2015; 81 (1): 75-77.
4. Braier J, Chantada G, Rosso D, Bernaldez P, Amaral D, Latella A, Balancini B, Masautis A, Goldberg J. Langerhans cell histiocytosis: retrospective evaluation of 123 patients at a single institution. Pediatr Hematol Oncol. 1999;16(5):377-385.
5. Meıer JD, Grımmer JF. Evaluation and Management of Neck Masses in Children. Am Fam Physician. 2014;89(5):353- 358.
6. Kwon SH, Choı JW, Kım HJ, Youn SW. Langerhans cell histiocytosis: A retrospective analysis in a Korean tertiary hospital from 2003 to 2012. Journal of Dermatology 2013; 40: 824–828.

Adress for correspondence: Ayşenur Bahadır, Karadeniz Teknik Üniversitesi, Pediatrik Hematoloji-Onkoloji Bilim Dalı, Trabzon, Türkiye
e-mail:aysenurkbr@yahoo.com
Available at www.actaoncologicaturcica.com

Intracranial Mesenchymal Chondrosarcoma: A Case Report

İntrakranial Mezenkimal Kondrosarkom: Bir Olgu Sunumu

Ayşe Gök Durnalı[1], Fisun Ardıç Yükrük[2], Nurten Kandemir[1], Saadet Tokluoğlu[3], Nuran Süngü[4], Ülkü Yalçıntaş Arslan[1], Kaan Helvacı[1], Necati Alkış[1]

[1]Department Of Medical Oncology, Dr A. Y. Ankara Oncology Training And Research Hospital, Ankara, Turkey
[2]Department Of Pathology, Dr A. Y. Ankara Oncology Training And Research Hospital, Ankara, Turkey
[3]Department Of Medical Oncology, Güven Hospital, Ankara, Turkey
[4]Department Of Pathology, Atatürk Training And Research Hospital, Ankara, Turkey

Dergiye Ulaşma Tarihi:27.02.2015 Dergiye Kabul Tarihi:14.07.2015 DOI: 10.5505/aot.2016.26349

ÖZET:
İntrakranial Kondrosarkomlar çok nadir görülen malign tümörlerdir, intrakranial tümörlerin sadece %15'ini oluştururlar. Bu tümörlerin tedavisinde, cerrahi rezeksiyon ve adjuvan radyoterapi temel yaklaşımlardır. Kemoterapinin rolü iyi tanımlanmamıştır. Biz burada intrakranial mezenkimal kondrosarkom tanılı 26 yaşında erkek hastayı sunduk.
Anahtar Kelimeler: İntrakranial, Kemoterapi, Mezenkimal kondrosarkom, Tedavi

ABSTRACT:
Intracranial chondrosarcomas are very rare malignant tumors, account for only 0.15% of all intracranial tumors. Surgical resection and adjuvant radiotherapy are main approaches of treatment in the treatment of these tumors. The role of chemotherapy is not well defined. We presented a 26 year-old- man diagnosed with intracranial mesenchymal chondrosarcoma.
Keywords: Chemotherapy, Intracranial, Mesenchymal chondrosarcoma, Treatment

Introduction

Chondrosarcoma is a rare malignant tumor that originates from cartilaginous tissue. It is mostly located in long bones and pelvic region, only 7% of chondrosarcomas grow in the craniocervical region and it accounts only 0.15% of all intracranial tumors (1,2,3). Microscopically tumor displays a dimorphic pattern characterized by well differentiated cartilage with abrupt boundary from undifferentiated stroma composed of small/round oval cells resembling lymphoma, hemangiopericytoma or Ewing's sarcoma/ Primitive neuroectodermal tumor (PNET). Differential diagnosis includes small blue round cell tumors, small cell osteosarcoma. Surgical resection and irradiation is mainstay of treatment (4). Because of the rarity of intracranial chondrosarcomas, the role of chemotherapy is not well defined.
Herein we reported our intracranial mesenchymal chondrosarcoma patient and treatment outcomes.

Case Report

A 26 year-old- man was admitted to hospital in with the history of progressive headache and sudden loss of consciousness. Cranial imaging showed intracranial mass in right temporoparietal region. He underwent surgical excision of this intracranial mass and pathological evaluation of excision material reported as mesenchymal chondrosarcoma, grade 4, according to WHO 2000. Microscopically tumor displayed a dimorphic pattern characterized by well differentiated cartilage with abrupt boundary from undifferentiated stroma composed of small/round oval cells (Figures 1, 2, 3, 4)
Immunohistochemically there was no staining with S100 (S100 positivity only in chondroid areas), desmin, actin, cytokeratin, EMA and synaptohysin.
A local recurrence was detected during postoperative 4th month, and the patient received radiation therapy at a dose of 60 Gy

Adress for correspondence: Doç. Dr. Ayşe Gök Durnalı. Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Kliniği13. Cadde, No: 56, Yenimahalle Ankara – Türkiye
e-mail: aysadurnali@gmail.com
Available at www.actaoncologicaturcica.com

with the response of partial regression. Approximately 3 years later, there was progressive mass in the same region and surgical excision followed by stereotactic radiation therapy was performed. Two months later, the patient underwent third surgical excision procedure for rapid local recurrence, but total excision was impossible due to multiplicity of lesions. After this last operation, no additional radiation therapy was planned and he was admitted to our department to be evaluated for chemotherapy. On imaging studies performed at that time, there was no distant metastasis and cranial magnetic resonance imaging showed recurrent mass lesions on occipital lobe and partial herniation of brain parenchyma from craniotomy line (Figure 5).

As doxorubicin is essential drug for the treatment of most types of sarcomas and also mesenchymal chondrosarcomas of bone and soft tissue (5), doxorubicin and ifosfamide with mesna protection was started. After 3 weeks of 4th cycle of this chemotherapy regimen, progressive disease was detected. Second line 4 cycles of cisplatin based chemotherapy regimen (cisplatin and doxorubicin was given with the response of stable disease. After 2 months of last chemotherapy cycle, there was progressive disease and the patient died 1 month later. Survival time of our patient from the beginning of chemotherapy cycles was 9 months and from first operation was 51 months.

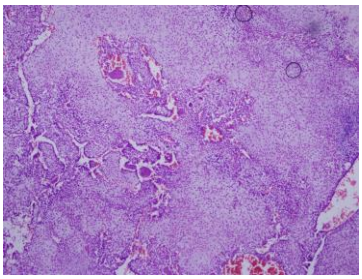


Figure 1. Islands of cartilage admixed with undifferentiated small ovoid cells HEx40

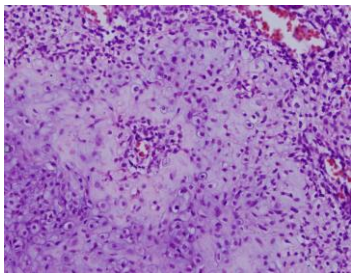


Figure 2. Low grade cartilaginous areas HEX200

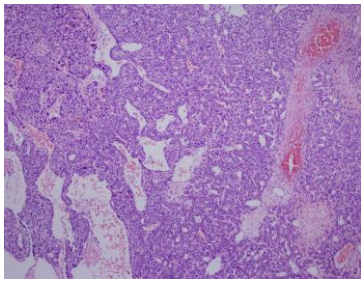


Figure 3. Undifferentiated round cell tumor with a typical hemangiopericytomatous vascular pattern HEX40

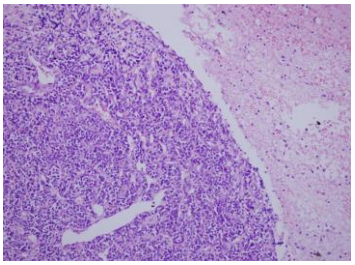


Figure 4. Undifferentiated small round cell tumor adjacent to brain tissue

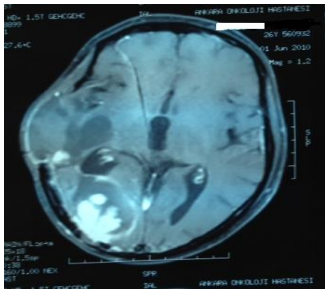


Figure 5. Cranial magnetic resonance imaging showed recurrent mass lesions on occipital lobe and partial herniation of brain parenchyma from craniotomy line

Adress for correspondence: Doç. Dr. Ayşe Gök Durnalı. Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Kliniği13. Cadde, No: 56, Yenimahalle Ankara – Türkiye
e-mail: aysadurnali@gmail.com
Available at www.actaoncologicaturcica.com

Discussion

Chondroid tumors infrequently originate from extra skeletal regions. Intracranial chondrosarcomas constitute only 0.15% of all intracranial tumors (3). There are different theories for the development of intracranial chondrosarcoma. Some reports have postulated that they might develop from chondrocytes in rests of endochondral cartilage, others have suggested that they might be arising from primitive multifunctional mesenchymal cells in embryogenesis of skull base or temporal bone or from metaplastic mature fibroblasts of from undifferentiated cells from cartilaginous synchondroses (1,2,6). Histopathologically they are subclassified into conventional, dedifferentiated, clear cell and mesenchymal types (1). Conventional subtype is most common type, usually locates at the base of skull (6,7). Mesenchymal subtype is more anaplastic type, may spread to distant sites (1). Prognosis is determined mainly by its WHO histological grade (1).

Intracranial chondrosarcomas sometimes mimics meningiomas, present with symptoms of mass effect such as increased intracranial pressure, nerve palsies, seizures (1,8). CT scans show iso-hyperdense lesion, variable degrees of heterogeneous enhancement and varying amounts of calcification (7). MR imagines show better demarcation and the pattern of heterogeneous enhancement which is typical for this malignancy (7,9). On pathological examination, S100 and vimentin positive, epithelial markers such as EMA and cytokeratin are negative (2).

Surgical resection is the mainstay in treatment of cranial chondroid tumors (1,4,7) and postoperative adjuvant radiation may reduce mortality (1,4,7,10). But for low grade chondrosarcomas, to determine the role of adjuvant therapy, investigations must be performed (1).

In a review, 5-year mortality rate was found to be 26% for patients treated with only surgery, addition of postoperative radiation therapy reduced this rate to 4% (1). In the same study, 5-year mortality rates were 6% and 54% in patients with conventional and mesenchymal chondrosarcomas respectively, overall 5-year mortality was 11%; median survival was 24 months (1).

The data about the role of chemotherapy for treatment of intracranial chondrosarcomas is very limited. Rapidis et al. also reported that chemotherapy was not effective (11). La spina et al suggested that adjuvant chemotherapy, a "sarcoma-like" course of chemotherapy: CEV, IVE, CEV, CAV-HDx3 (carboplatin, etoposide, vincristine, ifosfamide, and adriamycin), might have a role in the local control of intracranial mesenchymal chondrosarcoma, especially when total surgery was not possible (12). Aksoy et al, reported that a 31 –year-old patient with recurrent intracranial mesenchymal chondrosarcoma who had no further surgery or radiation therapy options, achieved a good clinical response with temozolomide (13). In a systematic review of 107 patients with mesenchymal chondrosarcoma of bone and soft tissue, it was reported that highly variable regimes were used as adjuvant treatment, including dactinomycin, carboplatin, cisplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, high-dose methotrexate, and vincristine; and there was no general agreement on the regimen of chemotherapy as the adjuvant therapy of mesenchymal chondrosarcoma, except for doxorubicin as a cornerstone (5).

With these limited literature data and outcomes of our patient, prognosis of intracranial chondrosarcoma depends mostly on grade, histopathological subtype, and treatment type (surgical excision is mandatory, adjuvant radiation therapy for complete or incompletely resected tumor is likely to be beneficial). The role of chemotherapy at adjuvant or metastatic settings may be important for high grade intracranial chondrosarcomas, especially mesenchymal subtype. For patients with recurrent tumor and with no further surgery or radiotherapy options, studies for effective chemotherapy regimens are required.

Conflict of interest: None

References

1. Bloch OG, Jian BJ, Yang I, et al. A systematic review of intracranial chondrosarcoma and survival. J Clin Neurosci. 2009;16: 1547-51
2. Oruckaptan HH, Berker M, Soylemezoglu F, Ozcan OE. Parafalcine chondrosarcoma: an unusual localization for a classical variant. Case report and review of the literature. Surg Neurol. 2001; 55: 174-9

Adress for correspondence: Doç. Dr. Ayşe Gök Durnalı. Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Kliniği13. Cadde, No: 56, Yenimahalle Ankara – Türkiye
e-mail: aysadurnali@gmail.com
Available at www.actaoncologicaturcica.com

3. Cianfriglia F, Pompili A, Occhipinti E. Intracranial malignant cartilaginous tumours. Report of two cases and review of literature. Acta Neurochir (Wien). 1978; 45: 163-75
4. Cherekaev VA, Golbin DA, Gasparyan TG, Shishkina LV, Tsukanova TV. Management of craniofacial chondroid tumors. J Craniofac Surg. 2015; 26: 10-8
5. Xu J, Li D, Xie L, Tang S, Guo W. Mesenchymal Chondrosarcoma of Bone and Soft Tissue: A Systematic Review of 107 Patients in the Past 20 Years**.** PLoS One. 2015; 10: e0122216
6. Chandler JP, Yashar P, Laskin WB, Russell EJ. Intracranial chondrosarcoma: a case report and review of the literature. J Neurooncol. Review. 2004; 68: 33-9
7. Güneş M, Günaldi O, Tuğcu B, Tanriverdi O, Güler AK, Cöllüoğlu B. Intracranial chondrosarcoma: a case report and review of the literature. Minim Invasive Neurosurg. 2009; 52: 238-41
8. Boccardo M, Bavaresco E, Sola S, Vitali A. Parafalcine chondrosarcoma: report of a case and review of the literature. J Neurosurg Sci. 2009; 53: 137-40
9. Kothary N, Law M, Cha S, Zagzag D. Conventional and perfusion MR imaging of parafalcine chondrosarcoma. AJNR Am J Neuroradiol. 2003; 24: 245-8
10. Kan Z, Li H, Zhang J, You C. Intracranial mesenchymal chondrosarcoma: case report and literature review. Br J Neurosurg. 2012; 26: 912-4.
11. Rapidis AD, Archondakis G, Anteriotis D, Skouteris CA. Chondrosarcomas of the skull base: review of the literature and report of two cases. J Craniomaxillofac Surg. 1997; 25: 322-7.
12. La Spina M, Dollo C, Giangaspero F, Bertolini P, Russo G. Intracranial mesenchymal chondrosarcoma with osteoid formation: report of a pediatric case. Childs Nerv Syst. 2003; 19: 680-2
13. Aksoy S, Abali H, Kiliçkap S, Güler N. Successful treatment of a chemoresistant tumor with temozolomide in an adult patient: report of a recurrent intracranial mesenchymal chondrosarcoma. J Neurooncol. 2005; 71: 333-4

Adress for correspondence: Doç. Dr. Ayşe Gök Durnalı. Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Kliniği13. Cadde, No: 56, Yenimahalle Ankara – Türkiye
e-mail: aysadurnali@gmail.com
Available at www.actaoncologicaturcica.com

A Case of Bilateral Malignant Ovarian Brenner Tumor

Bilateral Malign Brenner Tümörü: Olgu Sunumu

Emine Zeynep Uçar, Alper Karalök, Işın Üreyen, Tolga Taşçı, Derman Başaran, Osman Türkmen, Mehmet Çelik, Taner Turan, Gökhan Tulunay

Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi, Jinekolojik Onkoloji Bölümü

Dergiye Ulaşma Tarihi:04.01.2016 Dergiye Kabul Tarihi: 06.06.2016 DOI: 10.5505/aot.2016.53825

ÖZET

Giriş: Brenner tümörü nadir olarak görülen bir yumurtalık kanseridir ve tüm kanserlerin %1'ni oluşturur. Bu tümörler genelde iyi huyludur ve Brenner tümörlerinin sadece %1'i kötü (malign) karakterdedir. Nadir olarak görülen bilateral malign brenner tümörlü bir olguyu sunacağız.

Olgu: 55 yaşında hasta son bir aydır olan karında şişlik ve ağrı şikâyeti ile başvurdu. Hastanın fizik muayenesinde pelvik kitle ve asit sıvısı mevcuttu. Ultrasonografik incelemede yumurtalıktan kaynaklanan kitlesi mevcuttu. Ameliyat öncesi serum CA-125: 64 IU/ml'idi. Laparotomi yapılan hastanın bilateral yumurtalık kitleleri mevcuttu, frozen section incelemesi malign olan hastaya geride tümör kalmayacak şekilde evreleme cerrahisi yapıldı. FIGO 2009 evrelemesine göre evre IIIC olarak kabul edilen hasta adjuvan 6 kür platin bazlı kemoterapi aldı. On üç ay sonra bilateral ve çok sayıda akciğer metastazı gelişen hasta kurtarma kemoterapisi aldı. Sonrasında çok defa kemoterapi rejimleri almasına rağmen hastalığın ilerlemesi nedeniyle tanıdan 53 ay sonra hastalığından dolayı eksitus oldu.

Tartışma: İyi huylu lezyonlar basit eksizyonla tedavi edilebilir. Çok nadir görülmesinden dolayı malign brenner tümörünün cerrahi sonrası adjuvan tedavisi konusunda fikir birliği yoktur. Buna benzer yumurtalık patolojilerini içeren çok merkezli çalışmalar, bu hastalık ile olan bilgimizi artıracaktır.

Anahtar Kelimeler: Malign brenner tümörü, yumurtalık kanseri, sitoredüktif cerrahi, kemoterapi

ABSTRACT

Background: Brenner tumor of ovary is a rare neoplasm which constitutes almost 1 percent of all ovarian tumors. These tumors are usually benign, with only 1% being malignant. Here, we report a very rare case of bilateral malignant Brenner tumor.

Case: A 55 year-old woman admitted to our center with complaints of abdominal distention and pain. Her physical examination was remarkable for pelvic mass and ascites. Sonographic examination showed a complicated pelvic mass of ovarian origin. Her preoperative serum CA-125 level was 64 IU/ml. An exploratory laparotomy revealed bilateral ovarian masses and frozen section of the ovarian tumors was reported to be malignant. There was no peritoneal disease and she underwent a standard staging procedure. Final pathology revealed FIGO 2009 stage IIIC bilateral malignant Brenner tumor of the ovary. Patient received 6 cycles of platinum based chemotherapy. After 13 months of diagnosis multiple metastatic lesions in lungs were found and she underwent salvage chemotherapy. She received multiple chemotherapy regimens however disease progressed gradually and she succumbed to disease 53 months after initial diagnosis.

Discussion: In the vast majority of ovarian Brenner tumors, surgical resection provides a cure for benign disease. Owing to its low incidence there is not established adjuvant treatment algorithm for malignant ovarian Brenner tumors. Multicenter trials of ovarian cancer should aim to include this rare pathology to increase our knowledge.

Keywords: Malignant brenner tumor, ovarian carcinoma, cytoreductive surgery, chemotherapy

Giriş

Brenner tümörü büyük oranda fibroma benzeyen, nadir olarak görülen bir yumurtalık tümörüdür ve tüm tümörlerin %1,4-2,5'unu oluşturur (1). Mikroskobik incelemede belirgin olarak hiperplastik fibromatöz matriks arasına yayılmış epiteloid hücre adacıkları görülür. Epiteloid hücreler, uzunlamasına yarıklanan çekirdekleri nedeniyle kahve çekirdeği "coffee bean" yapısı gösterir. Brenner tümörünün basit Walthard hücre artıklarından köken aldığına inanılmasına rağmen, yüzey epitelinin rete ovarii ve ovaryan stromanın kendisi gibi farklı

Adress for correspondence: Uzm. Dr. Emine Zeynep Ucar. Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi, Jinekolojik Onkoloji Bölümü, Etlik Caddesi, Posta kodu: 06010, Keçiören / Ankara / TÜRKİYE
e-mail: ezyilmaz@gmail.com
Available at www.actaoncologicaturcica.com

dokulardan da kaynaklanabileceği gösterilmiştir (2).
Brenner tümörünün genel olarak benign olarak kabul edilmesine rağmen son birkaç dekatta olguların %1'inin malign olduğu rapor edilmiştir (1). Brenner tümörü genel olarak hormon salgılamaz. Fakat son yıllarda yapılan yayınlarda postmenopozal endometrial hiperplazi gelişen bazı hastalardaki hiperplazi brenner tümörünün östrojenik salgı yapmasıyla ilişkilendirilmiştir (3). Brenner tümörünün virilizm ile ilişkili olabileceği de rapor edilmiştir (4).
Brenner tümörlerinin çoğu cerrahiye adaydır. Genelde sınırlı bir tümör olması dolayısıyla yerinin tespit edilmesi kolaydır ve çevreleyen dokuyu etkilemez. Cerrahi rezeksiyon çoğu hastada tedavi edicidir ve semptomların gerilemesine yardımcı olur. Malign Brenner tümörleri ise çevre dokuyu etkileyebilir ve diğer yapılara yayılım gösterebilir ancak çok nadir görüldüğünden standart tedavi oluşturulamamıştır. Farklı kemoterapi rejimleri düşük başarı oranları ile uygulanmaktadır. Bu olgu sunumunda da nadir olarak görülen ve görüntüleme tetkikleriyle tanınamayan bilateral malign brenner tümöründen bahsedilmektedir.

Olgu sunumu

55 yaşında kadın hasta, kasık ağrısı ve karında şişme şikâyeti ile merkezimize başvurdu. Yapılan ultrasonografik incelenmede sol yumurtalık, 150x84 mm büyüklüğünde düzgün sınırlı içinde soliter ekolu alanlar içeren kitle lezyonu ve kitlenin alt kısmında 33x34 mm'lik kistik alan bulunmaktaydı. Sağ adneksiyel alanda 110x90 mm büyüklüğünde solid-kistik alanlar içeren komplike kitle mevcuttu. Batın alt kadranda 30 mm serbest sıvı saptandı. Tümör belirteçlerinden CA125: 64 IU/ml'di.
Hastaya laparotomi yapıldı. İntraoperatif gözlemde batında 600 cc seröz nitelikte serbest sıvı bulunmaktaydı, serbest sıvıdan sitoloji için örnek alındı. Sol yumurtalıkta 20x15 cm rüptüre sağda 10x8 cm rüptüre tümoral kitle mevcuttu. Hastaya total abdominal histerektomi, bilateral salpingooforektomi, omentektomi, appendektomi, alt para-aortik bölgede şüpheli lenf nodu eksizyonu operasyonu yapıldı. Cerrahi ile tam olarak maksimal debulking sağlandı. Hastanın postoperatif patolojisi bilateral malign brenner tümörü, barsak mezosundaki lenf nodunda metastatik karsinom ve batın sıvısında malignite yönünden şüpheli hücreler olarak raporlandı. FIGO (International Federation Gynaecology Obstetrics)'a göre Evre IIIC olarak tanımlandı. Hastaya 6 kür sisplatin ve paklitaksel kemoterapisi verildi. Tedavi sonrası alt-üst abdomen tomografi normal olarak raporlandı. 13 ay sonra hasta boyunda şişlik yakınmasıyla başvurdu. Lenf nodu biyopsisi yapıldı ve hastanın sistemik taranmasında akciğer tomografisinde "her iki akciğer alanında yaygın ve en büyükleri 12 mm çapa ulaşan çok sayıda solid metastatik kitle izlendi. Boyundaki skalen lenf nodu biyopsi patolojisi nonspesifik lenfadenit" olarak raporlandı. Hastaya 6 kür sisplatin, etoposid kemoterapisi verildi. Tedavi sonrası tam cevap veren hasta tedaviden 6 ay sonra yapılan ultrasonografide mesane sol altta 52x43 mm solid kitle oluşumu mevcuttu. Alt-üst abdomen tomografisinde; sol adneksiyel bölgede 55x50 mm büyüklüğünde kısmen düzensiz konturlu, septalı, kistik solid komponentli kitle, retroperitoneal alanı dolduran ve konglomere lenf nodlarına ait olduğu düşünülen yumuşak doku kitlesi izlendi ve solda böbrek hidronefrotik ve afonksiyoneldi. Hastaya pelvik eksternal radyoterapi verildi. Tedavi sonrası alt-üst abdomen tomografisi değerlendirilen hastanın pelviste sol adneksiyel alanda 50x45 mm çapta kitle ve paraaortik alanda büyümüş konglomere lenf nodları izlendi. Yapılan tedaviye rağmen tümörde ilerleme izlenen hasta opere edildi. Pelvisteki nüks kitle ve paraaortik bölgedeki konglomere lenfatik metastazlar çıkarıldı ve maksimal debulking sağlandı. Adjuvan BEP (bleomisin+ etoposid+ sisplatin) kemoterapisi verildi. 9 ay sonra akciğer ve alt-üst abdomen tomografilerinde; pelviste 66x64 mm boyutlarında solid oluşum, sağ akciğer orta lobda ve sol bazalde büyüğü 48 mm çapa ulaşan metastaz ile uyumlu nodüler lezyonlar, karaciğer içinde en büyüğü 37x32 mm olan çok sayıda lezyonlar, sol sürrenal lojda 53x50 mm yumuşak doku kitleleri saptandı. Hastaya palyatif 5 kür sisplatin, adriamisin ifosfamid planlandı. Kemoterapiye cevap vermeyen hastaya oral etoposid tedavisi başlandı ve bu tedaviden 2 ay sonra karaciğer yetmezliği nedeni ile hasta exitus oldu.

Adress for correspondence: Uzm. Dr. Emine Zeynep Ucar. Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi, Jinekolojik Onkoloji Bölümü, Etlik Caddesi, Posta kodu: 06010, Keçiören / Ankara / TÜRKİYE
e-mail: ezyilmaz@gmail.com
Available at www.actaoncologicaturcica.com

Tartışma

Yumurtalık tümörleri 2013 yılında yapılan WHO sınıflandırılmasına göre; epitelyal stromal tümörler, germ hücreli tümörler, sex-kord stromal tümörler ve ikincil (metastatik) tümörler olarak gruplara ayrılmıştır. Brenner tümörü epitelyal stromal tümörlerin transizyonel hücreli tümörler alt grubunda yer alır.

Brenner tümörü, genelde benign olsa da bir kısmı borderline veya malign olabilir (1). Brenner tümöründe malign tümör tanımı ilk kez Von Numers tarafından 1945 yılında yapılmıştır. Malign Brenner tümörünün kriterleri o zamandan beri oluşturulmaya çalışılmaktadır ve 1973 yılında Hall ve Campbellin sıraladığı kriterler şunlardır: 1) malign histopatolojik bulguların varlığı 2) malign komponent ile benign Brenner tümör arasında açık bir ilişki varlığı 3) müsinöz kistadenomun olmaması, varsa da benign ve malign Brenner tümöründen kesin bir şekilde ayrı olması 4) Brenner tümörün epitelyal elementlerinin stromal invazyonun gösterilmesidir (1).

Malign brenner tümörünün en sık görülme yaşı medyan 55'dir ve başvuru esnasında en sık gözlenen semptom karın ağrısıdır (5). Bizim olgumuz da literatür ile uyumlu olarak 55 yaşında idi ve karın ve kasık ağrısı semptomlarıyla başvurdu. Brenner tümörünün nonspesifik komponentlerinden dolayı görüntüleme yöntemlerinden ultrasonografi veya tomografi ile tanınması zordur (6). Olgumuzda da ovaryan kitle preoperatif olarak gösterilmiş fakat tümörün tipi konusunda bir yorum yapılamamıştır. Benign Brenner tümörleri düzgün kenarlı, sert veya fibromatöz gri, beyaz veya açık sarı renkte yüzeylidir. Doku kalsifik depolanmadan ötürü sertleşir. Borderline Brenner tümörleri kistiktir ve bir ya da çok loküle uzanan karnıbahar şeklinde papillomatöz uzantılar içerir. Malign Brenner tümörleri solid veya mural nodüller içeren kistler şeklinde olabilir ve genelde ayırt edici özellikleri yoktur (7). Brenner Tümörlerinin %4-14'de endometrial hiperplazinin eşlik ettiği gösterilmiştir (8). Olgumuzda hastada endometrial patoloji saptanmamıştır. Malign brenner tümörlerinin %10'unda kitleye asit eşlik eder(11), bizim olgumuzda da 600 cc seröz nitelikte asit mayi bulunmaktaydı.

Malign brenner tümörlerin başlangıç tedavisi diğer epitelyal yumurtalık kanserlerindeki gibi cerrahidir (9). Definitif cerrahi total abdominal histerektomi+ bilateral salpingo-ooferektomi+ bilateral pelvik para-aortik lenf nod diseksiyonu ve omentektomiyi içeren sitoredüktif cerrahidir (9). Sunulan olguda tam bir sitoredüktif cerrahi yapılmıştır. Cerrahi sonrası adjuvan tedavi yaklaşımında tam bir fikir birliği yoktur.

Benign brenner tümörleri genelde tek taraflı olarak görülmesine karşın malign brenner tümörleri bilateral ve kistik yapıların daha fazla olduğu solid-kistik kitleler olarak gözlenir (10). Olgumuzda kitle, bilateral ve komplike solid-kistik olarak izlenmekteydi. Gezginç ve ark yaptığı malign brenner vaka serisinde olguların %46.2'de tümörün evresi FIGO'a göre evre IIIC'di ve bu hastaların hepsi adjuvan tedavide paklitaksel+ karbo-platin kemoterapisi almıştır (11). Evre IIIC olan bu hasta grubunun %16.6'sı hastalıktan dolayı kaybedilmiştir. Olgumuzda da, hasta cerrahi tedavi sonrası paklitaksel + sisplatin tedavisi almış ve rekürrenslerinde çeşitli cerrahi ve kemoterapi tedavileri sonrasında 53 ay takip edilip bu hastalıktan dolayı kaybedilmiştir. Malign brenner tümörü olan 10 hastayı içeren bir çalışmada kemoterapinin rekürrenste umut verici olduğu (12) yazılsa da bu konuda daha çok çalışmaya ihtiyaç vardır.

Malign Brenner tümörü nadir görülen epitelyal orijinli yumurtalık malignitesidir. Genel olarak kabul edilen cerrahi yaklaşım sitoredüktif cerrahidir. Adjuvan tedavi konusunda fikir birliği yoktur. Cerrahi genelde erken evrelerde küratif olsa da malign Brenner tümörleri çevre veya uzak dokulara metastaz yapabilir ve hastalar bu hastalıktan dolayı kaybedilebilir. Bu tümör konusundaki bilgi birikiminin ve tedavi yaklaşımının yazılan olgu sunumları ve olgu serileri ile artacağını umuyoruz.

Referanslar:

1. Yamamoto R, Fujita M, Kuwabara M, Sogame M, Ebina Y, Sakuragi N, Kato H, Fujimoto S. Malignant Brenner tumors of the ovary and tumor markers: case reports. Jpn J Clin Oncol. 1999; 29: 308-13
2. Lamping JD, Blythe JG. Bilateral Brenner tumors: a case report and review of the literature. Hum Pathol. 1977; 8: 583-5

Adress for correspondence: Uzm. Dr. Emine Zeynep Ucar. Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi, Jinekolojik Onkoloji Bölümü, Etlik Caddesi, Posta kodu: 06010, Keçiören / Ankara / TÜRKİYE
e-mail: ezyilmaz@gmail.com
Available at www.actaoncologicaturcica.com

3. Kühnel R, Rao BR, Stolk JG, van Kessel H, Seldenrijk CA, Willig AP. Estrogen synthesizing rare malignant Brenner tumor of the ovary with the presence of progesterone and androgen receptors in the absence of estrogen receptors. Gynecol Oncol. 1987; 26: 263-9
4. de Lima GR, de Lima OA, Baracat EC, Vasserman J, Burnier M Jr. Virilizing Brenner tumor of the ovary: case report. Obstet Gynecol.1989; 73: 895-8
5. Driss M, Mrad K, Dhouib R, Doghri R, Abbes I, Ben Romdhane K. Ascitic fluid cytology in malignant Brenner tumor: a case report. Acta Cytol. 2010; 54: 598-600
6. Moon WJ, Koh BH, Kim SK et al. Brenner tumor of the ovary: CT and MR findings. J Comput Assist Tomogr. 2000; 24: 72–76
7. Clemet PB, Young RH. Ovarian Surface Epithelial – Stromal Tumors. In: Mills SE, editor. Sternberg's Diagnostic Surgical Pathology. 5th ed. Philadelphia: Lippincott Williams and Wilkins, A Wolters Kluwer business; 2010; 2278–308
8. Seldenrijk CA, Willig AP, Baak JP et al. Malignant Brenner tumor. A histologic, morphometrical, immunohistochemical,and ultrastructural study. Cancer. 1986; 58: 754–760
9. Verleye L, Ottevanger PB, van der Graaf W, Reed NS, Vergote I, Gynaecological Cancer Group(GCG) of European Organisation for Research and Treatment of Cancer (EORTC), et al. EORTC-GCG process quality indicators for ovarian cancer surgery. Eur J Cancer 2009; 45: 517e26
10. Ben Aissia N, Sadfi A, Youssef A et al. Malignant Brenner's tumor particularities and coverage. Tunis Med. 2004; 82: 701–707
11. Gezginç K, Karataylı R, Yazici F, Acar A, Çelik Ç, Çapar M et al. Malignant Brenner tumor of the ovary: analysis of 13 cases. Int J Clin Oncol 2012; 17: 324-9
12. Han JH, Kim DY, Lee SW, Park JY, Kim JH, Kim YM, Kim YT, Nam JH. Intensive systemic chemotherapy is effective against recurrent malignant Brenner tumor of the ovary: An analysis of 10 cases within a single center. Taiwan J Obstet Gynecol. 2015; 54: 178-82

Adress for correspondence: Uzm. Dr. Emine Zeynep Ucar. Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi, Jinekolojik Onkoloji Bölümü, Etlik Caddesi, Posta kodu: 06010, Keçiören / Ankara / TÜRKİYE
e-mail: ezyilmaz@gmail.com
Available at www.actaoncologicaturcica.com

Bilateral breast cancer and stomach metastasis: A Case Report

Bilateral meme kanseri ve mide metastazı: Olgu sunumu

Erdinç Nayır[1], Tolga Köşeci[2], Ali Arıcan[3]

[1]Kahramanmaraş Necip Fazıl Şehir Hastanesi, Tıbbi Onkoloji Kliniği, Kahramanmaraş, Türkiye
[2]Numune Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Kliniği, Adana, Türkiye
[3]Acıbadem Atakent Hastanesi, Tıbbi Onkoloji Kliniği, İstanbul, Türkiye

Dergiye Ulaşma Tarihi: Dergiye Kabul Tarihi: 04/02/2016 DOI: 10.5505/aot.2016.74046

ÖZET

Meme kanseri kadınlarda en sık görülen kanserdir. Tüm meme kanserlerinin %0,5-3'ü bilateral olarak görülmektedir. Meme kanserli hastalar genellikle erken evrede tanı almaktadır, yalnız metastatik dönemde de karşımıza çıkabilmektedir. Metastaz alanları genellikle kemik, akciğer ve karaciğerdir. Gastrointestinal sistemde metastaz nadir görülmekle birlikte sıklıkla kolon, rektum, mide ve özefagusa metastaz yapmaktadır. Kliniğimizde bilateral meme kanseri tanısıyla takip ettiğimiz ve tanı esnasında mide metastazı saptadığımız olguyu sizlere sunmayı amaçladık.

Anahtar Kelimeler: Bilateral meme kanseri, mide metastazı, senkron metastaz

ABSTRACT

Breast cancer is the most commonly seen cancer in women. 0.5-3% of the all breast cancer cases occur bilaterally. Breast cancer is generally diagnosed in early stages, but it can be recognised in metastatic period. Most commonly seen metastasis sites are bone, lung and liver. Although metastasis in gastrointestinal system is rare; it may be seen in colon, rectum, stomach and esophagus. We aimed to present a woman who has the diagnosis of bilateral breast cancer and stomach metastasis at diagnosis.

Keywords: bilateral breast cancer, stomach metastasis, synchron metastasis

Giriş:

Meme kanseri kadınlarda en sık görülen kanserdir(1). Hastalar tanı anında genellikle erken evrededir. Meme kanseri sıklıkla lenf nodu akciğer, plevra ve karaciğere metastaz yapar (2). Gastrointestinal sisteme nadir olarak metastaz yapmakla birlikte sıklıkla kolon, rektum, mide ve özefagusa metastaz yapmaktadır (3). Bilateral meme kanseri görülme oranı %0,5-3 arasındadır. Meme kanserinin mideye metastazı oldukça nadir olarak görülmekte olup bilateral meme kanseri ile eş zamanlı mide metastazı tanısı alan nadir olarak görülen bu olguyu sizlere sunmayı amaçladık.

Olgu:

52 yaşında kadın hastanın rutin sağlık kontrolleri sırasında her iki memesinde kitle saptandı. Meme ultrasonografisinde sol memede yaklaşık 21x14mm, sağ memede yaklaşık 30x17mm boyutunda solid lezyon görüldü. Sol memeden alınan biyopsi sonucu invaziv duktal karsinom, ER %70 pozitif, PR %80 pozitif, cerb-B2 negatif, e-cadherin pozitif tespit edildi. Sağ memeden alınan biyopsi sonucu ise invaziv duktal karsinom, ER %20 pozitif, PR %70 pozitif, cerb-B2 negatif tespit edildi. Hastanın CA15-3 düzeyi 44 U/mL, CEA düzeyi 1.76 ng/mL idi. 1 yıldır dispeptik şikâyetleri olan hastanın kanser evrelemesi için istenilen tomografisinde mide duvarında kalınlaşma

Adress for correspondence: Uzm. Dr. Erdinç Nayır Kahramanmaraş Necip Fazıl Şehir Hastanesi 46050 Kahramanmaraş - Türkiye
e-mail: drerdincnyr@gmail.com
Available at www.actaoncologicaturcica.com

saptandı. Yapılan üst gastrointestinal sistem endoskopisinde mide korpus pilileri hipertrofik, ödemli, dokunmakla frajildi ve nodüler lezyon izlendi. Alınan biyopside atipik hücre grupları görüldü. Meme karsinomu tanısı olması üzerine mide biyopsisinde immünohistokimyasal olarak östrojen, progesteron ve sitokeratin 7'ye bakıldı. Pozitif saptanması üzerine meme kanseri metastazı ile uyumlu olduğu düşünüldü. Kemik sintigrafisi ve SPECT'inde birden çok odakta kemik metastazı ile uyumlu görünüm saptandı. Metastatik bilateral meme kanseri tanısı konulan hastaya ibandronik asit başlandı ve 6 kür doksorubisin - siklofosfamid - dosetaksel kemoterapi rejimi uygulandı. Hastalığın stabil seyretmesi üzerine hormonal tedavi ile devam edilmektedir.

Tartışma:

Meme kanseri kadınlarda en sık olarak görülen kanserdir. Meme kanseri sıklıkla kemik, akciğer, karaciğer metastaz yapmakla birlikte mide, kolon, peritonada yayılım gösterebilir (2). Gastrointestinal sistemde en sık metastaz yaptığı bölgeler kolon, rektum, mide, ileum ve özefagustur (3). Yapılan postmortem çalışmalarında meme kanserinin mideye metastaz oranı %2-18 oranında saptanmıştır (4).Meme kanserinin mideye metastazı genellikle tanı anından yıllar sonra görülmektedir. Sunduğumuz vakamızda ise meme kanseri ile eş zamanlı olarak açığa çıkmıştır. Mide metastazı olan meme kanserli hastalarda genellikle diğer organlarda da metastaz saptanmaktadır (5). Bizim vakamızda da iskelet sisteminde multipl metastatik lezyonlar saptandı.

Mideye metastaz yapmış olan meme kanserli hastaların kliniği primer mide kanseri tanısı almış hastaların kliniği ile benzerdir. Hastalar genellikle epigastrik bölgede şişkinlik, erken doyma, ağrı, kilo kaybı, kusma ve kanama şikâyeti ile başvururlar. Meme kanserinin mideye metastazı genellikle linitis plastika şeklinde olup nadiren de nodüler lezyonlar şeklinde olabilmektedir. İnvaziv lobuler karsinoma bağlı mide metastazın endoskopik bulgusu ülser, erezyon ya da polipoid lezyon olurken; invaziv duktal karsinoma bağlı metastazlarda nodüler lezyon şeklinde görülmektedir (6). Bizim vakamızda ise hastamızın dispeptik yakınmaları mevcuttu ve yapılan endoskopisinde nodüler lezyon saptandı. Meme kanserinin en sık olarak görülen histopatolojik alt tipi invaziv duktal karsinom olup invaziv lobüler karsinom daha nadir olarak görülmektedir. Her iki alt tipinin öncelikle metastaz yaptığı organlar farklılık göstermektedir. İnvaziv duktal karsinom daha çok akciğer, plevra ve kemiğe metastaz yaparken, invaziv lobuler karsinom ise kemik iliği ve peritona metastaz yapma eğilimindedir (7). Literatürde mide metastazı saptanan meme kanserli hastalarda histopatolojik alt tipin daha çok invaziv lobuler karsinom olduğu saptanmıştır. Taa ve arkadaşları 24 mide metastazı olan meme kanserli hastada yaptıkları histopatolojik alt tipi incelemesinde 20 hastada invaziv lobüler karsinom saptarken diğer hastalarda invaziv duktal karsinom olduğu gösterilmiştir (8).Bizim vakamızda ise saptanan histopatolojik alt tipi invaziv duktal karsinomdu.

Mide metastazı tanısını koyabilmek için lezyondan biyopsi alınıp, primer memedeki lezyon ile karşılaştırmalı olarak incelenmesi gerekmektedir. İnvaziv lobuler karsinomuna bağlı mide metastazlarının histopatolojik incelemesinde taşlı yüzük hücre görünümü saptanabilmektedir ve primer mide kanserinden ayırımı zor olabilmektedir. Bu nedenle bu hastalarda immünohistokimyasal boyama yöntemleri kullanılmalıdır. Östrojen ve progesteron reseptör pozitifliği meme kanserini düşündürmekle birlikte mide kanserli hastalarda

Adress for correspondence: Uzm. Dr. Erdinç Nayır Kahramanmaraş Necip Fazıl Şehir Hastanesi 46050 Kahramanmaraş - Türkiye
e-mail: drerdincnyr@gmail.com
Available at www.actaoncologicaturcica.com

da %12-32 oranında östrojen ve progesteron reseptör pozitifliği olabileceği unutulmamalıdır (9). Bu hastalara mutlaka mamoglobulin ve GCDFP-15 bakılmalıdır. Eğer bu iki marker pozitif ise midedeki lezyonun meme kanseri metastazından kaynaklandığı gösterilmiş olur (10).

Meme kanseri tanısı almış bir kişide kontrolateral meme kanser açığa çıkma oranı %0.5 ile 3 arasında değişim göstermektedir. Primer lezyon ile eş zamanlı olarak açığa çıkarsa senkron eğer farklı bir zaman diliminde diğer memede kanser saptanırsa metakron olarak adlandırılır. Bizim vakamızda ise senkron bilateral meme kanseri mevcuttu (11). Bilateral meme kanseri olan hastalarda mide metastazı literatürde olgu sunumu şeklinde bulunmakta olup bu vakalarda mide metastazı hastalığın seyri esnasında açığa çıkmıştır. Bizim vakamızda ise mide metastazı, primer meme kanseri tanısıyla aynı dönemde tespit edilmiştir.

Bu hastaların tedavisinde sistemik kemoterapi ve hormon reseptör durumuna göre endokrin tedavi verilmesi önerilmektedir. Mide metastazına cerrahi müdahale yapılmasının sağkalıma katkısının olmadığı gösterilmiş olup sadece palyatif tedavi amacıyla cerrahi müdahale önerilmektedir. Mide metastazı olan meme kanserli hastalarda ortalama sağkalım yaklaşık olarak 2 yıldır (6).

Sonuç olarak; meme kanseri tanısı alan hastalarda dispeptik yakınmalar eşlik ediyorsa mutlaka metastaz açısından değerlendirilmesi gerekmektedir. Mideden alınan biyopsi ile memedeki lezyondan alınan biyopsi mutlaka birlikte değerlendirilmelidir. Bu hastaların tedavisinde sistemik kemoterapi tedavisi önerilmektedir. Mide metastazı olan bilateral meme kanserli vaka sayısı literatürde birkaç olgu sunumu şeklinde bulunmakta olup bu vakalarda mide metastazı hastalığın takibi esnasında saptanmıştır. Bizim vakamız ise bilateral meme kanseri ile eş zamanlı mide metastazı olması açısından literatürde ilk vaka olarak yerini almaktadır.

Çıkar Çatışması: Yok

Referanslar:

1. Sakamoto G, Noguchi M, Inaji H, Hiraoka M, Kurosumi M, Itou Y. Disease of the breast. 1st ed. Tokyo: Kaneharasyuppann; 2006. p. 22–4.
2. Winston CB, Hadar O, Teitcher JB et al. Metastatic lobular carcinoma of the breast:Patterns of spread in the chest, abdomen and pelvis on CT.Am J Roentgenol2000; 175:795-800
3. Borst MJ, Ingold JA. Metastaticpatterns of invasive lobular versus invasive ductal carcinoma of the breast. Surgery. 1993; 114:637–41
4. Cormier WJ, Gaffey TA, Wech JM, Wech JS, Edmonson JH. Linitis plastica caused by metastatic lobular carcinoma of the breast. Mayo ClinProc1980;55:747-753
5. McLemore EC, Pockaj BA, Reynolds C et al. Breast cancer: presentation and intervention in women with gastrointestinal metastasis and carcinomatosis. AnnSurgOncol. 2005;12:886–94
6. Taal BG, Peterse H, Boot H. Clinical presentation, endoscopic features, and treatment of gastric metastases from breast carcinoma. Cancer2000;89:2214-21
7. Jain S, Fisher C, Smith P, Millis RR and Rubens RD. Patterns of metastatic breast cancer in relation to histological type. Eur J Cancer1993;29:2155-57
8. Hoff J, Portet R, Becue J, Fourtanier G, Bugat R. Digestive tract metastases of breast cancers. AnnChir1983;37:281-4
9. Raju U, Ma CK, Shaw A. Signet ring variant of lobular carcinoma of the breast: a clinicopathologic and immunohistochemical study. ModPathol. 1993;6:516–20.
10. Takeda Y, Tsuta K, Shibuki Y et al. Analysis of expression patterns of breas tcancer-specificmarkers (mammaglobin and gross cystic disease fluid protein15) in lung and pleural tumors. ArchPatholLabMed. 2008;132:239–43.
11. Banelli B, Casciano I, Di Vinci A. et al. Pathologica land molecular characteristics distinguishing contralateral metastatic from new primary breast cancer. Ann. Oncol. 2010;21:1237–42

Adress for correspondence: Uzm. Dr. Erdinç Nayır Kahramanmaraş Necip Fazıl Şehir Hastanesi 46050 Kahramanmaraş - Türkiye
e-mail: drerdincnyr@gmail.com
Available at www.actaoncologicaturcica.com

A Rare Cause of Acute Abdomen: Duodenal Perforation of Gastrointestinal Stromal Tumors

Nadir Bir Akut Batın Nedeni: Duodenal Gastrointestinal Stromal Tümör Perforasyonu

Yasemin Cihan[1], Talha Sarigöz[2], Tamer Ertan[2], Ömer Topuz[2], Yusuf Sevim[2]

[1]Kayseri Eğitim Ve Araştırma Hastanesi, Radyasyon Onkoloji Bölümü, Türkiye
[2]Kayseri Eğitim Ve Araştırma Hastanesi, Genel Cerrahi Anabilim Dalı, Türkiye

Dergiye Ulaşma Tarihi: 19.9.2015 Dergiye Kabul Tarihi: 24.8.2016 Doi: 10.5505/aot.2016.03511

Dear Editor,

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract (1). They grow from the interstitial cells of Cajal which are located in the submucosal and myentric plexus (2). They may occur from lower esophagus to anus but a great majority (50–70%) is seen in the stomach followed by small intestines (33%). Duodenal origin makes 6-21% of small intestinal GIST and mostly second portion is involved (3,4). In this letter, we want to evaluate diagnosis and surgical treatment of duodenal GIST in emergency setting by presenting a rare case.

A 42 year-old male patient admitted to emergency department with history of acute abdominal pain of one day's duration. On abdominal examination, it was tender generally and right upper quadrant rebound tenderness was present.

Computed tomography scan with intravenous contrast was performed. In the axial tomography images, there were a hypodense 9x5 cm tumoral mass with intratumoral gas and fluid densities, perihepatic free gas, heterogeneous increase in mesenteric fat, mesenteric lymph nodes and pelvic free fluid. After the initial investigation, diagnosis of duodenal mass perforation was made and patient went to urgent surgery.

Surgery consisted of diagnostic laparotomy and it revealed perforated hemoragic 10x8 cm mass originated from the second portion of the duedonum. Whipple procedure was performed.

On literature review, most data on duodenal GIST are either from single case reports or from a few small series and most of them treated with elective surgery. But also

Adress for correspondence: Yasemin Cihan, Kayseri Eğitim Ve Araştırma Hastanesi, Radyasyon Onkoloji Bölümü, Türkiye
e-mail:cihany@erciyes.edu.tr
Available at www.actaoncologicaturcica.com

they may require urgent intervention. Although they are usually asymptomatic, while the tumor enlarges, it causes variable symptomatology like gastrointestinal bleeding which may be chronic and mild or sudden and massive (5). The next most common presentations are abdominal discomfort, pain and swelling. Gastroscopy is a useful procedure for duodenal GIST diagnosis. During upper gastrointestinal endoscopy if the tumor is smaller than 2 cm and heavily accompanied with blood clots, it is difficult to dissociate hemobilia, ampulla or duodenal ulcer from GIST (6). For these reasons, a complete examination should be conducted during upper gastrointestinal bleeding to prevent misdiagnosis.

Either elective or urgent, the treatment of choice for duodenal GIST is complete surgical excision. This can be performed by local or segmental duodenal resection with preservation of the pancreas for small tumors. For big tumors, a pancreatico-duodenectomy (Whipple procedure) is required (7). No lymph node dissection is required since they are very unlikely to be involved (8). Yet, the optimal surgical treatment for duodenal GIST has never been fully assessed. With the implementation of tyrosine kinase inhibitors as an adjuvant therapy, better quality of life and overall-survival have been reported (9).

Conflict of interest: None

References

1. Joensuu H, Fletcher C, Dimitrijevic S, Silberman S, Roberts P, Demetri G. Management of malignant gastrointestinal stromal tumours. Lancet Oncol. 2002 30;3:655-64
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors–definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Archiv. 2001;438:1-2
3. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg. 2000;231:51
4. Winfield RD, Hochwald SN, Vogel SB, Hemming AW, Liu C, Cance WG, et al. Presentation and management of gastrointestinal stromal tumors of the duodenum. Am Surg. 2006;72:719-23
5. Roberts PJ, Eisenberg B. Clinical presentation of gastrointestinal stromal tumors and treatment of operable disease. Eur J Cancer, 2002;38:Suppl5:pS37-8
6. Lin C, Chang Y, Zhang Y, Zuo Y, Ren S. Small duodenal gastrointestinal stromal tumor presenting with acute bleeding misdiagnosed as hemobilia: Two case reports. Oncol Lett. 2012;4:1069-71
7. Chung JC, Kim HC, Hur SM. Limited resections for duodenal gastrointestinal stromal tumors and their oncologic outcomes. Surgery today. 2015;10:1-7
8. Connolly EM, Gaffney E, Reynolds JV. Gastrointestinal stromal tumours. Br J Surg, 2003; 90:1178-86
9. DeMatteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373:1097-104

Adress for correspondence: Yasemin Cihan, Kayseri Eğitim Ve Araştırma Hastanesi, Radyasyon Onkoloji Bölümü, Türkiye
e-mail:cihany@erciyes.edu.tr
Available at www.actaoncologicaturcica.com

Serum Tumor Marker Levels in Rheumatoid Arthritis

Romatoid Artritli Hastalarda Serum Tümör Belirteçleri Düzeyleri

Selcuk Şeber[1], Dilek Solmaz[2], Tarkan Yetişyiğit[1]

[1]Namik Kemal University Hospital, Medical Oncology Clinic, Tekirdag, Turkey
[2]Namik Kemal University Hospital, Rheumatology Clinic, Tekirdag, Turkey

DergiyeUlaşma Tarihi: 11/08/2016 Dergiye Kabul Tarihi: 29/11/2016 Doi: 10.5505/aot.2016.26234

ÖZET

Giriş ve Amaç: Romatoid Artrit (RA) eklemleri etkileyen ve görece sık rastlanılan inflamatuar bir hastalıktır. Bu çalışmada RA tanılı hastalarda serum tümör belirteçleri olan karsinoembriyonik antijeni (CEA) ,CA 125, CA 19.9 ve CA15.3 düzeylerinin belirlenmesi amaçlanmıştır

Yöntem: Bir üniversite hastanesinin romatoloji kliniğinde RA tanısı ile takip edilmekte olan toplam 148 hasta çalışma grubuna ve osteoartrit tanılı 36 hasta ise kontrol grubuna dâhil edilmiştir. Çalışmaya katılan bireylerden alınan kan örneklerinden romatoid faktör (RF), eritrosit sedimantasyon hızı (ESR), anti siklik sitrilünepeptid (anti CCP) ve serum tümör belirteçleri olan CEA,CA19.9,CA 125 ve CA 15.3 düzeyleri ölçülmüştür. Hastalık aktivite skoru çalışmaya dâhil edilme sırasında ilgili romatoloji uzmanı tarafından değerlendirilmiştir.

Bulgular: Serum CEA,CA19.9,CA 125 ve CA15.3 düzeyleri RA tanılı hastalarda kontrollere göre anlamlı olarak daha yüksek saptanmıştır. Hem aktif hem de inaktif hasta grubunda tümör belirteç düzeyleri kontrol grubuna göre anlamlı olarak yüksek ölçülmüştür ancak tümör belirteçleri ile hastalık aktivite skoru arasında bir korelasyon saptanamamıştır. Tümör belirteçleri arasında yalnızca CEA ile RF arasında bir korelasyon saptanmıştır(r 0.165, p >0.049).

Tartışma ve Sonuç: Serum tümör belirteçleri RA tanılı hastalarda sıklıkla yüksek seviyelerde saptanabilir. Hastaların takibinden sorumlu olan hekimlerin bu durumdan haberdar olmaları, bu hasta grubunda malignite varlığı araştırma amacı ile yapılabilecek olan gereksiz işlemlerin önüne geçilmesine yardımcı olacaktır.

Anahtar kelimeler: Tümör belirteçleri, Romatoid Artrit, İnflamasyon

ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a relatively common inflammatory disease generally affecting the joints. This study aimed to assess the levels of various serum tumors markers; carcinoembryonic antigen (CEA), CA 125, CA 19.9 and CA15.3 in patients with a known diagnosis of RA.

Methods: A total of 148 patients who were being followed in the rheumatology clinic of a tertiary academic center with a diagnosis of RA and 36 controls were included in the study group. Measurement of rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), anti CCP and serum tumor markers including CEA, CA 19.9, CA 125, CA 15.3 were made from the blood samples obtained from the participants. Disease activity score at the time of study entry was also evaluated by the attending rheumatologist.

Results: Serum levels of CEA, CA19.9, CA 125 and CA 15.3 were found to be significantly higher in RA patients compared to controls. This difference was statistically significant in both patient groups with active and inactive disease compared to the control group. However a correlation between tumor markers and disease activity score was not found. Among tumor markers only serum CEA levels were found to be associated with RF levels (r 0.165, p >0.049)

Discussion and Conclusion: Serum tumor markers are frequently elevated in patients with RA and caring physicians should be aware of this phenomenon to avoid the use of unnecessary evaluative procedures for searching presence of malignancy in these group of patients.

Key words: Tumor markers, Rheumatoid Arthritis, Inflammation

Adressforcorrespondence: SelcukSeber, Namik Kemal University Hospital Medical Oncology Department, Tekirdag, Suleymanpasa, Turkey 59000
e-mail:esseber@nku.edu.tr
Available at www.actaoncologicaturcica.com

Introduction

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis affecting nearly %1 of the population. Chronic inflammation affecting synovial tissue is a major causes of disability in the adult population. Although the exact etiology behind RA is still obscure, RA associated antibody formation against RA related antigens is thought to be the primary initiating factor for development of overt clinical RA. In genetically susceptible individuals, autoantibody formation is followed by chronic immune system activation(1).

Through this chronic overstimulation of immune system production of several proinflammatory cytokines such as tumor necrosis factor alpha and interleukin one alpha are increased. These cytokines in return induce upregulation of cellular adhesion molecules such as intercellular adhesion molecule (ICAM) within synovial stroma and result in structural changes in the joints(2).

Presence of circulating antibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated antibody (anti CCP) are commonly present in high titer in the serum of RA patients and their presence along with elevated levels of inflammatory markers such as erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) play a role in the diagnosis and evaluation of disease activity(3).

On the other hand tumor markers are monoclonal antibodies directed to soluble glycoproteins that are produced by tumor cells in various types of cancer. Their serum levels are used as an adjunct for evaluation of diagnosis and treatment response in several malignant diseases (4).

CA 125 and CA 15.3 are transmembrane mucin glycoproteins and their cell surface expression is found in epitheal cells, digestive and respiratory tracts. CA 125 is encoded by the MUC16 musin gene and was initially thought to be overexpressed exclusively in ovarian cancer cells. However recent studies have identified that high CA125 serum levels can be found in several other types of cancer(5). CA 15.3 is the antigen product of the MUC1 gene and is generally used as a tumor marker for breast cancer. However, CA 15-3/MUC 1 overexpression is found in several other cancer types as well(6).

CA 19.9 is another mucin glycoprotein with a carbohydrate like structure which is called as sialy Lewis A (a member of the Lewis type blood group antigens). CA 19.9 antigen is commonly overexpressed in pancreatic cancer cells however it is not specific to pancreas cancer. Like other antigens high serum levels can be found in various other cancer types and inflammatory conditions such as hepatitis(7).

Carcinoembryonic antigen (CEA) is an oncofetal antigen which is normally expressed in fetal digestive tract. It plays an important role cell adhesion process. However, its abnormal expression is found in cancers of the colon, stomach, breast and lung as well as its serum level is elevated in inflammatory conditions such as cigarette smoking(8).

In this study we aimed to evaluate serum CA 15.3, CA 19.9, CA 125 and CEA levels in patients diagnosed with RA and their association with disease activity and acute phase reactants.

Methods

148 consecutive RA patients who were being followed in a tertiary academic centers' rheumatology clinic were included in the study group. RA diagnosis was made according to 1987 American College of Rheumatology Criteria(9). All of the patients were receiving active treatment for RA. Control group consisted of volunteers who were recruited from patients followed in the same clinic with diagnosis of osteoarthritis or other non-inflammatory joint disorders. Patients who have a history of malignancy were excluded from the study group. Written informal consent was taken from all of the study participants and the procedures were performed in accordance with the guidelines of the Helsinki Declaration. In all of the patients, acute phase reactants (ESR and CRP) and serum tumor markers (CA15-3, CA19-9, CA 125, CEA) were evaluated from the blood samples taken from the participants. Rheumatoid factor (RF) and anti-Anti- Cyclic Citrullinated Peptide levels were also recorded if available.

Serum levels of CA15-3, CA 19-9, CA 125 and CEA were evaluated with electrochemiluminescence method (Hitachi E170 automated analyzer, Roche, Basel, Switzerland). ESR was determined by

Adressforcorrespondence: SelcukSeber, Namik Kemal University Hospital Medical Oncology Department, Tekirdag, Suleymanpasa, Turkey 59000
e-mail:esseber@nku.edu.tr
Available at www.actaoncologicaturcica.com

Westergen method while CRP was measured with nephelometry (Behring 100, Behring, Germany). Anti CCP IgG autoantibodies were detected with ELISA method (Euroimmun, Germany). Disease activity score was measured with Disease Activity Score 28 - erythrocyte sedimentation rate (DAS28-ESR) criteria.

Statistical Analysis: All data were analyzed with SPSS Statistics 16.0 for Windows. Normality distribution of variables were assessed by Kolmogorov –Smirnov test. Variables with a continuous distribution were analyzed with the "t" test while analysis for nominal variables were done by using Mann-Whitney U test. Distributions of continuous variables were shown as mean and standard deviation. Categorical variables were recorded as percentages Ki square test was used for their analysis. Correlations between variables were evaluated with Spearman test. Results were considered statistically significant, when the obtained P-value was <0.05. Institutional Ethical Committee approval was obtained for this study.

Results:

148 RA patients and 36 controls were included in the study group. Distribution of the demographic variables between the two groups was statistically similar (Table 1). RF was found positive in %56.7 and anti CCP antibody levels were found positive in %60.6 of the patient group. The median duration of symptoms in RA patients were 6.8 ±6.9 years. Tumor marker levels and levels of acute phase reactants were significantly higher in the patient group compared to controls (Table 2). %50 of the patient group was categorized as having active disease according to DAS 28 ESR criteria. Levels of serum tumor markers was not statistically different between RA patients with active (DAS 28 ESR ≤2.6) and inactive (DAS 28>2.6) disease (Table 3). Among serum tumor markers CA 15-3, CA 19-9 and CEA had a positive correlation with increasing age while CEA levels were found to be correlated with smoking and serum RF levels. However, no significant correlation was found between tumor marker levels and CRP level and DAS 28 – ESR activity scores.

Table 1: Demographical variables of RA and control group

	RA (n: 148)	Control (n:36)	p
Age, means	52±11.7	50±11.5	>0.05
Gender, F/M	128/29	30/6	>0.05
Years of education, means	7±3.8	6±4.2	>0.05
Smoking history, n; %	58;37.4	14;38.8	>0.05

Abb: RA rheumatoid arthritis, F female, M male

Table 2: Serum Acute phase reactant and tumor marker levels in RA control groups

	RA (n: 148)	Control (n:36)	p
ESR, means	23±18.6	16±11.0	0.036
CRP, mean ±SD	8.2±10.8	3.9±4.1	0.005
CA 125, mean ±SD	23.1±47.3	12.5±4.6	0.029
CA 15-3, mean ±SD	20.8±11.4	15.4±.9	0.005
CA 19-9, mean ±SD	15.8±23.4	10.7±8.0	0.043
CEA, mean ±SD	4.0±17.8	1.7±1.8	0.002

Abb: SD standard deviation, RA rheumatoid arthritis, CRP C reactive protein

Table 3: Tumor marker levels in patients with active and inactive disease

	İnactive disease (n:76)	Active disease (n: 72)	p
CA 125, mean±SD	17.8±15.6	29.3±67.8	>0.05
CA 15-3, mean ±SD	20.9±12.9	20.9±9.6	>0.05
CA 19-9, mean ±SD	10.8±30.6	10.9±11.1	>0.05
CEA, mean ±SD	2.1±1.5	5.6±24.4	>0.05

Abb: SD standard deviation

Adressforcorrespondence: SelcukSeber, Namik Kemal University Hospital Medical Oncology Department, Tekirdag, Suleymanpasa, Turkey 59000
e-mail:esseber@nku.edu.tr
Available at www.actaoncologicaturcica.com

Table 4: The correlations between serum tumor marker levels with disease activity, RF, CRP, age and smoking history

		age	Smoking history	CRP	RF	DAS28 ESR
CA 125	r	-.014	0.057	-.050	0.085	0.093
	p	0.869	0.498	0.548	0.318	0.273
CA 15-3	r	0.203	-.076	-.082	0.013	0.080
	p	0.016	0.363	0.322	0.873	0.337
CA 19-9	r	0.346	-.075	0.066	0.033	0.134
	p	<0.001	0.367	0.424	0.696	0.109
CEA	r	0.299	0.247	-.019	0.165	-.052
	p	<0.001	0.003	0.815	0.049	0.533

Abb: CRP C reactive protein, RF rheumatoid factor, DAS28 ESR Disease Activity Score 28 Erytocyte Sedimentation Rate

Conclusion

Theoretically production of various serum tumor markers is closely associated with inflammation besides the presence of cancer producing cells. In this study we aimed to investigate whether serum tumor markers are elevated in presence of RA which is itself an inflammatory condition and also evaluate whether their levels are associated with disease activity and other commonly used markers of systemic inflammation.

Carcinoembryonic antigen (CEA), an oncofetal protein normally expressed in mucosal tissues, is over expressed in tumoral tissue and therefore regarded as a marker of malignancy. High levels have been documented to be present in a wide array of different cancer types such as colonic, gastric, breast and lung cancers. However high CEA levels has also been associated with the presence of inflammatory conditions. Studies have shown that cigarette smoking can induce increased production of CEA expression at the cellular level in normal (non-cancerous) lung parenchyma. It was also suggested that in smokers high CEA levels were closely associated with high neutrophil levels which is a sign of presence of inflammation(10).

Therefore, we can hypothesize that increased CEA levels in patients with RA is a reflection of proinflammatuary state. In our findings, CEA levels have been found to be correlated with smoking history and serum RF levels however a correlation between disease activity score and CEA was not present. This finding is in accordance with another study also evaluating the level of serum tumor markers in RA patients in which disease activity was measured by DAS28 however in two other studies which also reported elevated CEA levels in RA patients, a correlation between RF and CEA levels were not found(11–13).

Of interest there are a few studies in the literature that suggest CEA itself by binding to monocytes can trigger increased secretion of proinflammatuary cytokines such as tumor necrosis factor alfa, interleukin 1 beta and interleukin 6. These cytokines have a pivotal role in the pathogenesis of RA (14,15).

Similarly, CA 125, a glycoprotein normally expressed in coelomic epithelium during fetal development, is overexpressed in ovarian cancer as well as many other benign or malign conditions which are associated with fluid collection in peritoneum such as peritoneal metastatic disease, cirrhosis or congestive heart failure or endometriosis. CA-125 is a glycoprotein which is also known as MUC16. It is expressed on the cell surface and is responsible for cell adhesion to neighboring tissues(16).

Although CA-125 expression is not present in the affected tissues by rheumatoid arthritis; it has been postulated that CA 125 secretion from the mesothelium can increase by stimulation of mesothelial cells by cytokines such as IL 1 alpha and TNF alpha(17).CA 125 levels in RA patients in comparison to normal controls has been previously evaluated by Berfamashi et al. and Szekanecz et al. While Berfamaschi et al. reported CA 125

Adressforcorrespondence: SelcukSeber, Namik Kemal University Hospital Medical Oncology Department, Tekirdag, Suleymanpasa, Turkey 59000
e-mail:esseber@nku.edu.tr
Available at www.actaoncologicaturcica.com

levels were not significantly elevated in RA patients compared to controls, Szekanecz et al. found that CA125 levels were significantly elevated in the patient group. In our study group CA 125 levels were found to be significantly higher in RA patients (11,12).

Carbohydrate antigen 19-9 (CA 19-9) is a tumor associated oligosaccharide oncofetal antigen which is closely related to the sialylated Lewis blood group antigen (sLea). High serum levels are commonly associated with pancreatic cancer or cholangiocarcinoma as well as many other cancer types (7). sLea plays a pivotal role in adhesion of leukocytes to the inflamed joint by acting as a ligand for various cell adhesion molecules. This process is a key event in the pathogenesis of RA. Studies have suggested that sLea and cell adhesion molecule expressions may be upregulated by the same pathway in the presence of pro inflammatory cytokines in patients with inflammatory arthritis (18).

Cancer antigen 15-3 (CA 15-3) is produced by the MUC-1 gene.MUC1 gene expression is widely expressed throughout the epithelial lining and responsible for maintaining integrity of the epithelial track.MUC1 gene is not normally expressed in the connective tissue however it has been shown that MUC1 gene expression is upregulated in response to proinflammatory cytokines such as s IL-1β, IL-6, TNF-α, and IFN-γ which are all found to be increased in patients with RA (19,20).

The common denominator between CEA, CA 19-9, CA125 and CA 15-3 is that they are all glycoprotein antigens and have pivotal roles in intercellular adhesion and in cellular migration. It is hypothesized that overexpression of these adhesive antigens in cancer may play roles in increased tumorigenicity and undifferentiation of cancer cells. It is also possible that in the presence of inflammatory conditions such as RA , a common upregulatory process could result in overexpression of these adhesive antigens and increase synovial intercellular adhesion in the affected joints (21–23).

The relatively small sample size of patients with active disease in the study group may have prevented us from observing the correlation between the disease activity score and tumor marker serum levels. Although cancerous disease was not diagnosed in any of the subjects during the study period; it is possible that with a sufficiently longer follow up duration developing malignancies in some of the subjects with high tumor markers could have been detected. These limitations should be taken into account when interpreting the results of this study.

In conclusion, the levels of serum tumor markers, CEA, CA 19-9, CA125 and CA 15-3 are frequently increased in patients with RA. Their levels can be elevated even in well controlled disease. Only CEA levels were found to be positively correlated with RF levels. Elevated tumor markers in RA patients can solely be a marker of inflammation and not necessarily indicate presence of cancer.

Conflict of Interest: None

REFERENCES

1. Gerlag DM, Norris JM, Tak PP. RA: from risk factors and pathogenesis to prevention: Towards prevention of autoantibody-positive rheumatoid arthritis: from lifestyle modification to preventive treatment. Rheumatology (Oxford) [Internet]. 2015;kev347.
2. Siebert S, Tsoukas A, Robertson J, Mcinnes I. Cytokines as Therapeutic Targets in Rheumatoid Arthritis and Other Inflammatory Diseases. Pharmacol Rev. 2015;67(April):280–309
3. Shen R , Ren X, Jing R, Shen X, Chen J, Ju S YC. Rheumatoid Factor, Anti-Cyclic Citrullinated Peptide Antibody, C-Reactive Protein, and Erythrocyte Sedimentation Rate for the Clinical Diagnosis of Rheumatoid Arthritis. Lab Med. 2015;46(3):226–9
4. Perkins GL, Slater ED, Sanders GK, Prichard JG. Serum tumor markers. Am Fam Physician. 2003;68(6):1075–82
5. Streppel MM, Vincent A, Mukherjee R, Campbell NR, Chen SH, Konstantopoulos K, et al. Mucin 16 (cancer antigen 125) expression in human tissues and cell lines and correlation with clinical outcome in adenocarcinomas of the pancreas, esophagus, stomach, and colon. Hum Pathol. 2012;43(10):1755–63
6. Kufe DW. MUC1-C Oncoprotein as a Target in Breast Cancer; Activation of Signaling Pathways and Therapeutic Approaches. Oncogene. 2013;32(9):1073–81
7. Yue T, Maupin KA, Fallon B, Li L, Partyka K, Anderson MA, et al. Enhanced discrimination of malignant from benign pancreatic disease by measuring the CA 19-9 antigen on specific protein carriers. PLoS One. 2011;6(12)
8. Ballesta AM, Molina R, Filella X, Jo J GN. Carcinoembryonic antigen in staging and follow-up of patients with solid tumors. Tumour Biol. 1995;16(1):36–41
9. Arnett FC, Edworthy SM, Bloch D a, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the

Adressforcorrespondence: SelcukSeber, Namik Kemal University Hospital Medical Oncology Department, Tekirdag, Suleymanpasa, Turkey 59000
e-mail:esseber@nku.edu.tr
Available at www.actaoncologicaturcica.com

classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315–24
10. Kashiwabara K, Nakamura H, Kiguchi T, Yagyu H, Kishi K MK. Carcinoembryonic antigen and neutrophils in healthy smokers. Nihon Kyobu Shikkan Gakkai Zasshi. 1997;35(2):154–9
11. Strange A, Capon F, Spencer CC, Knight J, Weale ME, Allen MH, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet [Internet]. 2010/10/19 ed. 2010;42(11):985–90
12. Szekanecz E, Sandor Z, Antal-Szalmas P, Soos L, Lakos G, Besenyei T, et al. Increased production of the soluble tumor-associated antigens CA19-9, CA125, and CA15-3 in rheumatoid arthritis: Potential adhesion molecules in synovial inflammation? In: Annals of the New York Academy of Sciences. 2007. p. 359–71
13. Unger A, Panayi GS LM. Carcinoembryonic antigen in rheumatoid arthritis. Lancet. 1974;1:791–3
14. Ganguly A, Yeltsin E, Robbins J. Identification of a carcinoembryonic antigen binding protein on monocytes. In: Biochemical and Biophysical Research Communications. 2003. p. 319–23
15. Aarons CB, Bajenova O, Andrews C, Heydrick S, Bushell KN, Reed KL, et al. Carcinoembryonic antigen-stimulated THP-1 macrophages activate endothelial cells and increase cell-cell adhesion of colorectal cancer cells. Clin Exp Metastasis. 2007;24(3):201–9
16. Rump A, Morikawa Y, Tanaka M, Minami S, Umesaki N, Takeuchi M MA. Binding of ovarian cancer antigen CA125/MUC16 to mesothelin mediates cell adhesion. J Biol Chem. 2004;279(10):9190–8
17. Zeillemaker a M, Verbrugh H a, Hoynck van Papendrecht a a, Leguit P. CA 125 secretion by peritoneal mesothelial cells. J Clin Pathol. 1994;47(3):263–5
18. Fabris C, Falleti E, Pirisi M, Soardo G, Toniutto P, Vitulli D, Bortolotti N, Gonano F BE. Non-specific increase of serum carbohydrate antigen 19-9 in patients with liver disease associated with increased circulating levels of adhesion molecules. Clin Chim Acta. 1995;243(1):25–33
19. Li X, Wang L, Nunes DP, Troxler RF, Offner GD. Pro-inflammatory cytokines up-regulate MUC1 gene expression in oral epithelial cells. J Dent Res [Internet]. 2003;82(11):883–7
20. Celeste S, Santaniello A, Caronni M, Franchi J, Severino A, Scorza R, et al. Carbohydrate antigen 15.3 as a serum biomarker of interstitial lung disease in systemic sclerosis patients. Eur J Intern Med. 2013;24(7):671–6
21. Dettke M, Pálfi G, Pursch E, Fischer MB, Loibner H. Increased expression of the blood group-related Lewis Y antigen on synovial fluid granulocytes of patients with arthritic joint diseases. Rheumatology (Oxford) [Internet]. 2001;40(9):1033–7
22. Koch AE, Burrows JC, Haines GK, Carlos TM, Harlan JM LS. Immunolocalization of endothelial and leukocyte adhesion molecules in human rheumatoid and osteoarthritic synovial tissues. Lab Invest. 1991;64(3):313–20
23. Ilantzis C, Demarte L, Screaton RA, Stanners CP. Deregulated Expression of the Human Tumor Marker CEA and CEA Family Member CEACAM6 Disrupts Tissue Architecture and Blocks Colonocyte Differentiatio. Neoplasia. 2002;4(2):151–63

Adressforcorrespondence: SelcukSeber, Namik Kemal University Hospital Medical Oncology Department, Tekirdag, Suleymanpasa, Turkey 59000
e-mail:esseber@nku.edu.tr
Available at www.actaoncologicaturcica.com

Diabetic Mastopathy and Breast Cancer in Type-2 Diabetes Mellitus Patient: A Case Report

Tip 2 Diyabetli Hastada Diyabetik Mastopati ve Meme Kanseri: Olgu Sunumu

Onur Can Güler[1], Melda Bulut[2], Cihangir Özaslan[1], Yavuz Selim Kahraman[1]

[1]Department of Surgery, Ankara Oncology Training and Research Hospital, Ankara, Turkey
[2]Department of Pathology, Ankara Oncology Training and Research Hospital, Ankara, Turkey

Dergiye Ulaşma Tarihi: 16/01/2016 Dergiye Kabul Tarihi 15/02/2016: Doi: 10.5505/aot.2016.09719

ÖZET

Diyabetik mastopati; lenfositik lobulit, duktit ve stromal fibrozisli perivaskülit tablosuyla karakterize nadir görülen bir fibroinflamatuar meme hastalığıdır. Bu meme lezyonu uzun süreli tip 1 diyabet ve diğer otoimmün hastalıkları olanlarda, genellikle unilateral veya bilateral palpe edilebilir. Memede kitle ile başvuran ve kliniği malign olan diyabetik mastopatili hastayı raporluyoruz. Bu tip 2 diyabetli hastamız 74 yaşındadır. Mamografisi ve ultrasonografisi malignite şüphesi uyandırdığından bu hastaya tel yardımıyla eksizyonel biyopsi uygulandı. Biyopsi sonucu invaziv karsinom olarak raporlandı. Bu biyopsi sonucuyla yapılan operasyon sonrası patoloji raporunda ise yoğun keloid benzeri stromal fibrozisin eşlik ettiği lenfoid değişimlerin diyabetik mastopati ile uyumlu olduğu bildirildi.

Anahtar kelimeler: diyabetik mastopati, memede kitle, lenfositik lobulit

ABSTRACT

Diabetic mastopathy is a rare inflammatory breast disease demonstrated with ductitis, lymphocytic lobulitis and perivasculitis with stromal fibrosis. This lesion often presents as a discretely palpable uni- or bilateral mass in traditional type I diabetes and other autoimmune diseases. We report a case of diabetic mastopathy, which presented clinically as an indeterminate breast lump suspicious for malignancy. The patient is a 74-year-old woman who had type 2 diabetes mellitus. Mammography and ultrasonography raised a suspicion of malignancy, and a wire-guided excisional biopsy was performed. The biopsy was reported as invasive carcinoma. Histopathological examination now showed dense keloid-like stromal fibrosis with lymphoid features consistent with diabetic mastopathy.

Key words: diabetic mastopathy, breast mass, lymphocytic lobulitis

Introduction

Diabetic mastopathy (DMP) is a collection of clinical, radiological and histological features found in dense fibrous masses of the breast initially described by Soler and Khardori (1). The disease is associated with long-standing traditional type 1 insulin-dependent diabetes mellitus (IDDM) but has been reported in other autoimmune disorders or rarely in type2 diabetes mellitus like in our patient. These patients present with a palpable hard, painless, irregular solitary mass in one breast or both. As inconclusive clinical and imaging findings, these lesions are often evaluated as breast carcinomas. A carefully examination of this disease is essential to avoid unnecessary surgical biopsies.

Case Presentation

The patient described is a 74-year-old female, who presented with a lump in her left breast of 2 months duration. There was no associated pain; she noticed the lump incidentally. She has been treated for type 2 diabetes for the last ten years with oral antidiabetic agent and had no secondary complication of diabetes; also, there was no history of autoimmune diseases,

The examination showed a hard palpable, relatively immobile, painless mass whose location appeared to be deep in the breast tissue. The mass was located 4cm lateral

Adress for correspondence: Dr.Onur Can Güler, Department of Surgery, Ankara Oncology Training and Research Hospital, Yenimahalle, Ankara, Turkey
e-mail:onurcguler@gmail.com
Available at www.actaoncologicaturcica.com

to the areolar region at 3 o'clock direction of the left breast. Axillary lymph nodes were not palpable, and there was no history of nipple discharge. The right breast examination was normal.

Mammography revealed increased fibro glandular densities in both breasts (type-2) with dense mass in the outer quadrant of the left breast. It was thought to be an intramammarian lymph node. There were no micro calcifications detected. Hypoechoic mass which was 4,5cm in size, in 3 o'clock direction at the lateral merge of the areolar region of left breast was detected at the location of the focus of micro calcification defined on ultrasonography. According to The Breast Imaging Reporting and Data System (BIRADS) categorization, the lesion was an indeterminate breast lump, and hence, the clinical impression was suspicious for breast carcinoma. Magnetic resonance imaging (MRI) revealed that a 7mm sized lesion near the anterior axillary line and it was 12cm away from the nipple, oval shaped and well demarcated, contrasted with type 2-3 pattern. MRI reported this lesion as the intramammarian lymph node described in mammography.

A wire-guided excisional biopsy was performed. Gross pathology of the excised specimen was a whitish irregular breast tissue. There was no visible mass lesion in the specimen. In microscopic examination, in an area of 2 mm in size, a tumor with tubule-like structures, hyperchromatic nuclei and eosinophilic cytoplasm represented the characteristic appearance of an invasive carcinoma(Figure-1). Because of the fractionation of the materials, surgical margins couldn't be detected. Peritumoral tissue consists of fibrosis and chronic inflammation.

In the aspect of this malignant pathology report, breast-conserving surgery and axillary sentinel lymph node biopsy were done on the left breast. The sentinel lymph node was reactive. In postoperative pathological macroscopic examination; a whitish, elastic lesion of 3.5 cm in diameter with irregular margins was reported. Around the lobules of the breast, mononuclear inflammatory cells, dominant lymphocytic infiltrations were noticed in microscopic details of the postoperative pathology report. These features were pathognomonic for sclerosing lymphocytic lobulitis. (Figure-2) There was no residual carcinoma.

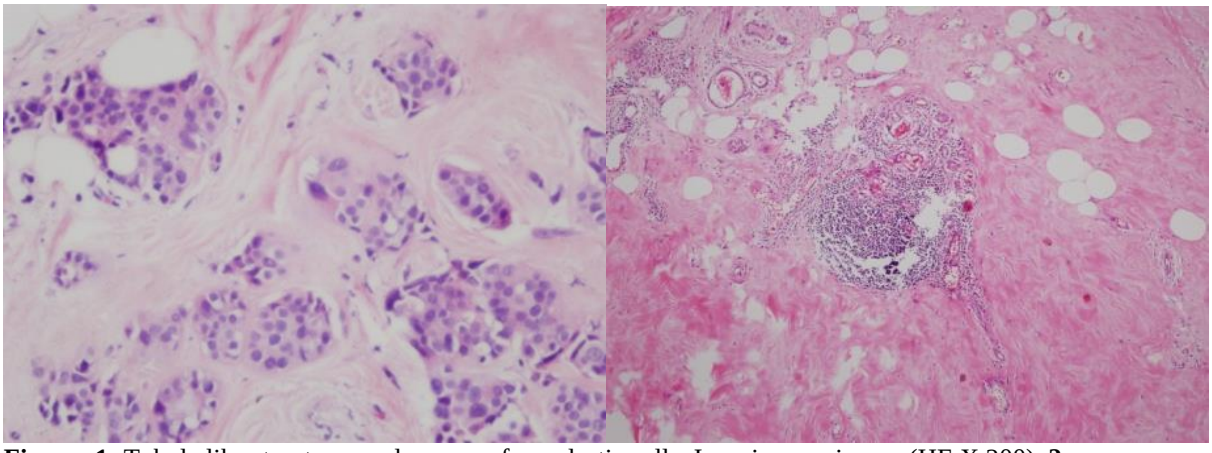


Figure -1: Tubule like structures and groups of neoplastic cells: Invasive carcinoma (HE X 200), **2:** Lymphocytic infiltration around the lobules in the breast stromal tissue; sclerosing lymphocytic lobulitis. (HEx100)

Discussion

Diabetic mastopathy (DMP) or sclerosing lymphocytic lobulitis, is a rare, benign tumor like the proliferation of fibrous tissue between lobules. DMP is further characterized by the presence of small lymphocytes in the lobules of the breasts. Recent studies reported that DMP is highly associated with type 1 diabetes mellitus and is often accompanied by other complications of diabetes, especially diabetic retinopathy (1). A few cases of DMP were reported in patients with a long-term history of type 2 diabetes in our patient (2,3). DMP is

Adress for correspondence: Dr.Onur Can Güler, Department of Surgery, Ankara Oncology Training and Research Hospital, Yenimahalle, Ankara, Turkey
e-mail:onurcguler@gmail.com
Available at www.actaoncologicaturcica.com

presented classically in premenopausal women, is less common in postmenopausal women, and is rare in men (4). Most reported female patients have been in their 30s; however, the patient presented here was much older and postmenopausal. Common clinical manifestations of DMP include multiple hard, mobile, bilateral, ill-defined, irregular breast lumps. Most patients have complained no pain, but a few have had serious pain (5). Some patients have presented with multiple unilateral lumps (6) or bloody nipple discharge (7).

In the beginning, breast ultrasonography usually demonstrates irregular, ill-defined, clear, hypoechoic shadowed breast nodules. Doppler flow imaging indicates no blood flow signal (8), which would be detected in the case of breast carcinoma. Mammography often shows asymmetric increased-density with disordered glandular structures, and no clear-cut mass or sand-like calcification. It is hard to differentiate DMP from breast cancer by under of mammography alone. The case in the present study had similar ultrasonographic and mammographic presentations compared with those described in other studies. Attitudes towards the effectiveness of breast magnetic resonance imaging (MRI) for the diagnosis of DMP vary (9); however, few individual case reports in the literature have covered the use, they concluded that MRI is not always useful in differentiating these lesions (10). Our patient's MRI was also ineffective, the lesion was reported as an intramammarian lymph node. From a clinical point of view, we recommended breast ultrasonography and mammography. Although the radiologists cannot clearly distinguish DMP from breast cancer, they provided some crucial clinical information and advice guided core needle biopsy or excisional biopsy (11-14).

Core needle biopsy can be performed to avoid unnecessary surgical biopsy as much as possible. In our study, excisional biopsy was performed. For patients with no complaints of discomfort, no further treatment is needed after diagnosis of DMP, but regular follow-up is recommended. Few cases of DMP have developed into breast cancer. A diabetic and kidney transplanted patient with DMP confirmed by excisional biopsy was found to have invasive breast cancer ten years later (15). Thorncroft et al considered it to be a coincidence as there is no clear pathologic evidence suggesting that breast cancer is associated with DMP (11). Our patient had malignant lesion synchronized with diabetic mastopathy.

DMP is a rare inflammatory disease of the breast that is difficult to identify from breast cancer by clinical manifestations. Regular follow-up is the main treatment. Breast ultrasonography and mammography are recommended. If the lesions become radiologically or clinically suspicious for malignancy core biopsy should be performed. If the core biopsy is inadequate, excisional biopsy is the diagnostic option.

Conflict of interest: None

References

1. Soler NG, Khardori R. Fibrous disease of the breast, thyroiditis and cheiroarthropathy in type I diabetes mellitus. Lancet 1984; 1(8370): 193-195.
2.Cirrito D, Orlando AA, Narese F, et al.Diagnostic and therapeutic management of diabetic mastopathy: a case report. Clin Ter. 2015; 166:e169-72.
3. Accurso A, Della Corte GA, et al. Unusual breast lesion mimicking cancer: diabetic mastopathy.Int J Surg. 2014; 12:S79-82.
4. Leroux-Stewart J, Rabasa-Lhoret R. Diabetic mastopathy: case report and summary of literature. Can J Diabetes 2014; 38:305-6.
5. Perret WL, Malara FA, Hill PA, et al. Painful diabetic mastopathy as a reason for mastectomy. Breast J 2006;12:559-62.
6.Utada Y, Watanabe T, Kajiwara T, Shimizu T, Imamura H, Watanabe O, et al. A case of diabetic mastopathy with multiple lesions mimicking breast cancer. BreastCancer 2003;10:371-3.
7. Wang Z, LeonardMHJr, Khamapirad T, et al. Bilateral extensive ductitis obliterans manifested by bloody nipple discharge in a patient with long-term diabetes mellitus. Breast J 2007;13:599-602.
8.Ricart Selma J, Camps Herrero C, Martínez Rubio R. et al. Diabetic mastopathy: Clinical presentation, imaging and histologic findings, and treatment. Radiología. 2011;53:349-354.
9. Isomoto I, Wada T, Abe K, et al. Diagnostic utility of diffusion-weighted magnetic resonance imaging in diabetic mastopathy. Clin Imaging 2009;33:146-9.
10. Sakuhara Y, Shinozaki T, Hozumi Y, et al. MR imaging in diabetic mastopathy. AJR Am J Roentgenol 2002;179:1201-3.
11. Thorncroft K, Forsyth L, Desmond S, et al. The diagnosis and management of diabetic mastopathy. Breast J 2007;13:607-13.
12. Seidman JD, Schnaper LA, Phillips LE. Mastopathy in insulin-requiring diabetes mellitus. Hum Pathol 1994;25:819-24.

Adress for correspondence: Dr.Onur Can Güler, Department of Surgery, Ankara Oncology Training and Research Hospital, Yenimahalle, Ankara, Turkey
e-mail:onurcguler@gmail.com
Available at www.actaoncologicaturcica.com

13. Tomaszewski JE, Brooks JS, Hicks D, et al. Diabetic mastopathy: a distinctive clinicopathologic entity. Hum Pathol 1992;23:780-6.
14. Camuto PM, Zetrenne E, Ponn T. Diabetic mastopathy: a report of 5 cases and a review of the literature. Arch Surg 2000;135:1190-3.
15. Mackey SP, Sinha S, Pusey J, et al. Breast carcinoma in diabetic mastopathy. Breast 2005;14:392-8.

Adress for correspondence: Dr.Onur Can Güler, Department of Surgery, Ankara Oncology Training and Research Hospital, Yenimahalle, Ankara, Turkey
e-mail:onurcguler@gmail.com
Available at www.actaoncologicaturcica.com

Management of Eyelid Defects after Tumor Excision

Tümör Eksizyonu Sonrasında Oluşan Göz Kapak Defektlerinin Yönetimi

Rahmi Duman, Reşat Duman
Afyon Kocatepe Üniveristesi Tıp Fakültesi, Göz Hastalıkları Ana Bilim Dalı, Afyonkarahisar, Türkiye

Dergiye Ulaşma Tarihi:24.11.2016 Dergiye Kabul Tarihi:01.12.2016 Doi: 10.5505/aot.2016.73745

ÖZET

Amaç: Göz kapak tümörlerinin eksizyonu sonrası oluşan kapak defektlerinin rekonstrüksiyonunda uygulanan yöntemlerin değerlendirilmesi.
Gereç ve Yöntem: Kapak tümörü nedeniyle 2010-2016 yılları arasında, total eksizyonel biyopsi uygulanan hastaların kayıtları retrospektif olarak değerlendirildi. Hastaların yaşı, cinsiyeti, kapak tümörü eksizyonu sonrası oluşan defektin büyüklüğü, defekti kapatmak için kullanılan yöntem ve oluşan komplikasyonlar değerlendirildi.
Bulgular: Çalışmaya 50 erkek 14 kadın hasta çalışmaya dâhil edildi. Hastaların yaş ortalaması 51,54 (5-84) idi. Ameliyat sonrası takipleri 35 ay (6-56 ay) olan hastaların büyük çoğunluğunda rekonstriksiyonda göz kapağının çevresindeki dokular kullanılarak primer olarak kapama metodu kullanıldığı saptandı.
Sonuç: Küçük kapak tümörlerinin cerrahisi sonrası oluşan defektlerin kapatılmasında herhangi bir greftyada flep dokusuna ihtiyaç olmadan primer kapamanın yeterli olduğu gösterildi. Kapak tümörlerinde uygun cerrahi teknik ile uygun bir anatomik sonuç elde edilebilmektedir.
Anahtar Kelimeler: Kapak, tümör, eksizyon, rekonstrüksiyon.

ABSTRACT

Aim: Evaluation of the methods applied in there construction of eyelid defects following eyelid tumor excision.
Material and Method: The medical records of patients who had undergone total excional biopsy between 2010-2016 were retrospectively reviewed. The age and sex, of the patients, the size of the defect after eyelid tumor excision, the method used to close the defect and the complications were evaluated.
Results: Fifty male and fourteen female patients were included in the study. The mean age of the patients was 51.54 (5-84). In the majority of patients with post-operative follow-up of 35 months (6-56 months), it was found that the method of closure as a primary using tissues around the eyelid was used in reconstruction.
Conclusion: It has been shown that primer closure without the need for any graft flap tissue is sufficient in the closure of defects after surgery of small eyelid tumors. An appropriate anatomical result can be obtained with appropriate surgical technique in the eyelid tumors.
Key Words: Eyelid, tumor, excision, reconstruction.

Giriş

Göz kapak tümörlerinin eksizyonu sonrası oluşan defektlerin doğru bir şekilde rekonstriksiyonu gözün korunması açısından önemlidir. Göz kapağı vücuttaki en ince cilt dokusudur, cilt altı bağ dokusu yağ doku içermez ve yapısı diğer bölgelerden farklılık göstermektedir. Göz kapağı, önden arkaya doğru cilt ve cilt altı dokular, orbikularis okuli, alt ve üst kapak retraktörleri, tars ve konjonktivadan oluşan kompleks bir yapıya sahiptir. Göz kapağının yapısını cilt ve orbikularis oküli kasından oluşan ön lamella, tars, retraktörler ve konjonktivadan oluşan arka lamella olmak üzere iki bölümde incelemek mümkündür. Göz kapağında oluşan defektlerin onarımı, göz kapaklarının gözü koruma görevlerinden ötürü ayrı bir önem taşır. Başarısız onarımlar sonucunda keratit, konjunktivit gibi ciddi komplikasyonlar oluşabilir (1). Göz kapak defektlerinin büyüklüğü, derinliği ve lokalizasyonu rekonstriksiyonda en önemli parametrelerdir. Hastanın yaşı ve genel sağlık durumu, kemik ve çevre dokuların tutulumu rekonstriksiyon sırasında göz önünde bulundurulması gereken diğer parametrelerdir. Bu çalışmada; tümör eksizyonu sonucu oluşan göz kapak defektlerinin rekonstriksiyonu için uygulanmış olan farklı onarım teknikleri ve sonuçları sunulmaktadır.

Adress for correspondence: Yrd. Doç. Dr. Rahmi Duman, Afyon Kocatepe Üniversitesi, Ali Çetinkaya Kampusü, Afyonkarahisar, Türkiye
e-mail: drrahmi42@yahoo.com
Available at www.actaoncologicaturcica.com

Materyal ve Metod

Göz kapağı tümörü nedeniyle Aralık 2010 - Eylül 2016 tarihleri arasında opere edilen, kapak rekonstriksiyonu uygulanan 64 hastanın dosyaları retrospektif olarak incelendi. Hastaların cinsiyeti, yaşı, opere edilen göz kapağı, uygulanan rekonstriksiyon metodu, operasyon sonrası oluşan komplikasyonları kaydedildi.

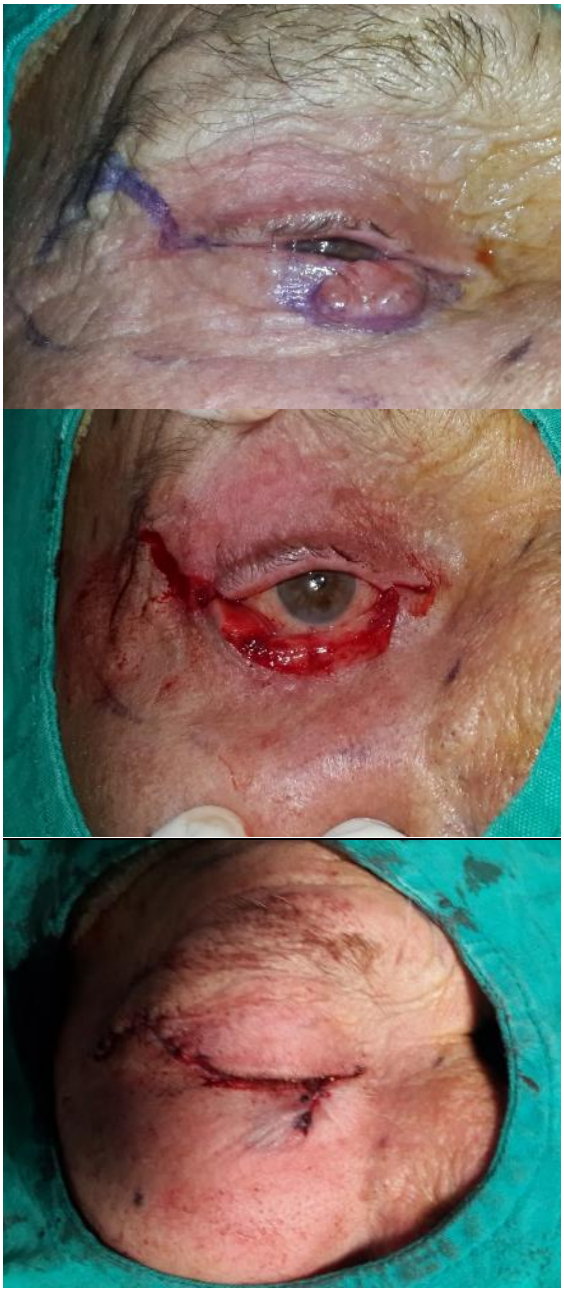
Göz kapak tümörü ilk operasyonda total olarak çıkarmayı planladığımız hastalarda total eksizyonel biyopsi yapılırken, büyük tümörlerde ise total eksizyon öncesi insizyonel biyopsi yapıldı. Cerrahi sınırda tümör olan hastalara, cerrahi sınırlar tümör negatif olacak şekilde reeksizyon uygulandı.

Bulgular

Çalışmaya 50 erkek 14 kadın hasta çalışmaya dâhil edildi. Hastaların yaş ortalaması 51,54 (5-84) idi. Kırk hastada tümör dokusu alt kapağı, yirmi dört hastada üst kapağı tutmuştu. Kırk dokuz hastada çeşitli tiplerde benign lezyon saptanırken (squamöz papillom, intradermal nevus, seboroik keratoz, epidermal inkülüzyon kisti, kapiller hemanjiom), 10 hastada bazal hücreli karsinom (BCC), 2 hastada skuamöz hücreli karsinom (SCC) ve 2 hastada sebase bez karsinomu,1'ine keratoakantom tanısı konuldu. Kırk altı hastada tümör göz kapağının %25'inden daha azını invaze etmişti, 14 hastada %25-50 arasında, 4 hastada yüzde 50 ve 80 arasında göz kapağında kayıp mevcuttu.

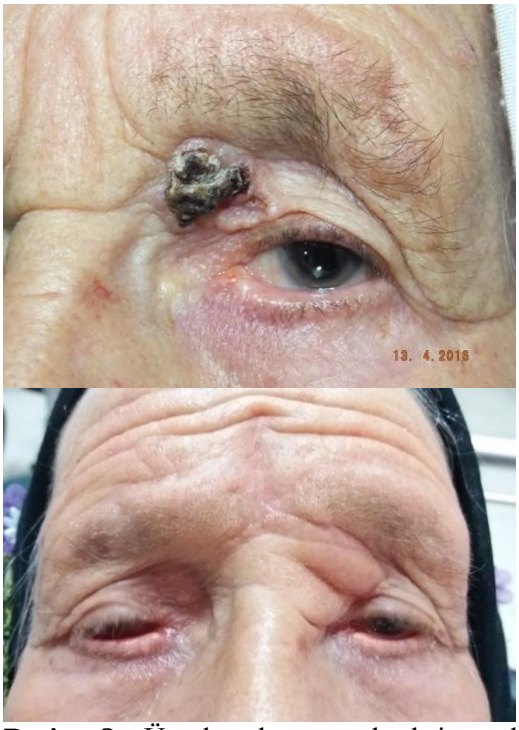
Göz kapak defektlerinin onarımında 46 hastada göz kapağının çevresindeki dokular kullanılarak primer olarak kapama yapıldı. Primer kapamanın yetersiz olduğu 6 hastada Tenzel flebi, 4 hastada Cutler-Beard flebi, 2 hastada Mustarde flebi ve 2 hastada lateral bazlı ilerletme flebi, 2 hastada glabellar flep, 1 hastada diğer kapaktan hazırlanan cilt grefti, 1 hastada karın ön duvarından hazırlanan greft kullanıldı (Resim 1-2). Arka lamel rekonstriksiyonunda ise 4 hastada tarsokonjonktival flep, 1 hastada sert damak grefti ve 2 hastada ağız içi mukoaza grefti kullanıldı.

Hastalar ameliyat sonrası ortalama 35 ay (6-56 ay) süresince takip edildi. Bir hastada greft nekrozu ile karşılaşıldı. Greft nekrozu olan hastaya reoperasyon yapılarak kaydırma flebi yapıldı. Kapak fonksiyon bozukluğuna hiçbir hastada karşılaşılmadı ve estetik olarak iyi sonuçlar elde edildi.



Resim 1: Alt kapaktan total eksize edilen tümör sonrasında tenzelsemisirküler flep uygulaması.

Adress for correspondence: Yrd. Doç. Dr. Rahmi Duman, Afyon Kocatepe Üniversitesi, Ali Çetinkaya Kampusü, Afyonkarahisar, Türkiye
e-mail: drrahmi42@yahoo.com
Available at www.actaoncologicaturcica.com



Resim 2: Üst kapaktan total eksize edilen tümör sonrasında Glabellar flep uygulaması.

Tartışma:

Kapak tümörlerinin malign veya benign olarak dağılımı toplumlar arasında farklılık göstermektedir. İsviçre'de %84 oranında benign kapak tümörüne rastlanırken, Yunanistanda % 59 oranında, ülkemizden yapılan bir çalışmada ise %90 oranında benign kapak tümörüne rastlanmıştır (2). Bizim çalışmamızdan elde ettiğimiz veriler ülkemizde yapılan Çevik ve arkadaşlarının yaptığı çalışmaya benzer oranlarda bulunmuştur.

Göz kapak tümörlerinde tümörün tamamının alınması ve oluşan defektlerin rekonstriksiyonunda korneayı ve gözü koruyacak düzgün kapak bütünlüğünün sağlanması önemlidir. Tümör eksizyonu sonrasında göz kapağında farklı büyüklüklerde ve farklı derinlikte defektler oluşabilmektedir. Göz kapak defektlerinin rekonstrüksiyonunda; defektin boyutu eksizyon sonrası değerlendirilmeli ve onarım bu kriterlere göre yapılmalıdır. Kapak rekonstrüksiyonu, mevcut olan kapak dokuların birleştirilmesi ile veya yeterli bir kapanmasının mümkün olmadığı durumlarda başka bir alandan getirilen greft veya fleplerle sağlanabilmektedir (3). Göz kapak rekonstriksiyonunda kapağın ön ve arka lamel olarak iki kısım olarak ele alınması, lamellerden birine serbest greft yerleştirildiğinde diğer lamellaya vaskülarizasyonu iyi olan transposizyon, rotasyon ya da ilerletme flebi tercih edilmesi önemlidir.

Ön lamelin %25 veya daha az defektlerinde mevcut olan göz kapağı dokuları kullanılarak primer olarak veya lateral kantolizis yaparak çevre dokulardan faydalanılıp primer onarım sağlanabilmektedir. Primer olarak kapanmayan %25'den daha fazla ön lamella defektlerine de; ilerletme ya da rotasyon fleplerinden ya da greftlerden faydalanılabilmektedir. Total alt göz kapağı kayıplarında alın flebi, nazolabial flep, üst göz kapağından hazırlanan tek veya iki pediküllü kas-deri flebi, üst göz kapağından tarsokonjonktival flep, infraorbital bölgeden hazırlanan fasyokutanöz V-Y ilerletme veya rotasyon flebi, temporoparyetalfasya flebi, semisirküler Tenzel flebi veya Mustardé yanak flebi ile rekonstriksiyon yapılabilmektedir (1-8). Total üst kapak kayıplarında ise alın flebi, glabellar flep, Cutler-Beard flebi ve McCord yöntemleri ile rekonstriksiyon yapılabilmektedir (9-10).

Alt kapağın ön lamel rekonstrüksiyonu için sayısız alternatif lokal perioküler flepler kullanılmaktadır. Biz özellikle %50'den fazla ön lamel kayıplarında öncelikli olarak tenzel semisirküler flebini tercih etmekteyiz. Tenzel semisirküler flebinin en önemli avantajları minimal morbidite (verici bölge için), kolay hazırlanabilmesi (diseksiyon alanının az olması) doku uyumunun yüksek olmasıdır (11-14).

Üst kapaktaki %50'den fazla oluşan tam kat defektlerde Cutler-Beard Flebi tercih etmekteyiz. Cutler-beard flebi çok kullanılan bir yöntem olmamasına rağmen bizim yaptığımız çalışmalarda doku uyumunun ve kapak fonksiyon kaybının minimal olması nedeniyle başarımız yüksek bulunmuştur. Cutler-Beard flebi kolay hazırlanmamasına rağmen ön ve arka lamellanın bir bütün halinde taşınması ve doku reddinin neredeyse hiç olmaması avantajları olarak sayılabilmektedir (15).

Alt kapaktaki yüzde elliden fazla oluşan tam kat defektlerde ise Mustarde flebi tercih etmekteyiz. Mustarde flebinin en önemli avantajları ise renk ve doku uyumunun yüksek olduğu temporal bölgenin kullanılması ve neredeyse totale yakın kapak rekonstriksiyonuna yetecek doku sağlamasıdır (16-18). İlerletme flebi ise çok fazla doku

Adress for correspondence: Yrd. Doç. Dr. Rahmi Duman, Afyon Kocatepe Üniversitesi, Ali Çetinkaya Kampusü, Afyonkarahisar, Türkiye
e-mail: drrahmi42@yahoo.com
Available at www.actaoncologicaturcica.com

kaybının olmadığı özellikle ön lamel defektlerinin fazla olduğu olgularda kullanıldı. Üst ve alt kapakta tarsal desteğe ihtiyaç duyulan durumlarda nazal septal kondromukozal greft, nazal üst lateral kondromukozal greft, sert damak mukoza grefti, kulaktan konkal kartilaj greftleri kullanılabilinir. Biz çalışmamızda tarsal desteğe sadece bir hastada ihtiyaç duyduk ve bu hastada sert damak mukoza grefti kullandık.

Sonuç olarak göz kapak defektlerinin rekonstrüksiyonunda; %25 fazla daha az kapak defektlerinde primer onarımın yeterli olduğu unutulmamalıdır. Daha büyük kapak defektlerinde ise defektin büyüklüğü, diğer kapağın durumu ve aynı seansta yapılabilecek en basit yöntemlerin uygulanması ve cerrahın tecrübesi önemlidir.

Kaynaklar:

1. Kesiktaş E, Kerimov R, Tabakan İ, Eser C, Aslaner EE. Alt Göz Kapak Rekonstrüksiyonundaki Klinik Deneyimlerimiz ve Rekonstrüksiyon Yöntemlerin Karşılaştırılması. Cukurova Medical Journal (Çukurova Üniversitesi Tıp Fakültesi Dergisi) 2011;36(1):15-23.
2. Çevik SG, Yücel E, Çevik M, Mutlu N. Göz kapağı ve konjoktiva tümörlerinde histopatolojik sonuçlarımız. Acta Oncologica Turcica, 2015;48(3), 114-117.
3. Banu MH, Özlem EA, Zeliha Y, Gürsel E. Malign kapak tümörlerinde kapak rekonstrüksiyonu sonuçlarımız. T Klin Oftalmoloji 2001;10:165-170.
4. Carraway JH. Reconstruction of the eyelids and correctionptosis of the eyelid. In: Aston SJ, Beasley RW, Thorne HC (eds): Grabb and Smith's Plastic Surgery. New York: Lippinco Raven, 1997, 5th ed p.529-44.
5. Codner M.A. Reconstruction of theeyelidsandorbit. Coleman, JJ in PlasticSurgery. London, Mosby, 2000, 1425p.
6. Mustarde JC. Repair and Reconstruction in the Orbital Region. A Practical. Guide. New York, Churchill Livingstone Inc, 1980;
7. Siegel R.J. Severe ectropion: repairwith a modified Tripier flap. PlastRecSurg 1987; 80: 21-28.
8. Hughes WL. New method for rebuilding a lowerlid; report of a case. Arch Ophthalmol. 1937;17:1008-17.
9. Maden A. Oküloplastik cerrahi. İzmir; Özden ofset:1995:106-132
10. Collin JRO. Tumor excision and eyelid reconstruction. A manual of systemic eyelid surgery. Edinburg: Churcill Livingstone, 1983:76-95
11. Carraway JH, Vincent MP. Reconstruction of eyelid deformities In: Gregory SG and Nicholas GG, eds. Textbook of Plast Maxillofacial and Reconstructive Surgery. Baltimo Williams and Wilkins, 1992, 2nd ed. p. 551-65.
12. Carraway JH. Reconstruction of the eyelids and correctionptosis of the eyelid. In: Aston SJ, Beasley RW, Thorne HC (eds): Grabb and Smith's Plastic Surgery. New York: Lippinco Raven, 1997, 5th ed p.529-44.
13. Tenzel RR. Eyelid reconstruction by these micircular flap technique. Ophthalmology 1978; 85:1164.
14. Tenzel RR. Semicircular flap in reconstruction of upper and lower eyelid defects. In: Berish Strauch, Luis O Vascones, Elizabeth J Hall Findlay (eds). Grabb's Encyclopedia of Flaps. Boston: Little Brown and Company, 1990, 1st ed p. 57-9.
15. Duman R, Balcı M, Başkan C, Özdoğan S. Management of the Large Upper Eyelid Defects with Cutler-Beard Flap. Journal of Ophthalmology. 2014,
16. Kesiktaş E, Kerimov R, Tabakan İ, Eser C, Aslaner EE. Alt Göz Kapak Rekonstrüksiyonundaki Klinik Deneyimlerimiz ve Rekonstrüksiyon Yöntemlerin Karşılaştırılması. Cukurova Medical Journal (Çukurova Üniversitesi Tıp Fakültesi Dergisi), 2011; 36:15-23
17. Güzel MZ., Yıldırım I, Aygit AC ve ark. Reconstruction of the total lower eyelid defect-Useful modifications. Eur J PlasticSurg 1995; 18: 171-174
18. Mustarde JC. Repair and Reconstruction in the Orbital Region. A Practical. Guide. New York, Churchill Livingstone Inc, 1980;
19. Kumar S, Medeiros F, Dowdy SC, Keeney GL, Bakkum-Gamez JN, Podratz KC, Cliby WA, Mariani A. A prospective assessment of the reliability of frozen section to direct intraoperative decision making in endometrial cancer. Gynecol Oncol. 2012 Dec;127(3):525-31.
20. Karalok A, Ureyen I, Reis Y, Oktay O, Turan T, Boran N, Bülbül D, Tulunay G, Köse MF. Prediction of staging with preoperative parameters and frozen/section in patients with a preoperative diagnosis of grade 1 endometrioid tumor in endometrial cancer. J Turk Ger Gynecol Assoc. 2014 Jan 30;15(1):41-8.
21. Acikalin A, Gumurdulu D, Bagir EK, Torun G, Guzel AB, Zeren H, Vardar MA. The guidance of intraoperative frozen section for staging surgery in endometrial carcinoma: frozen section in endometrial carcinoma. Pathol Oncol Res. 2015 Jan;21(1):119-22.
22. Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 2015 Review.

Adress for correspondence: Yrd. Doç. Dr. Rahmi Duman, Afyon Kocatepe Üniversitesi, Ali Çetinkaya Kampusü, Afyonkarahisar, Türkiye
e-mail: drrahmi42@yahoo.com
Available at www.actaoncologicaturcica.com

Porphyria; A Rare Cause of Neurological Symptoms in Cancer Patient

Porfiri; Kanser Hastasında Nörolojik Semptomların Nadir Bir Sebebi

Ali Alkan[1], Ebru Karcı[1], Betül Yavuz[2], Abdullah Akdağ[1], Nalan Akıncı[1], Arzu Yaşar[1], Güngör Utkan[1]

[1]Ankara University School of Medicine, Department of Medical Oncology, Ankara, Turkey
[2]Ankara University School of Medicine, Department of Internal Medicine, Ankara, Turkey

Dergiye Ulaşma Tarihi:20.11.2015 Dergiye Kabul Tarihi:08.02.2016 Doi: 10.5505/aot.2016.18209

ÖZET

Onkoloji pratiğinde nörolojik semptomlar genellikle direkt tümör etkisi veya paraneoplastik sendrom olarak karşımıza çıkmaktadır. Nörolojik semptomlara neden olan nadir hastalıkların tanısı özellikle metastatik kanser hastasında zordur. Burada kırmızı idrar ve nörolojik semptomlarla değerlendirilen bir metastatik akciğer kanseri olgusu sunulmuştur. Metastaz ve paraneoplastik patolojilerin ekartasyonu sonrasında bulgular porfiri tanısı ile ilişkilendirilmiştir. Tecrübemiz porfiri tanı ve tedavi hakkında klinik ipuçları verirken, onkoloji hastasında nörolojik semptomların ayırıcı tanısında tanısal yaklaşımın önemini vurgulamaktadır.
Anahtar kelimeler: Porfiri; Akciğer kanseri; Nörolojik semptomlar

ABSTRACT

In cancer patient neurological symptoms are mostly due to direct tumor effect or paraneoplastic syndromes. The diagnosis of rare diseases causing neurological symptoms is challenging, especially in a metastatic cancer patient. Here we discussed a metastatic lung cancer patient who presented with red urine and neurological symptoms. After exclusion of metastasis and paraneoplastic pathologies, the findings were associated with the diagnosis of porphyria. While our experience is giving clinical clues about a rare pathology, it also reminds us the importance of work up in the face of neurological symptoms in oncology patients.
Key words: Porphyri; Lung Cancer; Neurological symptoms

Introduction

In oncology practice, especially in metastatic disease, neurological symptoms usually lead the clinician to search brain metastasis or a compressive pathology in vertebral column. Besides common causes, rarely paraneoplastic syndromes may present with progressively deteriorating neurological symptoms. Although paraneoplastic syndromes especially Lambert Eaton syndrome, subacute sensory neuropathy and encephalomyeloneuritis and subacute cerebellar degeneration have been associated with lung cancer, neurological symptoms are usually a consequence of direct metastatic tumor effect (1).

Here we present a nonsmall cell lung cancer patient presenting with insignificant neurological symptoms and a diagnostic process resulting in a diagnosis of porphyria.

Case Presentation

A 62-year-old male patient, without any comorbidities, presented with dsypnea and hemoptysis. Nodular lesions detected in pulmonary imaging, further conveyed us to a diagnosis of squamous cell carcinoma of the lung with multiple bone metastasis. Patient was hospitalized for palliative intent with a plan of palliative radiotherapy and systemic chemotherapy. In the initial evaluation, patient was apathic and sometimes having difficulty in communication. Intermittent syncope history and progressive mood changes led us for a diagnostic work up. Thyroid, renal and hepatic functions were normal. Cranial imaging was free of either a metastatic lesion or vascular pathology. Behavioral changes and intermittent

Adress for correspondence: Ali Alkan, Ankara University School of Medicine, Department of Medical Oncology, Ankara, Turkey
e-mail: alkanali@yahoo.com
Available at www.actaoncologicaturcica.com

agitation couldn't be explained with an underlying psychiatric pathology and he was treated with a diagnosis of delirium. Due to inconclusive work-up and improvement in neurological symptoms, the patient was treated with palliative radiotherapy for vertebral metastasis and systemic cisplatin- gemcitabin regimen. After 2 courses of chemotherapy, pleural effusion ensued and second line regimen with docetaxel was planned. The patient was treated with drainage of the effusion with thorax tube insertion. During follow up, the patient was treated with numerous antibiotics and palliative medication, especially for emesis and constipation. Chronic dyspepsia was treated with symptomatic medication and intermittent mild abdominal pain was associated with chronic constipation after exclusion of organic pathology with gastroscopy and colonoscopy. During 2 months of follow up, the patient was intermittently sleepy, having speech problems and agitations.

At the end of 2 months of follow up, the patient complained about a 4 days history of reddish urine messing his underwear (Figure-1a/b). Thrombocytopenia due to docetaxel suggested a gross hematuria but it's excluded with urine microscopy. Hemoglobin levels of 8.6g/dl and normal bilirubin, LDH, haptoglobulin, reticulocyte levels excluded hemolysis. Patient was free of a medication, specific food and herbal medicine history that may cause red urine. Nonspecific fluctuating neurological symptoms, intermittent mild diffuse abdominal pain, red urine and increased urobilinogen in urine analysis conveyed the work up for porphyria. Daily porphobilinogen in urine was 4.7mg (0-2mg/d). Coproporphyrin I: 90.2 µg /d (0-25 µg /d), Coproporphyrin III: 80.5 µg/d (0-75 µg/d), total pophyrine: 182.75 µg/d (0-150 µg/d). Symptoms and laboratory results were consistent with the diagnosis of porphyria. Patient medication, especially metoclopramide and antibiotherapy aggravating porphyria was discontinued and red urine improved completely in 1 week (Figure 1c). In the follow up of patient chemo refractory disease progressed and debilitated patient progressively deteriorated and died.

Discussion

Management of neurological pathology due to metastatic disease is an important part of oncology practice. While direct tumor effect on nervous system is the most encountered cause of symptoms, rarely paraneoplastic syndromes, thrombo-embolism and electrolyte disorders may cause neurological deficit. Preexisting rare metabolic disorders may be aggravated by tumor itself, chemotherapeutic agents or by supportive medication during management.

Porphyrias are a group of disorders in haem biosynthesis, resulting from genetic enzyme defects in haem synthesis pathway. Seven different types with different enzyme defects have been defined in the pathway. Neuropsychiatric and dermatological problems with different intensity are the clinical results of the accumulating metabolites (2). Accumulation of toxic metabolites and symptoms are usually precipitated. Whereas drugs are the most documented precipitants; infections, malignancy, alcohol and fasting may cause porphyria attack. Besides not exactly defined, Aminolevulinic acid accumulation is hypnotized to be the cause of neurological symptoms. Especially during attacks patient may present with different neurological symptoms such as minor muscle weakness, motor deficits, blood pressure disturbances and dyspepsia. Although dermatological symptomatology may resolve with vesicles, patients may experience severe tissue damage causing digital amputation (3).

Knowledge about porphyrias and cancer is limited in literature. An increased risk for hepatocellular carcinoma in porphyria patients has been reported and screening for primary liver malignancy in pophyric patients has been recommended (4,5). Liver metastasis has been

Adress for correspondence: Ali Alkan, Ankara University School of Medicine, Department of Medical Oncology, Ankara, Turkey
e-mail: alkanali@yahoo.com
Available at www.actaoncologicaturcica.com

documented as a triggering factor of porphyria attacks. In addition to relation with hepatic malignancies, porphyria has been reported as a risk factor for lung cancer in a cohort study from Denmark and Sweden (6).

Management of a cancer patient with a diagnosis of porphyria is difficult. Especially selecting the best effective regimen in potential precipitant chemotherapeutic and palliative medications is challenging. The data about the cytotoxic drug used in porphyric patients is limited and safety data is only a total of experiences in case reports. Taxanes; docetaxel and paclitaxel, cyclophosphamide, busulfan, methotrexate, anastrazole, letrozole, tamoxifen are the porphyrinogenic drugs. Fluorouracil, Doxorubucin, Epirubicin, carbolatin, Capecitabine are drugs that are probably not porphyrinogenic (7). Palliative medications such as 5HT3 antagonists, metoclopramide, steroids, paracetamol, tramadol, fentanil are in the "probably not porphyrinogenic" group. Aprepitant is in the probably porphyrinogenic group (2). Different experiences with different drugs have been reported in literature. Before chosing drug it must be carefully discussed.

In our patient, management of neurological symptoms caused by a rare disease was challenging. Due to nonspecific findings, age of the patient and possible metastatic or paraneoplastic syndrome postponed the diagnosis. The analysis of the drugs used for detection of the precipitant was inconclusive. Second line regimen docetaxel has been reported to be precipitant in literature but the absence of symptoms during therapy and nearly 2 weeks period between symptoms and therapy decreases the likelihood of it. The ongoing nasocomial pneumonia was thought to be the precipitating factor. While our experience is giving clinical clues about a rare pathology, it also reminds us the importance of work up in the face of neurological symptoms in oncology patients.

Conflict of interest: None

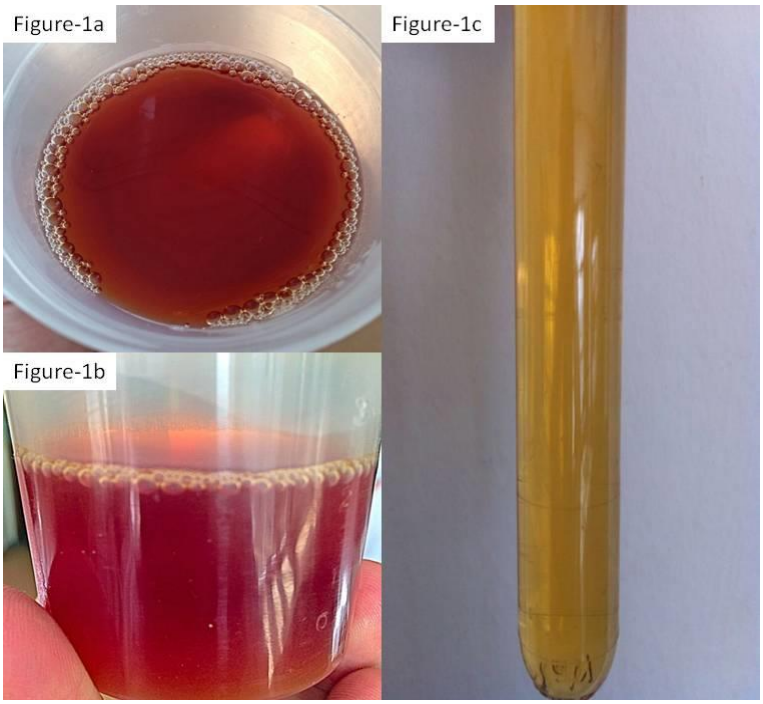


Figure 1: Reddish urine observed during exacerbation(1ab), Normal color urine after resolution of attack of porphyria(1c)

Adress for correspondence: Ali Alkan, Ankara University School of Medicine, Department of Medical Oncology, Ankara, Turkey
e-mail: alkanali@yahoo.com
Available at www.actaoncologicaturcica.com

Referanslar

1. Dropcho EJ. Neurologic complications of lung cancer. Handbook of clinical neurology. 2014;119:335-61
2. Palmieri C, Vigushin DM, Peters TJ. Managing malignant disease in patients with porphyria. QJM : monthly journal of the Association of Physicians. 2004;97:115-26
3. Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2012;2012:19-27
4. Kaczynski J, Hansson G, Thunell S, Wetterberg L, Wallerstedt S. Erythrocyte porphobilinogen deaminase activity and primary liver cancer. Journal of internal medicine. 1995;237:309-13
5. Innala E, Andersson C. Screening for hepatocellular carcinoma in acute intermittent porphyria: a 15-year follow-up in northern Sweden. Journal of internal medicine. 2011;269:538-45
6. Linet MS, Gridley G, Nyren O et al. Primary liver cancer, other malignancies, and mortality risks following porphyria: a cohort study in Denmark and Sweden. American journal of epidemiology. 1999;149:1010-5
7. Thiery-Vuillemin A, Chaigneau L, Meaux-Ruault N et al. Anticancer therapy in patients with porphyrias: evidence today. Expert opinion on drug safety. 2008;7:159-65

Adress for correspondence: Ali Alkan, Ankara University School of Medicine, Department of Medical Oncology, Ankara, Turkey
e-mail: alkanali@yahoo.com
Available at www.actaoncologicaturcica.com