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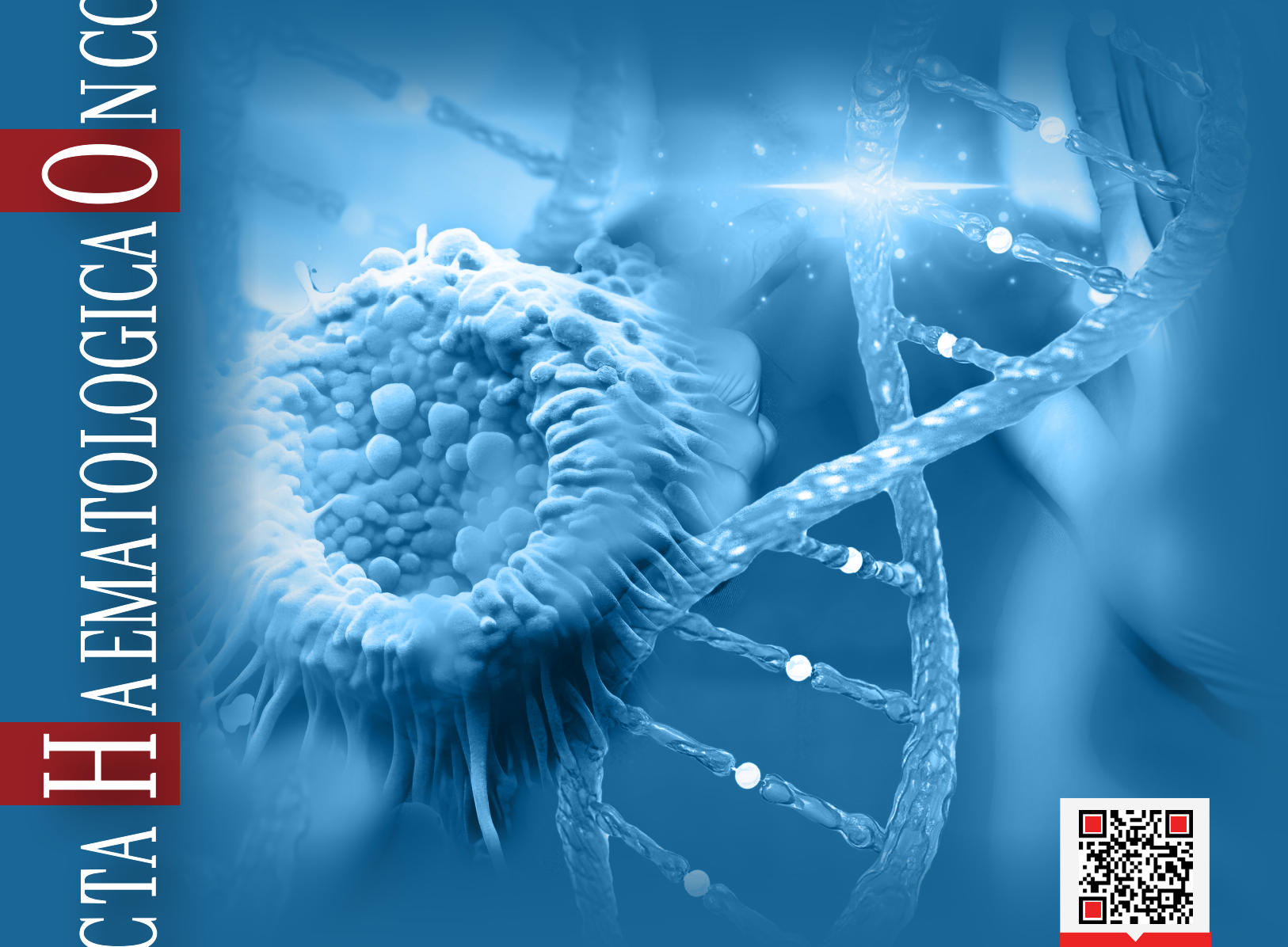

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Original Article

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Serum Periostin Levels in Newly Diagnosed Multiple Myeloma: Preliminary Observations and Treatment-related Changes

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ABSTRACT

Aim: This study aimed to perform a descriptive evaluation of serum periostin levels in newly diagnosed, treatment-naive multiple myeloma (MM) patients and to explore short-term changes following induction therapy.

Methods: Between May 2020 and May 2021, patients diagnosed with MM and healthy volunteers were recruited from the Hematology Unit of the Faculty of Medicine, Necmettin Erbakan University. Demographic characteristics, MM-related clinical findings, and treatment response data of the patients were documented. Serum periostin levels in MM patients before treatment were compared with those in healthy controls. Additionally, baseline periostin levels in the patient group were compared with post-treatment values.

Results: Thirty-six MM patientswere included in our study (17 females, 47.2%; 19 males, 52.8%), with an average age of 63.11±12.13 years. The control group consisted of 18 males (50%) and 18 females (50%), with a mean age of 61.94±10.53 years. Serum periostin levels were significantly elevated in the MM group compared with controls healthy (25.25 ng/mL vs. 14.84 ng/mL, p<0.001). No statistically significant associations were observed between baseline periostin levels and disease stage, cytogenetic risk groups, survival, or treatment response. In the 28 patients who completed induction chemotherapy, the median periostin value decreased from 24.96 (11.21-94.87) ng/mL at diagnosis to 17.97 (3.16-47.7) ng/mL after three courses of treatment (p<0.001).

Conclusion: In MM patients, serum periostin levels were elevated at diagnosis and decreased significantly following induction therapy. This study is the first to demonstrate a significant reduction in periostin levels after induction therapy in MM. These findings should be considered preliminary and hypothesis-generating. Larger, well-designed studies are required to clarify the clinical relevance of periostin in MM.

Keywords: Biomarkers, multiple myeloma, inflammation, periostin.

Introduction

Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by bone marrow infiltration, monoclonal protein production, and end-organ damage, including anemia, renal failure, hypercalcemia, and osteolytic bone disease. Despite advances in therapy, MM remains a heterogeneous disease with variable clinical outcomes, highlighting the importance of understanding disease-related biological markers and microenvironmental factors [1]. Periostin, an extracellular matrix protein, was first isolated as an adhesion molecule from mouse osteoblastic cells. Although initially described as an osteoblast- specific factor, it was last renamed following the discovery of its predominant expression in the periosteum [2]. Periostin has been implicated in various pathological processes, including fibrosis, atherosclerosis, tumor progression, and ultimately metastatic spread. When produced by fibroblasts, periostin contributes to tissue

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remodeling by influencing collagen deposition, modifying the biomechanical properties of connective tissue, and modulating chronic inflammatory responses [3]. Beyond inflammatory disorders, periostin has been investigated in numerous malignancies. Elevated periostin levels have been reported in cancers of the gastrointestinal tract, bladder, and breast, and increased expression is often associated with unfavorable clinical outcomes. Additionally, a study involving patients with non-small-cell lung cancer found that elevated periostin levels increased the likelihood of developing bone metastases [4]. Uncontrolled monoclonal proliferation in the bone marrow contributes to the pathogenesis of MM [5]. MM accounts for approximately 10% of hematological cancers and 1% of all cancers. Although its pathogenesis is multifactorial, chromosomal abnormalities are recognized as key contributors. In MM, prognosis is influenced by cytogenetic risk factors and laboratory markers, such as serum albumin, lactate dehydrogenase (LDH), and β2-microglobulin (β2-MG); these parameters also form the basis of current staging systems [6]. Abnormal changes in the bone marrow microenvironment play an important role in MM progression. Stromal cells, along with osteoblasts and osteoclasts, promote plasma cell survival and drive the formation of MM-related bone lesions through the secretion of cytokines including vascular endothelial growth factor, insulin-like growth factor-1, tumor necrosis factor-alpha and interleukin-6 [7]. Bone complications—especially lytic lesions—are present in nearly 90% of patients with MM [8]. Given the established involvement of periostin in tissue remodeling, inflammation, and malignancy-related bone dynamics, our study aimed to explore the relationship between serum periostin levels and clinical parameters in patients with newly diagnosed MM.

Methods

The study was prospective and observational. Power analysis indicated that with an effect size of 0.5, 80% power, and a type I error rate of 5% ($p<0.05$), a minimum sample size of 34 individuals per group was required , yielding a 1:1 ratio. Ethical approval for the study was obtained from the Necmettin Erbakan University Ethics Committee (approval no: 2020/2467, date: 08.05.2020). Patients newly diagnosed with MM at the Adult Hematology Department of Necmettin Erbakan University between May 2020 and May 2021 were screened.

Inclusion criteria for the study were newly diagnosed MM and age over 18 years.

Exclusion criteria were; a pathology affecting heart or lung function, an active infection, a chronic systemic disease, and a chronic bone disease.

The control group consisted of healthy volunteers over 18 years of age who reported no systemic illness, were not taking regular medications, and had normal blood counts and biochemical parameters during the same period. Informed consent was obtained from all participants. Following informed consent, serum samples were collected from both groups prior to treatment initiation to determine periostin concentrations. Demographic information, complete blood count results, standard biochemical analyses, MM subtype, disease stage, cytogenetic risk category, clinical characteristics, and treatment response after three chemotherapy cycles were documented for all participants. The primary aim of the study was to compare serum periostin levels in patients with MM to those in healthy individuals. For this purpose, baseline periostin concentrations in the patient group were compared with those in the healthy controls. The secondary objective was to investigate the clinical associations between periostin and MM and to evaluate changes in serum periostin levels following three cycles of therapy.

Periostin Measurement

After collection, Blood samples from patients and healthy individuals were centrifuged at 4000 rpm for 10 minutes at 37 °C. The collected samples were kept at -80 °C until analyzed. Periostin levels were measured in the central biochemistry laboratory using an ELISA-based assay (Human Periostin, POSTN ELISA kit, BTLAB, Atlas Biotechnology Ltd.).

Statistical Analysis

IBM SPSS Statistics for Windows, version 22.0 (USA), was used to analyze the study's statistical data. The distribution of continuous numerical variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were presented as median (minimum-maximum) for variables that were not normally distributed and as mean ± standard deviation for variables that were normally distributed. To compare two independent groups, the Mann-Whitney U test was used for variables that were not normally distributed, and the independent samples t-test was used for variables that were normally distributed. The Wilcoxon signed-rank test was applied for comparisons of dependent (paired) data. Categorical variables were expressed as percentages (%) and compared using chi-square test. In the correlation analyses, the Spearman correlation coefficient (rho) was used, and correlation strength was interpreted as follows: weak (0.2-0.4), moderate (0.4-0.6), strong (0.6-0.8), and very strong (0.8-1.0). A p value <0.05 was considered statistically significant.

Results

Our study included 36 participants in two groups. The mean age was 63.11±12.13 years and 61.94±10.53 years in the patient and healthy groups, respectively. The median periostin level was significantly higher in the group of patients (14.84 ng/mL vs. 25.25 ng/mL, $p<0.001$). Baseline laboratory and demographic data for the patient and healthy groups are shown in Table 1.

Eight (22.2%) of the MM patients died during remission-induction treatment. The remaining 28 (77.8%) patients reached the response evaluation stage. Although initial periostin levels were higher in the 8 patients who died than in the 28 surviving patients, the difference was not statistically significant (25.1 ng/mL vs. 21.1 ng/mL; $p=0.158$). Table 2

Table 1. Laboratory and demographic findings of the MM group and the control group

Parameters	Control (n= 36)	MM (n= 36)	p
Age	61.9±10.5	63.11±12.13	0.664
Sex (female/male)	18/18	17/19	0.815
Periostin (ng/mL)	14.84 (4.16-32.11)	25.25 (11.21-94.87)	**<0.001***
WBC (µLx10³)	7.75±1.6	7.30±2.54	0.372
Neutrophil (µLx10³)	4.77±1.29	4.51±1.79	0.489
Platelet (µLx10³)	257±57.7	247.97±124.92	0.696
Hb (g/dL)	14.8 (11-17)	10.75 (5.2-16)	**<0.001***
Basophil (µLx10³)	0.03 (0.00-0.07)	0.02 (0.01-0.1)	**0.008***
Total protein (g/dL)	74.15 (24.2-85)	78.2 (10.45-145.5)	0.110
Albumin (mg/dL)	4.5 (3.7-5.2)	3.7 (1.8-5.1)	**<0.001***
AST (U/L)	13.55 (7.5-76)	19.6 (9.8-99.6)	**0.001***
ALT (U/L)	13.15 (5.7-154)	14.4 (6.1-155.3)	0.182
CRP (mg/dL)	2.62 (0.1-130)	5.05 (0.5-193.2)	**<0.001***
Ca (mg/dL)	9.3 (8.15-10.10)	9.51 (7.3-14.7)	0.156
Ürea (mg/dL)	30.35 (12.7-68.4)	42.5 (7.7-186.6)	**<0.001***
Creatinine (mg/dL)	0.88 (0.5-1.3)	1.23 (0.66-5.18)	**<0.001***
Uric acid (mg/dL)	5.15 (3-8.7)	6.6 (3.1-15.8)	**<0.001***
Mg (mg/dL)	2.11 (1.52-2.94)	2.05 (1.51-2.4)	**<0.049***
Na (mmol/L)	139.5 (133-144)	137 (129-148)	**0.001***
K (mmol/L)	4.42 (3.55-9.3)	4.5 (3.2-5.87)	0.279
P (mg/dL)	3.42 (2.12-4.41)	4 (2.31-7.21)	**<0.001***
LDH (U/L)	190 (137-261)	241.5 (123-530)	**0.002***
IgG (g/dL)	12.05 (7.93-19)	10.8 (1.42-124)	0.702
IgM (g/dL)	0.84 (0.4-2.3)	0.17 (0.16-28.8)	**<0.001***
IgA (g/dL)	2.75 (0.71-5.5)	0.37 (0.24-72)	**<0.001***

*: The Mann-Whitney U test, WBC: White blood cell, Hb: Hemoglobin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, MM: Multiple myeloma, LDH: Lactate dehydrogenase, IgG: Immunoglobulin G, IgA: Immunoglobulin A, IgM: Immunoglobulin M

Table 2. Comparison of baseline periostin level between subgroups

	N (%)	Periostin level	p
Sex			
Female	17 (52.8)	23.2 (11.2-94.8)	0.176
Male	19 (47.2)	21.5 (11.4-52)	
ISS			
I-II	14 (38.9)	25.3 (11.2-94.8)	0.284
III	22 (61.1)	21.5 (11.4-46.3)	
R-ISS			
I-II	18 (50.0)	23.3 (11.2-94.8)	0.486
III	18 (50.0)	21.5 (11.4-46.3)	
Genetic risk			
Standard	22 (61.1)	22.05 (11.2-94.8)	0.673
High	14 (38.9)	22.4 (11.4-46.8)	
Survival			
Death	8 (22.2)	25.1 (12.5-46.8)	0.158
Alive	28 (77.8)	21.1 (11.2-94.8)	

Patients who could not complete their treatment were not included, ISS: International Staging System Revised, R-ISS: Revised International Staging System Revised

Table 3. Correlation of periostin value at the time of diagnosis with other parameters

Parameters	Rho (correlation coefficient)	P
WBC (μLx10^3)	-0.432	0.009
Neutrophil (μLx10^3)	-0.420	0.011
Monocytes (μLx10^3)	-0.352	0.035
Urea (mg/dL)	-0.339	0.043
B2 microglobulin (mg/L)	-0.371	0.026

WBC: White blood cell

compares periostin levels by sex, stage, genetic risk group, and patient survival.

According to the Spearman correlation analysis, serum periostin levels demonstrated a moderate negative correlation with both neutrophil count and white blood cell count (rho=-0.420, p=0.011; rho=-0.432, p=0.009, respectively). The statistically significant correlations are summarized in Table 3.

The median initial periostin level of 28 patients who underwent interim evaluation was 24.96 (11.21-94.87) ng/mL, and the serum periostin level of these patients after 3 cycles of treatment was 17.97 (3.16-47.7) ng/mL. The decrease in periostin level after treatment was statistically significant (p<0.001). Additionally, post-treatment serum periostin levels in the patient group were compared with those in the healthy control group, and no statistically significant difference was observed (p=0.457).

Discussion

MM is characterized by the uncontrolled monoclonal proliferation of plasma cells and predominantly affects older adults. The median age at diagnosis is approximately 66-70 years, and fewer than 40% of cases occur in individuals younger than 65 years. This illness is also more frequently observed in men [1]. In our study, the mean age of the patient cohort was 63.11±12.13 years, and the female-to-male ratio was 1.11; these findings are consistent with existing epidemiological data. A key result of our study was that serum periostin levels were significantly higher in MM patients than in healthy individuals. According to our information, only one study to date has evaluated the relationship between periostin and MM [9], making our research likely one of the first from Türkiye to examine this association. Periostin is known to be involved in extracellular matrix remodeling, inflammation, and bone metabolism; elevated levels of periostin have been reported in various malignant and inflammatory conditions [2-4]. Given the profound alterations in the bone marrow microenvironment in MM, increased periostin levels may reflect disease-related stromal and inflammatory changes. However, this finding should be interpreted descriptively, as the present study was not designed to establish mechanistic pathways. Despite the elevated periostin levels observed at diagnosis, no statistically significant associations were identified between serum periostin concentrations and clinical or laboratory parameters commonly used to define disease burden, including anemia, renal dysfunction, or hypercalcemia. Similarly, periostin levels did not differ significantly across the International Staging System (ISS), the Revised ISS (R-ISS), the cytogenetic risk categories, or the survival status. Although non-significant trends were observed in some subgroup analyses, these findings cannot support conclusions regarding disease severity or prognostic relevance. This lack of association may be attributable to the heterogeneity of the patient population and the relatively limited sample size. Additionally, since MM is typically diagnosed at an advanced age, age-related factors such as nutritional deficiencies or comorbid renal dysfunction may confound the interpretation of anemia-related findings [10]. In the R-ISS scoring system, elevated LDH levels and high-risk cytogenetic abnormalities contribute to upstaging [11]. Correlation analyses revealed weak to moderate negative associations between periostin levels and certain hematological and biochemical parameters, including white blood cell count, neutrophil count, monocyte count, urea, and β2-MG. These correlations were statistically significant but biologically inconsistent, particularly the inverse relationship observed with β2-MG, a well-established marker of tumor burden in MM. Given the small effect sizes and the exploratory nature of these analyses, no mechanistic or clinical inferences can be drawn. These findings should therefore be interpreted with caution. Existing studies investigating the relationship between periostin and laboratory markers, such as albumin, LDH, and C-reactive protein (CRP), have yielded inconsistent results. Massy et al. [12] reported a negative correlation between periostin and albumin and a positive association with CRP, whereas another study found no statistically significant relationships between periostin and LDH or CRP [13]. In our study, periostin levels were not significantly associated with albumin, LDH, CRP, or cytogenetic abnormalities. The role of periostin in survival outcomes has been explored in several solid tumors. Massy et al. [12], in a cohort of 133 patients with lung adenocarcinoma, demonstrated that high periostin levels were strongly associated with increased mortality in patients with bone metastases. In our study, periostin levels in the 28 patients evaluable for treatment response were lower than in the eight patients who died during follow-up; however, this difference was not statistically significant. This finding positions our study as the first to explore the prognostic implications of periostin in MM. A reduction in serum periostin levels following symptom improvement has previously been described in asthma patients treated with corticosteroids [13]. However, no prior study has compared pre- and post-treatment periostin levels in MM. In our investigation, serum periostin levels decreased significantly after three cycles of induction therapy and reached levels comparable to those of healthy controls. This appears to be the first report in the literature showing such treatment-related changes in MM. This observation suggests that periostin levels may be dynamically influenced by treatment-related changes in the disease microenvironment. However, the clinical significance of this decrease remains unclear, and

whether periostin reflects treatment response or merely secondary inflammatory changes cannot be determined from the current data.

In summary, while serum periostin levels were elevated at diagnosis and decreased following treatment, the absence of statistically significant associations with established prognostic markers limits the clinical interpretation of these findings. Larger prospectively designed studies with appropriate control groups and longer follow-up are required to clarify the potential role of periostin in the biology of MM.

Study Limitations

This study has several important limitations that should be acknowledged. First, the relatively small sample size limits the statistical power of subgroup and correlation analyses, reducing the ability to detect clinically meaningful associations. Second, multiple subgroup comparisons and correlation analyses were performed without adjustment for multiple testing, increasing the risk of type I error. Therefore, statistically significant findings should be interpreted cautiously. Another limitation relates to the control group. Healthy controls were not matched for inflammatory status, renal function, or comorbidities, all of which may influence serum periostin levels. This lack of matching may have affected the observed differences between patients and controls. In addition, periostin measurements were limited to baseline and post-induction time points; longitudinal changes during long-term follow-up were not assessed. Finally, the observational design of the study precludes causal or mechanistic interpretations. The study was not designed to evaluate the prognostic or predictive value of periostin, and survival analyses were limited by short follow-up duration.

Conclusion

Serum periostin levels were significantly higher in newly diagnosed MM patients than in healthy individuals, and decreased significantly in patients following induction therapy. However, no statistically significant associations were observed between periostin levels and disease stage, cytogenetic risk, survival, or treatment response. These findings should be regarded as preliminary and hypothesis-generating. Further studies with larger sample sizes, methodologically matched control groups, and longer follow-up are required to determine the clinical relevance of periostin in MM.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Necmettin Erbakan University Ethics Committee (approval no: 2020/2467, date: 08.05.2020).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: A.K.T., A.T., Design: A.K.T., A.T., İ.K., Data Collection or Processing: A.K.T., İ.K., S.D., Ö.Ç., Analysis or Interpretation: A.K.T., A.T., Literature Search: A.K.T., A.T., Writing: A.K.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Changes in Inflammatory Markers before and after Neoadjuvant Chemotherapy and Their Association with Pathological Complete Response in Breast Cancer

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ABSTRACT

Aim: This study aimed to investigate the association between pre- and post-neoadjuvant chemotherapy (NAC) inflammatory indices and pathological complete response (pCR) in breast cancer patients.

Methods: In this retrospective study, we reviewed the medical records of 412 patients with breast cancer who received NAC between January 2013 and January 2023. We recorded the following indices: pan-immune systemic inflammatory index (PIV), systemic immune-inflammation index (SII), prognostic nutritional index; neutrophil-to-lymphocyte, platelet-to-lymphocyte, and lymphocyte-to-monocyte ratios; hemoglobin and counts of white blood cells, neutrophils, platelets, monocytes, and lymphocytes; and pre-NAC-to-post-NAC ratios of these parameters. Pre-NAC and post-NAC values and their ratios were analyzed. Receiver operating characteristic analysis was used to explore optimal cut-off values. Univariate and multivariate logistic regression analyses were performed to identify factors associated with pCR.

Results: 119 (29%) patients achieved pCR. Cut-off values were explored for the pre-NAC/post-NAC ratios of PIV, SII, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, neutrophil, and hemoglobin. Multivariate analysis showed that HER2 positivity, hormone receptor negativity, earlier T stages, and elevated pre-NAC/post-NAC platelet-to-lymphocyte ratios and hemoglobin levels were independently associated with pCR.

Conclusion: The pre-NAC-to-post-NAC ratios of inflammatory markers were statistically associated with pCR following NAC in breast cancer patients. In addition to established clinicopathological factors such as HER2 positivity, hormone receptor negativity, and earlier T-stage, higher pre-NAC and post-NAC platelet-to-lymphocyte and hemoglobin ratios were associated with pCR. However, the discriminative performance of these markers was limited, as reflected by relatively low area under the curve values. Therefore, these findings represent statistical associations rather than predictive capability, and these markers should not be interpreted as standalone predictive biomarkers. Instead, they may serve only as complementary parameters alongside established clinicopathological factors.

Keywords: Breast cancer, inflammatory indices, neoadjuvant chemotherapy, pathological complete response

Introduction

Neoadjuvant therapies are a key component of breast cancer treatment protocols, owing to their ability to downstage the disease and minimize the extent of interventions in the breast and axilla. The pathological evaluation of the treatment response can inform the design of the regimen. In this sense, pathological complete response (pCR) is recognized as a pivotal prognostic indicator [1,2]; it refers to the absence of residual tumors in the breast and axilla in the resection material following neoadjuvant chemotherapy (NAC) [3]. Patients with HER2-positive and triple-negative

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breast cancers are widely regarded as ideal candidates for neoadjuvant treatments and exhibit notably high rates of pCR following NAC [4]. It should also be noted that it is imperative to select the most suitable patients for NAC, as those who can achieve pCR often demonstrate improved overall survival and disease-free survival compared to their counterparts [1,5].

The host systemic inflammatory response is key in tumor formation, progression, metastasis, and chemotherapy resistance [6,7]. A variety of serum markers influence this response, and the prognostic and predictive value of the response has been extensively examined in a plethora of studies [8,9]. The inflammatory markers include peripheral blood components such as neutrophils, lymphocytes, and platelets, as well as acute-phase proteins (e.g., albumin). In addition, the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), systemic immune-inflammation index (SII), pan-immune systemic inflammatory index (PIV), prognostic nutritional index (PNI), and systemic inflammation response index (SIRI) hold prognostic significance [10-15]. Although the literature hosts research exploring the response to neoadjuvant treatment in breast cancer [16-18], only a few studies evaluated the changes in these inflammatory factors in the treatment response [19,20].

Ultimately, the present study aimed to explore the association between routinely available peripheral blood-derived inflammatory indices and pCR in breast cancer patients receiving NAC. To this end, we evaluated both baseline values and changes from pre- to post-chemotherapy in these inflammatory markers. In this context, the study contributes to the limited body of literature examining the dynamic changes of inflammatory parameters in relation to treatment response.

Methods

In this study, we analyzed data from a cohort of 412 breast cancer patients who underwent surgical procedures following NAC between January 2013 and January 2023 at a tertiary oncology center. Nevertheless, we excluded incomplete records and patients who were unable to complete neoadjuvant therapy, had metastatic disease, or had surgical, traumatic, infectious, or immune-system disorders (e.g., autoimmune diseases and human immunodeficiency virus), because their parameters would have been affected before NAC. The data collection and methods used in this study adhered to the ethical guidelines established by both the institutional and national research committees. Furthermore, they complied with the principles outlined in the 1964 Helsinki Declaration and its subsequent revisions or equivalent ethical standards. The Research Ethics Committee of University of Health Sciences Türkiye, Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, granted ethical approval to our study (approval number: 2024-07/104, date: 25.08.2022). The data collection program for this study was approved by ethics committee with a waiver for individual informed consent for this retrospective study.

We defined pCR as the absence of residual disease in the breast or axilla on pathological examination of specimens obtained during surgery. According to the residual cancer burden (RCB) index, RCB-0 patients were classified as pCR, whereas other patients were classified as non-pCR. We then generated a comprehensive dataset, including patient age, T-stage, pre-NAC nodal status, histopathology, grade, hormone receptor status, HER2 status, molecular subtype, and Ki-67 level. The pathological staging of patients was established according to the American Joint Committee on Cancer tumor, node, metastasis staging manual (8th edition) [21].

We retrospectively extracted the following parameters from pre-NAC and preoperative blood samples in the hospital database: neutrophil count, platelet count, lymphocyte count, hemoglobin, and albumin. We calculated the following pre- and post-NAC parameters for the NAC response:

PIV = (neutrophil×platelet×monocyte)/lymphocyte

SII = (platelet×neutrophil)/lymphocyte

PNI = [10×serum albumin (g/dL)]+[0.005×lymphocyte count(/mm^3)]

NLR = neutrophil/lymphocyte

PLR = platelet/lymphocyte

LMR = lymphocyte/monocyte

Statistical Analysis

We performed a comparative analysis to reveal alterations in these parameters before and after NAC. The optimal cut-off values for inflammatory markers were calculated through receiver operating characteristic (ROC) curve analysis. Accordingly, we designated the value at the point with the highest Youden index as the optimal cut-off value and performed categorization based on this cut-off value. While examining the relationships between pCR and clinicopathological variables using a chi-square test, we performed logistic regression analysis to identify factors affecting pCR. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and Jamovi; a p value<0.05 was considered statistically significant. Model discrimination was evaluated using the area under the ROC curve (AUC). Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. Multicollinearity among predictors was evaluated using variance inflation factors (VIF). VIF values below 5 were considered to indicate the absence of significant multicollinearity.

Results

Comparison of Patients' Clinicopathological Features

Of 412 patients, 119 (29%) demonstrated pCR (pCR group), while 293 (71%) did not (non-pCR group). We found that 233 (39%) of the patients were older than 50 years. The patients were further categorized based on their follow-up status: 50 (12%) were T1, 270 (66%) were T2, and 92 (22%) were T3. 24 (48%) of T1 patients, 76 (28%) of T2 patients, and 19 (21%) of T3 patients achieved pCR (p=0.002). Pre-NAC node positivity

was noted in 205 patients (50%) and 379 patients (92%) had no special type histopathology. While 252 (61%) were Grade III, 160 (39%) were Grades I and II. Additionally, 113 (27%) were hormone-negative. 55 (49%) of hormone-negative and 64 (21%) of hormone-positive cases achieved pCR (p=0.001). Of the patients, 251 (61%) were HER2-negative; pCR was achieved by 42 (17%) of HER2-negative and 77 (48%) of HER2-positive patients (p=0.001) (Table 1).

Findings of ROC Analysis on Inflammatory Markers

In the ROC analysis, we could not determine significant cut-off values for pre-NAC blood parameters: hemoglobin; white blood cell (WBC), neutrophil, platelet, monocyte, and lymphocyte counts; PIV; SII; PNI; neutrophil/lymphocyte; platelet/lymphocyte; and lymphocyte/monocyte. It was also the case for post-NAC blood parameters: hemoglobin, WBC, neutrophil, platelet, monocyte, and lymphocyte counts; and PNI, neutrophil/lymphocyte, platelet/lymphocyte, and lymphocyte/monocyte. However, we calculated the optimal cut-offs to be 281 for post-NAC PIV (sensitivity =47%, specificity =32%, p=0.024, AUC=0.429) and 685.37 for SII (sensitivity =55%, specificity =45%, p=0.021, AUC=0.428).

We also determined pre- and post-NAC values of PIV, SII, NLR, PLR, neutrophil count, hemoglobin level, platelet count, and PNI and evaluated changes in these parameters. Accordingly, we calculated optimal cut-off values for the following pre-NAC/post-NAC ratios: PIV=0.8564 (sensitivity =54%, specificity =46%, p=0.01, AUC=0.575); SII=0.8853 (sensitivity =54%, specificity =46%, p=0.01, AUC=0.581); neutrophil/lymphocyte =0.8766 (sensitivity =54%, specificity =46%, p=0.03, AUC=0.568); platelet/lymphocyte =0.7560 (sensitivity =57%, specificity =43%, p=0.03, AUC=0.568); neutrophil =1.2173 (sensitivity =56%, specificity =44%, AUC=0.563); and hemoglobin =1.1245 (sensitivity =57%, specificity =43%, AUC=0.575) (Table 2). The ROC curves of the variables for which the optimal cut-off was determined are shown in Figures 1-6.

Univariate and Multivariate Analyses

The parameters were then categorized into two groups (i.e., < cut-off and ≥ cut-off). In univariate analysis, the pre-NAC/post-NAC ratios of PIV (p=0.025), SII (p=0.011), platelet/lymphocyte (p=0.011), neutrophil (p=0.018), and hemoglobin (p=0.011) were associated with pCR to neoadjuvant treatment (Table 3). The logistic regression analysis showed that the pre-NAC/post-NAC ratios of platelet/lymphocyte and hemoglobin, together with hormone receptor status, HER2 status, and T-stage, were independent factors associated with pCR following neoadjuvant treatment. The multivariable model demonstrated good discrimination with an AUC of 0.798. Model calibration was acceptable according to the Hosmer-Lemeshow goodness-of-fit test (χ^2=8.99, df=8, p=0.343). Multicollinearity analysis showed no significant correlation among predictors (all VIF values <2). Furthermore, elevated pre-NAC platelet/lymphocyte ratio and hemoglobin, along with HER2 positivity, hormone negativity, and earlier T stages, were associated with pCR to neoadjuvant therapy (Table 4). These findings indicate statistical associations between certain inflammatory marker ratios and pCR; however, the observed relationships should not be interpreted as evidence that these markers function as independent predictive biomarkers.

Discussion

In this study, we retrospectively reviewed the medical records of 412 breast cancer patients receiving NAC and evaluated the association between inflammatory markers and pCR, including PIV, SII, and PNI; NLR, PLR, and LMR; hemoglobin, WBC, neutrophil, platelet, monocyte, and lymphocyte counts; and pre-NAC/post-NAC ratios of these parameters. The pCR to neoadjuvant treatment was more prevalent among patients whose pre-NAC/post-NAC PLR and hemoglobin ratios exceeded the cut-off values. Moreover, the multivariate analysis revealed that HER2 positivity, hormone negativity, and earlier T-stages were associated with increased pCR to

Table 1. Patients' clinicopathological features

Clinicopathological variables	pCR (%) n=119	Non-pCR (%) n=293	p value
Age (years)			
<50	52 (44)	127 (43)	0.517
≥50	67 (56)	166 (57)	
T-stage			
T1	24 (20)	26 (9)	0.002*
T2	76 (64)	194 (66)	
T3	19 (16)	73 (25)	
Pre-NAC nodal status			
Negative	57 (48)	148 (51)	0.710
Positive	62 (52)	145 (49)	
Histopathology			
NST	114 (96)	265 (91)	0.122
Lobular	4 (3)	18 (6)	
Others	1 (1)	10 (3)	
Grade			
Grade III	83 (70)	169 (58)	0.003*
Grades I and II	36 (30)	124 (42)	
HR status			
Negative	55 (46)	58 (20)	<0.001*
Positive	64 (54)	235 (80)	
Ki-67			
≤14	10 (8)	30 (10)	0.713
>14	103 (87)	246 (84)	
Missing	6 (5)	17 (6)	
HER2 status			
Negative	42 (35)	209 (71)	<0.001*
Positive	77 (65)	84 (29)	
Molecular sub-type			
HR(+) HER2(+)	44 (37)	65 (22)	<0.001*
HR(+) HER2(-)	20 (17)	173 (59)	
HR(-) HER2(+)	33 (28)	20 (7)	
Triple negative	22 (18)	34 (12)	

*: Statistically significant (p<0.05)
pCR: Pathologic complete response, NAC: Neoadjuvant chemotherapy, HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2, Ki-67: Ki-67 proliferation index, NST: No special type

neoadjuvant treatment. However, the discriminative ability of these markers was limited. The ROC analyses demonstrated relatively low AUC values (<0.60), indicating a modest ability to distinguish between patients who achieved pCR and those who did not. Therefore, these findings should be interpreted as exploratory associations rather than evidence of clinically useful predictive biomarkers.

Inflammation plays a key role in cancer pathogenesis. The alterations in inflammatory cells have therefore been scrutinized for many years, as they serve as a reflection of the tumor's inflammatory response [7]. Moreover, the routine evaluation of pre-treatment blood parameters has been investigated for potential associations with treatment response. As is widely acknowledged, NAC, high grade, hormone negativity, and HER2/neu amplification are the factors that predict pCR in breast cancer [22]. Similarly, we found that hormone receptor status, T-stage, and HER2 amplification status were significant predictors of pCR in both univariate and multivariate analyses.

Numerous studies have explored the relationship between blood parameters and pCR in breast cancer patients receiving NAC. In their study, Yang et al. [10] found significant associations between low neutrophil/lymphocyte (<2.46), platelet/lymphocyte (<118.78), and SII (<403.20) with pCR in breast cancer. While Ma et al. [23] showed lymphocyte/monocyte (>6.2) to be associated with pCR to NAC, Goto et al. [24] could not find a significant correlation between them. Similarly, Ma et al. [25] found a significant correlation between

Table 2. Findings of ROC analysis

	Value	AUC (95%)	Cut-off	p value	Sensitivity %	Specificity %
RATES pre-NAC/post-NAC	PIV (pre-NAC/post-NAC) ratio	0.575	0.8564	0.01*	54	46
	SII (pre-NAC/post-NAC) ratio	0.581	0.8853	0.01*	54	46
	Neutrophil/lymphocyte (pre-NAC/post-NAC) ratio	0.568	0.8766	0.03*	54	46
	Platelet/lymphocyte (pre-NAC/post-NAC) ratio	0.568	0.7560	0.03*	57	43
	Pre-NAC/post-NAC neutrophil ratio	0.563	1.2173	0.04*	56	44
	Pre-NAC/post-NAC hemoglobin ratio	0.575	1.1245	0.01*	57	43
	Pre-NAC/post-NAC platelet ratio	0.560	-	0.055	-	-
	Pre-NAC/post-NAC PNI ratio	0.472	-	0.365	-	-
PRE-NAC	Pre-NAC PIV	0.514	-	0.666	-	-
	Pre-NAC SII	0.516	-	0.617	-	-
	Pre-NAC PNI	0.500		0.997		
	Pre-NAC neutrophil/lymphocyte	0.508	-	0.797	-	-
	Pre-NAC PLT/lymphocyte	0.526	-	0.405	-	-
	Pre-NAC lymphocyte/monocyte	0.501	-	0.968	-	-
	Pre-NAC hemoglobin	0.494	-	0.843	-	-
	Pre-NAC WBC	0.493	-	0.840	-	-
	Pre-NAC neutrophil	0.499	-	0.986	-	-
	Pre-NAC PLT	0.541	-	0.204	-	-
	Pre-NAC monocyte	0.494	-	0.856	-	-
	Pre-NAC lymphocyte	0.480	-	0.542	-	-
POST-NAC	Post-NAC PIV	0.429	281	0.024*	47	32
	Post-NAC SII	0.428	685.37	0.021*	55	45
	Post-NAC PNI	0.516		0.618		
	Post-NAC neutrophil	0.436	-	0.042*	-	-
	Post-NAC PLT/lymphocyte	0.463	-	0.234	-	-
	Post-NAC lymphocyte/monocyte	0.538	-	0.232	-	-
	Post-NAC hemoglobin	0.459	-	0.917	-	-
	Post-NAC WBC	0.470	-	0.343	-	-
	Post-NAC neutrophil/lymphocyte	0.443	-	0.71	-	-
	Post-NAC PLT	0.468	-	0.312	-	-
	Post-NAC monocyte	0.470	-	0.338	-	-
	Post-NAC lymphocyte	0.516	-	0.606	-	-

*: Statistically significant (p<0.05)
ROC: Receiver operating characteristic, AUC: Area under the curve, NAC: Neoadjuvant chemotherapy, PIV: Pan-immune-inflammation value, SII: Systemic immune-inflammation index, PNI: Prognostic nutritional index, PLT: Platelet, WBC: White blood cell

high pre-NAC platelet counts and treatment response; however, this was not the case in the study by Corbeau et al. [26]. Şahin et al. [27] identified a significant relation between pCR in patients with low PIV. Marín et al. [28] and Losada et al. [29] discovered no significant link between neutrophil/monocyte and pCR. Therefore, among the abovementioned variables, we could not identify useful parameters with optimal cut-off values for predicting pCR. Although most individual inflammatory parameters were not significantly associated with pCR, ratios reflecting changes between pre- and post-NAC values were significantly associated with treatment response. This observation may suggest that dynamic changes in inflammatory markers reflect treatment-related biological responses more than single baseline measurements. However, given the limited discriminative performance observed in the current study, these findings should be interpreted cautiously and confirmed in larger prospective cohorts.

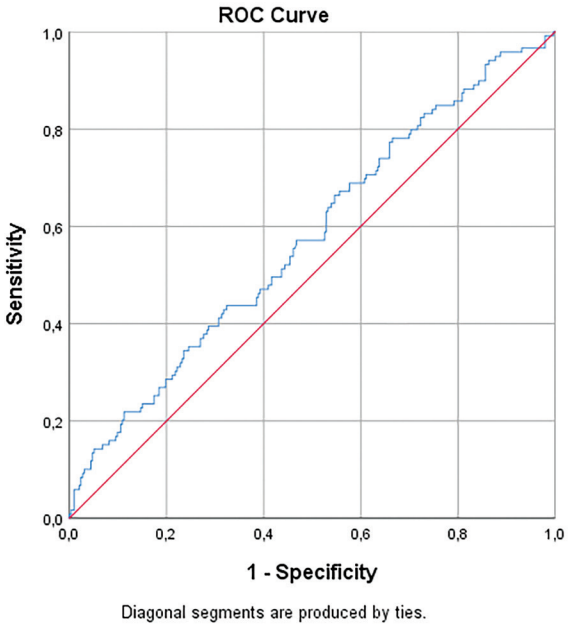

Figure 1. PIV (pre-NAC-post-NAC) ratio

Pre-NAC: Pre- and post-neoadjuvant chemotherapy, ROC: Receiver operating characteristic, PIV: Pan-immune systemic inflammatory index

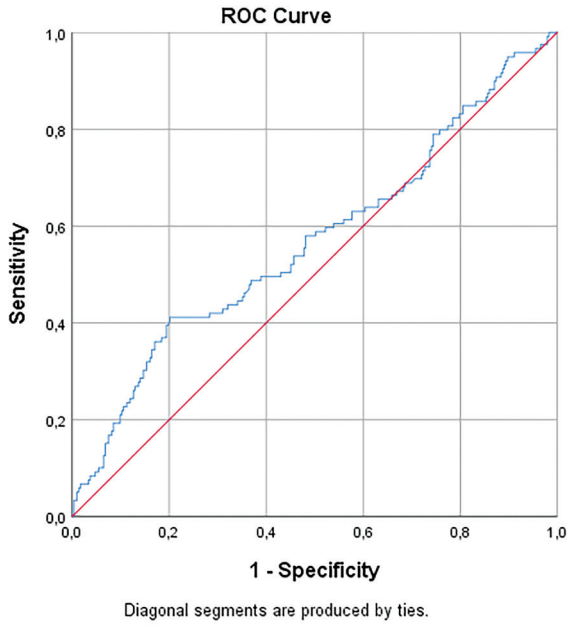

Figure 3. Neutrophil/lenfosit (pre-NAC-post-NAC) ratio

Pre-NAC: Pre- and post-neoadjuvant chemotherapy, ROC: Receiver operating characteristic

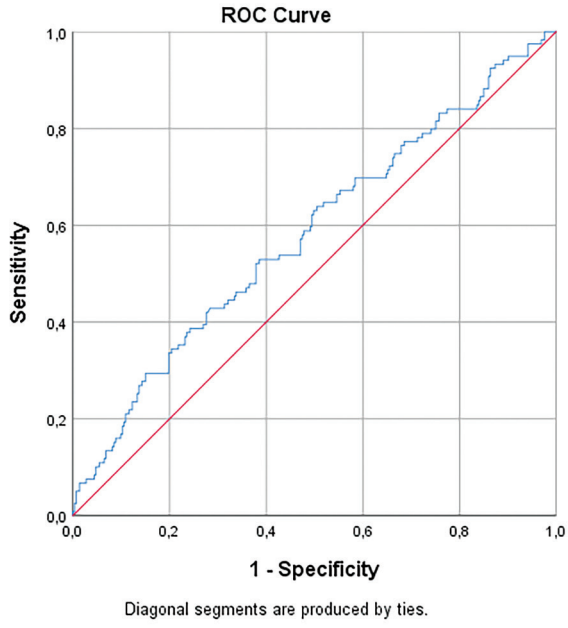

Figure 2. SII (pre-NAC-post-NAC) ratio

Pre-NAC: Pre- and post-neoadjuvant chemotherapy, ROC: Receiver operating characteristic, SII: Systemic immune-inflammation index

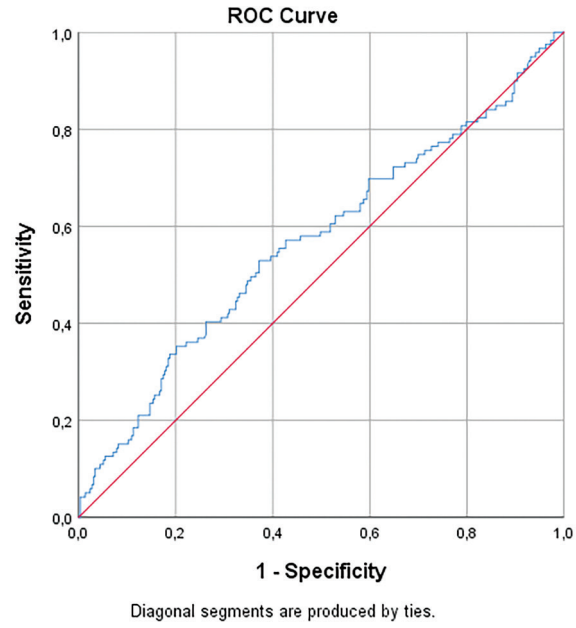

Figure 4. PLT/lenfosit (pre-NAC-post-NAC) ratio

Pre-NAC: Pre- and post-neoadjuvant chemotherapy, ROC: Receiver operating characteristic, PLT: Platelet

In this study, we observed that pre-NAC/post-NAC ratios of PIV (p=0.01), SII (p=0.01), neutrophil/lymphocyte (p=0.03), platelet/lymphocyte (p=0.03), neutrophil (p=0.04), and hemoglobin (p=0.01) were significantly associated with pCR following NAC based on derived cut-off values.

The significance of this study may lie in its pioneering attempt to elucidate the impact of changes in inflammatory markers on pCR to NAC, as a review of the extant literature reveals a paucity of studies addressing this subject. In their study, Dan et al. [20] reported an association between pre- and post-treatment alterations in NLR and pCR following NAC in breast cancer patient. In another study, Omarini et al. [19] focused on the association between the decline in hemoglobin and pCR to NAC and found a >2 g/dL decrease in hemoglobin level to be linked with a diminished pCR (15% vs. 43%, p=0.047). In contrast, we could not identify a significant association between NLR and pCR; however, we found that high pre-NAC/post-NAC hemoglobin ratios were statistically associated with pCR in our cohort.

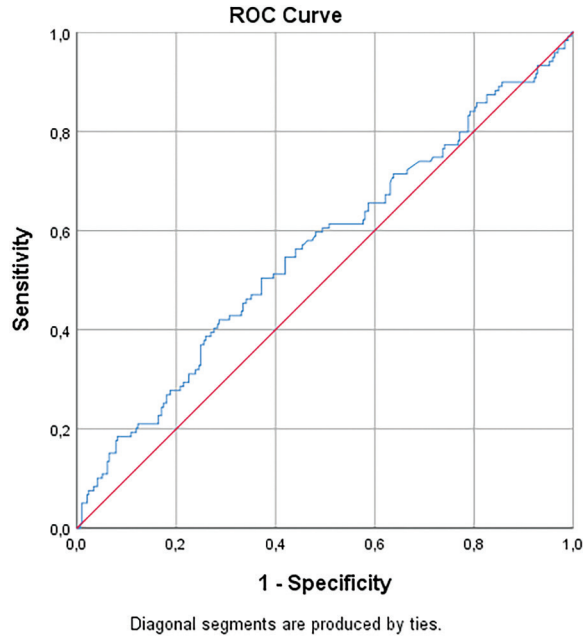

Figure 5. Neutrophil (pre-NAC-post-NAC) ratio

Pre-NAC: Pre- and post-neoadjuvant chemotherapy, ROC: Receiver operating characteristic

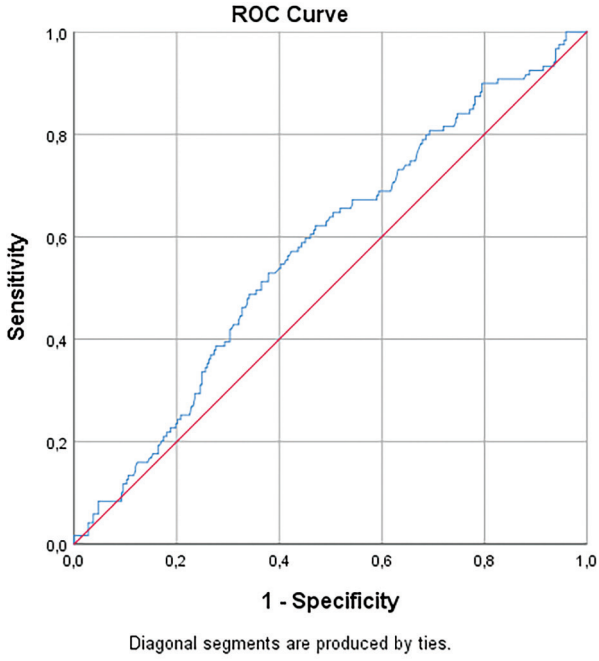

Figure 6. Hemoglobin (pre-NAC-post-NAC) ratio

Pre-NAC: Pre- and post-neoadjuvant chemotherapy, ROC: Receiver operating characteristic

This study has notable strengths. The analysis was conducted in a relatively large cohort of patients treated in routine clinical practice over a 10-year period, and it systematically assessed multiple inflammatory indices derived from standard blood tests. Importantly, we focused on changes from pre- to post-treatment, which may better reflect treatment-related biological dynamics than baseline values alone. Importantly, the results of this study demonstrate statistical associations rather than causal or predictive relationships. Therefore, inflammatory marker dynamics should not be considered standalone predictive biomarkers. Instead, they may be incorporated as complementary variables in future multivariable prediction models alongside established clinicopathological factors.

Study Limitations

This study has several limitations. First, its retrospective, single-center design may introduce selection bias and limit the generalizability of the findings. Second, although several inflammatory marker ratios showed statistically significant associations with pCR, their discriminative performance was limited. The ROC analyses yielded relatively low AUC values, indicating that these markers have only a modest ability to discriminate between patients achieving pCR and those who do not. Third, cut-off values were derived from the same dataset, and the study lacked an external validation cohort, which raises the possibility of overfitting and limits the applicability of these thresholds to other populations. Therefore, the possibility of model overfitting cannot be excluded, and the derived thresholds should be interpreted with caution, as their generalizability to other patient populations remains uncertain. Fourth, the timing of post-NAC blood sampling and potential unmeasured confounders (e.g., intercurrent infections, concomitant medications, nutritional status, and treatment-related toxicities) may have influenced inflammatory markers. The sample size within molecular subgroups was relatively limited, which may have reduced the power of subgroup analyses. Prospective multicenter studies with standardized sampling time points and external validation are warranted to confirm these findings and clarify the incremental value of inflammatory marker dynamics beyond established clinicopathological predictors. The multivariable model also demonstrated acceptable calibration according to the Hosmer-Lemeshow test; however, external validation was not performed, and the results should therefore be interpreted cautiously.

Table 3. Pairwise comparisons of inflammatory markers

	pCR (%) n=119	Non-pCR (%) n=293	p-value
PIV ratio (pre-NAC/post-NAC)			
<0.8564	52 (44)	161 (55)	0.025*
≥0.8564	67 (56)	132 (45)	
SII ratio (pre-NAC/post-NAC)			
<0.8853	49 (41)	159 (54)	0.011*
≥0.8853	70 (59)	134 (46)	
Neutrophil/lymphocyte ratio (pre-NAC/post-NAC)			
<0.8766	55 (46)	157 (54)	0.193
≥0.8766	64 (54)	136 (46)	
Platelet/lymphocyte ratio (pre-NAC/post-NAC)			
<0.7560	52 (44)	166 (57)	0.011*
≥0.7560	67 (56)	127 (43)	
Neutrophil ratio (pre-NAC/post-NAC)			
<1.2173	52 (44)	163 (56)	0.018*
≥1.2173	67 (56)	130 (44)	
Hemoglobin ratio			
<1.1245	46 (39)	165 (56)	0.011*
≥1.1245	73 (61)	128 (44)	
Post-NAC PIV			
<281	63 (53)	139 (47)	0.329
≥281	56 (47)	154 (53)	
Post-NAC SII			
<685.37	65 (55)	130 (44)	0.065
≥685.37	54 (45)	163 (56)	

*: Statistically significant (p<0.05)
pCR: Pathologic complete response, NAC: Neoadjuvant chemotherapy, PIV: Pan-immune-inflammation value, SII: Systemic immune-inflammation index

Table 4. Model coefficients - pCR

						95% confidence interval	
Predictor	**Estimate**	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
Intercept	-0.904	0.546	-1.656	0.09	0.405	0.139	1.180
T Stage							
T3-T1	1.027	0.448	2.2906	0.022	2.792	1.160	6.722
T2-T1	0.794	0.372	2.1337	0.033	2.212	1.067	4.587
Grade							
Grade II - Grade III	0.456	0.286	1.5958	0.111	1.578	0.901	2.764
PIV pre-NAC/post-NAC)							
Ref.<Cut-off value	0.121	0.357	0.3397	0.734	1.129	0.561	2.274
SII pre-NAC/post-NAC)							
Ref.<cut-off value	0.373	0.439	0.8508	0.395	1.453	0.615	3.434
Neutrophil/lymphocyte ratio							
Ref.<cut-off value	-0.377	0.384	-0.9829	0.326	0.686	0.323	1.455
Platelet/lymphocyte ratio							
Ref.<cut-off value	0.714	0.331	2.1585	0.031	2.042	1.068	3.905
Neutrophil ratio (pre-NAC/post-NAC)							
Ref.<cut-off value	-0.525	0.326	-1.6098	0.107	0.592	0.312	1.121
Hemoglobin ratio (pre-NAC/post-NAC)							
Ref.<cut-off value	0.544	0.268	2.0283	0.043	1.722	1.018	2.912
HR status							
Negative-positive (ref)	-1.064	0.271	-3.9223	<0.001	0.345	0.203	0.587
HER2 status							
Negative-positive (ref)	1.475	0.263	5.6093	<0.001	4.370	2.610	7.315

pCR: Pathologic complete response, NAC: Neoadjuvant chemotherapy, HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2

Conclusions

Changes in inflammatory marker ratios before and after NAC were significantly associated with pCR among breast cancer patients. However, these results demonstrate only associations and do not support the use of these markers as standalone predictive biomarkers. This limitation is further supported by the relatively low AUC values observed in ROC analyses and the absence of an independent validation cohort. Therefore, inflammatory markers should be interpreted as complementary indicators alongside established clinicopathological factors. Higher pre-NAC/post-NAC platelet-to-lymphocyte and hemoglobin ratios, HER2 positivity, hormone receptor negativity, and earlier T-stage were independently associated with pCR. However, given their limited discriminative performance, these inflammatory markers should not be considered standalone predictive tools but rather complementary to established clinicopathological factors; further prospective validation is required.

Ethics

Ethics Committee Approval: The Research Ethics Committee of University of Health Sciences Türkiye, Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, granted ethical approval to our study (approval number: 2024-07/104, date: 25.08.2022).

Informed Consent: The data collection program for this study was approved by ethics committee with a waiver for individual informed consent for this retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.F.S., A.K., C.Ö., Concept: M.F.S., A.K., C.Ö., Design: M.F.S., A.K., C.Ö., Data Collection or Processing: M.F.S., E.G., C.Y.B., F.A., A.K., C.Ö., Analysis or Interpretation: M.F.S., A.K., C.Ö., Literature Search: M.F.S., E.G., C.Y.B., A.K., C.Ö., Writing: M.F.S., A.K., C.Ö.

Conflict of Interest: No conflict of interest was declared by theauthors.

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Original Article

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Retrospective Evaluation of Patients with Acute Myeloid Leukaemia in the Trakya Region of Türkiye

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ABSTRACT

Aim: Acute myeloid leukaemia (AML) is an aggressive haematological malignancy that primarily affects older adults. Its prognosis varies widely depending on cytogenetic and molecular risk profiles, as well as age, performance status, and comorbidities. This study aimed to examine the demographic and clinical characteristics, treatment responses, and prognostic factors of patients diagnosed with AML at the Hematology Clinic of Trakya University Health Application and Research Hospital and to assess their role in treatment decision-making.

Methods: This retrospective cohort study included 111 patients (out of 185 adults aged ≥18 years diagnosed between 2017 and 2021) for whom complete data were available. The diagnosis was established according to the World Health Organization 2016/2022 criteria. Collected data encompassed age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, Charlson comorbidity index, European LeukemiaNet 2022 risk group, induction therapies, and treatment response. Statistical analyses were conducted using SPSS v.26; $p<0.05$ was considered significant.

Results: The median age was 66 years, with 59.5% of patients aged 60 or older. The male-to-female ratio was 1.36. Among the patients, 46% were from outside Trakya (Edirne: 29%; Kırklareli: 17%) and 8% were from abroad. Annual incidence ranged from 5.9 to 7.4 per 100,000. Among the 80 evaluable patients, 66.3% (n=53) achieved complete remission (CR), 2.5% had a partial response, and 31.3% had refractory disease. In the CR group, age and Charlson comorbidity index were significantly lower, while the proportion with ECOG 0 was significantly higher (p=0.016). The "3+7" regimen achieved a markedly higher CR rate than hypomethylating agent monotherapy (p=0.002); azacitidine + venetoclax showed comparable efficacy to "3+7" (p=0.431).

Conclusion: Advanced age and a high comorbidity burden adversely affect treatment response. The "3+7" regimen remains the gold standard for fit patients, while azacitidine + venetoclax emerges as a promising, lower-toxicity alternative for elderly or unfit individuals. This study provides the first comprehensive real-world AML data from our region and may serve as a foundation for prospective research.

Keywords: Acute myeloid leukaemia, cytogenetics, prognosis, Trakya, venetoclax

Introduction

Acute myeloid leukaemia (AML) is a heterogeneous group of aggressive haematological malignancies that typically occur in older adults. It is characterised by the uncontrolled clonal proliferation of leukemic cells in the bone marrow, along with impaired maturation of myeloid progenitor cells, leading to their accumulation there and, less commonly, in extramedullary tissues.

The aetiology involves multiple contributing factors, including genetic abnormalities (such as chromosomal translocations and gene mutations), exposure to ionising radiation, and prior treatment with certain chemotherapeutic agents (especially alkylating agents or topoisomerase II inhibitors).

AML is the common type of acute leukaemia in adults, accounting for roughly 80% of cases in this age group [1,2]. In contrast, it accounts for less than 10% of acute leukaemias in children under 10 years old. Globally, the incidence is reported to be about 3-5 cases per 100,000 population [3-5]. According to global data, the median age at diagnosis among adults is approximately 65 years, with 60% of patients aged 65 or older. However, in Türkiye, the average age is slightly younger, at

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around 58 years, and 45.5% of cases occur in people aged 60 and above [6]. The incidence rises sharply with age: it's approximately 2 per 100,000 in those under 65, but increases to around 20 per 100,000 in those over 65 [7]. The male-to-female ratio is approximately 5:3. While AML epidemiology in Türkiye follows similar global patterns, national registry data indicate that the median age at diagnosis is somewhat lower than in many other countries [6].

Mortality increases with age, and about 72% of deaths occur in people aged 65 years and older. The average age at death for AML patients is around 72 years.

Treatment decisions depend on several factors, including the patient's overall performance status, comorbidity burden, and cytogenetic/molecular risk profile. The classic induction regimen "3+7" (cytarabine plus an anthracycline) remains curative in fit patients. For older adults, those with high comorbidities, or frail individuals, lower-toxicity options like hypomethylating agent (HMA) (e.g., azacitidine or decitabine) tend to take priority. In recent years, adding venetoclax to these HMA regimens has yielded promising results, thereby opening a valuable new treatment pathway, particularly for patients who are not candidates for allogeneic stem cell transplantation. When considering intensive chemotherapy for AML, clinicians should assess two key criteria to determine the patient's tolerance to the treatment. The patient's performance status, as measured by the Eastern Cooperative Oncology Group (ECOG) score [8], and the presence of comorbidities that may affect life expectancy, evaluated using the Charlson comorbidity index [9], should always be carefully reviewed.

This retrospective study, drawing on hospital-based data, aims to evaluate the demographic and clinical characteristics and treatment responses of patients diagnosed with AML in the Trakya region over 5 years, thereby contributing to national AML data in Türkiye.

Methods

This retrospective cohort study included 111 of 185 adults aged 18 years and older diagnosed with AML between January 2017 and December 2021, for whom complete clinical and laboratory data were available. These patients were seen at the Division of Haematology, Department of Internal Medicine, Trakya University Faculty of Medicine. Ethical approval for this study was obtained from the Scientific Research Ethics Committee of the Trakya University Faculty of Medicine, and the study was conducted in accordance with the principles of the Helsinki Declaration (decision no: TÜTF-BAEK 2020/350, date: 14.09.2020). Committee under protocol number 2020/350.

AML diagnosis was established according to the World Health Organisation 2016/2022 classification systems [10, 11]. Bone marrow aspiration and biopsy were performed in patients presenting with laboratory abnormalities such as anaemia (Hb <12 g/dL), thrombocytopenia (<100,000/mm^3), thrombocytosis (>450,000/mm^3), leukopenia (<4,000/mm^3), or leukocytosis (>10,000/mm^3). The diagnosis relied primarily on the presence of blast cells constituting ≥20% of total bone marrow cellularity, along with immunophenotyping results (by flow cytometry) consistent with AML. In cases where defining genetic abnormalities were present (e.g., specific translocations), the blast threshold was evaluated according to the revised criteria [12]. The demographic characteristics of the patients, performance status (ECOG score [8]), comorbidity burden (Charlson comorbidity index [9]), and European LeukemiaNet 2022 risk groups, as well as administered induction therapies, treatment responses, and complications, were retrospectively collected in anonymised form from the electronic medical record system.

Statistical Analysis

Statistical analyses were performed using SPSS version 26; p values <0.05 were considered statistically significant.

Results

Demographic characteristics are summarised in Table 1. Among the patients, 64 (57.7%) were male and 47 (42.3%) were female, yielding a male-to-female ratio of 1.36. The median age of the cohort was 66 years (25th-75th percentiles: 48.0-75.0). When stratified by gender, median ages were 60 years (47-71.8) in males and 68 years (56-76) in females. Patients were dichotomised at 60 years: 45 patients (40.5%) were <60 years old, while 66 patients (59.5%) were ≥60 years old. Among females, 70.2% (n=33) were in the ≥60 years group, compared with 51.6% (n=33) of males; this difference was statistically significant (chi-square test: χ^2=3.910, p=0.048). The distribution of patients by place of residence was as follows: 29% from Edirne, 17% from Kırklareli, 10% from İstanbul, 8% from Tekirdağ, 8% from abroad, 6% from Çanakkale, 2% from Bursa, and the remaining 20% from various other provinces in Türkiye (each contributing <1%). The proportion of patients coming from outside the Trakya region was 46%. The geographic distribution of patients' residences is shown in Figure 1.

As shown in Figure 2, in 2017, of 444,515 patients presenting to our hospital, 9,178 were referred to the haematology clinic and 33 were diagnosed with AML. Among 521,876 hospital admissions in 2018, 9,650 patients were seen in Haematology, of whom 31 received an AML diagnosis. Of 554,764 hospital admissions in 2019, 11,662 were managed in haematology and AML was confirmed in 40 patients. In 2020, of the 367,393 total presentations, 8,685 were evaluated by haematology, which resulted in 26 AML diagnoses. Of 455,409 hospital admissions in 2021, 10,163 patients were referred to haematology and 32 were diagnosed with AML. The crude, age-independent AML incidence rates at our hospital (per 100,000 hospital admissions) were calculated as follows: 7.4 in 2017, 5.9 in 2018, 7.2 in 2019, 7.0 in 2020, and 7.0 in 2021 (Figure 3). The incidence rate was determined using the formula: (incidence rate per 100,000) = (number of new AML cases diagnosed in

that year ÷ total number of patients presenting to the hospital in that year) ×100,000.

Among the 80 patients for whom response evaluation was possible, the complete remission (CR) rate was 66.3% (n=53). This group included 29 patients aged <60 years and 24 aged ≥60 years. Partial response (PR) was observed in only 2 patients (2.5%), whereas the non-responsive group comprised 25 patients (31.3%), with 8 in the <60 years group and 17 in the ≥60 years group. Given the small number of partial responders, patients were classified into two groups: CR and non-responders. The distributions of demographic and clinical parameters for the two groups are shown in Table 2. The distribution of administered treatment regimens was as follows: 20 patients (18%) received the azacitidine + venetoclax combination and 28 patients (25.2%) received azacitidine monotherapy. Among cases achieving CR, those on azacitidine ± venetoclax regimens accounted for 22.6% of the group.

When evaluating responses to induction therapy, non-responders were significantly older and had higher Charlson index scores than complete responders. For ECOG scores, the categories "1," "2," and "3" were combined for analysis, and the complete response group had a notably higher proportion of patients with a score of "0" than the non-responsive group (p=0.016). In subgroup analysis by treatment received, the complete response rate in the "3+7" treatment group was significantly higher than that in the azacitidine monotherapy group (p=0.002). No significant difference in response rate was found between the "3+7" group and the azacitidine + venetoclax group (p=0.431). Similarly, there was no significant difference in treatment response rates between the azacitidine monotherapy group and the azacitidine + venetoclax group.

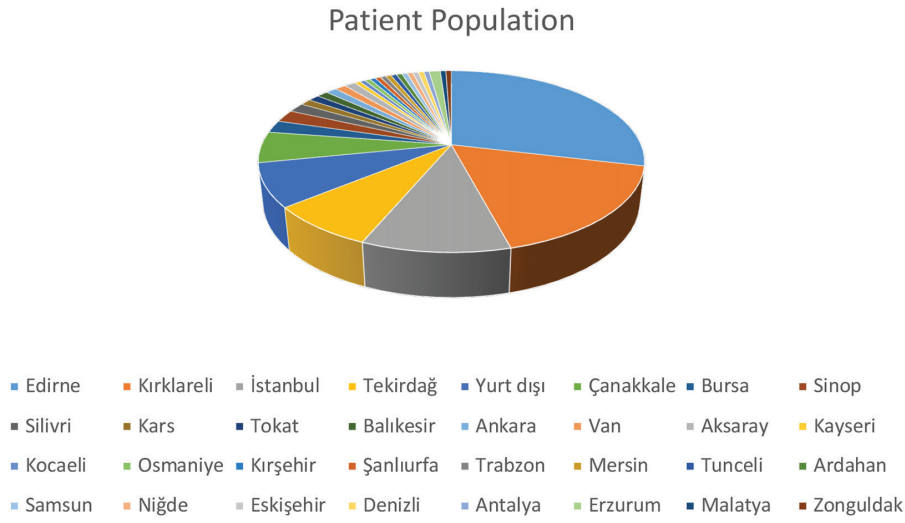

Figure 1. Distribution of patients according to their place of residence

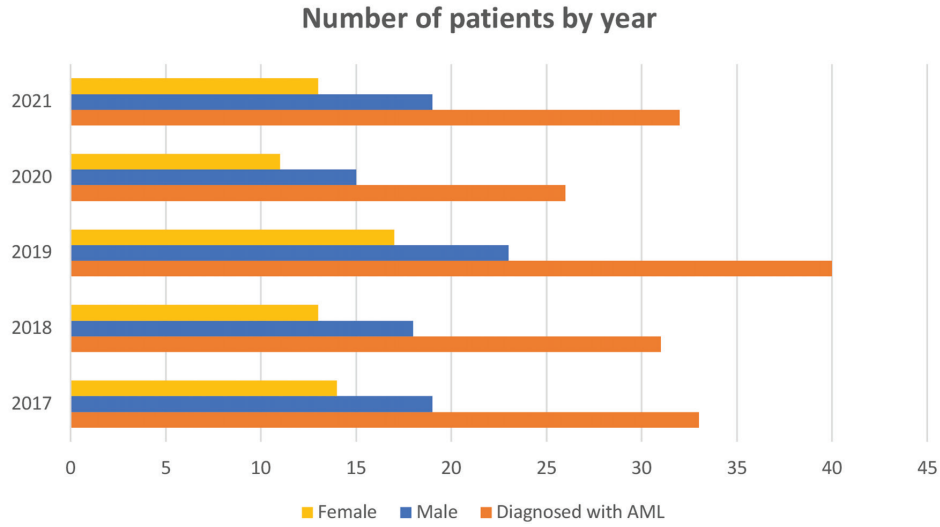

Figure 2. Number of patients by year
AML: Acute myeloid leukaemia

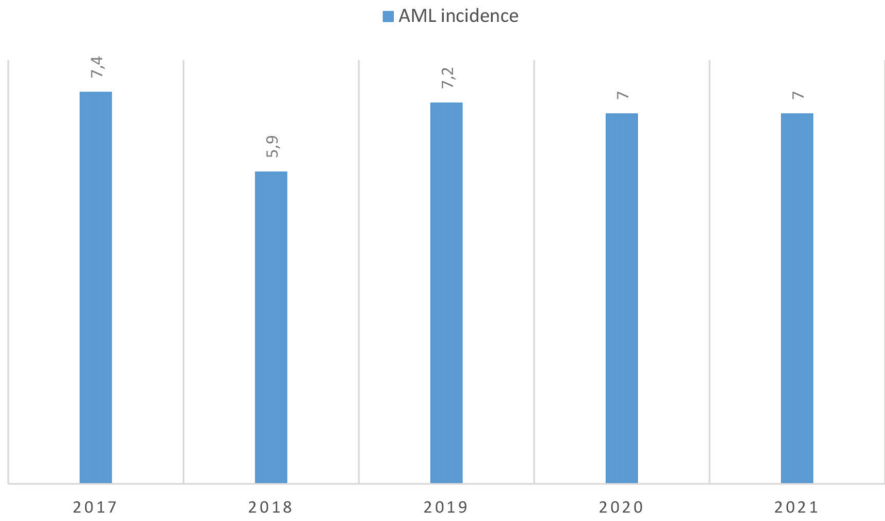

Figure 3. AML incidence by year
AML: Acute myeloid leukaemia

Discussion

AML is an aggressive haematological malignancy that typically occurs in older adults, and its treatment is individualised based on factors such as age, performance status, comorbidities, and cytogenetic and molecular risk profile. The classic "3+7" induction regimen still holds curative potential in fit patients, whereas in elderly and frail individuals, HMA-based therapies come to the forefront due to their lower toxicity. In recent years, the addition of venetoclax to HMAs has notably improved response rates and survival, particularly among patients ineligible for allogeneic transplantation. This study retrospectively evaluated the demographic, clinical, and therapeutic characteristics of 111 patients with AML diagnosed in the Trakya region, thereby highlighting the role of prognostic factors in treatment response.

Globally, the incidence of AML has been gradually increasing over the past few years. According to the Global Burden of Disease (GBD) 2017 data, the number of new cases increased from approximately 63,840 in 1990 to 119,570 in 2017, representing an 87.3% increase. More recent GBD 2021 analyses indicate a rise from 79,372 cases in 1990 to 144,645 cases in 2021 (an 82% increase). This upward trend is largely attributable to population growth and ageing [13]. Higher case numbers have been reported in Western Europe and South Asia. At the country level, India, China, and the United States (USA) stand out as the countries with the highest absolute numbers of cases. According to the United States National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data, the incidence rate during 2012-2016 was 4.3 cases per 100,000 population per year. The most recent SEER data for 2018-2022 show that this rate has remained stable at the same level (4.3 per 100,000) [13,14]. In our study, the hospital-based crude incidence rates ranged from 5.9 to 7.4 per 100,000 admissions. This figure likely reflects the referral pattern to our tertiary referral centre, which receives more advanced-stage cases. 46% of patients came from outside the Trakya Region, and 8% from abroad, highlighting that our centre has become a leading and trusted institution in regional health tourism.

Table 1. According to the studies, the median age

	Median age (years)
NCI SEER 21 [15]	68
Medeni et al. [16]	53±15.3
Cömert et al. [17]	52.44
TSD AML Working Group [6]	58
Our study	66

NCI: National Cancer Institute, SEER: Surveillance, Epidemiology, and End Results, AML: Acute myeloid leukaemia, TSD: Turkish Society of Hematology

According to an analysis of NCI SEER-21 data, the median age of patients diagnosed with AML was 68 years [15]. In a Turkish study by Medeni et al. [16], a 2015 study including 140 patients reported a median age of 53±15.3 years. Another local study by Cömert et al. [17], published in 2014 and comprising 87 patients, reported a mean age of 52.44 years. In our group of 111 patients, the median age was 66,0 years (25^{th}-75^{th} percentile: 48-75), being 60,0 years (47-71.8) for males and 68,0 years (56-76) for females, as shown in Table 1. The interim results of the Turkish Society of Haematology AML registry study [6], which included 891 patients, reported a median age of 58 years (45.5% aged ≥60 years). The higher age at diagnosis in our Trakya cohort may reflect regional demographic differences, such as an older population and referral patterns to our tertiary centre. According to NCI SEER-21 data, the male-to-female ratio among AML patients is 1.44 [15]. In our study, 64 patients (57.7%) were male and 47 (42.3%) were female, yielding a male-to-female ratio of 1.36, consistent with existing literature. Patients in the studies by Medeni et al. [16] and Cömert et al. [17] were notably younger

than those in our series, whereas our median age and gender distribution align more closely with international figures.

Among patients for whom response evaluation was possible, the CR rate was 66.3%, consistent with rates reported in large series. In the study by Chang et al. [18]. Among 379 patients, the CR rate was 59.8%. In our series, PR remained limited (n=2, 2.5%); therefore, the patients were divided into two groups—CR and non-responsive—and the distribution of parameters between these groups is presented in Table 2. Twenty patients (18%) received the azacitidine + venetoclax regimen, and 28 patients (25.2%) received the azacitidine monotherapy. Among the cases achieving CR, these regimens accounted for 22.6% of the total. Response rates by treatment group are also shown in Figure 4.

In recent years, the identification of genetic abnormalities and recognition of the role of hypermethylation in pathophysiology have led to the introduction of new treatment modalities. The incorporation of the two molecules classified as HMAs has been shown to alter the course of myeloproliferative disorders [19]. This observation aligns with findings from randomised trials, such as VIALE-A, supporting the view that the HMA + venetoclax combination represents an effective alternative for low-intensity treatment [12].

Study Limitations

The main limitations of this work are: the limited number of patients in our study, the predominance of the "3+7" protocol among participants, and the absence of subgroup analysis

Table 2. Patient characteristics according to induction response

Parameters		Grouping based on induction response		p
		Complete response (%)	Non-response (%)	
Gender	**Male**	32 (60.4)	14 (56.0)	0.714
	Female	21 (39.6)	11 (44.0)	
Age		59.0 (43.0-69.0)*	69.0 (53.0-76.5)*	**0.025**
Age groups	**<60 years**	29 (54.7)	8 (32.0)	0.061
	≥60 years	24 (45.3)	17 (68.0)	
ECOG	**0**	40 (75.5)	12 (48.0)	-
	1	10 (18.9)	7 (28.0)	
	2	2 (3.8)	5 (20.0)	
	3	1 (1.9)	1 (4.0)	
Charlson index		3.0 (2.0-4.0)*	4.0 (3.0-6.0)*	**0.037**
Treatmet	**3+7**	39 (73.6)	11 (44.0)	-
	Azacitidine	6 (11.3)	10 (40.0)	
	Azacitidine + venetoclax	6 (11.3)	3 (12.0)	
	3+7+ ATRA**	2 (3.8)	1 (4.0)	

*: Median (25th-75th percentile), **: ATRA: All-trans retinoic acid, ECOG: Eastern Cooperative Oncology Group

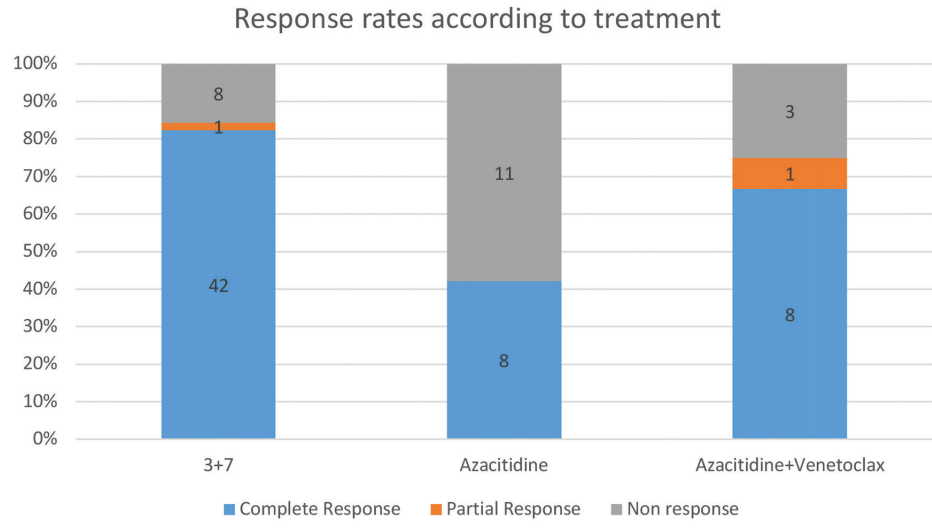

Figure 4. Response rates accordin

of induction treatment response by cytogenetic risk group. In patients over 60 years of age, treatment with HMA is considered an important option because of its markedly lower complication rate compared to the "3+7" regimen.

Conclusion

In this retrospective study, the demographic distribution, year-by-year incidence, and referral patterns of AML patients diagnosed in the Trakya region were evaluated with respect to age, performance status, comorbidities, and treatment regimens, revealing significant associations with treatment response. The findings confirm that AML is predominantly a disease of advanced age and that the age at diagnosis is significantly higher among female patients. The age and gender ratios observed in our study were consistent with those reported in the national and international literature. Furthermore, the fact that a substantial proportion of AML cases presenting to our hospital originated outside the Trakya region, both indicates that our centre has become a regional referral hub and reflects the trust placed in the healthcare services we provide. The increase in diagnosed cases over the years suggests improvements in both diagnostic capabilities and the capacity of our haematology clinic.

The strong negative associations between age and comorbidity index scores and between age and treatment response, once again, underscore the importance of individualised treatment approaches. The "3+7" regimen remains effective in younger, medically fit patients, whereas the azacitidine + venetoclax combination is a promising alternative for older adults and those with significant comorbidities. These data constitute the first comprehensive dataset of demographic and therapeutic information specific to our region and provide a foundation for future studies.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Scientific Research Ethics Committee of the Trakya University Faculty of Medicine, and the study was conducted in accordance with the principles of the Helsinki Declaration (decision no: TÜTF-BAEK 2020/350, date:

14.09.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: A.M.D., Design: A.M.D., Data Collection or Processing: F.Y., Analysis or Interpretation: F.Y., A.M.D., Literature Search: F.Y., Writing: F.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Prevalence of Neuropathic Pain and Its Association with Clinical and Laboratory Findings in Sickle Cell Disease

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ABSTRACT

Aim: Pain in sickle cell disease (SCD) has traditionally been attributed to acute vaso-occlusive events; however, chronic pain with neuropathic features is increasingly recognized. This study aimed to determine the prevalence of neuropathic pain (NP) in adult patients with SCD and to evaluate its association with clinical and laboratory parameters.

Methods: This cross-sectional observational survey included adult patients with SCD and age- and sex-matched healthy controls. NP was assessed using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique en 4 Questions (DN-4), and painDETECT questionnaires. Clinical characteristics, laboratory findings, and treatment-related variables were recorded and analyzed.

Results: A total of 56 patients with SCD and 56 healthy controls were included. NP prevalence ranged from 33.9% to 50% depending on the assessment tool used. LANSS, DN-4, and painDETECT scores were significantly higher in patients with SCD compared with controls (p=0.001). No statistically significant associations were identified between NP and laboratory parameters; however, female sex (p=0.058), comorbidities (p=0.067), and frequent vaso-occlusive crises (p=0.060)showed trends toward higher NP prevalence.

Conclusion: NP is highly prevalent in adults with SCD and represents an important component of the chronic pain phenotype. Routine assessment of NP using validated tools may improve individualized pain management strategies and patient outcomes.

Keywords: Sickle cell disease, neuropathic pain, LANSS, DN-4, painDETECT

Introduction

Sickle cell disease (SCD) is an inherited hemoglobinopathy characterized by the formation of hemoglobin S (HbS) due to a single point mutation in the β-globin chain, and is associated with high morbidity and mortality [1,2]. Polymerization of HbS during deoxygenation reduces erythrocyte deformability, leading to microvascular occlusion, tissue ischemia, and recurrent pain episodes [1,3]. Over time, these pain episodes are associated with progressive organ damage, increased complication burden, and premature mortality [2,4].

SCD continues to represent a major public health problem worldwide, particularly in regions with high prevalence, where it imposes a substantial burden on healthcare systems [2]. In Türkiye, hemoglobinopathies—especially in the Mediterranean region—have long been recognized as an important public health concern [5,6].

Neuropathic pain (NP) is pain that arises as a direct consequence of a lesion or disease affecting the somatosensory nervous system and is characterized by distinctive sensory symptoms, such as burning and stabbing sensations, electric shock-like pain, numbness, paresthesia, and allodynia. This type of pain is associated with structural and functional alterations in the peripheral and/or central nervous systems and often follows a chronic course. Clinically, NP is characterized by poor response to conventional analgesics, a discrepancy between pain intensity and tissue damage, and a marked reduction in quality of life [7-9].

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In clinical practice, several screening and assessment tools have been developed to identify NP. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale is designed to differentiate NP by combining patient-reported symptoms with findings from clinical sensory examination. The Douleur Neuropathique en 4 Questions (DN-4) questionnaire is a brief and practical tool that integrates symptom-based questions with simple physical examination findings and is widely used for NP screening. The painDETECT questionnaire, originally developed for patients with low back pain, has been validated in various chronic pain conditions and serves as a self-report instrument providing a detailed assessment of pain characteristics. These tools are particularly useful in conditions with complex pain mechanisms, such as SCD, as they facilitate more accurate classification of pain phenotypes and support the selection of appropriate treatment strategies [7-11].

Although pain in SCD was long considered to be solely a consequence of vaso-occlusive processes, accumulating evidence has demonstrated that pain may become chronic and acquire neuropathic features over time [7,8]. In this context, diagnostic frameworks for chronic sickle cell-related pain have been developed, emphasizing that the neuropathic component should not be overlooked in clinical practice [8].

The reported prevalence of NP in patients with SCD varies depending on the assessment methods used; however, studies employing screening tools such as DN-4, LANSS, and painDETECT have reported prevalence rates ranging from 20% to 40% [7-9]. These findings suggest that pain in adult patients with SCD is heterogeneous in nature and that a substantial subgroup exhibits neuropathic characteristics [9].

The development of NP has been attributed to multiple mechanisms, including repeated tissue ischemia and reperfusion injury affecting peripheral nerve fibers, chronic inflammation, oxidative stress, endothelial dysfunction, and disturbances in nitric oxide metabolism [12,13]. Moreover, pain in SCD has been reported to be associated not only with peripheral mechanisms but also with alterations in central pain processing pathways and central sensitization at the level of the central nervous system [8,12].

Clinically, NP is associated with increased emergency department visits, frequent hospitalizations, long-term opioid use, risk of dependency, and significant impairment in quality of life [14,15]. Therefore, pain assessment in SCD should extend beyond acute vaso-occlusive crises and incorporate chronic and NP components. Current national and international guidelines recommend systematic evaluation of NP in addition to acute pain management and advocate for multidisciplinary treatment approaches integrating both pharmacological and non-pharmacological strategies [4,15].

The aim of this study was to evaluate the prevalence of NP in individuals with SCD using multidimensional assessment tools and to investigate the possible associations between NP and clinical and laboratory parameters. In addition, this study aims to contribute to the limited data available from Türkiye and to highlight the importance of the neuropathic component in pain management among patients with SCD.

Methods

Study Design and Participants

This cross-sectional observational study was conducted in adult patients diagnosed with SCD who were followed at outpatient clinics. Clinical and laboratory data were collected retrospectively from hospital records. Age- and sex-matched healthy individuals without a history of chronic pain or neurological disease were included as a control group. Demographic characteristics, clinical history, treatment data, and laboratory parameters were recorded for all participants.

Neuropathic Pain Assessment

NP was evaluated using three validated screening tools: the LANSS, the DN-4 questionnaire, and the painDETECT questionnaire. These instruments were administered during routine clinical visits, and scoring was performed according to standard guidelines.

Ethical Considerations

Written informed consent was obtained from all participants prior to enrollment. Ethics approval for the study was obtained from the Ethics Committee of Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, and the study was conducted in accordance with the principles of the Declaration of Helsinki (approval no: 09, date: 20.02.2020).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using appropriate parametric or non-parametric tests depending on data distribution. A p value <0.05 was considered statistically significant.

Results

A total of 56 patients diagnosed with SCD and 56 age- and sex-matched healthy individuals were included in the study. The mean age of the patient group was 33.9±9.9 years, while that of the control group was 32.1±6.6 years, with no statistically significant difference between the groups ($p>0.05$). The proportion of male participants in the patient group (62.5%) was higher than that of female participants (37.5%) (Table 1).

The most frequently reported clinical complications in patients' medical histories were avascular necrosis (25%) and acute chest syndrome (12.5%). Cerebrovascular events (3.6%), leg ulcers (12.5%), and priapism (8.9%) were observed less frequently. Overall, 75% of patients were receiving regular hydroxyurea (HU) therapy, and 44.6% had a history of ≥3 vaso-occlusive crises per year (Table 2).

Table 1. Demographic characteristics of the participants

Characteristic	Patient group (n=56)	Control group (n=56)	Total participants (n=112)
Sex, n (%)			
Female	21 (37.5%)	29 (51.8%)	50 (44.6%)
Male	35 (62.5%)	27 (48.2%)	62 (55.4%)
Age, mean ± SD (years)	33.98±9.96	32.13±6.62	33.05±8.47

SD: Standard deviation

The mean hemoglobin level was 8.67±1.47 g/dL, lactate dehydrogenase (LDH) was 535.2±262.4 U/L, C-reactive protein (CRP) was 28.0±35.9 mg/L, and ferritin was 1092.8±1041.1 ng/mL. Other hematological and biochemical parameters are presented in Table 3. No statistically significant association was found between laboratory variables and the presence of NP (p>0.05).

In the assessment of NP, the mean LANSS, DN-4, and painDETECT scores in the SCD group were 12.0±7.0, 3.7±2.8, and 14.3±8.1, respectively. In the control group, the corresponding scores were 0.9±1.9, 0.5±1.1, and 2.8±4.1. The differences between the patient and control groups were statistically significant across all scales (p=0.001) (Table 4). According to the LANSS scale, NP was identified in 50% of patients, whereas the DN-4 questionnaire and the painDETECT scale indicated prevalences of 33.9% and 41.1%, respectively.

Table 2. Clinical characteristics of the patients

Clinical characteristics	Present, n (%)	Absent, n (%)
History of acute chest syndrome	7 (12.5)	49 (87.5)
History of cerebrovascular disease	2 (3.6)	54 (96.4)
History of avascular necrosis	14 (25.0)	42 (75.0)
History of leg ulcer	7 (12.5)	49 (87.5)
History of priapism	5 (8.9)	51 (91.1)
Hydroxyurea use	42 (75.0)	14 (25.0)
≥3 vaso-occlusive crises per year	25 (44.6)	31 (55.4)

Table 3. Laboratory findings of the patients

Laboratory parameters	Mean ± SD
Hemoglobin (12-16 g/dL)	8.67±1.47
WBC (4-10 ×10^3/µL)	9.78±4.48
Platelets (150-450 ×10^3/µL)	417.76±241.78
Ferritin (10-290 ng/mL)	1092.75±1041.09
CRP (0-5 mg/L)	28.04±35.88
LDH (120-246 U/L)	535.21±262.41
Vitamin B12 (210-910 pg/mL)	440.55±351.08
Folate (5-16 ng/mL)	24.25±84.39

SD: Standard deviation, WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase

Analysis based on the LANSS scale evaluated the association between the presence of NP and selected clinical and laboratory variables (Table 5). The prevalence of NP was higher in female patients (66.7%) than in male patients (40.0%). Similarly, the rate of NP was higher in patients with comorbid conditions (63.2%) than in those without comorbidities (3.2%).

Patients experiencing ≥3 pain crises per year had a higher prevalence of NP (64.0%) compared with those experiencing <3 crises per year (28.7%); however, this difference did not reach statistical significance, although it approached significance (p=0.060). This finding suggests that the neuropathic component of pain may be more pronounced in patients with frequent crises.

With respect to laboratory parameters, the prevalence of NP was slightly higher in patients with hemoglobin levels ≥8 g/dL (51.1%) compared with those with levels <8 g/dL (44.4%). Likewise, NP was more frequent in patients with CRP levels ≥5 mg/L (53.0%) than in those with lower CRP levels (40.0%). Nevertheless, none of these differences were statistically significant (p>0.05).

No statistically significant association was observed between the presence of NP and the use of HU or folic acid (FA) (p>0.05). The prevalence of NP was identical in patients who were receiving HU and those who were not (50.0%) (Table 5).

Table 6 presents a comparative analysis of NP presence and selected clinical and laboratory variables according to the DN-4 scale. The prevalence of NP was higher among female patients, those with comorbid conditions, patients receiving HU, those not using FA, patients with an annual crisis frequency of <3, those with hemoglobin levels ≥8 g/dL, and those with CRP levels <5 mg/L. However, none of these differences reached statistical significance (p>0.05). Notably, female sex (p=0.058) and the presence of comorbidities (p=0.067) demonstrated trends toward statistical significance (Table 6).

Table 4. Comparison of scale scores between the patient and control groups*

Scales	Patient (Mean ± SD)	Control (Mean ± SD)	Z-score	p value
LANSS	12.0±7.0	0.9±1.9	-8.477	0.001
DN-4	3.7±2.8	0.5±1.1	-6.676	0.001
PainDETECT	14.3±8.1	2.8±4.1	-7.695	0.001

*: Mann-Whitney U test was used, SD: Standard deviation, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, DN-4: Douleur Neuropathique en 4 Questions

Table 5. Analysis of neuropathic pain prevalence according to the LANSS scale and selected variables*

Variables	NP present, n (%)	NP absent, n (%)	p value
Sex			0.533
Female	14 (66.7)	7 (33.3)	
Male	14 (40.0)	21 (60.0)	
Comorbidity			0.158
Present	12 (63.2)	7 (36.8)	
Absent	16 (43.2)	21 (56.8)	
Hydroxyurea			1.000
Yes	21 (50.0)	21 (50.0)	
No	7 (50.0)	7 (50.0)	
Folic acid			0.577
Yes	19 (52.8)	17 (47.2)	
No	9 (45.0)	11 (55.0)	
Annual crisis frequency			0.060
<3	12 (28.7)	19 (61.3)	
≥3	16 (64.0)	9 (36.0)	
Hemoglobin (g/dL)			0.716
<8	4 (44.4)	5 (55.6)	
≥8	24 (51.1)	23 (48.9)	
CRP (mg/L)			0.365
<5	6 (40.0)	9 (60.0)	
≥5	22 (53.0)	19 (47.0)	

*: Chi-square test was used, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, NP: Neuropathic pain, CRP: C-reactive protein

Table 6. Analysis of neuropathic pain prevalence according to the DN-4 scale and selected variables*

Variable	NP present, n (%)	NP absent, n (%)	p value
Sex			0.058
Female	12 (57.1)	9 (42.9)	
Male	11 (31.4)	24 (68.6)	
Comorbidity			0.067
Present	11 (57.9)	8 (42.1)	
Absent	12 (32.4)	25 (67.6)	
Hydroxyurea			0.638
Yes	18 (42.9)	24 (57.1)	
No	5 (35.7)	9 (64.3)	
Folic acid			0.311
Yes	13 (36.1)	23 (63.9)	
No	10 (50.0)	10 (50.0)	
Annual crisis frequency			0.884
<3	13 (41.9)	18 (58.1)	
≥3	10 (40.0)	15 (60.0)	
Hemoglobin (g/dL)			0.210
<8	2 (22.2)	7 (77.8)	
≥8	21 (44.7)	26 (55.3)	
CRP (mg/L)			0.607
<5	7 (46.7)	8 (53.3)	
≥5	16 (39.0)	25 (61.0)	

*: Chi-square test was used, DN-4: Douleur Neuropathique en 4 Questions, CRP: C-reactive protein

Table 7 presents a comparative analysis of NP levels assessed by the painDETECT scale and selected clinical and laboratory variables When patients with *suspected* and *positive* NP were evaluated together, the prevalence of NP was higher among female patients, those with comorbid conditions, patients receiving HU, those not using FA, patients with an annual crisis frequency ≥3, those with hemoglobin levels ≥8 g/dL, and those with CRP levels ≥5 mg/L. However, none of these differences reached statistical significance (p>0.05) (Table 7).

Discussion

This study demonstrated that the prevalence of NP is high among adult patients with SCD and that NP occurs significantly more frequently in this population than in healthy controls. The significantly higher scores observed in the SCD group across all three assessment tools—LANSS, DN-4, and painDETECT—support the notion that pain in SCD is not limited to acute vaso-occlusive processes but frequently evolves into a chronic pain phenotype with neuropathic features [7-9,16-18].

In our study, the prevalence of NP ranged from 33.9% to 50% depending on the assessment scale used; these findings are largely consistent with previously reported rates in adult SCD populations. These results highlight that the neuropathic component of pain constitutes a substantial clinical burden, particularly in adult patients with SCD [7-9,16,17].

Although the pathophysiology of pain in SCD has traditionally been attributed to microvascular occlusion and tissue ischemia resulting from erythrocyte sickling, accumulating evidence suggests that this model alone is insufficient to explain the full spectrum of pain experienced by patients. Recurrent ischemic episodes are thought to induce structural and functional damage to peripheral nerve fibers, thereby facilitating the development of NP. In addition, chronic inflammation, oxidative stress, and endothelial dysfunction have been reported to increase neural sensitization and contribute to pain chronicity [12,16-19].

Functional neuroimaging and quantitative sensory testing studies have further demonstrated alterations in central pain-processing pathways and the development of central sensitization in patients with SCD. These findings indicate that pain in SCD is sustained not only by peripheral mechanisms but also by central nervous system-mediated processes [14,16,18-20].

The use of three different validated NP scales represents an important strength of this study, as it enhances the robustness and reliability of the findings. The observed variability

Table 7. Analysis of neuropathic pain according to the painDETECT scale and selected variables*

Variable	Negative, n (%)	Suspected, n (%)	Positive, n (%)	p value
Sex				0.434
Female	19 (47.6)	3 (14.3)	8 (38.1)	
Male	19 (54.3)	8 (22.9)	8 (22.9)	
Comorbidity				0.538
Present	8 (42.1)	4 (21.1)	7 (36.9)	
Absent	21 (56.8)	7 (18.9)	9 (24.3)	
Hydroxyurea				0.359
Yes	20 (47.6)	10 (23.8)	12 (28.6)	
No	9 (64.3)	1 (7.1)	4 (28.6)	
Folic acid				0.979
Yes	19 (52.8)	7 (19.4)	10 (27.8)	
No	10 (50.0)	4 (20.0)	6 (30.0)	
Annual crisis frequency				0.284
<3	19 (61.3)	5 (16.1)	7 (22.6)	
≥3	10 (40.0)	6 (24.0)	9 (36.0)	
Hemoglobin (g/dL)				0.441
<8	6 (66.7)	2 (22.2)	1 (11.1)	
≥8	23 (48.9)	9 (19.1)	15 (31.9)	
CRP (mg/L)				0.702
<5	9 (60.0)	2 (13.3)	4 (26.7)	
≥5	20 (48.8)	9 (22.0)	12 (29.3)	

*: Chi-square test was used, CRP: C-reactive protein

in NP prevalence across the scales may be attributed to methodological differences in sensitivity and specificity among these instruments. In particular, the LANSS scale includes a clinical examination component, which may explain the higher prevalence rates detected with this tool, whereas DN-4 and painDETECT rely primarily on symptom-based assessments [15,17].

With regard to clinical variables, no statistically significant associations were identified between NP and sex, comorbidity status, HU use, or FA supplementation. Previous studies have reported inconsistent findings regarding the effect of HU on chronic and NP, suggesting that its benefits may be more pronounced in reducing acute vaso-occlusive events rather than NP mechanisms [4,15,18]. Female sex and the presence of comorbid conditions showed trends toward statistical significance in some analyses. While previous studies have suggested that women may be more susceptible to chronic pain syndromes due to hormonal and psychosocial factors, evidence specific to SCD remains inconsistent [10,14,17].

The relationship between annual crisis frequency and NP was another notable finding of this study. Although patients experiencing more than three vaso-occlusive crises per year exhibited higher NP prevalence, this association did not reach statistical significance. Nonetheless, prior studies have emphasized that frequent crises may contribute to the development of NP through repeated nerve ischemia and sustained inflammatory responses [8,12,16,19].

The lack of significant associations between laboratory parameters (Hb, CRP, ferritin, and LDH) and NP suggests that NP cannot reliably be predicted from routine biochemical markers. Systemic inflammatory markers such as CRP may not adequately reflect localized neuroinflammatory processes involved in NP [12,17,19]. Consistent with current literature, NP appears to be more closely related to chronic nerve injury, central sensitization, and neuroinflammatory mechanisms rather than conventional laboratory indicators [12,17-20].

The relatively high prevalence of complications such as avascular necrosis, acute chest syndrome, leg ulcers, and priapism observed in our cohort indicates a substantial disease burden. These complications have previously been shown to prolong pain duration and increase analgesic requirements in patients with SCD [9,10].

The clinical impact of NP extends beyond pain intensity alone. NP has been associated with increased emergency department visits, frequent hospitalizations, long-term opioid use, risk of dependency, and marked impairment in quality of life [1,8,10,17]. Furthermore, chronic pain in SCD has been strongly linked to depression, anxiety, and sleep disturbances [14].

Overall, our findings underscore the heterogeneous nature of pain in SCD and emphasize the clinical importance of the neuropathic component. Pain assessment in patients with SCD should extend beyond acute vaso-occlusive crises to include chronic and neuropathic dimensions, thereby facilitating the development of multidisciplinary and individualized treatment strategies [1,8,17].

Study Limitations

This study has several limitations. First, its single-center, cross-sectional design limits the ability to establish causal relationships between NP and clinical or laboratory parameters. Second, the relatively small sample size may have reduced the statistical power to detect significant associations. In addition, psychiatric comorbidities, opioid use patterns, and pain duration were not evaluated, which may have influenced the assessment of NP. Despite these limitations, the inclusion of a matched control group and the use of three validated NP assessment tools strengthen the reliability and clinical relevance of the findings.

Conclusion

The findings of this study indicate that NP has a high prevalence in SCD and is more prominent in patients experiencing frequent vaso-occlusive crises and clinical complications. These results demonstrate that the pathophysiology of pain in SCD cannot be explained solely by acute vaso-occlusive mechanisms, but rather involves a chronic pain phenotype with significant neuropathic features. Accordingly, systematic assessment of NP using validated tools during routine follow-up, and the

implementation of multidisciplinary, individualized treatment approaches for appropriate patients are crucial for optimizing patient management and improving patients' quality of life.

Ethics

Ethics Committee Approval: Ethics approval for the study was obtained from the Ethics Committee of Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, and the study was conducted in accordance with the principles of the Declaration of Helsinki (approval no: 09, date: 20.02.2020).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.D.G., G.İ., İ.M.M., H.K., Concept: G.İ., İ.M.M., H.K., Design: G.İ., İ.M.M., H.K., Data Collection or Processing: A.D.G., Analysis or Interpretation: A.D.G., İ.M.M., Literature Search: A.D.G., G.İ., H.K., Writing: A.D.G., G.İ.

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Original Article

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Are Changes in PET/CT SUV_{max} Associated with Pathologic Complete Response in Breast Cancer Patients Receiving Neoadjuvant Therapy?

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ABSTRACT

Aim: Non-invasive predictors of pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) are needed in breast cancer (BC). We evaluated whether serial fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) maximum standardized uptake value (SUV_{max}) metrics [baseline, preoperative, and the percentage change of SUV_{max} (ΔSUV_{max} %)] and complete metabolic response (CMR) are associated with pCR.

Methods: This retrospective single-center cohort included patients treated with NAC followed by surgery who underwent paired baseline and preoperative ^{18}F-FDG PET/CT. Primary tumor SUV_{max} was recorded on both scans, ΔSUV_{max} % was calculated, and CMR was defined as complete resolution of pathologic FDG uptake on the preoperative scan. pCR was defined as ypT0/is ypN0.

Results: Fifty-six patients were included (median age, 51.5 years). Subtypes were HR^+/HER2- (50%), $HER2^+$ (30.3%), and triple-negative BC (TNBC) (19.7%). Overall, pCR occurred in 25% (14/56) and CMR occurred in 35.7% (20/56). Baseline SUV_{max} differed by subtype (highest in TNBC), and pCR rates varied significantly (lowest in luminal, highest in HER2+). Compared with the non-pCR group, the pCR group had lower preoperative SUV_{max} (0.68 vs 4.33; p=0.001) and higher ΔSUV_{max}% (95.89% vs 54.10%; p=0.001). In univariate logistic regression, lower preoperative SUV_{max} [odds ratio (OR): 0.64; p=0.04]., higher ΔSUV_{max}% (OR: 1.06 per 1% increase; p=0.01), and CMR (OR: 6.75; p=0.01) were associated with pCR.

Conclusion: In this retrospective cohort, end-of-NAC ^{18}F-FDG PET/CT findings—especially a low preoperative SUV_{max} and CMR—were associated with a higher likelihood of pCR while ΔSUV_{max}% contributed incremental predictive signal.

Keywords: Breast cancer, complete metabolic response, neoadjuvant therapy, pathologic complete response, PET-CT

Introduction

Neoadjuvant chemotherapy (NAC) has become a key component of modern breast cancer (BC) treatment, offering tumor downstaging and providing an *in vivo* assessment of treatment sensitivity [1]. In this setting, achieving a pathologic complete response (pCR) is strongly associated with improved outcomes, especially in triple-negative BC (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive BC [2]. Thus, regulatory authorities (drug agencies) have accepted pCR as an endpoint that can support accelerated approval of new therapies in high-risk early-stage BC, underscoring the clinical and translational (bench-to-bedside) importance of pCR.

However, pCR can only be confirmed postoperatively, and there remains a practical need for non-invasive biomarkers that can predict the pathologic response during neoadjuvant treatment. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) provides a quantitative measure of tumor metabolism, while PERCIST defines response based on uptake changes from baseline to follow-up imaging [3]. Prior studies suggest that declines in FDG uptake—often summarized by pre- to post-treatment

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changes in standardized uptake value (SUV) metrics [e.g., absolute or percent maximum SUV (SUV_{max}) reduction]—may help predict pCR [4,5]. Moreover, pooled evidence indicates that PET-defined metabolic response provides prognostic information beyond pCR, with interim and end-of-treatment PET response correlating with survival outcomes [6].

Although metabolic changes on PET/CT may help predict response to NAC, reported performance varies across studies, likely reflecting differences in patient populations, subtype distribution, treatment regimens, scan timing, and response definitions. To address the gap in real-world evidence with paired baseline and preoperative imaging, we conducted an exploratory single-center study to evaluate whether PET-derived SUV_{max} metrics are associated with pCR after NAC.

Methods

Study Design and Patients

This retrospective, single-center cohort study evaluated the association between serial ^{18}F-FDG PET/CT parameters and pCR in patients with BC treated with NAC. The analysis focused on patients who had paired baseline and preoperative ^{18}F-FDG PET/CT scan performed in routine practice to quantify treatment-related changes in tumor metabolic activity. Eligible patients were those who (i) were diagnosed with BC, (ii) were treated with NAC followed by definitive surgery, and (iii) underwent both a baseline PET/CT (prior to NAC) and a preoperative PET/CT (after completion of NAC and before surgery), with available clinicopathologic data. Patients with missing key imaging or pathology data, non-interpretable PET/CT studies or evidence of metastatic disease at baseline were excluded. Demographic and baseline clinicopathologic variables were abstracted from medical records and pathology reports. Tumors were categorized into subtypes consistent with the study tables: luminal (HR^+/HER2-), HER2 positive, and TNBC; (ER-/PR-/HER2-).

^{18}F-FDG PET/CT Acquisition and Image Analysis

All patients underwent whole-body ^{18}F-FDG PET/CT according to institutional clinical protocols. Patients fasted prior to tracer injection; serum glucose was assessed before imaging; PET acquisition was performed after an uptake period. PET images were reconstructed using standard corrections (attenuation, scatter, and decay) and reviewed on a dedicated workstation by experienced nuclear medicine physicians. For each scan, the primary tumor SUV_{max} was recorded. Percent change of SUV_{max} (ΔSUV_{max}) between baseline and preoperative scans was calculated as follows:

$$\Delta SUVmax\ (\%) = \frac{SUVmax_{baseline} - SUVmax_{preop}}{SUVmax_{baseline}} 100$$

A binary metabolic response variable was also defined as a complete metabolic response (CMR), indicating complete resolution of pathologic FDG uptake at the primary tumor site on the preoperative scan.

Pathologic Assessment and Study Endpoint

After completion of NAC, surgical specimens were evaluated by breast pathologists according to routine institutional standards. The primary endpoint was pCR, defined as no residual invasive carcinoma in the breast and in sampled axillary lymph nodes, while allowing residual *in situ* disease (ypT0/is ypN0), consistent with common definitions used in NAC trials.

This study was conducted in accordance with institutional and national ethical standards and the Declaration of Helsinki. Ethical approval was obtained from the Ankara University Faculty of Medicine Human Research Ethics Committee (approval no: İ09-644-23, date: 02.11.2023). Given the retrospective nature of the study, the ethics committee waived the requirement for written informed consent.

Statistical Analysis

Continuous variables were summarized using appropriate descriptive statistics. Comparisons of metabolic parameters across BC subtypes were performed using parametric or non-parametric tests, depending on the distributional assumptions; categorical variables were compared using the χ^2 test or Fisher's exact test. Associations between PET-derived variables (baseline SUV_{max}, preoperative SUV_{max}, ΔSUV_{max}%, and CMR) and pCR were explored using univariate logistic regression, reporting odds ratios (ORs) with 95% confidence intervals (CIs). Because of the limited sample size and relatively low number of pCR events, multivariable modeling was not emphasized, as any adjusted model would likely be underpowered and prone to overfitting. Two-sided p values <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Fifty-six patients were included. The median age was 51.5 years (interquartile range 43.5-57.7). Most patients were postmenopausal (57.2%), had invasive ductal carcinoma, no special type (invasive ductal carcinoma/no special type) histology (92.8%), and presented with clinically node-positive disease (91.1%). Clinical stage was II in 60.7% of patients and III in 39.3%. The cohort comprised 50.0% luminal, 30.3% HER2-positive and 19.7% TNBC tumors (Table 1).

Baseline tumor metabolic activity differed significantly across tumor subtypes (p=0.001), with the highest SUV_{max} in TNBC and the lowest in luminal tumors (Table 2). In contrast, preoperative SUV_{max} and ΔSUV_{max} % did not differ significantly by subtype (p=0.71 and p=0.39, respectively). Overall, pCR was achieved in 25.0% of patients, and CMR was observed in 35.7% of patients. Response rates varied by subtype: pCR was lowest in luminal tumors (7.7%) and highest in HER2-positive disease (52.0%) (p=0.03). CMR rates were numerically higher in the luminal and HER2-positive subgroups than in TNBC, although the difference was not statistically significant (p=0.46) (Table 2). Notably, although CMR was relatively frequent in luminal tumors, the pCR rate remained low.

Table 1. Baseline clinicopathological characteristics of the study cohort (n=56)

Variables	n, %
Age, years (IQR)	51.5 (43.5-57.7)
Menopausal status	
Premenopausal	24 (42.8)
Postmenopausal	32 (57.2)
Histology	
IDC, NST	52 (92.8)
Other	4 (7.2)
cT	
T1-T2	37 (71.1)
T3-T4	15 (28.9)
cN	
Positive	51 (91.1)
Negative	5 (8.9)
Subtype	
Luminal	28 (50)
HER2- positive	17 (30.3)
TNBC	11 (19.7)
Grade	
2	35 (62.5)
3	21 (37.5)
Ki-67, %	
≤20	6 (12.2)
>20	43 (87.8)

IQR: Interquartile range, cT: Clinical tumor stage, cN: Clinical nodal stage, HER2: Human epidermal growth factor receptor 2, IDC, Invasive ductal carcinoma, NST: No special type, Ki-67, Proliferation index, TNBC: Triple-negative breast cancer

Overall, CMR was significantly associated with pCR; patients who achieved CMR had higher pCR rates than patients without CMR (Figure 1; p=0.004). Using pCR as the reference standard among patients with complete paired CMR and pCR data (n=51), CMR demonstrated 71.4% sensitivity, 73.0% specificity, 50.0% PPV, and 87.1% NPV for predicting pCR; performance varied by subtype, with particularly low PPV in luminal disease (Table 3).

Compared with patients without pCR, those with pCR showed a markedly greater metabolic decline (ΔSUV_{max} %, 95.89% vs 54.10%; p=0.001). In univariate logistic regression, lower preoperative SUV_{max} (OR: 0.64, 95% CI: 0.42-0.98; p=0.04), higher ΔSUV_{max} % (OR: 1.06, 95% CI: 1.01-1.11; p=0.01), and CMR (OR: 6.75, 95% CI: 1.71-26.50; p=0.01) were associated with higher odds of pCR, while baseline SUV_{max} showed a borderline association (OR: 1.09, 95% CI: 1.00-1.20; p=0.05) (Table 4).

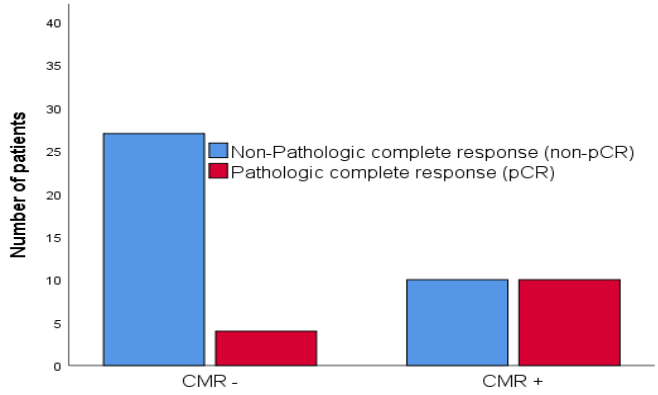

Figure 1. Relationship between CMR and pCR
CMR: complete metabolic response, pCR: Pathologic complete response

Table 2. Metabolic PET parameters and treatment response outcomes by breast cancer subtype

Variables	Luminal type (n=28)	HER2⁺ (n=17)	TNBC (n=11)	p value
Baseline SUV_{max}, (median)	7.99 (3-17.6)	13.53 (3.1-24)	17.84 (9.7-40.1)	0.001
Preoperative SUV_{max}, (median)	2.2 (0-8)	0 (0-13)	2.8 (0-25.6)	0.71
ΔSUV_{max}, %	63.9	77.4	47.6	0.39
pCR, %	2 (7.7)	9 (52)	3 (33)	0.03
CMR, %	10 (35)	8 (47)	2 (18)	0.46

P values were calculated using the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables: as appropriate
HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer, SUV_{max}: Maximum standardized uptake value, ΔSUV_{max}: Percent change of SUV_{max} (baseline to preoperative), pCR: Pathologic complete response, CMR: Complete metabolic response

Table 3. Diagnostic performance of CMR for predicting pCR

Group	n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall	51	71.4	73.0	50.0	87.1
Luminal	25	100.0	65.2	20.0	100.0
HER2-positive	17	66.7	75.0	75.0	66.7
TNBC	9	66.7	100.0	100.0	85.7

Overall analysis includes patients with complete paired CMR and pCR data (n=51)
PPV: Positive predictive value, NPV: Negative predictive value, TNBC: Triple-negative breast cancer, HER2: Human epidermal growth factor receptor 2, pCR: Pathologic complete response, CMR: Complete metabolic response, TNBC, Triple-negative breast cancer

Table 4. Univariate logistic regression analysis of FDG PET/CT metabolic parameters associated with pathologic complete response (pCR)

Variables		pCR	
	OR	95% CI	p
Baseline FDG/PET SUV_{max}	1.09	1.00-1.20	0.05
Preoperative FDG/PET SUV_{max}	0.64	0.42-0.98	0.04
ΔSUV_{max} %	1.06	1.01-1.11	0.01
CMR	6.75	1.71-26.50	0.01

ORs are expressed per 1-unit increase. For ΔSUV_{max} %: the OR reflects the change in odds of pCR per 1% increase in $\Delta SUVm_{ax}$ %. For clinical interpretability: ΔSUV_{max} % can also be modeled per 10% increase (ΔSUV_{max} %/10), %: Percentage
pCR: Pathologic complete response, OR: Odds ratio, CI: Confidence interval, FDG: Fluorodeoxyglucose, PET: Positron emission tomography, SUV_{max}: Maximum standardized uptake value, ΔSUV_{max}: Percent change of SUV_{max} (baseline to preoperative), CMR: Complete metabolic response

Discussion

In this retrospective single-center cohort with paired baseline and preoperative ^{18}F-FDG PET/CT, metabolic response measures were significantly associated with pCR. Compared with the non-pCR group, patients achieving pCR had a markedly lower preoperative SUV_{max} and a substantially greater metabolic decline (ΔSUV_{max}: 95.89% vs 54.10%; p=0.001). Achieving CMR was associated with higher odds of pCR, suggesting that marked suppression of FDG uptake after NAC may increase the likelihood of a pathologic response at surgery. This is consistent with prior studies showing that residual FDG uptake and the degree of metabolic decline can indicate chemosensitivity in BC, especially in aggressive subtypes [7,8].

Our data underscore the importance of end-of-NAC PET, consistent with Akimoto et al. [9], who reported that post-NAC SUV_{max} predicted pCR (and recurrence-free survival) in HER2-positive and TNBC, whereas baseline SUV_{max} and ΔSUV_{max} did not. In our cohort, however, metabolic change also carried a signal: compared with the non-pCR group, patients achieving pCR exhibited a greater metabolic decline, reflected by a significantly higher ΔSUV_{max} % (95.89% vs 54.10%; p=0.001). Conceptually, post-treatment uptake is closest to a "metabolic residual disease" readout and may therefore map more directly to residual viable tumor than baseline avidity or relative change alone-especially when cohorts include luminal disease where pCR is intrinsically uncommon [10]. Notably, we observed a subtype-dependent discordance between metabolic and pathologic responses, most evident in luminal tumors, where CMR occurred relatively frequently despite a low pCR rate. This likely reflects lower, heterogeneous FDG avidity and the possibility that microscopic residual invasive disease remains below PET detectability, underscoring that PET-defined CMR should be interpreted cautiously as a surrogate for pCR in luminal disease. Although absolute post-treatment SUV may be more informative in heterogeneous populations, several studies have shown that marked metabolic declines can also help identify responders [11]. In TNBC, Kiyoto et al. [12] reported that a ΔSUV_{max} cut-off of 81.3% provided meaningful discrimination for pCR (area under the curve ~0.79)-poor metabolic response consistently indicated non-pCR. Similarly, the multicenter Japanese study identified an optimal peak SUV normalized to lean body mass (SUL_{peak}) decrease of 84.3% for predicting pCR and showed that CMR and pCR were associated with longer PFS [13]. Overall, ΔSUV-based thresholds may be particularly informative in selected aggressive phenotypes and when implemented as pre-specified decision rules.

Our study focuses on pCR, but the broader evidence base supports the prognostic significance of end-of-NAC PET [14]. Emmering et al. [15] demonstrated that residual FDG uptake on preoperative PET was inversely associated with disease-free survival (DFS) (HR 4.09) and appeared superior to histopathology-based response grading in their dataset. More contemporary analyses reinforce this theme using quantitative cut-offs and node-focused assessment. García Vicente et al. [16] (n=132) found that end-of-treatment PET predicted nodal histopathologic response and that binary nodal assessment was associated with both overall survival (OS) and DFS; they also reported cut-offs for ΔSUV change at early and end timepoints and noted an end-of-treatment ΔSUV threshold linked to DFS. Taken together, these data support the biological plausibility of our finding that lower post-treatment SUV is associated with pCR, while also underscoring the heterogeneity in PET metrics across studies. Indeed, the "best" PET metric likely depends on subtype (luminal vs. $HER2^+$/TNBC), scan timing (interim vs end-of-NAC), and endpoint (pCR vs DFS/OS); accordingly, post-treatment SUV_{max} may perform best in $HER2^+$/TNBC cohorts, whereas ΔSUV-based cut-offs and PERCIST-defined CMR may be particularly informative in selected settings, such as TNBC. One possible explanation is that $HER2^+$ and triple-negative tumors are often more FDG-avid at baseline and may undergo more pronounced metabolic changes during neoadjuvant treatment, making post-treatment SUV_{max} and response-based metrics such as ΔSUV and PERCIST-defined CMR more informative in these settings. However, these observations should be interpreted cautiously, given the limited sample size and the exploratory nature of the subgroup analyses.

Study Limitations

This study has limitations typical of retrospective single-center analyses, including a modest sample size, potential selection bias (inclusion of only patients with paired PET/CT), and heterogeneity in systemic therapy regimens and in the timing of imaging relative to treatment and surgery. While

our study does not report long-term survival outcomes, pCR is widely regarded as a robust surrogate endpoint for prognosis in high-risk BC, particularly in the $HER2^+$ and TNBC subtypes. In addition, we used SUV_{max}-based metrics (rather than the PERCIST-preferred SUL_{peak}), which may increase susceptibility to noise. Nonetheless, SUV_{max} remains widely reported and clinically intuitive. The absence of statistically significant differences in CMR rates across subtypes should be interpreted cautiously because of the small number of cases in the TNBC subgroup. The study may have been underpowered to detect moderate subtype-specific differences in metabolic response. Finally, multivariable modeling may have been underpowered, and the observed associations—especially for categorical CMR—should be interpreted with appropriate caution.

Conclusion

Overall, our results support a practical and clinically intuitive message: very low residual uptake on preoperative PET/CT (and/or achievement of CMR) is associated with a higher likelihood of pCR, whereas substantial residual uptake suggests persistent viable disease. Taken together, these findings support end-of-NAC PET/CT as a pragmatic adjunct for response assessment, but not a substitute for surgical pathology-particularly in luminal disease.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ankara University Faculty of Medicine Human Research Ethics Committee (approval no: İ09-644-23, date: 02.11.2023).

Informed Consent: Given the retrospective nature of the study, the ethics committee waived the requirement for written informed consent.

Footnotes

Authorship Contributions

Concept: B.D., H.A.Y., Design: B.D., H.A.Y., A.D., Data Collection or Processing: B.D., Ç.S., Analysis or Interpretation: B.D., H.A.Y., Ç.S., A.D., Literature Search: B.D., Writing: B.D., A.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Second Primary Malignancies in Patients with Hematologic and Solid Tumors: Risk Factors

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ABSTRACT

Aim: This study aimed to evaluate time to second primary malignancy (SPM) development and associated clinical factors in adults with a PM.

Methods: This retrospective study included patients with hematologic malignancies (HM) and a prior history of solid organ malignancy (SOM) who had complete clinical data available. We recorded demographic characteristics; diagnoses of the PM and SPM; the interval between PM and SPM; treatments received; and survival outcomes. Time to SPM was calculated for the overall cohort and for predefined subgroups, and comparisons were performed according to demographic variables and treatment exposures.

Results: A total of 101 patients were included. Median age was 61 years (26-88). Median time to SPM was 42.9 months overall, longer in the primary hematologic malignancy than primary SOM (54.9 vs. 26.8 months, p=0.018). Patients <60 years had longer time to SPM than those ≥60 (66 vs. 21.4 months, p<0.001), a difference consistent across subgroups (<60: 96 vs. 37 months, p=0.001; ≥60: 41 vs. 8.9 months, p=0.036). Patients receiving chemotherapy (CT) and/or radiotherapy had longer SPM times than untreated patients (CT: 54.5 vs. 18.9 months, p=0.007). Among SPMs, the most frequent HM was chronic lymphocytic leukemia (chronic lymphocytic leukemia, 24.4%), while lung cancer (17.9%) was the most frequent solid tumor. In multivariate regression, the only independent predictor of shorter SPM time was age ≥60 years (odds ratio=0.34, 95% confidence interval: 0.12-0.88, p=0.023).

Conclusion: Advanced age is the main determinant of SPM development in adult cancer survivors, highlighting the need for closer surveillance in elderly patients.

Keywords: Chemotherapy, hematologic malignancies, medical oncology, onco-hematology

Introduction

In addition to conventional chemotherapy (CT), targeted therapies such as monoclonal antibodies, immunomodulatory drugs, tyrosine kinase inhibitors (TKIs), and checkpoint inhibitors have significantly contributed to the treatment of hematologic and solid cancers over the past two decades. With these agents, survival has improved [1-4], but attention to treatment-related adverse effects and secondary malignancies has also increased [5,6]. Drugs causing direct deoxyribonucleic acid damage, including alkylating agents, topoisomerase II inhibitors, and platinum compounds, are well recognized for inducing secondary cancers by affecting hematopoietic cells [7]. Data on targeted therapies are less consistent. Some studies suggest an increased risk of malignancy with imatinib in chronic myeloid leukemia (CML) and lenalidomide in maintenance therapy for multiple myeloma (MM) [8,9]. However, attributing secondary cancers solely to therapy may be misleading. These cases could represent therapy-related cancers or independent second primaries. Multiple factors, including age, genetic predisposition, radiotherapy (RT), hormone replacement therapy (HRT) and immune status, contribute to new cancer development [10].

This study evaluated clinical and treatment-related factors influencing the time to second cancer in patients with prior

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malignancy. Understanding these risks is crucial for identifying high-risk groups and guiding individualized follow-up. Findings are expected to support improved management of secondary malignancies and inform future surveillance strategies.

Methods

This retrospective study involved review of the medical records of patients followed at the Necmettin Erbakan University Faculty of Medicine between 2002 and 2024. The medical documents were reviewed between 01.07.2023 and 01.07.2025. This study was conducted in accordance with the principles of the 1964 Helsinki Declaration and its subsequent amendments. The study was approved by the Non-interventional Research Ethics Committee of Necmettin Erbakan University (approval no: 177, date: 02.06.2023).

Patients diagnosed with hematologic malignancies (HM) who either had a prior diagnosis of solid organ cancer or who developed solid organ cancer during follow-up and for whom complete data were available were included in the study.

Demographic characteristics of the patients (age and sex), diagnoses of primary malignancy (PM) and second PM (SPM), interval between diagnoses, treatments received (CT, RT, HRT, TKI use, etc.), and survival times were recorded. For patients who received CT, the use of alkylating agents and topoisomerase inhibitors was specifically noted.

The time between diagnosis of PM and diagnosis of SPM was calculated. This duration was evaluated for all patients and separately for those with a primary HM (PHM) or primary solid organ malignancy (PSOM). The interval to SPM development was compared across PM diagnosis, demographic characteristics, and treatment modalities.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA). Descriptive data are presented as median (minimum-maximum). Continuous numerical variables were compared using the Mann-Whitney U test. Categorical variables were expressed as percentages (%) and analyzed with the chi-square test or Fisher's exact test. Survival analysis was conducted using the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. A binary logistic regression analysis was performed to determine the factors influencing the development of second cancers. For this purpose, patients were divided into two groups based on the median time to the development of a SPM (42.9 months): early development (<43 months) and late development (≥43 months). Independent variables included age (<60 and ≥60), sex, diagnosis of PM, and treatment modalities. All variables were entered into the model using the Enter method. Results were reported as odds ratios (ORs) with 95% confidence intervals. A p value <0.05 was considered statistically significant.

Results

A total of 101 patients were included. The median age was 61 years (range, 26-88); 37 (36.6%) were women and 64 (63.4%) were men. Of the patients, 56 (55.4%) had PHM and 45 (44.6%) had PSOM. In these two groups, the numbers of females and males were 18 (38.1%)/38 (67.9%) and 19 (42.2%)/26 (57.8%) respectively, while the median ages were 60 years (range 26-82) and 63 years (range 34-88). No statistically significant differences in age or sex were observed between the groups (p=0.296 and p=0.672). The distribution of patients by PM and treatment characteristics is presented in Table 1.

Accordingly, the rates of CT administration differed significantly between the PHM and PSOM groups (87.5% vs. 37.8%; Pearson chi-square =27.240; p<0.001). Among patients who received CT, the rate of alkylating agent use was markedly higher in the PHM group (69.4%) than in the PSOM group (5.9%) (Pearson chi-square =20.435; p<0.001). Similarly, the rate of topoisomerase II inhibitor use was significantly higher among patients with PHM (30.6%) than among those with PSOM (Pearson chi-square =6.735; p=0.009).

No patients in the PHM group received RT or HRT. Regarding TKI use, 6 patients (10.7%) in the PHM group and 3 patients (6.7%) in the PSOM group received TKI therapy, reflecting similar rates between the groups. All patients in the PHM group were diagnosed with CML and treated with imatinib as first-line therapy. Among the PSOM patients, two had gastrointestinal stromal tumors (GIST) and were treated with imatinib, while one patient with lung adenocarcinoma received afatinib.

Table 1. Primary malignancy and characteristics of treatment

Treatment	PHM (n=56)	PSOM (n=45)	p
CT-treated patient, n(%)	49 (87.5)	17 (37.8)	<0.001[a]
Alkylating agent topoisomerase II inhibitors	34 (69.4) 15 (30.6)	1 (5.9) 0	<0.001[a] 0.009[a]
RT-treated patient, n (%)	0	6 (13.3)	0.006[b]
KT and/or RT-treated patient, n (%)	49 (87.5)	20 (44.4)	<0.001[a]
HRT-treated patient, n (%)	0	5 (11.1)	0.005[b]
TKI-treated patient, n (%)	6 (10.7)	3 (6.7)	0.727[b]

[a]: Pearson chi-square test
[b]: Fisher's exact test
PHM: Primary hematologic malignancy, PSOM: Primary solid organ malignancy, CT: Chemotherapy, RT: Radiotherapy, HRT: Hormone replacement therapy, TKI: Tyrosine kinase inhibitors

The median time to the development of SPM was 42.9 months (4-315.5) for all patients. This duration was significantly longer in the PHM group (54.9 months; range, 5.5-315.5) than in the PSOM group (26.8 months; range, 4-240) (p=0.018). When all patients were evaluated, the time to SPM development was longer in patients aged <60 years compared with those aged ≥60 years: 66 months (5-315.5) vs. 21.4 months (4-178.7), respectively (p<0.001). Similarly, in both the PHM and PSOM groups, patients younger than 60 years had a significantly time to development of SPM. In patients aged <60 years, the time was 96 months (6-315.5) vs. 37 months (5.5-169.9) (p=0.001), while in those aged ≥60 years, the time was 41 months (5-240) vs. 8.9 months (4-178.7) (p=0.036). When all patients were analyzed according to treatment status, the time to SPM development was significantly longer in patients who received CT and those who received CT and/or RT, compared with untreated patients. Among CT-treated and untreated patients, median times were 54.5 months (range 4.7-315.5) and 18.9 months (range 4-178.7), respectively (p=0.007). Similarly, among patients who received CT and/or RT compared with those who did not, the durations were 54 months (4-315.5) and 18.5 months (4-178.8), respectively (p=0.012). However, when patients were evaluated separately according to PM diagnosis, the time to SPM development was similar across treatment groups. The comparison of time to second cancer across PM, sex, and treatment groups is summarized in Table 2.

The median estimated overall survival (OS) for all patients was 178.3 months (113.2-243.5). In the PHM group, the duration was 283 months (41.6-524.4), whereas in the PSOM group it was 126.2 months (81.8-170.7), with no significant difference between the two groups (p=0.454).

Among SPMs, the most frequently reported HM was chronic lymphocytic leukemia (CLL, 24.4%), whereas the most common solid organ tumor was lung cancer (17.9%). The primary and secondary malignancy diagnoses of the patients are summarized in Table 3. Among the 34 PHM patients who received alkylating agent therapy, the most common second cancers were lung (20.6%), breast (14.9%), prostate (11.8%), bladder (8.8%), skin (8.8%), hepatocellular carcinoma (HCC, 5.9%), rectum (5.9%), endometrium (5.9%), and other tumors (Kaposi sarcoma, malignant melanoma, pleura, and

Table 2. Comparison of time to second primary malignancy

	All patients		PHM		PSOM	
Parameter	**Time to SPM (month)**	**p***	**Time to SPM (month)**	**p***	**Time to SPM (month)**	**p***
Sex						
Female	57.9 (5-315.5)	0.98	69.4 (5.9-315.5)	0.380	49.4 (5-240)	0.063
Male	36.7 (2-250)		53 (5.5-250.9)		13.9 (4-178.8)	
Age						
<60	66 (5-315.5)	<0.001	96 (6-315.5)	0.001	41 (5-240)	0.036
≥60	21.4 (4-178.7)		37 (5.5-169.9)		8.9 (4-178.7)	
CT						
Treated	54.5 (4.7-315.5)	0.007	56 (5.5-315.5)	0.408	39.9 (4.7-240)	0.122
Un-treated	18.9 (4-178.7)		37 (6.5-170.9)		14.9 (4-178.7)	
Alkylating agent						
Treated	54.9 (5.3-315.5)	0.07	55.4 (5.9-315.5)	0.540	-	0.771s
Un-treated	36.2 (2-250.9)		46 (5.5-250.9)		29.4 (4-240)	
Topo II inhibitor						
Treated	54.9 (6-315.5)	0.189	54.9 (6-315.5)	0.598	-	-
Un-treated	39.5 (4-250.9)		54.9 (5.5-250.9)		26.8 (4-240)	
RT						
Treated	32.5 (4-101.9)	0.464	-	-	32.4 (4-101.9)	0.961
Un-treated	47.1 (4-315.5)		54.9 (5.5-315.5)		26.8 (4-240)	
CT and/or RT**						
Treated	54 (4-315.5)	0.012	56 (5.5-315.5)	0.408	56.4 (4-240)	0.185
Un-treated	18.5 (4-178.8)		37 (6.5-170.9)		12 (4-178.7)	
HRT						
Treated	57.9 (5.4-89)	0.657	-	-	57.9 (5.4-89)	0.857
Un-treated	42.9 (4.0-315.5)		54.9 (5.5-315.5)		25.9 (4-240)	
TKI						
Treated	35.9 (5-250.9)	0.872	67.8 (23.9-250.9)	0.427	15.9 (5-26.8)	0.275
Un-treated	45 (4-315.5)		54.5 (5.5-315.5)		34.2 (4-240)	

*: Mann-Whitney U test
**: Three patients received both CT and RT. In the time comparisons, patients without treatment and those who received CT and/or RT were evaluated together
PHM: Primary hematologic malignancy, PSOM: Primary solid organ malignancy, CT: Chemotherapy, RT: Radiotherapy, HRT: Hormane replacement therapy, TKI: Thyrosine kinase inhibitors, SPM: Second primary malignancy

Table 3. Distribution of diagnosis

	Second primary malignancy	Primary malignancy
Hematological malignancies, n (%)		
CLL	11 (24.4)	15 (26.8)
MDS	8 (17.8)	4 (7.1)
AML	7 (15.6)	3 (5.4)
NHL	5 (11.1)	14 (25)
CML	5 (11.1)	6 (10.7)
MM	4 (8.9)	8 (14.3)
ALL	3 (6.7)	1 (1.8)
HL	1 (2.2)	2 (3.6)
PMF	1 (2.2)	-
ET	-	2 (3.6)
PV	-	1 (1.8)
Solid organ malignancies, n (%)		
Lung	10 (17.9)	5 (11.1)
Breast	9 (16.1)	10 (22.2)
Prostate	7 (12.5)	4 (8.9)
Skin	7 (12.5)	3 (6.7)
Bladder	4 (7.1)	-
Gastric	3 (5.4)	1 (2.2)
Pancreas	2 (3.6)	-
HCC	2 (3.6)	1 (2.2)
Colon	2 (3.6)	6 (13.3)
Rectal	2 (3.6)	3 (6.7)
Endometrium	2 (3.6)	4 (8.9)
Caposi's Sarcoma	2 (3.6)	-
Malignant melanom	1 (1.8)	1 (2.2)
Meningioma	1 (1.8)	-
Thyroid	1 (1.8)	-
Pleural mesothelioma	1 (1.8)	-
Larynx (SCC)	1 (1.8)	-
Timoma	-	1 (2.2)
Lip (SCC)	-	1 (2.2)

CLL: Chronic lymphocytic leukemia, MDS: Myelodysplastic syndromes, AML: Acute myeloid leukemia, NHL: Non-Hodgkin lymphoma, CML: Chronic myeloid leukemia, MM: Multiple myeloma, ALL: Acute lymphoblastic leukemia, HL: Hodgkin lymphoma, PMF: Primary myelofibrosis, ET: Essential thrombocythemia, PV: Polycythemia vera, HCC: Hepatocellular carcinoma, SCC: Squamous cell carcinoma

meningioma). Among patients treated with topoisomerase inhibitors, the most common second cancers were lung cancer (26.7%), breast cancer (20%), and HCC (13.3%). Of the 6 oncology patients who received RT, 3 (50%) developed acute myeloid leukemia (AML), 2 (33.3%) developed CLL, and 1 (16.7%) developed non-Hodgkin lymphoma. Among the 6 patients with CML treated with imatinib, 2 developed breast cancer, while the remaining four developed lung, skin, bladder, and thyroid cancers. AML and CLL developed in 2 patients with GIST treated with imatinib, whereas acute lymphoblastic leukemia (ALL) was diagnosed in a patient with lung adenocarcinoma treated with afatinib. Of the 5 solid-organ cancer patients who received HRT, 3 were female; the second cancers reported in these patients were CML, CLL, and myelodysplastic syndrome (MDS). ALL and MDS developed in the two male patients.

In the multivariable logistic regression analysis, factors influencing the time to SPM development (<43 months vs. ≥43 months) were evaluated. The overall model was found to be borderline significant (Omnibus test χ^2=18.1, p=0.053), with a classification accuracy of 69.7%. Among the analyzed variables, only age was statistically significant. Patients aged ≥60 years had a significantly lower likelihood of late SPM development (≥43 months) (OR=0.34, 95% CI: 0.12-0.88, p=0.023). This finding suggests that SPM may occur at an earlier stage in older patients. Gender (OR=1.99, p=0.156), PM type (PHM vs. PSOM, OR=1.27, p=0.733), topoisomerase inhibitor use (OR=1.72, p=0.490), CT (OR=0.88, p=0.943), RT (OR=0.35, p=0.451), CT+RT (OR=1.64, p=0.796), and TKI treatment (OR=0.64, p=0.596) were not significantly associated with early SPM development.

Discussion

In our study, the median age of the 101 patients was 61 years, and the majority were male (63.4%). These demographic characteristics are consistent with previously reported data on patients developed SPM in adult cancer populations [11]. Furthermore, the age and sex distributions were similar in the PHM and PSOM subgroups. In the large cancer survival cohort conducted by Kjaer et al. [12], the median age for SPM development was reported as 68.3 years, which is in line with our findings.

There are large-cohort epidemiological studies emphasizing that exposure to CT is one of the main factors increasing the risk of SPM [13]. In our study, follow-up without systemic therapy or surgical resection sufficed for most PSOM patients, and CT was unnecessary. In contrast, the markedly higher CT rate in the PHM group (87.5%) compared with the PSOM group (37.8%) aligns with the literature, suggesting that CT is a potential risk factor for SPM. Reviewing CT data, Pedersen-Bjergaard et al. [14] reported in the Danish cohort that after high cumulative etoposide doses, the 5.7-year cumulative risk of AML/MDS was 4.7%. Similarly, in the German cohort by Bokemeyer and Schmoll, the cumulative incidence of SPM was 1.0% in patients treated with regimens containing topoisomerase II inhibitors [15]. Notably, in our study, although no PSOM patients received topoisomerase II inhibitors, 17.8% developed MDS and 15.6% developed AML. Alkylating agents are also major chemotherapeutic culprits and significant risk factors, particularly for AML and MDS [16]. In our study, while most PHM patients received alkylating agents, only one PSOM patient was treated with this regimen. Despite the PHM-PSOM comparison and our cohort's relatively smaller size compared with that reported in the literature, our findings suggest that CT may not be the sole determinant of SPM. It has been demonstrated that RT is an important risk factor for the development of SPM in solid organ cancers [17]. However, in our study, only 6 PSOM patients received RT, which limits our ability to draw strong conclusions about this matter. Similarly, the number of patients receiving HRT was limited, making it difficult to draw inferences.

In CML, evidence on whether imatinib increases SPM risk remains conflicting, with some studies reporting elevated risk and others showing no difference from the general population [8,18]. In our study, the SPMs that developed in patients receiving imatinib were heterogeneous, whereas ALL was identified in the patient treated with afatinib.

When assessing the time to SPM development, the median duration in our study was 42.9 months (≈3.6 years), consistent with Halamkova et al. [19], who reported 1.7-5.2 years in an adult cancer survival cohort. A noteworthy finding in our study was that the time to SPM development was longer in the PHM group than in the PSOM group (54.9 vs. 26.8 months). In the Swiss cancer cohort, Feller et al. [20] reported that SPM risk became more pronounced after 5 years in PHM patients, whereas it could be observed earlier in PSOM patients. Although our dataset included fewer cases, our findings support these observations.

In the data reported by Wood et al. [21], SPMs occurred at a higher rate particularly within the first 2 years in patients aged ≥60 years, whereas this period was considerably longer in younger adults. In our study, time to SPM development was 66 months in patients aged <60 years and 21.4 months in those aged ≥60 years, consistent with this finding. Factors influencing time to SPM development were also evaluated using a regression model. The only factor associated with SPM duration <43 months was age ≥60 years.

In contrast, in the Swiss cohort, the risk of SPM was found to be higher in younger patients [20]. On the other hand, in our study, the longer time to SPM development in patients who received CT±RT may initially appear contradictory. However, large population-based data have also reported earlier SPM development in untreated groups [19,21]. This situation may be related to the higher mean age and shorter follow-up among untreated patients. In the elderly, more frequent genetic mutations and genomic instability, along with greater cumulative environmental exposures such as smoking and chemicals, are possible mechanisms explaining this difference [7,21]. Therefore, the shorter time to SPM development observed in older patients in our study may be attributable not only to the PM itself but also to age-related biological and environmental factors.

In the adult population, although survival in patients who developed SPM is somewhat shorter compared to those who did not, the 10-year OS remains 45-50%, and the median survival exceeds 10 years [20-22]. In our study, the median survival for all patients was 178.3 months and was similar in the PHM and PSOM groups.

A review of the literature shows that SPM diagnoses are highly heterogeneous. SPMs that develop after PHM have been particularly investigated in patients with MM. In one analysis of MM follow-up data, the most common solid organ cancers were reported as prostate (25%) and breast (13%) [23]. In a study evaluating patients who received chimeric antigen receptor T-cell therapy and had a median age of 66 years, the most common SPM was non-melanoma skin cancer. MDS and AML were identified as the most frequent hematologic SPMs [24]. In our study, the most common solid-organ SPM was lung cancer, which closely matched the 18% rate reported by Donin et al. [25]. The most frequently observed hematologic SPM was CLL. No data in the literature report CLL as the most common SPM. However, in our study, malignancy diagnoses were categorized into two distinct groups: SOMs developing after PHM and HMs developing after PSOM. Although this represents a limitation, it also provides a different contribution to the literature.

The main strengths of our study are the inclusion and comparison of solid-organ and HM, the broad age range of the study population, and the use of multivariable analysis.

Study Limitations

The limitations of our study include its single-center design, limited number of patients (n=101), retrospective design, lack of genetic data, and evaluation of cases in two separate groups.

Conclusion

Our study demonstrated that advanced age was an important determinant of the development of SPM, while the independent effects of other clinical and treatment-related parameters were limited. Our findings suggest that SPMs may occur at an earlier stage particularly in patients aged ≥60 years. These results highlight the need to consider age as a critical factor in follow-up care for adult cancer patients.

Ethics

Ethics Committee Approval: The study was approved by the Non-interventional Research Ethics Committee of Necmettin Erbakan University (approval no: 177, date: 02.06.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T., O.Y., C.D., S.D., M.M., M.K.E., Concept: A.T., S.D., M.K.E., Desing: A.T., O.Y., C.D., S.D., M.M., M.K.E., Data Collection or Processing: A.T., O.Y., C.D., Analysis or Interpretation: A.T., M.M., Literature Search: A.T., O.Y., C.D., S.D., M.M., M.K.E., Writing: A.T., O.Y., C.D., S.D., M.M., M.K.E.

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Hereditary Multiple Exostoses: Genetic, Radiologic, and Oncologic Insights from Twenty-one Patients

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ABSTRACT

Aim: To characterize the clinical, radiological, and genetic features of genetically confirmed hereditary multiple exostoses (HME) in patients presenting with multiple exostoses and to contribute to the understanding of the phenotypic and genotypic spectrum.

Methods: This retrospective cohort study included 21 patients from 13 unrelated families referred to a pediatric genetics clinic for multiple exostoses, with an HME diagnosis confirmed by molecular genetic testing. Clinical findings and available skeletal survey radiographs were reviewed. Identified variants were classified, and segregation analysis was performed when feasible.

Results: Ages at presentation ranged from 2.27 to 59.6 years; 14 patients were female, and 7 were male. The most common reasons for referral were a palpable mass and imaging findings. Skeletal survey radiographs were available for 17 patients, all of whom showed multiple exostoses of variable severity. Exostoses most frequently involved the forearm (ulna and radius), femur, lower leg (tibia and fibula), and humerus; involvement of the hands and pelvis was observed at an intermediate frequency. The feet, ribs, scapula, and clavicle were less commonly affected, and no vertebral lesions were identified. As of the most recent follow-up, no malignant transformation has been identified among patients in our cohort (0%). In one of our patients (P21), a stable, non-growing mass was detected in the mesencephalon. Thirteen distinct variants were detected, five of which were novel. Fifteen patients were classified as *EXT1*-related HME type 1 and six as *EXT2*-related HME type 2. Variant types comprised seven frameshift variants, four nonsense variants, one missense variant, and one splice-site variant; all were classified as pathogenic/likely pathogenic. Among eight probands with segregation testing available, two variants (25%) were confirmed to be de novo.

Conclusion: HME exhibits marked clinical and genetic heterogeneity. Careful assessment of skeletal surveys supports the clinical diagnosis, while molecular confirmation is critical for accurate genetic counseling. The novel variants and the associated phenotypic and radiological findings reported here further expand the disease spectrum.

Keywords: Hereditary multiple exostoses, bone pain, *EXT1*, *EXT2*, osteochondroma

Introduction

In European populations, the reported prevalence of hereditary multiple exostoses (HME) is approximately 1 in 100,000 [1,2]. HME is characterized by the development of osteochondromas, benign cartilage-capped bony tumors that typically arise from the metaphyseal regions of long bones and grow outward from the bone surface. Lesions are most often multiple and, in addition to long bones, may also involve the ribs, clavicle, and pelvis [1-3]. Most patients present with a

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palpable mass, whereas others are referred after lesions are detected incidentally on skeletal radiographs obtained for an alternative indication or during evaluation prompted by a positive family history [2]. The number of osteochondromas, the extent and distribution of skeletal involvement, and the severity of resulting deformities may vary considerably among individuals [1,2]. On average, approximately six lesions are observed per patient; the skeletal distribution of lesions may follow an asymmetric or symmetric pattern across cases [2]. During skeletal growth, osteochondromas enlarge and progressively ossify; after skeletal maturity is reached, growth typically ceases, and the development of new osteochondromas is not expected thereafter [1,2]. Osteochondromas in multiple hereditary exostoses may lead to a broad clinical spectrum, including pain, limb deformities, limb-length discrepancy, scoliosis, reduced skeletal growth, restricted joint range of motion, short stature, early-onset osteoarthritis, and neurological symptoms secondary to peripheral nerve compression [1,2].

Although the primary malignancy risk in HME is well defined as an increased risk of secondary chondrosarcoma, evidence regarding an association with hematologic malignancies (e.g., leukemia) remains limited, with only a few cases reported; the potential contribution of *EXT1/EXT2* through heparin sulfate biosynthesis and related pathways is currently being investigated [4]. Molecular genetic advances have substantially facilitated the genetic diagnosis of this syndrome. Using next-generation sequencing (NGS) and deletion/duplication analyses, genetic testing can identify heterozygous disease-causing pathogenic/likely pathogenic variants or copy-number variations (CNVs) in the *EXT1* and *EXT2* genes, thereby establishing the diagnosis of autosomal dominant HME [1,2,5].

The retrospective study discusses the clinical characteristics, radiological findings, and genetic results of 21 patients from 13 unrelated families with genetically confirmed HME.

Methods

Between February 2022 and December 2025, we enrolled 21 patients from 13 unrelated families who were referred to the Pediatric Genetics Department of Universty of Health Sciences Türkiye, Ankara Etlik City Hospital. The study cohort comprised patients in whom multiple exostoses were identified on radiographs and/or a disease-causing variant was detected in either the *EXT1* or *EXT2* gene by genetic testing. This retrospective study was approved by the Clinical Research Ethics Committee of the University of Health Sciences, Ankara Etlik City Hospital (approval no: AEŞH-BADEK1-2025-349, date: 02.09.2025). Written informed consent for genetic testing was obtained from the patients and their legal guardians prior to testing. Clinical and anthropometric data included medical and family histories, dysmorphic features, age at presentation, sex, weight, height, and head circumference. These measurements were reported as standard deviation scores (SDS) using nationally validated reference standards for children in Türkiye [6]. For participants older than 18 years, height, weight, and head circumference SDS values were calculated using the reference standards for age 18 years [6]. To ensure analytical accuracy, patients who could not be evaluated for specific variables (denoted as “NA: not available” throughout the tables and text) were excluded from percentage calculations for those variables within the cohort. With the exception of four patients (P2, P7, P10, and P18), systematic skeletal survey radiographs were obtained for the remaining 17 patients. The routine skeletal survey protocol included skull radiographs in two projections, anteroposterior radiographs of the upper and lower extremities, hand and foot radiographs, spine radiographs in two projections, a pelvic radiograph, and a posteroanterior chest radiograph. The survey was used to assess the location of skeletal abnormalities (e.g., exostoses) and evaluate radiographic features of spondylar, epiphyseal, and metaphyseal dysplasia. In addition, anthropometric measurements and skeletal survey radiographs of parents with identified exostoses were reviewed.

Diagnostic evaluation was performed using NGS-based clinical exome sequencing (CES) and Sanger sequencing. Genomic deoxyribonucleic acid was extracted from the patient’s peripheral blood following standard procedures. The sequencing library was prepared using the Clinical Exome Solution v3 capture kit (SOPHiA Genetics SA, Switzerland), and sequenced on the MiSeq platform (Illumina Inc., CA, USA). The generated data were interpreted using current databases (PubMed, OMIM, DGV, ClinVar, DECIPHER, and ClinGen), and variant pathogenicity was classified according to the American College of Medical Genetics and Genomics criteria [7]. Variants were reported with reference to the NCBI RefSeq transcripts NM_000127.3 (*EXT1*) and NM_207122 (*EXT2*), respectively. For candidate variants with the potential to explain the observed phenotype, Sanger sequencing was performed for validation in the proband and for segregation analysis in affected parents and siblings. Sanger sequencing was carried out using the Applied Biosystems 3500 Genetic Analyzer (Thermo Scientific, USA).

In this study, genetic diagnoses were established by CES in 12 patients (P1, P3, P6, P9, P11, P13-P17, P19, and P20). Variant confirmation was performed by Sanger sequencing in 19 patients (all except P16 and P19). In some cases, both CES and Sanger sequencing were performed.

Statistical Analysis

No formal statistical analysis was performed in this study. Accordingly, no statistical software was used; the results are presented descriptively.

Results

Of the 21 patients included in the study, 14 (66.7%) were female and 7 (33.3%) were male. The reasons for presentation included family screening, a history of exostoses, a palpable, hard mass in the extremities, joint pain, detection of exostoses on skeletal survey radiographs obtained for screening purposes, short stature, limb bowing, hypoglycemia, and onset of puberty. Age at presentation ranged from 2.27 to 59.6

years. Among patients with available information, no prenatal problems were identified; with respect to birth history, only one patient (P6) was small for gestational age. Only one of the 13 families (P21) was consanguineous.

Based on anthropometric evaluation, two patients (P4, P16) had a body weight ≤-2 SDS, and one patient (P14) had a head circumference <-2 SDS. Five patients (P3-P5, P7, P17) were classified as having short stature (height ≤-2 SDS). Three patients (P5, P11, P17) exhibited variable dysmorphic facial features. None of the patients reported hearing- or vision-related complaints, and no developmental or cognitive impairments were observed.

Cranial imaging was performed in selected patients; brain magnetic resonance imaging (MRI) findings were normal in P1 and P6, the latter of whom was followed for complex febrile seizures. Chiari type 1 malformation was identified in P14, and a benign-appearing, non-growing mass in the mesencephalon was observed in P21. Abdominal ultrasonography was performed in five patients (P1, P3, P15, P17, P21), and findings were normal in all patients. On echocardiography, minimal mitral regurgitation was detected in P14 (who was subsequently diagnosed with acute rheumatic fever) and in two other patients (P15 and P21). A secundum atrial septal defect was identified in P7. Echocardiography was normal in P3 and P17. In addition, epileptiform activity was detected on EEG in P6. One patient (P21) was receiving treatment for anorexia nervosa and an anxiety disorder.

Genetic testing identified a point mutation in either *EXT1* or *EXT2* in all patients. No CNV-related etiology was detected. Overall, 13 distinct pathogenic or likely pathogenic variants were identified in 15 (71.4%) patients with *EXT1* and *in* six (28.6%) patients with *EXT2*. Of these variants, seven were frameshift, four were nonsense, one was missense, and one affected a splice site. Eight variants had been previously reported in ClinVar, whereas the remaining five were novel. Family segregation analysis was performed on eight probands; only two (25%) were found to harbor *de novo* variants. For P14, P16, and P19, parental inheritance was suspected; however, segregation analysis could not be performed. In P15, segregation analysis in the mother was negative, whereas paternal testing could not be undertaken because the father was deceased. The medical history indicated that the father did not report similar symptoms. The patients' clinical and anthropometric characteristics are summarized in Table 1. Skeletal survey radiographs from 17 patients were evaluated for exostoses, and the findings are presented in Table 2 and Figures 1-3. The genetic analysis results are compared in Table 3.

Discussion

HME is a syndrome that is predominantly caused by pathogenic/likely pathogenic variants in the *EXT1* or *EXT2* genes and typically shows an inherited pattern, with sporadic cases occurring less frequently [8-11]. Whereas the diagnosis was historically based on clinical findings, the widespread use of molecular testing now facilitates diagnostic confirmation and enables provision of appropriate genetic counseling, including discussion of preimplantation genetic testing options for families [1]. Hematologic, renal, central nervous system, and cardiac findings may rarely accompany the condition. These manifestations are often not intrinsic features of the disease; rather, they may result from compressive mass effects due to lesions in uncommon locations or may reflect incidental/secondary conditions [1,3,12-14]. In our cohort, exostoses were most frequently identified in the forearm (ulna and radius), the femur, the lower leg (tibia and fibula), and the humerus. They were observed with moderate frequency in the hand and pelvis. More rarely, exostoses were detected in the foot, ribs, scapula, and clavicle, but no vertebral exostoses were observed in any patient. When interpreting radiographs, priority should be given to the extremities; however, it should be kept in mind that exostoses may also occur in other anatomical regions.

Scoliosis has been reported in approximately 30% of individuals with HME, with some studies describing even higher rates [2,3,15]. In our series, the prevalence of scoliosis was 17.6% (3/17), lower than rates reported in the literature. On the other hand, the detection of heparan sulfate (HS) expression in human fetal vertebrae and intervertebral discs suggests that HS may influence axial skeletal development [16]. Moreover, the literature has also demonstrated that HME is a risk factor in the etiology of scoliosis [15]. The reported prevalence of scoliosis may vary depending on several factors, including the number and size of exostoses, patient age at assessment, and the Cobb angle threshold used to define scoliosis. In addition to axial deformities, cases of compressive myelopathy due to intraspinal exostoses—although less frequent—have also been reported [17]. Therefore, for patients with HME who present with symptoms suggestive of neurological deficits, we recommend advanced imaging modalities. In the long bones, osteochondromas are typically asymptomatic and most commonly present as cosmetic concerns or palpable, firm masses. When symptomatic, they may lead to complications related to mechanical compression of adjacent anatomical structures, including bursitis, tendinitis, neuropathy, and arterial or venous thrombosis, as well as pseudoaneurysm formation; in rare cases, chronic compartment syndrome has also been reported [18,19]. Exostoses that impair joint range of motion may increase shear forces across the joint during movement. In addition, cartilaginous hypertrophy secondary to HS deficiency is considered a potential risk factor for early-onset osteoarthritis [20]. HME can affect long-bone growth, leading to short stature, limb-length discrepancies, and angular deformities of the extremities. The most common deformities include coxa valga, genu valgum, and ankle valgus. Radial and ulnar deviation and progressive deformity may result in elbow dislocation. Additional deformity-related manifestations include shortening and angular deformities of the metacarpal and metatarsal bones, as well as hip-related pathology such as acetabular dysplasia, femoroacetabular impingement, hip subluxation or dislocation, and patellar dislocation, reflecting a broad spectrum of orthopedic conditions associated with HME [21-23].

Table 1. Clinical and anthropometric characteristics of the patients

Patient	Sex	Age (years)	Weight (kg/ SDS)	Height (cm/SDS)	Head circum-ference (cm/SDS)	Gestational age/birth weight	Presenting complaint (s)	Comorbidities US: ultrasonography ECHO: echocardiography EEG: electroencephalography
F1P1	Female	9.24	27/-0.54	127 /-1.09	53/0.38	38 weeks 3500 g	Puberty started	Brain MRI: normal, abdominal US: normal, non-dysmorphic
F1P2 (father)	Male	47.00	NA	NA	NA	NA	Family screening, exostosis history	Non-dysmorphic
F2P3	Female	10.92	26.1/-1.88	126/**-2.77**	52/-0.91	38 weeks 3000 g	Short stature, limb bowing	Abdominal US: normal ECHO: normal non-dysmorphic
F2P4 (sibling)	Male	9.83	22/**-2.29**	125/**-2.00**	53/-0.29	NA	Short stature, limb bowing	Non-dysmorphic
F2P5 (mother)	Female	35.00	NA	136/**-4.62**	NA	NA	Short stature	Dysmorphic features
F3P6	Female	5.54	20/0.14	112/-0.07	50/-0.62	37 weeks 1800 g	Recurrent febrile seizures	Abnormal EEG findings, brain MRI: normal, Hypoglycemia, non-dysmorphic
F3P7 (sibling)	Female	2.46	NA/-1.46	**NA/-2.74**	NA/-0.78	38 weeks 2400 g	Family screening, short stature	ECHO: Secundum atrial septal defect, non-dysmorphic
F3P8 (mother)	Female	30.00	NA	NA	NA	NA	Family screening, exostosis history	Non-dysmorphic
F4P9	Male	2.87	12/-1.58	91/-1.19	51/0.68	38 weeks 3400 g	Exostoses identified; family history present	Non-dysmorphic
F4P10 (mother)	Female	30.00	NA	NA	NA	NA	Family screening, exostosis history	Non-dysmorphic
F5P11	Female	4.84	16/-0.87	109/0.21	51/0.27	40 weeks 3300 g	Palpable hard mass in the extremities	Dysmorphic features
F6P12	Female	13.34	40/-1.71	151.5/-1.2	54.5/-0.27	38 weeks normal	Palpable hard mass in the extremities	Non-dysmorphic
F6P13 (father)	Male	50.20	73/0.12	165 /-1.82	57/-0.47	NA	Family screening, exostosis history	Non-dysmorphic
F7P14	Female	15.00	48/-1.17	160/-0.28	**52/-2.62**	38 weeks normal	History of acute rheumatic fever, arthralgia	Non-dysmorphic brain MRI: chiari type I malformation, ECHO: minimal mitral regurgitation
F8P15	Male	2.27	NA/**-0.91**	NA/**-0.50**	NA/1.16	38 weeks 3000 g	Palpable hard mass in the extremities	Abdominal US: normal, non-dysmorphic ECHO: minimal mitral regurgitation
F9P16	Female	11.23	27/**-2.0**	137/-1.5	55/0.30	38 weeks normal	Palpable hard mass in the extremities	Don-dysmorphic
F10P17	Female	13.84	31/-4.05	142/**-3.03**	54/-0.84	39 weeks 3500 g	Short stature	Dysmorphic features abdominal US: normal ECHO: normal
F10P18 (father)	Male	59.60	NA	NA	NA	NA	Family screening, exostosis history	Non-dysmorphic

Table 1. Continued

Patient	Sex	Age (years)	Weight (kg/ SDS)	Height (cm/SDS)	Head circum-ference (cm/SDS)	Gestational age/birth weight	Presenting complaint (s)	Comorbidities US: ultrasonography ECHO: echocardiography EEG: electroencephalography
F11P19	Female	18.21	NA	169/1.00	NA	NA	Palpable hard mass in the extremities	Non-dysmorphic
F12P20	Male	2.99	15,8/0.5	94/-0.69	51/0.65	38 weeks 3250 g	Palpable hard mass in the extremities	Non-dysmorphic
F13P21	Female	17.79	50/-1.33	158/-0.85	56/-0.05	38 weeks 2650 g	Palpable hard mass in the extremities	Brain MRI*, abdominal US: normal ECHO: minimal mitral regurgitation non-dysmorphic

*: A well-circumscribed solid lesion is identified in the left mesencephalon, measuring 1.2 cm (AP) ×1.1 cm (TV) ×1.1 cm (SI). The lesion is T2-hyperintense and T1-hypointense, demonstrates no appreciable contrast enhancement, and shows no acute diffusion restriction. There is mild superior extension toward the left thalamo-mesencephalic junction
NA: Not available, F: Family, P: Patient, US: Ultrasonography, ECHO: Echocardiography, EEG: Electroencephalography, MRI: Magnetic resonance imaging

Three of our patients (3/21, 14.3%) underwent surgery for osteochondromas. Patient P3 underwent bilateral hemiepiphysiodesis of the distal femur, proximal tibia, and distal tibia to address bilateral knee and ankle valgus deformities. In Patient P5, MRI was performed because of pain in the left iliac wing and right distal medial femur and demonstrated a cartilage cap thickness of 3 mm; excision was subsequently performed for pain palliation. Patient P21 underwent excision of painful osteochondromas located at the right distal medial femur and the lateral aspect of the proximal tibia.

Malignant transformation is one of the most concerning complications of osteochondromas. The association between HME and skeletal malignancies is well established, and approximately 5-10% of patients may develop low-grade chondrosarcoma with limited metastatic potential [24,25]. The most common sites of malignant transformation include the proximal femur, proximal humerus, scapula, and pelvis [26]. Less frequently, osteosarcoma, fibrosarcoma, and malignant fibrous histiocytoma have also been reported [27]. In addition, hematologic malignancies, cerebellar astrocytoma, atypical teratoid/rhabdoid tumor, and cancer of the lung, thyroid, and colon have been described in these patients [27-32]. As of the most recent follow-up, no malignant transformation has been identified in any patient in our cohort (0%). In one of our patients (P21), a non-growing, stable mass was detected in the mesencephalon.

The *EXT* gene family, comprising *EXT1* and *EXT2*, functions as a tumor suppressor and encodes critical glycosyltransferases involved in HS biosynthesis. HS proteoglycans, formed by the attachment of HS chains to core proteins, play an important role in regulating bone and cartilage development [25,33,34]. Heterozygous variants in *EXT1*/*EXT2* reduce HS levels by approximately 50%; however, this reduction alone is not sufficient for osteochondroma formation [35]. The development of a tumorigenic cell is consistent with Knudson's "two-hit" hypothesis, requiring an additional somatic event affecting the second allele (e.g., loss of heterozygosity, or a second pathogenic mutation) [1,8]. Loss-of-function variants in these genes provide the biological basis for osteochondroma development [1,2]. Variants in *EXT1*, compared with those in *EXT2*, have been reported to be associated with a more severe phenotype, a higher number of osteochondromas, and an increased risk of malignant transformation [1,36]. In this genetically heterogeneous syndrome, no underlying genetic etiology is identified in approximately 10-13% of cases, whereas variants are reported in *EXT1* in 65-70% and in *EXT2* in 30-35% of cases [1]. In our study, consistent with the literature, variants were most frequently detected in *EXT1* (15/21; 71.4%) and less commonly in *EXT2* (6/21; 28.6%). Although variants can be distributed throughout the genes, some reports indicate that exons 1 and 6 in *EXT1* and the first eight exons in *EXT2* constitute mutational "hot spot" regions [1]. Consistent with the literature, 80% of patients carrying an *EXT1* variant had variants in these two exons (60% in exon 1 and 20% in exon 6), whereas all patients with *EXT2* variants

Table 2. Distribution of exostoses across the skeletal system in patients

Patient	Femur	Lower leg (tibia and fibula)	Humerus	Forearm (ulna and radius)	Hand	Foot	Rib	Clavicle	Vertebra	Pelvis	Scapula
F1P1	+	+	+	+	+	+	-	-	-	+	-
F1P2	No imaging available										
F2P3	+	+	+	+	+	-	-	+	-	+	-
F2P4	+	+	+	+	+	-	+	+	-	+	+
F2P5	+	+	+	+	-	-	-	-	-	+	+
F3P6	+	+	+	+	+	-	-	-	-	-	-
F3P7	No imaging available										
F3P8	+	+	-	+	+	+	-	-	-	-	-
F4P9	+	+	+	+	-	-	-	-	-	-	-
F4P10	No imaging available										
F5P11	+	+	+	+	+	-	-	-	-	-	-
F6P12	+	+	+	+	-	-	-	-	-	-	-
F6P13 (Baba)	+	+	+	+	-	-	-	+	-	-	+
F7P14	+	+	-	-	-	-	-	-	-	-	-
F8P15	+	+	-	+	-	-	-	-	-	-	-
F9P16	-	-	+	+	-	-	-	-	-	-	-
F10P17	+	+	+	+	-	-	-	-	-	+	-
F10P18	No imaging available										
F11P19	+	+	+	+	-	-	-	-	-	-	-
F12P20	-	+	-	+	+	+	+	-	-	-	-
F13P21	+	+	+	+	-	-	-	-	-	-	-
	15/17	16/17	13/17	16/17	7/17	3/17	2/17	3/17	0/17	5/17	3/17

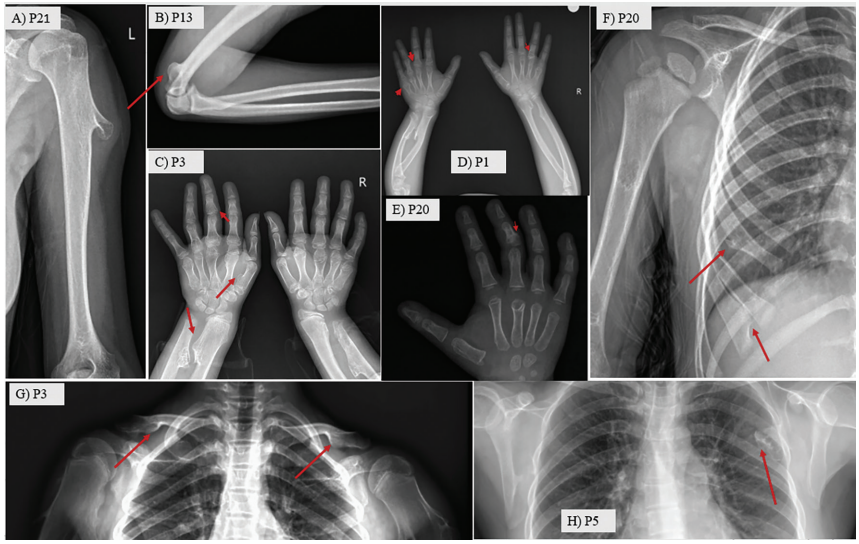

Figure 1. Representative examples of multiple exostoses/osteochondromas involving the upper extremities, clavicles, and ribs in patients with hereditary multiple exostoses. Red arrows indicate the lesions. A) P21: Exostosis of the proximal humerus. B) P13: Exostosis around the elbow (at the level of the proximal forearm). C) P3: Multiple exostoses of the hand and wrist, involving the metacarpals, phalanges, and distal forearm bones. D) P1: Multiple exostotic foci in both hands and the forearm, predominantly at the metacarpal/phalangeal level. E) P20: Exostosis at the level of the phalanx. F) P20: Rib-localized exostoses on the shoulder girdle and chest radiograph. G) P3: Bilateral clavicular exostoses on a shoulder girdle radiograph. H) P5: Exostosis in the scapular region on a shoulder girdle/chest radiograph

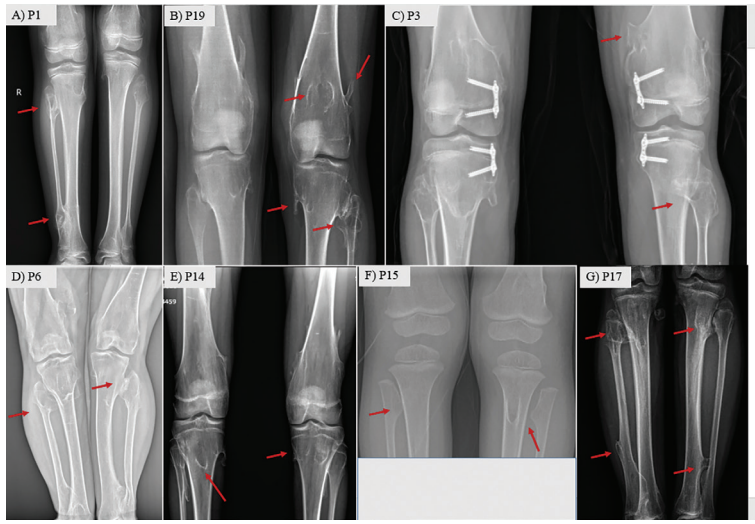

Figure 2. Representative examples of multiple exostoses/osteochondromas involving the lower extremities (distal femur, proximal tibia/fibula, and peri-knee region) in patients with hereditary multiple exostoses. Red arrows indicate the lesions. A) P1: Multiple exostoses along the tibia at the proximal and distal metaphyseal levels. B) P19: Multiple exostoses around the knee involving the distal femur and proximal tibia/fibula. C) P3: Exostoses around the knee at the distal femur and proximal tibia, with orthopedic fixation hardware *in situ*. D) P6: Multiple exostoses around the proximal tibia/fibula. E) P14: Prominent exostosis around the knee, most evident at the proximal fibular metaphysis. F) P15: Multiple exostoses at the level of the proximal tibia and fibula. G) P17: Multiple exostotic foci along the tibia and fibula

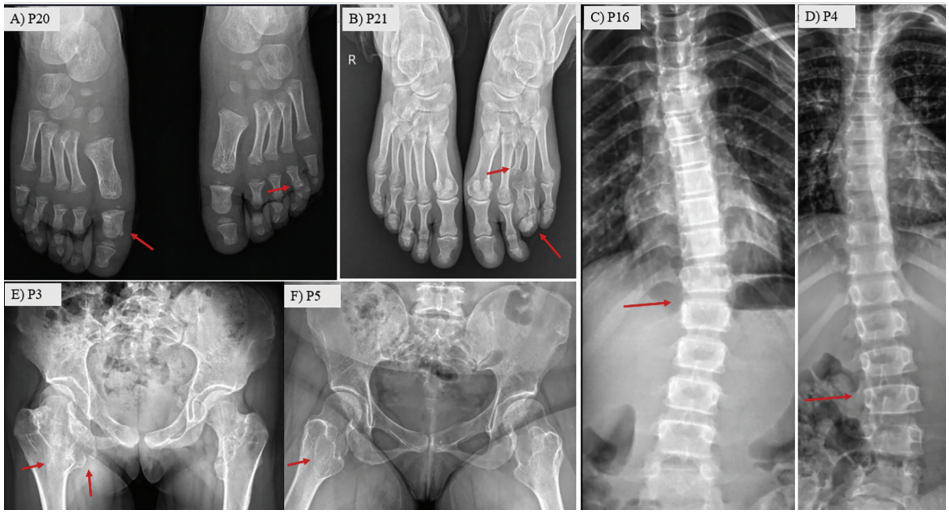

Figure 3. Findings observed in the feet, pelvis/proximal femur, and spine in patients with hereditary multiple exostoses. Red arrows indicate the relevant pathology. A) P20: Exostosis/osteochondroma foci in the foot at the metatarsal and phalangeal levels. B) P21: Multiple exostoses in the foot involving the metatarsals and phalanges. C) P16: Scoliosis on spine radiograph (arrows indicate the curvature). D) P4: Scoliosis on spine radiograph (arrows indicate the curvature). E) P3: Exostosis/osteochondroma foci around the proximal femur/hip on pelvic radiograph. F) P5: Exostosis/osteochondroma foci around the proximal femur/hip on pelvic radiograph

harbored variants within the first eight exons. *De novo* disease has been reported in the literature at a rate of approximately 10%; in our study, a higher frequency of 25% was observed [1]. This discrepancy may be related to the inability to perform genetic testing on the parents of all probands and the limited sample size.

Multilocus genomic variation is defined as the concurrent identification of pathogenic variants at more than one independent locus in patients presenting with complex clinical phenotypes [37]. In this context, in addition to the *EXT1* variant, other genomic variant were identified in our patients P1 and P3: a paternally inherited heterozygous variant of uncertain significance in *COL11A1* in P1, and a maternally inherited heterozygous, likely pathogenic variant in *NOG* in P3. These cases were published by Kablan et al. [37].

Follow-up of patients with HME should include documentation of growth parameters at each visit and a particularly thorough assessment of the musculoskeletal system. Given the variable clinical manifestations and potential complications, the management of HME requires a multidisciplinary approach. Optimal care, coordinated through a multidisciplinary team that includes specialists in pediatric oncology, orthopedic

Table 3. General characteristics of variants detected in the *EXT1* (NM_000127.3) and *EXT2* (NM_207122) genes in patients

Patient	Genomic Analysis	Variant (c./p.)	Exon	Molecular consequence	Classification ACMG Criteria	Parental segregation	ClinVar submission status (submitted/novel)
F1P1	CES, SS	*EXT1* c.325delT p.(Cys109Alafster27)	1/11	Frameshift	Pathogenic (PP1, PP4, PVS1, PM2)	Paternal	Novel
F1P2	SS	*EXT1* c.325delT p.(Cys109Alafster27)	1/11	Frameshift	Pathogenic	Paternal (no tested)	Novel
F2P3	CES, SS karyotyping	*EXT1* c.390_406del p.(Tyr131Glyfs*52)	1/11	Frameshift	Pathogenic (PP1, PP4, PVS1, PM2)	Maternal	Novel
F2P4	SS	*EXT1* c.390_406del p.(Tyr131Glyfs*52)	1/11	Frameshift	Pathogenic	Maternal	Novel
F2P5	SS	*EXT1* c.390_406del p.(Tyr131Glyfs*52)	1/11	Frameshift	Pathogenic	NA	Novel
F3P6	CES, SS	*EXT1* c.493C>T p.(Gln165*)	1/11	Nonsense	Pathogenic (PP1, PP4, PP5, PS4, PVS1, PM2)	Maternal	Submitted rs2130043213
F3P7	SS	*EXT1* c.493C>T p.(Gln165*)	1/11	Nonsense	Pathogenic	Maternal	Submitted rs2130043213
F3P8	SS	*EXT1* c.493C>T p.(Gln165*)	1/11	Nonsense	Pathogenic	Maternal (no tested)	Submitted rs2130043213
F4P9	CES, SS	*EXT1* c.1057-3C>G	3/11	Splice-site	Pathogenic (PP1, PP4, PP3, PP2)	Maternal	Submitted rs200927981
F4P10	SS	*EXT1* c.1057-3C>G	3/11	Splice-site	Pathogenic	NA	Submitted rs200927981
F5P11	CES, SS	*EXT1* c.1468del p.(Leu490Trpfs*9)	6/11	Frameshift	Pathogenic (PS4, PVS1, PM2, PP5, PM6, PP4)	*De novo*	Submitted rs886039355
F6P12	SS	***EXT2*** c.670C>T p.(Gln224*)	4/14	Nonsense	Pathogenic (PS4, PM2, PP1, PVS1, PP4, PP5)	Maternal	Submitted rs1565199251
F6P13	CES, SS	***EXT2*** c.670C>T p.(Gln224*)	4/14	Nonsense	Pathogenic	NA	Submitted rs1565199251
F7P14	CES, SS	***EXT2*** c.244dup p.(Asp82Glyfs*11)	2/14	Frameshift	Pathogenic (PS4, PVS1, PM2, PP5, PP4)	NA	Novel
F8P15	CES, SS	*EXT1* c.584T>G p.(Leu195*)	1/11	Nonsense	Pathogenic (PVS1, PM2, PP5)	NA	Submitted rs1586279621
F9P16	CES	***EXT2*** c.623del p.(Asp208Alafs*62)	3/14	Frameshift	Likely Pathogenic (PP4, PVS1, PM2)	Maternal (no tested)	Novel
F10P17	CES, SS karyotyping	*EXT1*.1469del p.(Leu490Argfs*9)	6/11	Frameshift	Pathogenic (PS4, PM2, PVS1, PP5)	Paternal	Submitted rs886039356
F10P18	SS	*EXT1* c.1469del p.(Leu490Argfs*9)	6/11	Frameshift	Pathogenic (PS4, PM2, PVS1, PP5)	NA	Submitted rs886039356
F11P19	CES	*EXT1* c.1019G>A p.(Arg340His)	2/11	Missense	Likely Pathogenic (PM1, PM5, PP3, PP4, PP5)	Paternal (no tested)	Submitted rs119103287
F12P20	CES, SS	***EXT2*** c.1187G>A p.(Trp396*)	8/14	Nonsense	Pathogenic (PVS1, PM2, PP5)	*De novo*	Submitted rs750542485
F13P21	SS	***EXT2*** c.1060del p.(Leu354PhefsTer11)	6/14	Frameshift	Likely Pathogenic (PM2, PVS1)	Paternal (no tested)	Novel

F: Family, P: Patient, NA: Not available, CES: Clinical exome sequencing, SS: Sanger sequencing, ACMG: American College of Medical Genetics and Genomics

surgery, pediatric genetics and medical genetics, pediatric neurology, pediatric radiology, and physiotherapy/rehabilitation, encompasses comprehensive clinical evaluation, the appropriate use of imaging modalities, an expanded differential diagnosis, and the integration of advanced molecular testing. This comprehensive collaboration facilitates early recognition of mild or atypical clinical features and complications and supports accurate genetic diagnosis. Diagnostic certainty can be enhanced through testing approaches such as *EXT1*/*EXT2*-focused NGS and deletion/duplication analyses. Management and follow-up are individualized according to parameters such as the number and location of lesions, the severity of the deformity, the symptom burden, and the age. Regarding the risk of secondary chondrosarcoma, warning signs such as new-onset or increasing pain, rapid growth, and thickening of the osteochondroma cartilage cap should be assessed meticulously. This approach enables effective management of HME-specific complications and improves quality of life; it also supports more accurate genetic counseling for families regarding prognosis and reproductive options in the context of autosomal dominant inheritance, penetrance, and variable expressivity.

Study Limitations

The main limitations of this study include its single-center design, limited sample size, and the inability to perform segregation analyses in some families. Nevertheless, our findings are expected to provide meaningful contributions to future research and patient management. Multicenter studies with larger cohorts will help clarify the pathogenesis of this syndrome more precisely and further expand its clinical spectrum.

Conclusion

HME is a clinically heterogeneous entity with variable expressivity. In the presence of a family history, patients should be monitored closely, given the high penetrance and risk of malignant transformation. Careful follow-up is warranted for restricted joint range of motion, cosmetic concerns, and associated skeletal abnormalities. In patients with these features, HME should routinely be considered in the differential diagnosis and comprehensive molecular testing should be prioritized to elucidate the underlying genetic etiology.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Clinical Research Ethics Committee of the University of Health Sciences, Ankara Etlik City Hospital (approval no: AEŞH-BADEK1-2025-349, date: 02.09.2025).

Informed Consent: This retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., M.A.K., T.D., F.D.B., A.Ka., G.Ş., Concept: A.K., M.A.K., T.D., S.D., G.Ş., Design: A.K., M.A.K., T.D., Ş.Y., Ş.Ye., Data Collection or Processing: A.K., M.A.K., F.D.B., A.Ka., Ş.Y., Ş.Ye., Analysis or Interpretation: A.K., M.A.K., F.D.B., A.Ka., A.D., Ş.Ye., G.Ş., Literature Search: A.K., T.D., G.Ş., Writing: A.K., T.D., F.D.B., A.Ka., Ş.Y., A.D., G.Ş.

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The Effect of Nutritional Support on Malnutrition and Muscle Loss in Hematological Cancer Patients: A Retrospective Single-center Study

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ABSTRACT

Aim: Malnutrition is frequently observed in patients with hematopoietic malignancies due to the effects of the primary disease and treatments. The aim of this study is to assess the nutritional status of patients who have undergone hematopoietic stem cell transplantation and to evaluate the effects of malnutrition on anthropometric measurements, muscle function, and skinfold thickness.

Methods: This retrospective study included 37 patients with hematological malignancies who were at risk of malnutrition and sarcopenia, as determined using the NRS2002. The nutritional status of the patients was evaluated before and after nutritional support using the Global Leadership Initiative on Malnutrition (GLIM) criteria. Additionally, triceps, calf, suprailiac, and subscapular skinfold thicknesses, as well as handgrip strength (HG), were measured before and after nutritional support. The patients' malnutrition universal screening tool (MUST) scores, sarcopenia levels, body mass index (BMI), and weight changes were compared before and after nutritional support.

Results: The participants' weight and BMI showed statistically significant changes after nutritional therapy. The median weight increased from 59 (38-88) kg to 61 (42-87) kg, and the median BMI rose from 21.75 (15.3-28.4) to 23 (16.8-28.2) ($p<0.001$). The MUST score, sarcopenia risk, skinfold thickness, and HG measurements showed significant decreases (all $p<0.001$). Increases in weight, BMI, hand-grip strength, and skinfold thickness measurements, and decreases in MUST score and sarcopenia risk were observed. The mean survival time was calculated as 10.89 months. The 6-month survival rate was 89.2%.

Conclusion: Providing nutritional support according to the GLIM criteria to patients with hematological malignancies can help protect them from sarcopenia.

Keywords: Malnutrition, hematologic malignancy, sarcopenia, NRS2002, MUST score

Introduction

Malnutrition is prevalent in patients with hematologic cancers and results from both the presence of the tumor and the medical treatments they undergo. This condition has a detrimental impact on patients' quality of life and on treatment-related toxicities. As a result, nutrition plays a crucial role in the care of hematologic cancer patients [1-3].

Nutritional status plays a critical role in the treatment of hemato-oncological patients. It is considered a valuable tool in the selection and process of treatment in hemato-oncology patients [4]. It is well-established that the metabolism and nutrition of patients with hematological malignancies are adversely affected by both their underlying diseases and the treatments they undergo [4]. Research has demonstrated that nutritional deficiencies can negatively impact the treatment outcomes of these patients [5].

The European Society for Clinical Nutrition and Metabolism (ESPEN) has issued guidelines recommending the periodic evaluation of nutritional intake, weight changes, and body

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mass index (BMI) should be regularly performed at the time of diagnosis and subsequent follow-ups to identify malnutrition [2].

Sarcopenia characterized by progressive and pervasive skeletal muscle disorder is confirmed by the presence of low muscle mass or quality [6]. All patients with hemato-oncological diagnoses should be screened for malnutrition and sarcopenia before and during treatment [7,8]. Patients at risk of sarcopenia should be carefully assessed for muscle mass, muscle strength and function [9]. Medical nutrition treatments for patients with malnutrition and sarcopenia should be carefully planned [10,11].

The Global Leadership Initiative on Malnutrition (GLIM) framework recommends a two-stage process for the diagnosis of malnutrition in adults: initially, risk is identified using a validated nutritional screening instrument; this is followed by a comprehensive assessment which requires the presence of at least one phenotypic indicator (such as unintentional weight loss, a low BMI, or reduced muscle mass) and at least one etiologic factor (such as inadequate dietary intake or absorption, or an underlying inflammatory condition or disease burden) to establish the diagnosis. Phenotypic measures are used to determine the severity of malnutrition. This model aims to harmonize the global definition of malnutrition and facilitate its consistent implementation in clinical settings [12].

There are limited data on functional and anthropometric changes after structured nutritional support in hematopoietic stem cell transplantation (HSCT) patients diagnosed using GLIM criteria. This study aimed to assess the nutritional status of patients with hematological malignancies who underwent HSCT and to explore the impact of malnutrition on anthropometric measurements, muscle function, and skinfold thickness.

Methods

Approval for conducting the study was obtained from the İnönü University Faculty of Health Sciences Non-Interventional Clinical Research Ethics Committee (approval no: 2024/6234, date: 16.07.2024). Patient data were collected retrospectively. Patients who underwent HSCT in our bone marrow transplantation unit were included in the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

The primary outcome of the study was the change in handgrip strength (HG) (kg) following structured nutritional support. Secondary outcomes included changes in BMI, weight, skinfold thickness, malnutrition universal screening tool (MUST) score, and sarcopenia risk. This study included 37 patients diagnosed with hematological malignancies who were deemed to be at risk of malnutrition and sarcopenia, determined using the NRS2002 [12]. The nutritional status of the patients was evaluated before and after nutritional support using GLIM criteria [13].

According to ESPEN guidelines, high-energy oral nutritional supplementation (ONS) was typically initiated at 1-2 bottles per day (300-600 kcal) and increased to 600-900 kcal/day depending on the patient's requirements and tolerance. The aim of oral nutritional support was to meet the patient's total energy needs of 25-30 kcal/kg/day and protein requirements of 1.2-1.5 g/kg/day. Intake, gastrointestinal tolerance, and weight were monitored regularly, and supplementation was continued until the nutritional targets were achieved.

Sarcopenia risk was assessed according to the NRS-2002 criteria. Values prior to nutritional support and at six months thereafter were compared. Triceps, calf, suprailiac, and subscapular skinfold thicknesses (triceps skinfold thickness, calf skinfold thickness, suprailiac skinfold thickness, subscapular skinfold thickness) and HG were recorded before and after nutritional support. The patients' MUST scores [14], sarcopenia levels, BMI, and weight changes were compared before and after six months of nutritional support.

Additionally, the survival analysis aimed to determine whether there was a difference between the groups that received nutritional support and those that did not.

Study Population

Inclusion criteria: Patients were eligible if they: were ≥18 years old, had a confirmed diagnosis of hematological malignancy, underwent autologous or allogeneic HSCT (allo-HSCT), were identified as being at risk of malnutrition using NRS-2002, received structured nutritional support during hospitalization.

Exclusion criteria: Severe organ failure preventing anthropometric evaluation, neuromuscular disorders affecting handgrip measurement, incomplete medical records, a total of 37 patients met the inclusion criteria.

Structured Nutritional Support Protocol

All patients received individualized, structured nutritional support which was supervised by a clinical nutrition team and initiated within the first 48 hours of hospitalization for HSCT.

The nutritional intervention included the following: energy targets of 25-30 kcal/kg/day, adjusted based on clinical condition and metabolic demand; protein targets of 1.2-1.5 g/kg/day, increased up to 1.5-2.0 g/kg/day in patients with severe catabolism; and ONS containing.

Nutritional support, including whey protein, essential amino acids, vitamins, and trace elements, was maintained throughout the hospitalization period (median duration: 180 days).

Statistical Analysis

Categorical variables in the study were summarized using frequencies (percentages). The normality of the quantitative data distribution was evaluated using the Shapiro-Wilk test. For quantitative data that did not show a normal distribution, the median (minimum-maximum) was used for summarization, while quantitative data that showed a normal distribution were summarized using mean ± standard deviation. In statistical analyses, two dependent quantitative variables were analyzed using either the dependent samples t-test or the Wilcoxon signed-rank test, depending on the normality

of the distribution. The relationship between variables was examined using the Spearman's rho correlation coefficient. A p value <0.05 was considered statistically significant in the statistical analyses. All analyses were performed using IBM SPSS Statistics 26.0 for Windows (New York, USA). Survival curves were visualized using Python (version 3.13.5) with the lifelines library (version 0.30.3).

Results

The median age of the patients included in the study was 56. Twenty-five (67.57%) of the patients were male, and 12 (32.43%) were female. The patients' demographic data are presented in Table 1.

As illustrated in Table 2, a comprehensive statistical analysis was conducted to assess changes in weight, muscle strength, and body fat measurements among all patients (p1), male patients (p2), and female patients (p3). The analysis showed statistically significant increases in weight and BMI over time. The median weight increased from 59 (38-88) kg to 61 (42-87) kg (p=0.001), and the median BMI increased from 21.75 (15.3-28.4) to 23 (16.8-28.2) (p<0.001).

A significant decrease was observed in the MUST score which decreased from 4 (0-6) to 2 (0-5) (p<0.001). Similarly, the risk of sarcopenia significantly decreasedreducing from 4 (1-9) to 2 (0-7) (p<0.001). In addition, a notable increase in arm muscle strength was observed. Specifically right arm strength increased from 18±9 kg to 22±9 kg (p<0.001), while left arm strength increased from 18±9 kg to 22±9 kg (p<0.001). Increases were also observed in the skinfold thickness measurements, indicating changes in body fat distribution: suprailiac skinfold thickness increased from 10 (2-22) mm to 11 (7-25) mm (p<0.001), triceps skinfold thickness increased from 12 (3-32) mm to 14 (2-33) mm (p<0.001), and subscapular skinfold thickness increased from 12 (3-25) mm to 13 (6-25) mm (p=0.002). These findings suggest that there were significant improvements in the participants' physical condition over time, with increases, particularly in weight, BMI, arm strength, and skinfold thickness, while the MUST score and sarcopenia risk decreased.

Table 1. Descriptive statistics table of demographic variables

		Mean ± SD	Median (min-max)
Age		53±18	56 (20-83)
Weight (before)		60±10	59 (38-88)
Weight (after)		62±9	61 (42-87)
Height		165±10	170 (145-180)
BMI (before)		21±3	21.75 (15.3-28.4)
BMI (after)		22±3	23 (16.8-28.2)
		Number	**Percentage (%)**
Gender	**Male**	25	67.57
	Female	12	32.43
Primary disease	**HL**	2	6
	Non-HL	1	3
	AML	4	10
	ALL	4	10
	CML	1	3
	MM	25	68
HSCT	**Autologuous**	14	38
	Allogeneic	23	62

SD: Standard deviation, min: Minimum, max: Maximum, HL: Hodgkin lymphoma, AML: Acute myeloid leucemia, ALL: Acute lymphoblastic leukemia, CML: Chronic myeloid leukemia, MM: Multiple myeloma, HSCT: Hematopoietic stem cell transplantation, BMI: Body mass index

In this study, changes in weight, muscle strength, and body fat distribution were analyzed separately for male and female patients. In male patients, weight exhibited a significant increase; the average weight rose from 63±10 kg to 66±8 kg (p<0.001). The BMI of male patients also exhibited a statistically significant increase, from 20.4 (15.6-28.4) to 21.38 (17.2-28.2) (p=0.001). The MUST score decreased significantly from 4 (0-6) to 2 (0-5) (p<0.001). Furthermore, the risk of sarcopenia also significantly decreased in men, dropping from 4.7±2 to 2±1 (p<0.001). Right arm muscle strength increased from 19±10 kg to 24±10 kg (p<0.001), while left arm muscle strength increased from 19±10 kg to 24±9 kg (p<0.001). Significant increases were also observed in suprailiac, triceps, and subscapular skinfold thicknesses in men: suprailiac increased from 11 (2-22) mm to 11 (7-25) mm (p=0.001), triceps increased from 10 (3-32) mm to 12 (2-33) mm (p=0.001), and subscapular increased from 11 (3-25) mm to 11 (6-25) mm (p=0.015).

In female patients, weight increase was not statistically significant; the average weight increased from 52±6 kg to 53±6 kg, but this increase was not significant (p=0.338). Women's BMI increased from 23 (15.3-25.68) to 24 (16.8-26.63); this increase was statistically significant (p=0.034). The MUST score also significantly decreased in women, dropping from 4 (2-5) to 2 (0-4) (p=0.007). The risk of sarcopenia significantly decreased in women as well, from 4±2 to 2±2 (p<0.001). Right arm muscle strength increased from 16±7 kg to 19±7 kg (p=0.004), and left arm muscle strength increased from 14±7 kg to 19±7 kg (p=0.003). Among women, suprailiac skinfold thickness changed from 10 (4-20) mm to 10 (8-20) mm; this change was not statistically significant (p=0.054). Triceps skinfold thickness increased from 19 (8-25) mm to 21 (10-30) mm (p=0.005). Subscapular skinfold thickness in women increased from 14.5 (8-25) mm to 18 (7-25) mm, and this increase was statistically significant (p=0.049).

These findings suggest that in men weight, BMI, muscle strength, and skinfold thicknesses showed statistically significant increases, whereas in women BMI, muscle strength, and certain skinfold thicknesses showed statistically significant increases; weight change was not significant.

Table 3 shows correlations between the pre-nutrition measurements of the variables. According to the findings in Table 3, a robust positive correlation was found between BMI and weight (r=0.667, p<0.001), while a negative correlation was observed between the MUST score and BMI (r=-0.694, p<0.001). Additionally, a positive relationship was identified

Table 2. Analysis table of changes in weight, muscle strength, and body fat measurements

Variables		p1	Male	p2	Female	p3
Weight (before)	59 (38-88)	0.001*	63±10	<0.001**	52±6	0.338**
Weight (after)	61 (42-87)		66±8		53±6	
BMI (before)	21 (15-28)	<0.001*	20 (15-28)	0.001*	22 (15-25)	0.034*
BMI (after)	23 (16-28)		21 (17-28)		24 (16-26)	
MUST score (before)	4 (0-6)	<0.001*	4 (0-6)	<0.001*	4 (2-5)	0.007*
MUST score (after)	2 (0-5)		2 (0-5)		2 (0-4)	
Sarcopenia risk (before)	4 (1-9)	<0.001*	4±2	<0.001**	4±2	<0.001**
Sarcopenia risk (after)	2 (0-7)		2±1		2±2	
Right arm strength (before)	18±9	<0.001**	19±10	<0.001**	16±7	0.004**
Right arm strength (after)	22±9		24±9		19±7	
Left arm strength (before)	18±9	<0.001**	19±10	<0.001**	14±7	0.003**
Left arm strength (after)	22±9		24±9		18±7	
Suprailiac skinfold (before)	10 (2-22)	<0.001*	11 (2-22)	0.001*	10 (4-20)	0.054*
Suprailiac skinfold (after)	11 (7-25)		11 (7-25)		10 (8-20)	
Triceps skinfold (before)	12 (3-32)	<0.001*	10 (3-32)	0.001*	19 (8-25)	0.005*
Triceps skinfold (after)	14 (2-33)		12 (2-33)		21 (10-30)	
Suprascapular skinfold (before)	12 (3-25)	0.002*	11 (3-25)	0.015*	14.5 (8-25)	0.049*
Suprascapular skinfold (after)	13 (6-25)		11 (6-25)		18 (7-25)	
Calf skinfold (before)	13 (3-39)	0.003*	12 (3-35)	0.012*	20 (6-39)	0.101*
Calf skinfold (after)	14 (7-40)		12 (8-36)		21.5 (7-40)	

Variables are presented as mean ± standard deviation or median (minimum-maximum) based on the normality of the distribution. p1: significance test result for measurements between all patients; p2: significance test result for measurements between male patients; p3: significance test result for measurements between female patients; *: Wilcoxon test; **: Paired sample t-test
BMI: Body mass index, MUST: Malnutrition universal screening tool

between the MUST score and sarcopenia risk (r=0.334, p=0.043). A negative relationship was found between right arm strength and sarcopenia risk (r=-0.482, p=0.003). Similarly, a negative correlation was observed between left-arm strength and sarcopenia risk (r=-0.518, p=0.001). Strong positive relationships were found between subscapular skinfold thickness and BMI (r=0.712, p<0.001), and between subscapular and triceps skinfold thickness (r=0.575, p<0.001). Furthermore, positive relationships were identified between calf skinfold thickness and triceps skinfold thickness (r=0.736, p<0.001), and between calf and subscapular skinfold thickness (r=0.762, p<0.001). These findings suggest significant relationships among increased sarcopenia risk, decreased muscle strength, and body fat thickness. A positive relationship was found between suprailiac skinfold thickness and BMI (r=0.409, p=0.012). Additionally, a positive relationship was found between triceps skinfold thickness and BMI (r=0.384, p=0.019). Conversely, a negative relationship was identified between subscapular skinfold thickness and sarcopenia risk (r=-0.451, p=0.005). These results suggest that an elevated risk of sarcopenia may be associated with increased body fat thickness.

Table 4 shows the correlations among the post-nutrition measurements. According to the table, a positive relationship was found between BMI and weight (r=0.486, p=0.002), while a negative relationship was observed between BMI and MUST score (r=-0.454, p=0.005). A positive correlation was also found between sarcopenia risk and the MUST score (r=0.467, p=0.004), whereas a negative correlation was found between sarcopenia risk and left arm strength (r=-0.416, p=0.010). A strong positive relationship was found between subscapular skinfold thickness and BMI (r=0.662, p<0.001), whereas triceps skinfold thickness was negatively associated with sarcopenia risk (r=-0.486, p=0.002). Additionally, positive correlations were found between calf skinfold thickness and both triceps skinfold thickness (r=0.734, p<0.001) and subscapular skinfold thickness (r=0.717, p<0.001). Positive relationships were also found between suprailiac skinfold thickness and BMI (r=0.346, p=0.036) and between triceps skinfold thickness and BMI (r=0.374, p=0.023). These findings highlight the effects of post-nutritional measurements on sarcopenia risk on and muscle strength. The significant relationships between BMI, sarcopenia risk, and muscle strength are important to consider in nutritional interventions and monitoring.

According to the Kaplan-Meier survival analysis, a total of 37 patients were included in the study: 4 patients (10.81%) experienced death, and 33 patients (89.19%) survived. The mean survival time was 10.89 months [standard error (SE): 0.524, 95% confidence interval (CI): 9.87-11.92 months]. The survival curve showed a gradual decline during the first 3 months, reaching approximately 89% by the 3rd month, and then remained stable at this level over the following 12

Table 3. Correlation table of pre-nutrition measurements of variables

Variables		Weight (before)	BMI	MUST score (before)	Sarcopenia risk (before)	Right arm strength (before)	Left arm strength (before)	Suprailiac skinfold (before)	Triceps skinfold (before)	Subscapular skinfold (before)	Calf skinfold (before)
Weight (before)	**r**	1.000									
	p	-									
BMI (before)	**r**	0.667**	1.000								
	p	**<0.001**	-								
MUST score (before)	**r**	-0.384*	-0.694**	1.000							
	p	**0.019**	**<0.001**	-							
Sarcopenia risk (before)	**r**	-0.164	-0.177	0.334*	1.000						
	p	0.332	0.295	**0.043**	-						
Right arm strength (before)	**r**	0.169	0.154	-0.231	-0.482**	1.000					
	p	0.319	0.364	0.168	**0.003**	-					
Left arm strength (before)	**r**	0.267	0.074	-0.197	-0.518**	0.874**	1.000				
	p	0.109	0.665	0.243	**0.001**	**<0.001**	-				
Suprailiac skinfold (before)	**r**	0.319	0.409*	-0.142	-0.114	0.197	0.196	1.000			
	p	0.054	**0.012**	0.402	0.501	0.242	0.244	-			
Triceps skinfold (before)	**r**	0.066	0.384*	-0.293	-0.129	0.084	-0.036	0.529**	1.000		
	p	0.698	**0.019**	0.079	0.447	0.623	0.835	**0.001**	-		
Suprascapular skinfold	**r**	0.428**	0.712**	-0.451**	0.010	0.021	-0.056	0.575**	0.564**	1.000	
	p	**0.008**	**<0.001**	**0.005**	0.955	0.902	0.741	**<0.001**	**<0.001**	-	
Calf skinfold (before)	**r**	0.209	0.526**	-0.331*	-0.225	-0.005	-0.159	0.489**	0.741**	0.762**	1.000
	p	0.215	**0.001**	0.045	0.181	0.977	0.348	**0.002**	**<0.001**	**<0.001**	-

r: Spearman's rho correlation coefficient, *: p<0.05, **: p<0.001, bolded values indicate statistical significance
BMI: Body mass index, MUST: Malnutrition universal screening tool

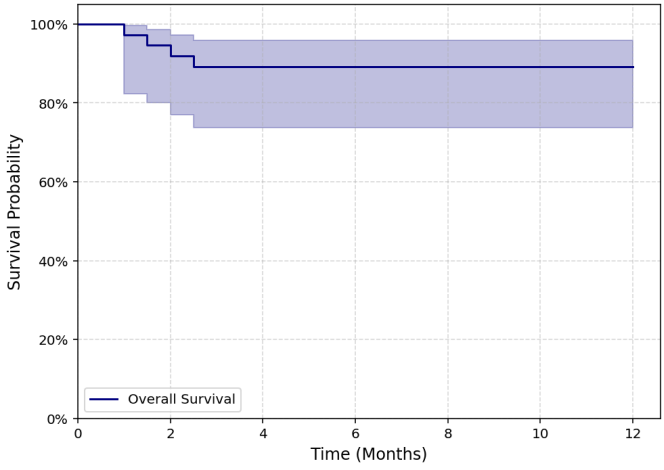

Figure 1. Survival outcomes of hematologic malignancy patients with weight loss

months. Thus, the 6-month survival rate was 89.2% (Figure 1, Table 5).

The mean survival time for male patients was 10.24 months (SE: 0.516; 95% CI: 9.228-11.252), while for female patients it was 10.33 months (SE: 1.077; 95% CI: 8.222-12.445). The log-rank test showed no statistically significant difference between the survival curves (p=0.45) (Figure 2, Table 6).

Discussion

There is limited information in the literature regarding sarcopenia and nutritional deficiencies in patients with hematological malignancies. Cachexia and sarcopenia are thought to play a significant role in the treatment process in this patient population. In addition to necessity of primary malignancy treatments, supportive treatments for cachexia and sarcopenia are well understood [8].

In the HSCT setting, patients are frequently exposed to profound metabolic stress, systemic inflammation, mucosal toxicity, and reduced nutritional intake, all of which predispose them to progressive weight loss and muscle wasting. In this context, the prevention of further decline may be clinically meaningful. Therefore, the observed median weight increase from 59 kg to 61 kg, although modest in absolute terms, may represent stabilization of nutritional status in a population typically at risk of ongoing catabolic deterioration rather than simple weight gain.

Importantly, minimal clinically important differences for anthropometric parameters and HG have not been clearly established in HSCT populations. As a result, while the observed changes reached statistical significance and were directionally consistent with improved functional status, their precise clinical magnitude remains uncertain. These findings should therefore be interpreted cautiously, and larger prospective

Table 4. Correlation table of post-nutrition measurements of variables

Variables		Weight (after)	BMI (after)	MUST score (after)	Sarcopenia risk (after)	Right arm strength (after)	Left arm strength (after)	Suprailiac skinfold (after)	Triceps skinfold (after)	Suprascapular skinfold (after)	Calf skinfold (after)
Weight (after)	r	1.000									
	p	-									
BMI (after)	r	0.486**	1.000								
	p	**0.002**	-								
MUST score (after)	r	-0.151	-0.454**	1.000							
	p	0.372	**0.005**	-							
Sarcopenia risk (after)	r	0.040	0.075	0.467**	1.000						
	p	0.813	0.657	**0.004**	-						
Right arm strength (after)	r	0.283	0.096	-0.239	-0.313	1.000					
	p	0.090	0.570	0.155	0.059	-					
Left arm strength (after)	r	0.289	0.040	-0.276	-0.416*	0.907**	1.000				
	p	0.083	0.812	0.098	**0.010**	**<0.001**	-				
Suprailiac skinfold (after)	r	0.237	0.346*	-0.227	0.095	0.199	0.154	1.000			
	p	0.157	**0.036**	0.177	0.574	0.239	0.363	-			
Triceps skinfold (after)	r	-0.041	0.374*	-0.486**	0.061	0.053	-0.024	0.427**	1.000		
	p	0.807	0.023	**0.002**	0.720	0.758	0.890	**0.008**	-		
Suprascapular skinfold (after)	r	0.201	0.662**	-0.365*	0.244	0.125	0.098	0.453**	0.599**	1.000	
	p	0.232	**<0.001**	**0.026**	0.146	0.462	0.563	**0.005**	**<0.001**	-	
Calf skinfold (after)	r	-0.054	0.456**	-0.409*	0.044	0.090	-0.035	0.341*	0.734**	0.717**	1.000
	P	0.751	**0.005**	**0.012**	0.797	0.596	0.839	**0.039**	**<0.001**	**<0.001**	-

r: Spearman's rho correlation coefficient, *: p<0.05, **: p<0.001, bolded values indicate statistical significance
BMI: Body mass index, MUST: Malnutrition universal screening tool

Table 5. Mean survival time of hematologic cancer patients with weight loss

Mean survival time	Standard error	95% CI
10.892	0.524	9.865 to 11.919
CI: Confidence interval		

Table 6. The effect of gender on survival time in hematologic cancer patients with weight loss

Factor	Mean survival time	Standard error (SE)	95% CI
Male	10.2	0.5	9.2 to 11.2
Female	10.3	1	8.2 to 12.4
CI: Confidence interval			

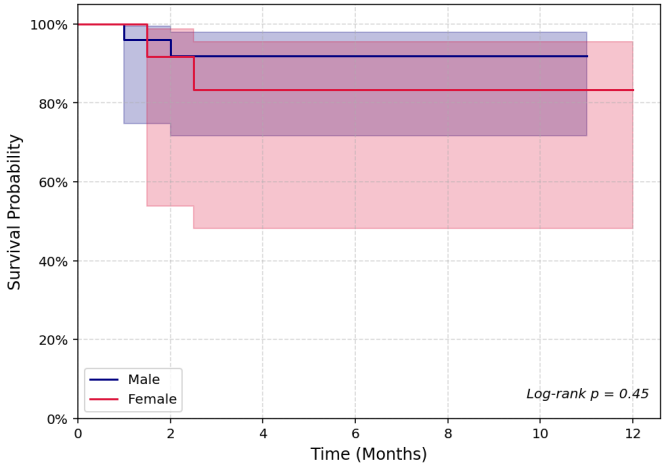

Figure 2. Effect of gender on survival time in hematologic cancer patients with weight loss

studies are required to define clinically meaningful thresholds for nutritional and func-tional recovery in this high-risk group.

The presence of cachexia and sarcopenia has been reported in patients with hematological malignancies, as well as in solid tumors [15]. A comprehensive review of the extant literature, encompassing 5,687 patients diagnosed with hematologic malignancies examined a total of 29 studies, the majority of which were diagnosed with diffuse large B-cell lymphoma [11]. A notable finding was the observation that, akin to patients with solid tumors, those with hematologic malignancies and cachexia or sarcopenia exhibited diminished overall survival and progression-free survival [16]. In our study, the mean survival time was calculated as 10.89 months. The survival curve showed a gradual decline within the first 3 months, reaching approximately 89% at the 3rd month, and remained stable at this level over the following 12 months. Thus, the 6-month survival rate was 89.2%. The mean survival times

for male and female patients were 10.24 months and 10.33 months, respectively. The log-rank test showed no statistically significant difference between the survival curves (p=0.45).

In a subsequent study, Yilmaz et al. [17] assessed the malnutrition risk in 120 patients with hematological malignancies using the NRS2002 criteria and re-evaluated them with the GLIM criteria. Measurements of mid-upper arm circumference, calf circumference, and HG were conducted. The results revealed that low HG (p=0.03), low albumin levels (p=0.001), and elevated C-reactive protein levels (p=0.002) were significantly associated with an increased risk of mortality [17]. In our study, nutritional support provided to the patients resulted in significant improvements in patients' HG (p<0.001).

In the study by Staxen et al. [18], which included 61 patients with hematological malignancies, weight loss and loss of muscle mass were detected in 64% and 59% of patients, respectively. Muscle mass was reported to be significantly positively correlated with increasing physical activity level (p=0.003) and negatively correlated with increasing age (p=0.03) [18]. In our study, patients demonstrated a statistically significant increase in both weight and BMI over the follow-up period. The median weight rose from 59 kg (38-88) to 61 kg (42-87) (p=0.001), while BMI increased from 21.75 (15.3-28.4) to 23 (16.8-28.2) (p<0.001).

Tanaka et al. [19] reported a statistically significant decrease in body weight after HSCT in their study of 34 HSCT patients (p<0.001). Additionally, bilateral hand-grip and knee-extensor strengths exhibited significant decreases after HSCT. Furthermore, oral caloric intake and gender (female) were found to be significantly associated with muscle weakness after HSCT (p=0.033 and 0.036, respectively) [19]. Among the women in our study, the MUST score declined significantly, from 4 (2-5) to 2 (0-4) (p=0.007). A comparable reduction was observed in the male patient population, with the MUST score decreasing from 4 (0-6) to 2 (0-5) (p<0.001).

Brotelle et al. [20] retrospectively examined 84 allo-HSCT patients and the mean follow-up period after allo-HSCT was 56.4±47.5 months. The prevalence of malnutrition at the end of follow-up was reported to be 20%. At the end of follow-up hospitalization, the proportion of malnourished patients was significantly higher in the malnourished group than in the well-nourished group (p=0.04). The probability of a statistically significant greater decrease in mid-arm muscle circumference and muscle strength was reported in the malnourished group compared to the well-nourished group (p=0.017; 0.005, respectively) [20]. In our study, measurements of arm muscle strength showed a significant increase, with right arm strength rising from 18.143±9.682 kg to 22.489±9.412 kg (p<0.001) and left arm strength increasing from 17.943±9.557 kg to 22.416±9.277 kg (p<0.001). Additionally, increases in skinfold thickness measurements, which indicate body fat distribution, were observed. Suprailiac skinfold thickness increased from 10 mm (2-22) to 11 mm (7-25) (p<0.001); triceps skinfold thickness increased from 12 mm (3-32) to 14 mm (2-33) (p<0.001); and subscapular skinfold thickness increased from 12 mm (3-25) to 13 mm (6-25) (p=0.002).

Eglseer et al. [21] conducted a retrospective cohort study involving 341 patients who underwent autologuous or Allo-HSCT. They used survival curves and COX proportional hazards models to evaluate whether the risk of malnutrition predicted overall and non-relapse mortality. The survival curves indicated that patients at risk of malnutrition prior to HSCT experienced higher overall and non-relapse mortality during the 1-year follow-up period. Among Allo-HSCT patients, the impact of malnutrition risk on mortality was found to be even more pronounced [21].

Yang et al. [22] conducted a study to determine the prevalence of malnutrition and sarcopenia in 171 Allo-HSCT patients. The prevalence of malnutrition in this patient group was reported to be 24.6% and the prevalence of sarcopenia was reported to be 13.5% [22].

Morishita et al. [23] reported that out of 164 allo-HSCT patients, 83 patients (50.6%) had sarcopenia prior to allo-HSCT. Patients with sarcopenia exhibited reduced muscle strength and increased fatigue in comparison to patients without sarcopenia (p<0.05). Additionally, patients with sarcopenia scored significantly lower in the physical function, bodily pain, and vitality domains of health-related quality of life than those without sarcopenia. Male sex and BMI were identified as significant factors associated with sarcopenia (p<0.01) [23]. Our study demonstrates statistically significant increases in weight, BMI, muscle strength, and skinfold thickness among male patients. In female patients, significant increases were observed in BMI, muscle strength, and certain skinfold thickness measurements; however, the change in weight was not statistically significant.

Study Limitations

The primary limitation of our study is its retrospective design. The small sample size and the study's single-center design constitute additional limitations.

The strengths of our study include addressing the limited available literature on nutritional support for hemato-oncological patients, particularly those undergoing HSCT, and having all patients followed by the same team at a single center. The weaknesses of the study are the relatively small sample size and the inability to assess effects on hospitalization duration and non-relapse mortality. The absence of a control group limits the ability to attribute the observed improvements solely to structured nutritional support. Potential confounding factors such as type of HSCT (autologous vs. allogeneic), underlying hematological diagnosis, chemotherapy intensity, corticosteroid exposure, inflammatory status, and hospitalization duration were not controlled for in the analysis.

The sample size was limited due to the inherent constraints of evaluating HSCT recipients in routine practice. HSCT is performed in a restricted number of eligible patients per center, and retrospective analyses are further affected by missingness of standardized func-tional and anthropometric measurements. In this study, inclusion required availability of paired measurements before and after a structured nutritional support period, which re-duced the number of eligible cases.

Importantly, the pre-post (within-subject) design in-creases efficiency by minimizing between-subject variability, and significant changes were observed even in this modest cohort. Nonetheless, the findings should be interpreted as exploratory and hypothesis-generating, and larger controlled studies are necessary to es-tablish causality and generalizability.

Conclusions

Sarcopenia is defined as the progressive decline in systemic muscle mass accompanied by a reduction in muscle strength or in physical function. In hemato-oncological patients, it may be associated with an increased risk of treatment-related toxicity and higher mortality due to infections. Studies indicate that low muscle mass in patients with hematological malignancies, particularly those undergoing HSCT, may contribute to adverse clinical outcomes. Therefore, the accurate identification of sarcopenia, the assessment of its risk factors and their impact on disease progression, and the implementation of effective treatment strategies are essential. Based on our study, we propose that given its reversible nature, nutritional support may be the most effective approach to managing sarcopenia. Based on our findings, structured nutritional support was associated with improvements in anthropometric parameters and muscle strength in HSCT patients. However, prospec-tive controlled studies are required to determine its comparative effectiveness in the man-agement of sarcopenia.

Ethics

Ethics Committee Approval: Approval for conducting the study was obtained from the İnönü University Faculty of Health Sciences Non-Interventional Clinical Research Ethics Committee (approval no: 2024/6234, date: 16.07.2024).

Informed Consent: Patient data were collected retrospectively.

Footnotes

Authorship Contributions

Concept: M.A.E., E.K., İ.K., B.D., E.H., Desing: A.S., E.K., İ.B., İ.B.Ç., Data Collection or Processing: A.S., M.A.E., İ.B., S.A., B.D., E.H., Analysis or Interpretation: S.A., İ.B.Ç., Literature Search: A.S., M.A.E., E.K., İ.K., B.D., İ.B.Ç., Writing: A.S., İ.K., İ.B., S.A., E.H.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Case Report

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Chyle Leak Following Revision Surgery for Recurrent Papillary Thyroid Carcinoma: Successful Conservative Management with Octreotide

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ABSTRACT

Chyle fistula is a rare but potentially serious complication that can occur after head and neck surgeries such as thyroidectomy and neck dissection. Conservative approaches are recommended as the first-line treatment, particularly for high-output lymphatic leaks following lateral neck dissection. This case report presents the successful conservative management of a high-output chyle fistula in a young female patient who previously underwent thyroidectomy and neck dissection due to recurrent papillary thyroid carcinoma. On postoperative day 3, chylous drainage of 1200 mL was observed, and octreotide therapy (100 µg three times daily, total 0.3 mg/day) was initiated. On day 5, oral intake was discontinued and total parenteral nutrition was started. During follow-up, a significant reduction in drainage was noted; serum albumin and total protein levels were monitored, and albumin supplementation was administered. Oral intake was reintroduced on day 12, and the patient was discharged on day 14 without complications or drainage. This case demonstrates that high-output lymphatic leaks can be successfully managed without surgical intervention through early diagnosis and appropriate conservative treatment.

Keywords: Chyle leak, conservative management, neck dissection, octreotide, papillary thyroid carcinoma

Introduction

Thyroidectomy and cervical lymph node dissection are widely performed surgical procedures for the treatment of differentiated thyroid carcinomas. Although generally considered safe, lateral neck dissections, particularly when performed near the course of the thoracic duct, increase the risk of the development of a chyle fistula, a rare but potentially serious complication [1].

Chyle leaks are typically characterized by milky-white drainage fluid in the postoperative period and are more commonly observed after left-sided neck surgeries [2]. The reported incidence ranges from 0.5% to 8.3%, with a significantly higher rate in patients undergoing lateral neck dissection [1,3]. If not promptly recognized and effectively managed, chyle fistulas may cause complications such as malnutrition, hypoproteinemia, electrolyte imbalances, immunosuppression, and impaired wound healing [2,4].

Treatment algorithms for chyle fistulas are usually based on the volume of daily drainage. Low-output leaks (<500 mL/day) are generally managed successfully with conservative measures such as dietary modification, bed rest, and octreotide therapy. However, in cases of high-output leaks (>1000 mL/day), surgical or interventional approaches (e.g., thoracic duct embolization) may be required [3,5]. Recent studies have shown that the use of octreotide, a somatostatin analog, reduces the need for surgery and accelerates clinical recovery in patients with chyle fistulas [5].

This report presents a case of high-output lymphatic leakage in a young patient who had previously undergone thyroidectomy and a repeat neck dissection for recurrent papillary thyroid carcinoma. The successful outcome achieved through conservative management is discussed in light of the current literature.

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Case Report

Written informed consent was obtained from the patient for all diagnostic and therapeutic procedures, as well as for the use of clinical data for academic and scientific purposes.

A 28-year-old female patient underwent fine-needle aspiration biopsy in 2023 after a suspicious nodule was identified in the left thyroid lobe during a routine neck ultrasound. The biopsy result was consistent with papillary thyroid carcinoma. The patient subsequently underwent total thyroidectomy with central and lateral neck dissection. Adjuvant radioactive iodine therapy was recommended postoperatively, but the patient declined. No complications were observed during follow-up.

In 2025, a follow-up ultrasound revealed a new lesion in the left neck posterior to the internal jugular vein and extending toward the thoracic inlet. The lesion measured approximately 22×35 mm and contained cystic and solid components with internal macrocalcifications. Pathology from a new biopsy confirmed metastasis of papillary thyroid carcinoma, and the patient underwent a revision lateral neck dissection.

A closed-suction drain (Hemovac) was placed in the left neck region postoperatively. On postoperative day 3, the drainage became milky and markedly increased in volume, leading to the diagnosis of a chyle fistula (Figure 1). Oral intake was discontinued, and subcutaneous octreotide (Sandostatin®) therapy was initiated at a dose of 100 µg three times daily [1.5 mg/day 300 µg/day (0.3 mg/day)]. Although drainage temporarily decreased on postoperative day 4, it increased again on postoperative day 5, prompting initiation of total parenteral nutrition (TPN) with an amino acid-glucose solution (Periolimel N4-600E, 1500 mL/day). From day 6 onward, a marked decrease in drainage was observed. By day 11, drainage had fallen below 100 mL/day. Oral feeding was resumed on day 12, and TPN was discontinued on day 13 (Figure 2).

Figure 1. Postoperative drainage content of the patient

Biochemical monitoring showed that serum albumin dropped to 2.1 g/dL and total protein to 4.8 g/dL on postoperative day 4. The patient received two doses of intravenous human albumin. As the drainage became minimal, the drain was removed on postoperative day 14, and the patient was discharged in good condition without complications (Figure 3).

Octreotide therapy was continued for 11 days based on published literature demonstrating its efficacy in treating high-output chyle leaks.

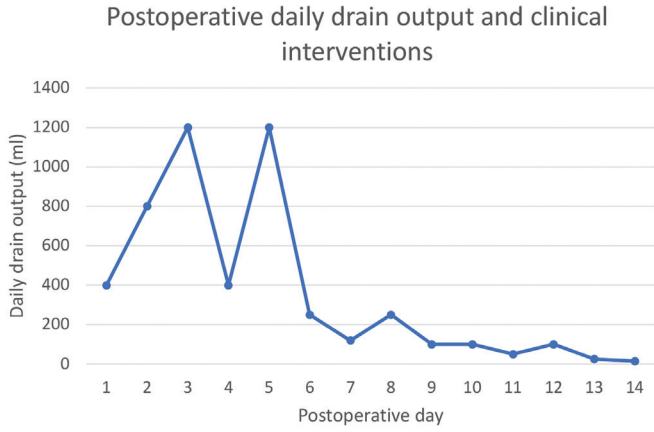

Figure 2. Daily drainage volumes monitored from the hemovac drain during the postoperative period are shown. High-output lymphatic leakage was observed on postoperative days 3 and 5, and conservative management interventions were implemented on these days

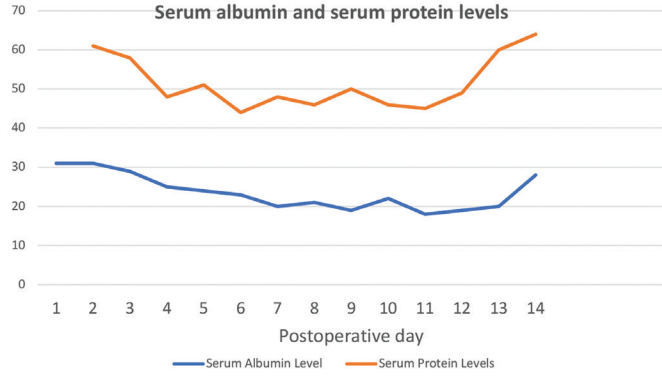

Figure 3. Serum albumin and total serum protein levels of the patient during the postoperative period

Discussion

Lymphatic leaks following neck dissection are rare but serious complications. Anatomical variations of the thoracic duct and the difficulty of its preservation during lateral neck dissection increase risk. Chyle fistulas typically occur after left-sided dissections but can also be seen on the right due to anatomical variants [2].

Clinically, chyle leaks are characterized by milky drainage fluid, high drainage volume, electrolyte disturbances, malnutrition, delayed wound healing, and infections [2,3]. In our case, a chyle fistula was confirmed on postoperative day 3 when the drainage volume increased to 1200 mL and the drainage became milky. High-output lymphatic leaks are initially managed conservatively, but surgical or interventional procedures may be necessary if conservative measures fail [3,4].

Conservative treatment includes cessation of oral intake, TPN, pressure dressings, and somatostatin analogs such as octreotide [2,3,5]. Octreotide reduces lymphatic flow by decreasing gastrointestinal secretions and thereby facilitates fistula closure [5]. Swanson et al. [5] reported that octreotide effectively reduces the need for surgery for chyle fistulas and increases the success rate of conservative management. In the literature, the duration of octreotide therapy varies with output level but generally ranges from 5 to 11 days in high-output cases [5]. In our case, octreotide was administered subcutaneously at 1.5 mg/day for 11 days, resulting in complete resolution without surgical intervention.

Studies have also shown that discontinuation of oral intake and initiation of TPN are effective in reducing chyle output in high-output leaks [3,4]. Chang et al. [3] emphasized that in patients with drainage exceeding 1000 mL/day, TPN combined with somatostatin analogs is an effective strategy. In our case, oral intake was discontinued on day 5 and TPN was started with Periolimel N4-600E, leading to a significant and sustained decrease in drainage.

Replacing protein losses due to chyle drainage is essential. The patient's albumin levels decreased starting on postoperative day 1 and reached critical levels by postoperative days 4 and 5. Intravenous albumin supplementation was administered. Park et al. [1] highlighted that in persistent chyle leaks, supportive therapy is necessary to prevent hypoproteinemia and hypovolemia.

Although conservative management is the established first-line approach, reports describing successful non-surgical treatment of high-output (>1000 mL/day) chyle leaks after revision neck dissection are scarce.

This case highlights that early initiation of octreotide and nutritional support can prevent the need for surgical or interventional treatment even in high-output scenarios.

The timing of surgical or interventional treatment in lymphatic leaks remains controversial. Yi et al. [4] reported high success rates with thoracic duct embolization in patients resistant to conservative therapy. However, due to its invasive nature, such interventions should be reserved for refractory cases [4]. In our case, conservative measures were effective early in the course, and no further intervention was required.

Conclusion

Conservative management is the first-line approach for high-output lymphatic leaks. The use of octreotide and the initiation of TPN after discontinuation of oral intake significantly reduce complications and may eliminate the need for surgical intervention. However, in cases where conservative therapy is insufficient, surgical or interventional procedures should be considered.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.G.A., F.U., V.B.T., M.H.D., M.S.K., Consept: E.G.A., F.U., V.B.T., B.K., Design: E.G.A., F.U., B.K., M.S.K., Desing: G.U, B.B.D., Data Collection or Processing: E.G.A., F.U., V.B.T., M.H.D., Analysis or Interpretation: E.G.A., F.U., B.K., Literature Search: E.G.A., F.U., V.B.T., B.K., M.H.D., M.S.K., Writing: E.G.A., F.U., M.S.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Case Report

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Primary Intracranial Oligosarcoma with IDH2 Mutation: A Rare Case Report

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ABSTRACT

Oligosarcoma is a rare malignant tumor of oligodendroglial origin that exhibits sarcomatous components and histological features consistent with World Health Organization grade III gliomas. Sarcomatous transformation of oligodendroglial components has only been reported in a small number of cases to date. In this report, we present a unique case of primary oligosarcoma diagnosed by histopathological examination after surgical resection.

Keywords: Oligosarcoma, oligodendroglioma, sarcomatoid transformation

Introduction

Oligosarcoma is a rare malignant tumor derived from oligodendroglial origin, exhibiting sarcomatous components and histological features consistent with World Health Organization grade III gliomas [1]. Oligodendroglioma is generally considered a relatively indolent neoplasm with a better prognosis than astrocytic tumors [2,3]. It accounts for approximately 0.5-1.2% of all primary brain tumors and histologically exhibits the classic "fried egg" appearance, characterized by smooth, round nuclei surrounded by prominent perinuclear halos. At the molecular level, its most distinctive feature is a deletion of all arms of chromosomes 1p and 19q (1p/19q codeletion), which is associated with increased response rates to chemotherapy and survival exceeding 14 years [2,4]. Although transformation to higher-grade lesions such as anaplastic oligodendroglioma has been described, sarcomatous transformation is extremely rare. The majority of oligosarcoma cases are reported as recurrences of previously diagnosed and treated oligodendrogliomas. Therefore, the occurrence of an oligosarcoma as a primary presentation is exceptional and should be evaluated with caution. Of the 36 oligosarcoma cases reported in the literature, only 5 were primary, with the remainder developing in the setting of previously resected oligodendroglioma or oligoastrocytoma [5]. This highlights the extremely rare occurrence of *de novo* oligosarcoma.

Case Report

A 69-year-old man presented with headache, unsteadiness, and urinary incontinence. The patient had no prior brain imaging studies. The patient also had no known pre-existing brain pathology or history of radiotherapy. Computed tomography of the brain revealed a tumor with calcification in the right frontal lobe. Radiologically, the tumor appeared hyperintense on T2-weighted imaging, hypointense on T1-weighted imaging, and showed contrast enhancement on gadolinium-enhanced T1-weighted imaging. Oligodendroglioma was suspected. Written informed consent was obtained from the patient for the surgical procedure and for the publication of this case report and case images. The mass was grossly excised using an interhemispheric approach (Figure 1). After the initial surgery, the histopathological diagnosis was oligosarcoma with IDH2

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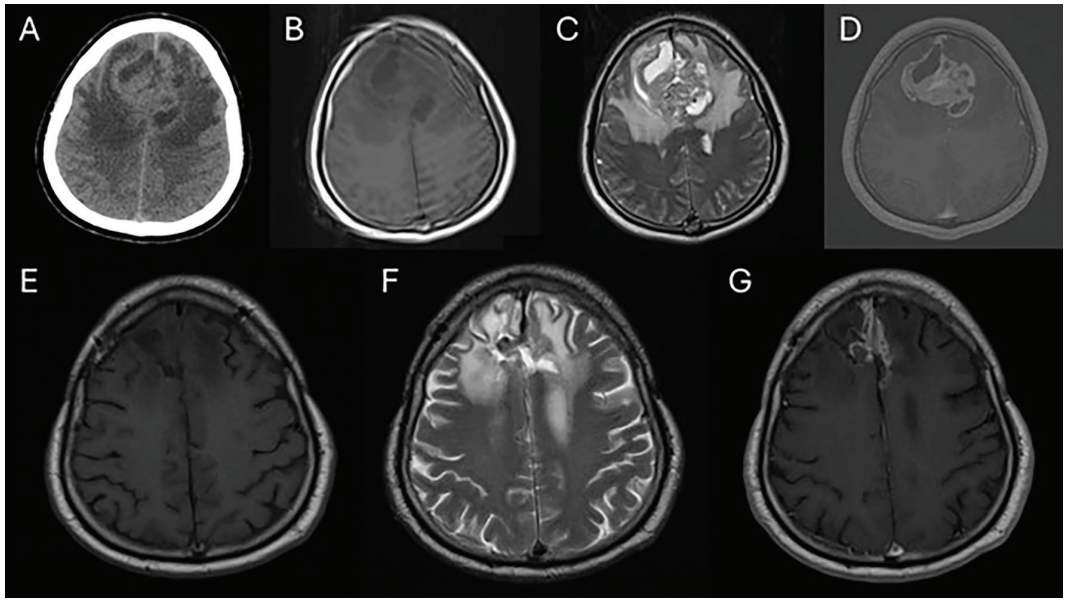

Figure 1. Preoperative (A-D) and postoperative (E-G) images of the first surgery. A: Cranial CT scan shows the frontal lobe lesion. T1-weighted (B), T2-weighted (C), and contrast-enhanced T1-weighted MRI (D) show the frontal mass. Postoperative MRI images [T1-weighted (E), T2-weighted (F), and contrast-enhanced T1-weighted magnetic resonance images (G)] show the postoperative surgical field
CT: Computed tomography, MRI: Magnetic resonance imaging

mutant an IDH2 mutation and 1p/19q loss. The patient was referred to the oncology department. No further genetic tests were performed on the patient. The patient received 60 Gy of curative radiotherapy over one month and was monitored with magnetic resonance imaging (MRI) every three months. The patient did not receive chemotherapy. Twenty months after the initial surgery, gadolinium-enhanced T1-weighted MRI revealed an enlarging mass at the site of the resected oligosarcoma. The mass grew rapidly over 3 months (Figure 2).

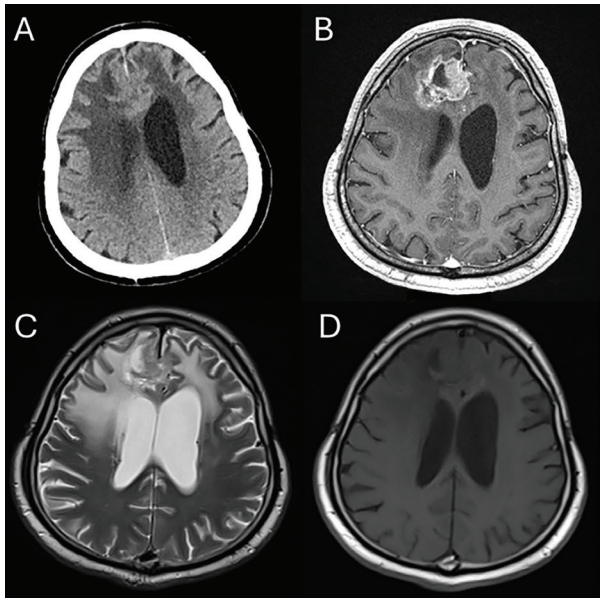

Figure 2. Preoperative images of the second surgery. Computed tomography (A), gadolinium-enhanced T1-weighted (B), T2-weighted (C), and T1-weighted magnetic resonance images (D) revealed a tumor with homogeneous contrast enhancement in the deep portion of the resection cavity

Initially diagnosed with recurrent oligosarcoma, he underwent a second surgery 24 months after the first, using the same approach. The tumor was also resected macroscopically during the second surgery. After the second surgery, histopathological examination again reported oligosarcoma. The patient had no preoperative or postoperative neurological deficits. He continues his oncological treatment as an outpatient.

Discussion

Oligosarcomas are generally defined as late complications of previously treated oligodendrogliomas and typically recur at the same anatomic site years after initial surgery. The present case is significant because it represents a primary oligosarcoma. They are frequently located in the frontal and temporal lobes and may present with non-specific symptoms such as headache, epileptic seizures, dizziness, nausea, and vomiting [6-9]. Imaging findings typically appear as solid, heterogeneous masses that are surrounded by significant edema and enhance on T1 with gadolinium. Extra-axial localization or meningeal involvement in oligosarcomas can also be misleading in the differential diagnosis [5]. Histopathologically, these tumors retain the features of oligodendrogliomas (monomorphic round nuclei, perinuclear halo, fine chromatin) while also showing signs of sarcomatous differentiation (eosinophilic cytoplasm, spindle cells, increased mitotic activity, and necrosis). Recurrent oligosarcomas generally reflect high-grade anaplastic morphology with increased cellularity, endothelial hyperplasia, atypical mitoses, hyperchromatic pleomorphic nuclei, and mucus-filled cystic areas [3,6,7,10]. Immunohistochemically, they exhibit glial and mesenchymal features; glial-derived glial fibrillary acidic protein (GFAP) and S-100 positivity, and alpha-smooth muscle actin (α-SMA) and desmin positivity in sarcomatous areas have been reported [6-9].

Additionally, publications report cluster of differentiation (CD34) and epithelial membrane antigen (EMA) positivity in sarcomatous areas. Additionally, as Rodriguez et al. [6] demonstrated, positivity for non-GFAP markers (e.g., CD34, α-SMA, EMA) in sarcomatous components can be helpful in the diagnosis of oligosarcoma, and routine evaluation of this panel is recommended during the diagnostic process. In the case presensted here, positivity for GFAP, S-100, OLIG-2, and EMA is also noteworthy (Figure 3).

The genetic profile of oligosarcoma can exhibit distinct molecular features that differentiate it from classic oligodendroglioma. Anomalies such as homozygous deletion of *CDKN2A/B* genes, regain of H3K27me3 expression, loss of 6q and *NF1*, and gain of *YAP1* have been frequently reported in these tumors [5]. In the case presented by Tanaka et al. [8], the presence of an IDH1 mutation and a 1p/19q codeletion in both oligodendroglial and sarcomatoid components strongly supports the oligodendroglial origin of the tumor and the development of a sarcomatoid component as a result of metaplastic transformation. In glial tumors, IDH1 mutations are more common than IDH2 mutations. Although IDH' mutations are rare, they are more common in oligodentrogliomas [11]. The presence of the rare IDH2 mutation in our case is noteworthy.

The main treatment approach is maximal safe surgical resection followed by adjuvant therapy. Conventional treatment comprises procarbazine, lomustine, and vincristine (PCV), together with radiotherapy. However, based on long-term data, the PCV regimen is preferred in some centers [12]. According to recent reports, despite aggressive surgery and adjuvant chemoradiotherapy, the median survival after oligosarcoma diagnosis has been reported as only 1.3 years (range, 0-5.2 years), confirming the poor prognosis of the disease [5]. The presence of the 1p/19q codeletion is associated with a better response to chemotherapy and radiotherapy and is considered a favorable prognostic factor [6,13]. The patient survived for 24 months, which is above the mean survival time. The primary explanation for this is 1p/19q codeletion. This genetic alteration is associated with a better prognosis in oligodendrogliomas. It contributes to the slower progression of the tumor and a better response to chemotherapy/radiotherapy [14]. The patient presented in this case was diagnosed with oligosarcoma without any prior history of surgery or oncologic treatment, suggesting that sarcomatous features may develop *de novo* in some cases.

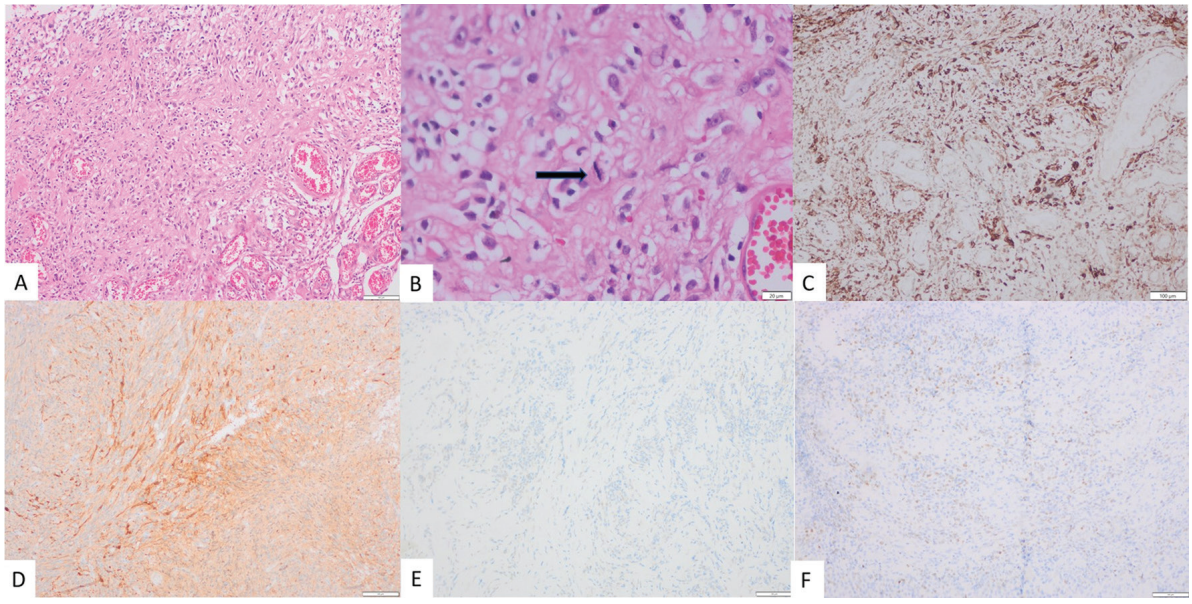

Figure 3. Oligosarcoma. A: Hematoxylin eosin, 100x. B: Hematoxylin eosin, 400x (black arrow: atypical mitosis). C: GFAP, 100x. D: S-100, 100x. E: EMA, 100x. F: OLIG-2, 100x
GFAP: Glial fibrillary acidic protein, OLIG-2: Oligodendrocyte transcription factor 2

Ethics

Informed Consent: Informed consent was obtained from all patients included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ş.S., M.E.Y., N.K., M.F.E., Concept: M.F.E., Design: M.Ş.S., M.F.E., Data Collection or Processing: M.Ş.S., N.K., Analysis or Interpretation: M.E.Y., N.K., Literature Search: M.Ş.S., M.E.Y., Writing: M.Ş.S., M.E.Y.

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Case Report

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Myeloid Sarcoma as a Manifestation of Lineage Switch from B-cell Acute Lymphoblastic Leukemia after Double Allogeneic Stem Cell Transplantation: A Case Report

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ABSTRACT

Phenotypic conversion between lymphoid and myeloid leukemic lineages is infrequent and generally associated with an unfavorable clinical prognosis. Most reported cases involve relapse of B-cell acute lymphoblastic leukemia (B-ALL) presenting as acute myeloid leukemia (AML). The development of extramedullary disease as myeloid sarcoma after lineage switch, particularly following sequential allogeneic hematopoietic stem cell transplantation (allo-HSCT), is exceedingly rare. A 36-year-old woman with Philadelphia chromosome-positive B-ALL achieved remission after chemotherapy and tyrosine kinase inhibitor-based therapy, but relapsed and underwent two consecutive allo-HSCTs from different donors. Eighteen months after the second transplantation, while in complete remission, she presented with localized knee pain. Imaging and histopathological evaluation confirmed myeloid sarcoma, and bone marrow analysis demonstrated AML, indicating a lineage switch. Treatment with local radiotherapy followed by venetoclax and azacitidine resulted in remission. This case highlights the importance of considering lineage switch in patients with atypical relapse patterns or isolated extramedullary lesions after allo-HSCT.

Keywords: Lineage switch, acute lymphoblastic leukemia, acute myeloid leukemia, myeloid sarcoma, allogeneic stem cell transplantation, extramedullary relapse

Introduction

Regulation of hematopoietic clones is fundamentally important for both normal and malignant hematopoiesis. Transitions between lymphoid and myeloid lineages in leukemia are rare and typically associated with poor clinical outcomes. Most lineage-switching cases involve a transition between acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). In addition, leukemic lineage switching is more commonly observed in infants and young patients with epigenetic and transcriptional regulatory lysine methyltransferase 2A (*KMT2A*; formerly *MLL1*) gene rearrangements [1].

Granulocytic sarcoma is a localized tumor mass composed of immature cells of the granulocytic lineage. Synonyms used for this disease include myeloblastoma, myelosarcoma, chloroma, or extramedullary myeloid tumor [2]. Granulocytic sarcoma may appear in isolation or may occur during the course of AML, chronic myeloid leukemia, myelodysplastic syndromes, or myeloproliferative disorders [3]. Granulocytic sarcoma, a rare entity in leukemia, is most frequently reported in AML; it is much rarer in T-cell or B-cell ALL [4,5]. The most common locations include the skin, soft tissues, bone, periosteum, and lymph nodes [5,6]. In this case report, we present a patient who developed AML with myeloid sarcoma while in remission following treatment for ALL.

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Case Report

A 36-year-old woman with no comorbidities presented to the emergency department with diffuse muscle pain. A complete blood count revealed white blood cell 199.5×10^3/µL, neutrophils 100.74×10^3/µL, monocytes 51.81×10^3/µL, hemoglobin 10^9 g/dL, and platelets 407×10^3/µL. Due to symptomatic hyperleukocytosis, urgent leukapheresis was performed. Bone marrow examination showed 38% lymphoid blasts with a TdT^+, $CD34^+$, $HLA\text{-}DR^+$, $CD19^+$, $CD79a^+$ phenotype; pathology confirmed B-lymphoblastic leukemia/lymphoma (B-ALL/LBL), $CALLA^+$, World Health Organization 2017. Cytogenetic work-up at diagnosis demonstrated t(9;22)(q34;q11.2) *BCR-ABL1* positivity, while fluorescence *in situ* hybridization and polymerase chain reaction, corroborated the presence of the Philadelphia chromosome, and no additional abnormalities were identified. The patient received two cycles of Hype-cyclophosphamide, vincristine, adriamycin (doxorubicin), dexamethasone; however, a relapse occurred, and salvage therapy with dasatinib plus fludarabine, cytarabine, granulocyte colony-stimulating factor (FLAG) achieved a second remission. Cytogenetics at relapse again demonstrated *BCR-ABL1* positivity, supporting clonal continuity between the first and second leukemic episodes. She underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) from her HLA-matched sister, and early post-transplant chimerism studies showed >98% donor chimerism. In the 4th month, she developed a coronavirus disease-2019 infection, and a relapse of B-ALL was subsequently confirmed. A further remission was obtained with dasatinib plus FLAG followed by dasatinib, vincristine, and dexamethasone consolidation; eight months after the first transplant, she underwent a second allo-HSCT from a 9/10 TÜRKÖK donor. Post-transplant follow-up revealed steroid-responsive, grade II, cutaneous graft-versus-host disease (GVHD).

Eighteen months after the second transplant, the patient developed left knee pain; ultrasound demonstrated a 3-cm soft-tissue mass with tibial tuberosity erosion. Fine-needle aspiration showed a myeloid sarcoma that was immunohistochemically positive for HLA-DR, CD117, CD13, and focally for myeloperoxidase (MPO), and negative for TdT, CD20, and CD5. Bone marrow flow cytometry revealed 21.4% myeloid blasts expressing MPO, HLA-DR, CD34, CD13, CD33, and CD117. At the time AML was diagnosed, post-transplant chimerism analysis demonstrated 85% donor chimerism, consistent with mixed chimerism. Cytogenetic and molecular reassessment at this stage demonstrated continued *BCR-ABL1* positivity and a newly acquired trisomy 8 abnormality, which had not been present in the initial B-ALL sample. The persistence of *BCR-ABL1*, together with the emergence of trisomy 8, indicates clonal evolution of the original leukemic clone, supporting a lineage switch rather than a *de novo* or therapy-related AML. Intensive AML induction chemotherapy was not preferred because the patient had undergone two allo-HSCTs, had steroid-treated GVHD, had a reduced performance status, and had a high risk of treatment-related mortality. Therefore, treatment with azacitidine plus venetoclax was initiated as a more appropriate and better-tolerated option. The patient also received 39 Gy of local radiotherapy to the myeloid sarcoma site. She has completed three cycles of azacitidine and venetoclax and remains in remission at the most recent evaluation. Written informed consent was obtained from the patient for the publication of this case report and the use of all related clinical data and images.

Discussion

Approximately 50% of adult ALL cases relapse after the first remission [7]. Relapsed disease is most often characterized by preservation of the original immunophenotypic and cytogenetic features, with occasional acquisition of secondary abnormalities indicative of clonal evolution. However, transformation from ALL to AML is rare. *Lineage switching* is defined as the transition of leukemia diagnosed in one lineage (lymphoid/myeloid) to the other at relapse. This phenomenon is characterized by the loss of markers specific to one lineage and the acquisition of markers specific to another lineage. In most reported lineage-switch cases, patients with B-ALL/LBL relapse with AML [8].

The biological basis of lineage switching has not been fully elucidated, and multiple explanatory mechanisms have been proposed [9-11]. A proposed explanation for lineage switching involves a common progenitor cell capable of divergent differentiation, with selective therapeutic pressure enabling leukemic stem cells to adopt an alternative lineage fate. Additional hypotheses include dedifferentiation and transdifferentiation.

Fujisaki et al. [10] transplanted myeloid cells obtained from a case of T-ALL that exhibited lineage switching into severe combined immunodeficiency mice.

The differential leukemic phenotypes observed under cytokine-free versus Granulocyte-Macrophage Colony-Stimulating Factor-supplemented conditions indicate that leukemic stem cell differentiation is highly dependent on the microenvironment.

A case report by Kishore et al. [12] described a lineage-switching event similar to ours: a 10-year-old child diagnosed with ALL who—four years later during relapse—was found to have AML.

Another case report by Ruiz-Delgado et al. [13] presented a 60-year-old adult who experienced lineage switching from ALL to AML.

In a case series published by Zhou et al. [14], lineage switching from ALL to AML occurred in 28 patients, and from AML to ALL in 4 patients.

Lineage switching is extremely rare. This case represents a lineage-switching event in which a patient initially diagnosed with ALL later relapsed with AML.

Conclusion

This case illustrates an exceptionally rare example of lineage switching from B-ALL to AML accompanied by extramedullullary

myeloid sarcoma following sequential allogeneic stem cell transplantation. The occurrence of myeloid sarcoma as the initial manifestation of relapse underscores the biological complexity and plasticity of leukemic stem cells. Clinicians should maintain a high index of suspicion for lineage switch in patients with atypical relapse patterns, particularly in the presence of isolated extramedullary lesions. Comprehensive immunophenotypic and histopathological evaluation is essential for accurate diagnosis and timely initiation of appropriate therapy. Increased awareness of this phenomenon may facilitate earlier detection and improve clinical decision-making in similarly complex cases.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and the use of all related clinical data and images.

Footnotes

Authorship Contributions

Concept: R.Ş., Design: R.Ş., Data Collection or Processing: R.Ş., Analysis or Interpretation: S.K., Literature Search: R.Ş., Writing: R.Ş., S.K., K.E., Y.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Case Report

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Early Surgical Excision Achieving Remission in Cutaneous B-cell Lymphoma

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ABSTRACT

Primary cutaneous diffuse large B-cell lymphoma, leg-type (PCDLBCL-LT), is an uncommon and aggressive form of non-Hodgkin lymphoma with a poor prognosis. We report the case of an 89-year-old woman who presented with a rapidly enlarging cutaneous nodule on her right thigh. The lesion, which appeared 1.5 months earlier, measured 2×2 cm and displayed homogeneous pink, structureless areas with hemorrhagic foci on dermatoscopy. The patient's history included Alzheimer's disease, epilepsy, a congenital solitary kidney, cerebrovascular disease resulting in a bedridden state, and a prior basal cell carcinoma. An excisional biopsy with a 0.5 cm margin was performed for diagnostic and therapeutic purposes. Histopathological analysis revealed diffuse infiltration by large atypical lymphocytes with hyperchromatic nuclei and frequent mitotic figures. Immunohistochemistry showed positivity for cutaneous diffuse-20 (CD20) and B-cell lymphoma-2 (BCL-2), while CD3, CD10, BCL-6, and cellular myelocytomatosis were negative. The Ki-67 proliferation index was notably high (90-95%), confirming the aggressive nature of the lymphoma. Based on these findings, a diagnosis of PCDLBCL-LT was established. Given the patient's advanced age, comorbidities, and the family's preference to avoid systemic therapy, no additional treatments such as chemotherapy or radiotherapy were pursued. The patient remained recurrence-free over a one-year follow-up period. This case underscores the importance of early recognition of atypical skin lesions in elderly patients and highlights that surgical excision alone may be an effective, minimally invasive treatment option in selected frail individuals. Early intervention not only aids in local disease control but may also help maintain quality of life without the risks associated with aggressive therapies.

Keywords: Early diagnosis, elderly patient, primary cutaneous B-cell lymphoma, surgery-only treatment

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive subtype of non-Hodgkin lymphoma [1]. Among its variants, primary cutaneous DLBCL, leg type (PCDLBCL-LT), is notable for its aggressive behavior and poor prognosis [2-4]. This report presents a case of an 89-year-old patient who was diagnosed with PCDLBCL-LT following the rapid growth of a cutaneous nodule.

Case Report

An 89-year-old woman presented with a rapidly enlarging nodule on her right upper thigh. The lesion had appeared approximately 1.5 months prior to her visit. Her medical history included Alzheimer's disease, epilepsy managed with valproic acid and quetiapine, a congenital solitary kidney, and severe hearing loss requiring a hearing aid since the age of 35. She had a history of basal cell carcinoma of the nose 15 years earlier and had been bedridden and receiving percutaneous endoscopic gastrostomy feeding for the past five years due to cerebrovascular disease.

On physical examination, a 2×2 cm, non-ulcerated, pink, well-demarcated nodular lesion was observed on the mid-right thigh (Figure 1). Dermatoscopic evaluation revealed homogeneous, pink, structureless areas, accentuated skin lines, and hemorrhagic foci (Figure 2). The patient did not exhibit any B symptoms such as fever, night sweats, pruritus, or weight loss. Physical examination revealed no hepatosplenomegaly or lymphadenopathy.

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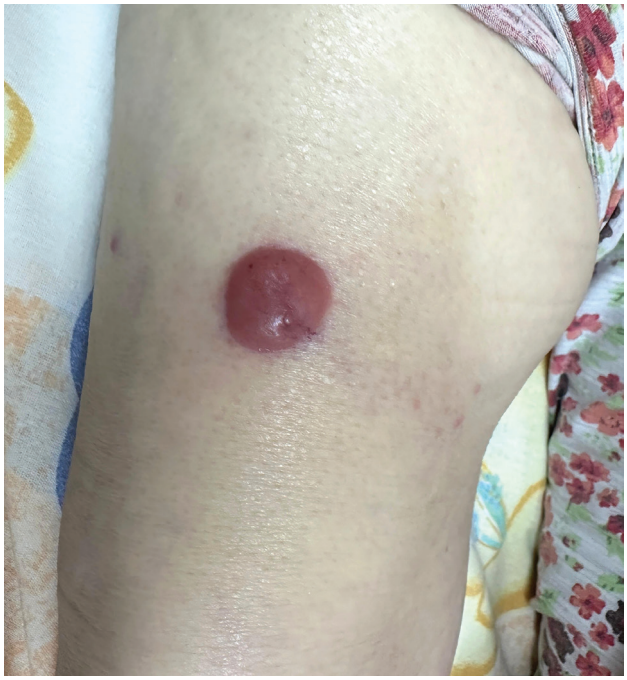

Figure 1. Macroscopic view of the lesion showing a painless, pink-colored, well-demarcated nodule on the lower leg

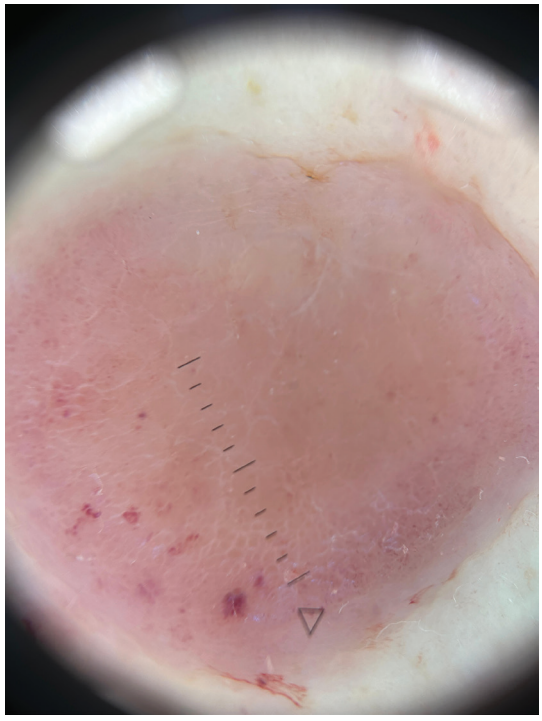

Figure 2. Dermoscopy of the lesion demonstrating homogeneous pink, structureless areas with accentuation of skin lines and focal hemorrhagic spots

Based on the clinical and dermatoscopic findings, the differential diagnosis included B-cell lymphoma, amelanotic malignant melanoma, and pseudolymphoma.

Because of the patient's advanced age, bedridden status, and limited access to healthcare, an excisional biopsy with a 0.5 cm surgical margin was performed for diagnostic and therapeutic purposes.

Histomorphological examination revealed a preserved epidermis and a diffuse lymphocytic infiltration, composed of atypical large cells, within the dermis. These cells exhibited hyperchromatic nuclei, prominent nucleoli, and frequent atypical mitotic figures. In the initial immunohistochemical panel, leukocyte common antigen (LCA) was used to highlight the lymphoid infiltrate, and cytokeratin 20 (CK20) was applied to exclude Merkel cell carcinoma. LCA was diffusely positive, while CK20 was negative.

In the subsequent panel, cutaneous diffuse-3 (CD3) showed positive staining in reactive T-cells, whereas the neoplastic cells demonstrated strong positivity for CD20 and B-cell lymphoma-2 (BCL-2). CD10, cellular myelocytomatosis, synaptophysin, and BCL-6 were negative. Although BCL-6 expression may be seen in PCDLBCL, it was absent in this case. The Ki-67 proliferation index was remarkably high (90-95%), consistent with a highly proliferative phenotype (Figure 3A-D).

Collectively, these histopathological and immunohistochemical findings confirmed the diagnosis of PCDLBCL-LT.

Following the diagnosis, the patient was referred to the hematology department for further evaluation and management. Given her general condition, comorbidities, family's reluctance to pursue aggressive treatment, and her bedridden state, the hematology team decided to forgo further interventions, such as positron emission tomography imaging or systemic chemotherapy.

The patient provided written informed consent for the publication of all clinical details and associated images in this report.

Discussion

PCDLBCL-LT is a rare and aggressive form of primary cutaneous B-cell lymphoma [1]. Large case series have reported a median age at diagnosis ranging from 70 and 76 years, indicating that the disease predominantly affects elderly individuals but rarely extends into the very advanced age group. For example, in a clinicopathologic analysis of 60 patients with PCDLBCL-LT, most were in their seventh decade of life, and only a limited number were older than 85 years [5].

A small number of case reports describing patients aged 90 years or older have been documented, suggesting that presentations at extremely advanced ages are uncommon. Therefore, an 89-year-old patient can reasonably be considered among the oldest reported cases of PCDLBCL-LT in the literature [6].

Histopathologically, PCDLBCL-LT is characterized by a diffuse lymphocytic infiltrate in the dermis. Tumor cells typically express CD20 and BCL-2, while T-cell markers (such as CD3) and germinal center markers (CD10, BCL-6) are usually negative [7]. A high Ki-67 proliferation index (90-95%) further supports its aggressive nature [3]. The absence of systemic involvement is a key feature that distinguishes primary cutaneous lymphomas from systemic lymphomas with secondary skin involvement [1].

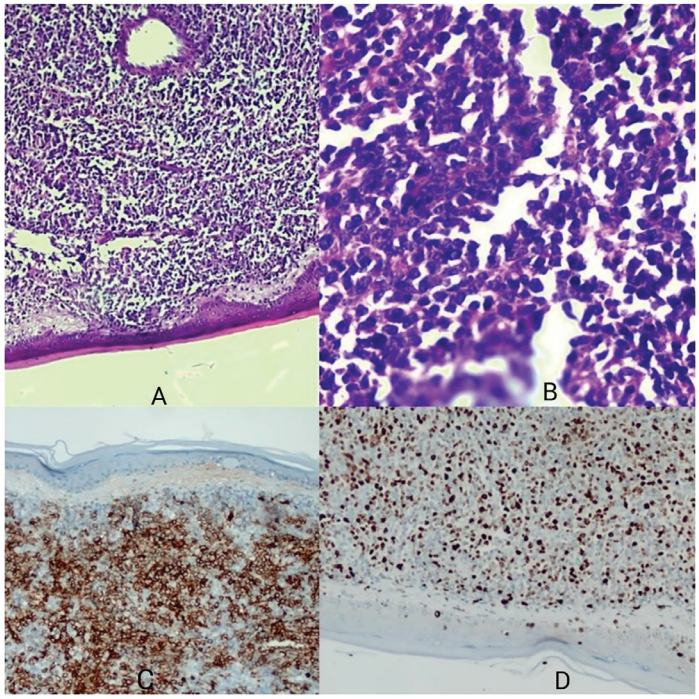

Figure 3. (A) Diffuse infiltration of large atypical lymphoid cells in the dermis (H&E, ×10), (B) atypical lymphocytes with hyperchromatic nuclei and prominent nucleoli (H&E, ×40), (C) positive staining of large neoplastic B cells with CD20, (D) high Ki-67 proliferation index in tumor cells
CD: Cutaneous diffuse, H&E: Hematoxylin and eosin

Early diagnosis plays a vital role in improving treatment response and reducing relapse risk in such aggressive lymphomas.

Current international guidelines from the European Organization for Research and Treatment of Cancer and the International Society for Cutaneous Lymphomas recommend systemic chemoimmunotherapy, most commonly rituximab combined with CHOP-based regimens, as the preferred first-line treatment for PCDLBCL-LT due to its aggressive biological behavior and high relapse rate [8].

Radiotherapy may be used as an adjunctive modality in patients with localized disease; however, surgery alone is generally not considered a curative approach in standard treatment algorithms because of the systemic relapse potential of the disease [9].

Although surgical excision is frequently performed as a diagnostic procedure, complete remission achieved with surgery alone has only rarely been described in the literature. In most reported cases, patients subsequently receive systemic therapy or radiotherapy due to the aggressive nature of the disease [10].

However, in this case, the patient's advanced age, Alzheimer's disease, immobility, and multiple comorbidities rendered aggressive therapies too risky [11]. Nevertheless, prompt surgical excision of the lesion shortly after clinical presentation (within 1.5 months) played a key role in achieving local control and preventing recurrence [11]. A conservative approach consisting of surgical excision alone was adopted in accordance with the patient's and family's preferences, resulting in a recurrence-free course over one year of follow-up. Although there are limited reports of surgical excision being curative on its own, this case highlights that, particularly in frail patients, early diagnosis and timely intervention can help balance disease control with quality of life [12].

From a molecular perspective, recent studies have shown that PCDLBCL-LT frequently harbors mutations in the *MYD88* and *CD79B* genes, which are involved in the activation of the NF-κB signaling pathway and may contribute to the aggressive biological behavior of the disease. MYD88 mutations have been reported in approximately 60-75% of cases, while CD79B mutations occur in nearly half of patients [13].

Genetic analysis of these mutations has been proposed as a useful tool for understanding disease pathogenesis and identifying potential therapeutic targets; however, molecular testing is not routinely performed in all reported cases due to technical and resource limitations. Genetic analysis was not performed, which represents a limitation of the study.

In cases diagnosed at an early stage, complete excision of the lesion may reduce the risk of local recurrence and delay the need for systemic treatment. As observed in this patient, rapid histopathological evaluation and individualized treatment planning are essential.

This case demonstrates that PCDLBCL-LT can occur even at a very advanced age and that early diagnosis combined with minimally invasive approaches can positively influence prognosis. Treatment decisions should not only consider the patient's physiological capacity and comorbidities but also

emphasize the importance of timely diagnosis and intervention in achieving recurrence-free survival.

Ethics

Informed Consent: The patient's data used in this study have been fully anonymized, and no identifiable information is included. Therefore, consent to publish is not required.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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Case Report

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Exceptional Long-term Survival in BRAF V600E-mutant Anaplastic Pleomorphic Xanthoastrocytoma: A Case Report with 12-year Disease-free Follow-up

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ABSTRACT

Anaplastic pleomorphic xanthoastrocytoma (APXA) is a rare World Health Organization (WHO) grade 3 glial neoplasm with limited long-term survival data. While grade 2 pleomorphic xanthoastrocytoma (PXA) demonstrates favorable 5-year overall survival rates of 80-90%, anaplastic variants carry a significantly worse prognosis with 5-year survival of approximately 55-57%. BRAF V600E mutations are detected in 50-78% of PXAs and have been associated with improved clinical outcomes; however, cases with follow-up exceeding 10 years are exceptionally rare in the literature, making long-term prognostic assessment challenging. We report an exceptional case of BRAF V600E-mutant APXA with 12-year disease-free survival following gross total resection and comprehensive multimodal adjuvant therapy. A 30-year-old woman presented in October 2014 with a generalized tonic-clonic seizure. Magnetic resonance imaging (MRI) revealed a 32×27 mm contrast-enhancing mass in the left temporal lobe. The patient underwent left temporal craniotomy with gross total resection. Histopathological examination demonstrated pleomorphic tumor cells with bizarre hyperchromatic nuclei, multinucleated giant cells, rhabdoid and spindle-shaped morphology, and lipid-laden xanthomatous cells with eosinophilic cytoplasm. Immunohistochemistry showed glial fibrillary acidic protein and S-100 positivity, Ki-67 proliferation index of 15%, and 13 mitoses per 10 high-power fields. BRAF V600E mutation was confirmed by molecular analysis, and the tumor was diagnosed as PXA, WHO grade III. The patient was lost to follow-up after the first surgery. Eight months postoperatively, the patient presented with tumor recurrence following another seizure, and second surgery achieved gross total resection. Upon histopathological re-evaluation, findings were consistent with APXA recurrence rather than malignant transformation. Ten days after the second surgery, adjuvant treatment was initiated with dynamic arc radiotherapy delivering a total dose of 6000 centigray, concurrent temozolomide 75 mg/m^2, followed by six cycles of adjuvant temozolomide 150 mg/m^2. Follow-up cranial MRI scans performed at regular intervals over the subsequent 12 years consistently demonstrated stable post-surgical changes without any evidence of tumor recurrence. At 12-year follow-up, the patient remains clinically stable and disease-free. This case demonstrates that exceptional long-term survival exceeding 12 years is achievable in BRAF V600E-mutant APXA with gross total resection and comprehensive multimodal adjuvant therapy. The BRAF V600E mutation may serve as a favorable prognostic biomarker and represents a potential therapeutic target. This case underscores the importance of molecular profiling for accurate prognostication and identification of targeted therapeutic options in this rare tumor entity.

Keywords: Neuro-oncology, pleomorphic xanthoastrocytoma, anaplastic, BRAF V600E, long-term survival

Introduction

Pleomorphic xanthoastrocytoma (PXA) is a rare astrocytic neoplasm first described by Kepes et al. [1] in 1979, accounting for less than 1% of all astrocytomas and predominantly affecting children and young adults [2]. The tumor typically arises in the superficial cerebral cortex, most commonly in the temporal lobe, and frequently involves the overlying leptomeninges. The 2021 World Health Organization (WHO) Classification of Central

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Nervous System Tumors categorizes PXA as either grade 2 or grade 3 (anaplastic) based on mitotic activity, with ≥5 mitoses per 10 high-power fields defining anaplastic histology [3]. While grade 2 PXA demonstrates favorable 5-year overall survival rates of 80-90%, anaplastic PXA (APXA) carries a significantly worse prognosis with 5-year survival of approximately 55-57% [2,4].

BRAF V600E mutations are detected in 50-78% of PXAs and have been associated with improved clinical outcomes compared to BRAF wild-type tumors [5,6]. The presence of this mutation also offers potential targeted therapeutic options with BRAF and mitogen-activated protein kinase kinase inhibitors, which have shown promising results in recurrent or refractory cases [7,8]. We present an exceptional case of BRAF V600E-mutant APXA with a 12-year disease-free survival following gross total resection and comprehensive, multimodal adjuvant therapy.

Case Report

A thirty-year-old woman with no significant past medical history presented in October 2014 with a generalized tonic-clonic seizure. Written informed consent was obtained from the patient for publication of this case report and accompanying images. The neurological examination was unremarkable. Magnetic resonance imaging (MRI) revealed a 32×27 mm space-occupying lesion in the left temporal lobe, demonstrating a hyperintense signal on T2-weighted and fluid-attenuated inversion recovery sequences, a hypointense signal on T1-weighted imaging, and an intense homogeneous contrast enhancement (Figure 1). The patient underwent a left temporal craniotomy with careful attention to language preservation, maintaining a posterior resection margin of less than 4.5 cm from the temporal pole to protect Wernicke's area.

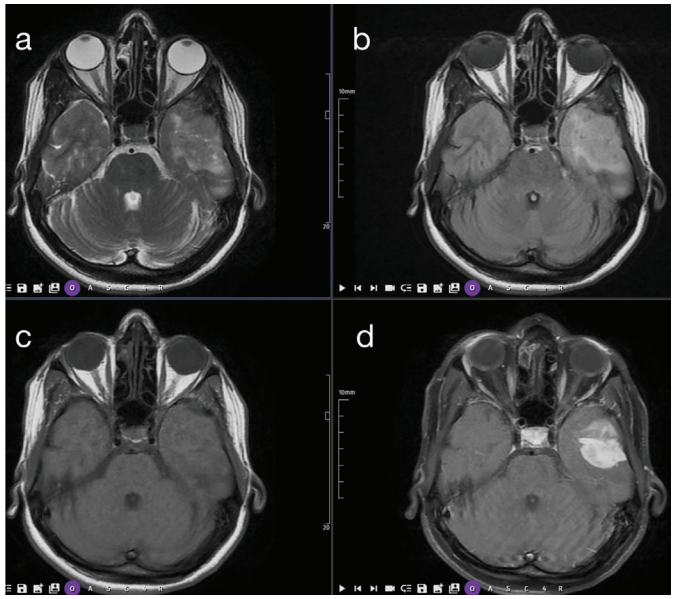

Figure 1. Preoperative magnetic resonance imaging of the left temporal lobe mass. A 32×27 mm space-occupying lesion demonstrates hyperintense signal on T2-weighted (a) and fluid-attenuated inversion recovery (b) sequences, hypointense signal on T1-weighted imaging (c), and homogeneous contrast enhancement on post-contrast fat-suppressed T1-weighted sequences (d) in axial planes. The lesion is located in the left temporal lobe with associated mass effect

Histopathological examination revealed pleomorphic tumor cells characterized by bizarre hyperchromatic nuclei, multinucleated giant cells, rhabdoid and spindle-shaped morphologies, and lipid-laden xanthomatous cells with eosinophilic cytoplasm (Figure 2a). Immunohistochemistry demonstrated glial fibrillary acidic protein and S-100 protein positivity; a Ki-67 proliferation index of 15%; p53 expression in 5% of tumor cells; and 13 mitoses per 10 high-power fields. BRAF V600E mutation was confirmed by molecular analysis. Based on these findings, the tumor was diagnosed as a PXA (WHO grade III). The patient was lost to follow-up after the first surgery.

Eight months postoperatively (June 2015), the patient presented with another generalized seizure. MRI demonstrated tumor recurrence at the previous resection site. A second surgery was performed, achieving gross total resection. Histopathological examination of the recurrent specimen showed lipid-laden xanthomatous cells with eosinophilic cytoplasm, and epithelioid/rhabdoid tumor cells (Figure 2b). The specimen was initially diagnosed as glioblastoma, WHO grade IV. However, upon re-evaluation, considering the same anatomical location, histological similarity, and clinical course, this diagnosis is now considered incorrect; the findings are more consistent with recurrence of the same APXA rather than a true malignant transformation to glioblastoma.

Ten days after the second surgery, adjuvant treatment was initiated according to the glioblastoma protocol, based on the initial pathological interpretation. Between June 11 and July 23, 2015, the patient received dynamic arc radiotherapy using 6 MV photons. Phase 1 delivered 4600 centigray (cGy) in 23 fractions (200 cGy/day) to the tumor bed with an edema margin, followed by Phase 2, which delivered 1400 cGy in 7 fractions (200 cGy/day) to the tumor bed with a reduced margin, for a total dose of 6000 cGy. Concurrent temozolomide 75 mg/m^2 was administered throughout radiotherapy, followed by six cycles of adjuvant temozolomide 150 mg/m^2. The patient tolerated the treatment well, with no significant acute or late toxicities. Follow-up cranial MRI

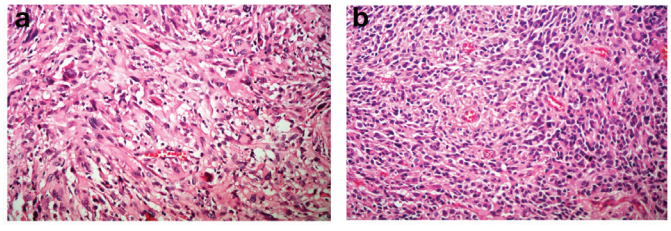

Figure 2. Histopathological findings from the surgical specimens. (a) Hematoxylin and eosin (H&E)- stained section from the first surgical specimen showing pleomorphic tumor cells with bizarre, hyperchromatic nuclei, including multinucleated giant cells, as well as pleomorphic, rhabdoid, and spindle-shaped cells (original magnification ×400). (b) H&E-stained section from the second surgical specimen demonstrating characteristic lipid-laden xanthomatous cells with eosinophilic cytoplasm and epithelioid/rhabdoid tumor cells (original magnification ×400)

scans, performed at regular intervals over the subsequent 12 years, consistently demonstrated stable post-surgical changes without any evidence of tumor recurrence (Figure 3). At the 12-year follow-up, the patient remains clinically stable and disease-free while on levetiracetam 500 mg daily for seizure prophylaxis.

Discussion

This case demonstrates exceptional 12-year disease-free survival in APXA, substantially exceeding the expected 55-57% 5-year survival reported in the literature [2,4]. The patient's age of 30 years is consistent with typical PXA demographics, as this tumor predominantly affects children and young adults with median ages ranging from 20 to 26 years [2,9]. Histopathological examination confirmed grade 3 PXA with characteristic features including xanthomatous cells with lipid accumulation, marked cellular pleomorphism, high mitotic activity (13 mitoses/10 high-power field), and Ki-67 proliferation index of 15%, fulfilling the WHO criteria for anaplastic designation [3,10].

The BRAF V600E mutation identified in this case is a well-established favorable prognostic factor in PXA. Multiple studies have demonstrated that BRAF-mutant tumors are associated with significantly improved survival compared to wild-type counterparts [2,5]. The underlying biological mechanisms may include distinct tumor behavior and enhanced sensitivity to conventional therapies including radiation and alkylating chemotherapy [11,12]. Although our patient was treated according to a glioblastoma protocol, the multimodal approach combining gross total resection, high-dose radiotherapy (6000 cGy), and temozolomide chemotherapy likely contributed to this exceptional outcome.

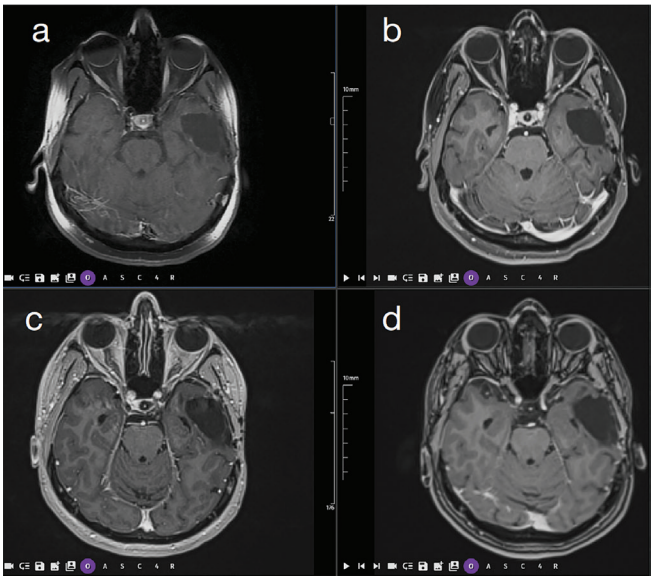

Figure 3. Follow-up magnetic resonance imaging (MRI). Post-contrast fat-suppressed T1-weighted MRI axial images obtained during follow-up show no evidence of residual or recurrent disease in the top row (a, 2018; b, 2020) or the bot tom row (c, 2022; d, 2026)

Treatment strategies for residual or recurrent grade III PXA remain a subject of ongoing debate. Radiotherapy with doses ranging from 45 to 60 Gy is frequently administered for patients with incomplete resection or anaplastic histology, with or without concurrent temozolomide. Gross total resection consistently emerges as the most important independent prognostic factor across multiple studies [2,4,9]. For BRAF V600E-mutant tumors, targeted therapy with vemurafenib has demonstrated response rates of approximately 50%, while dabrafenib and trametinib combination has shown significant benefit in recurrent cases [7,8].

Study Limitations

This case has certain limitations. Comprehensive molecular profiling including CDKN2A/B homozygous deletion and TERT promoter mutation status was not performed, which could provide additional prognostic information [11,13]. The differential diagnosis included epithelioid glioblastoma; however, the classic PXA features, BRAF V600E mutation, and favorable clinical course support the APXA diagnosis [1].

Conclusion

This case demonstrates that exceptional long-term survival exceeding 12 years can be achieved in a patient with BRAF V600E-mutant anaplastic PXA after gross total resection and comprehensive multimodal adjuvant therapy. The findings underscore the importance of molecular profiling for accurate prognostication and identification of potential therapeutic targets in this rare tumor entity.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.S., Concept: B.S., Design: B.S., Data Collection or Processing: B.S., Ö.M., İ.T.R., C.L., Analysis or Interpretation: B.S., Ö.M., İ.T.R., C.L., Literature Search: B.S., Writing: B.S., Ö.M., İ.T.R., C.L.

Conflict of Interest: No conflict of interest was declared by the authors.

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Letter to the Editor

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Therapeutic Response Heterogeneity in the Neoadjuvant Setting: Observations from a Case of HER2-positive, Hormone Receptor-negative Breast Cancer

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Keywords: Breast cancer, human epidermal growth factor receptor 2, targeted therapy, tumor biology, tumor heterogeneity

Dear Editor,

The neoadjuvant treatment period serves as a critical window for evaluating tumor biology and chemosensitivity, particularly in breast carcinomas characterized by well-defined molecular subtypes. Here, we present a case of human epidermal growth factor receptor 2 (HER2)-positive, hormone receptor-negative breast cancer that exhibited differential therapeutic sensitivity, which we interpret in light of current evidence regarding intratumoral heterogeneity.

Case Presentation

A 38-year-old female patient was diagnosed with invasive ductal carcinoma of the breast, stage cT2N2M0 (American Joint Committee on Cancer 8th edition), estrogen receptor- and progesterone receptor- negative, HER2-overexpressing, with a Ki-67 proliferation index of 60%. She received four cycles of neoadjuvant doxorubicin and cyclophosphamide (AC) chemotherapy. Contrary to expectations, interim breast magnetic resonance imaging revealed progressive disease. The regimen was subsequently intensified by adding carboplatin to a standard docetaxel-trastuzumab-pertuzumab combination, resulting in four cycles of docetaxel + carboplatin + trastuzumab + pertuzumab (TCHP). A near-complete radiologic response was achieved following this modification (Figure 1). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Inadequate Response to Anthracyclines: Indicative of Underlying Molecular Discordance?

Anthracycline-based chemotherapy remains a cornerstone in the treatment of highly proliferative breast tumors, particularly those overexpressing HER2 [1]. The high Ki-67 index in this case would typically suggest increased chemosensitivity [1]; however, disease progression following AC challenges this assumption. While HER2 positivity and high proliferation indices are generally associated with favorable treatment responses, this case highlights the limitations of relying solely on immunohistochemical markers for therapeutic prediction [2]. Increasing evidence supports the existence of distinct molecular subtypes within HER2-positive disease—such as "HER2-enriched," "luminal B-like," and "basal-like"—each displaying unique response patterns [2].

Implementation of TCHP as a Salvage Strategy in the Neoadjuvant Setting

Given the radiologically documented progression, the treatment regimen was escalated to TCHP. This strategy aimed not only to enhance cytotoxic effects but also to improve anti-HER2 efficacy through the synergistic interaction with carboplatin, a

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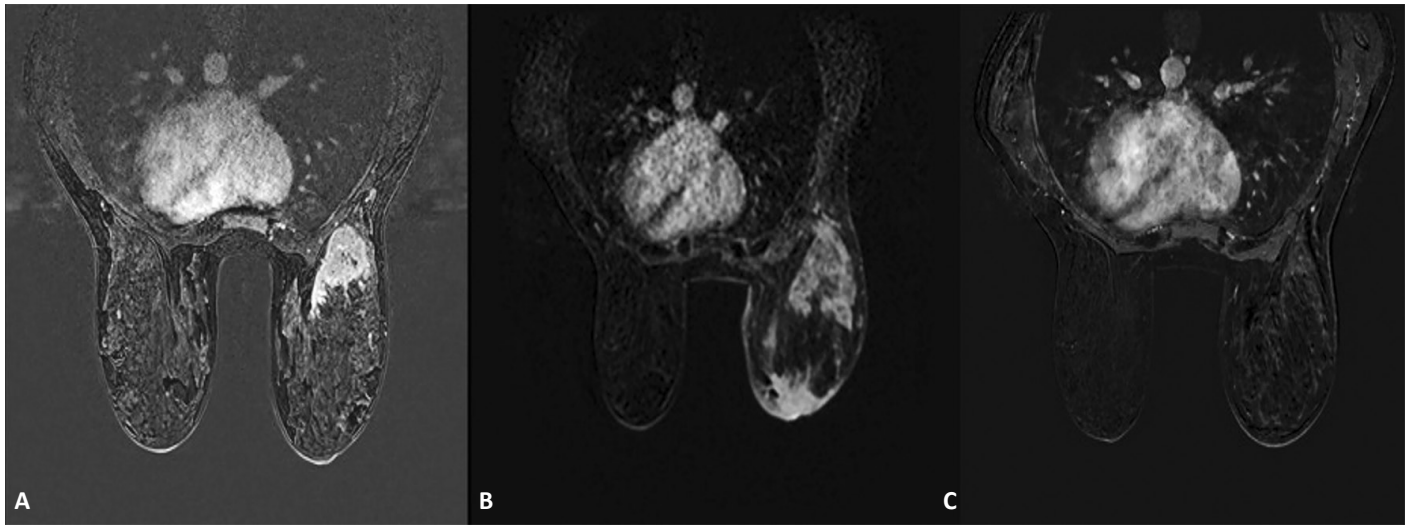

Figure 1. Serial breast MRI images demonstrate the radiological course of a HER2-positive malignant lesion in the right breast. At baseline (A), a malignant mass is observed in the upper outer quadrant of the right breast. At the 3-month follow-up (B), MRI reveals findings consistent with disease progression. Following the addition of anti-HER2 therapy (C), subsequent imaging shows a near-complete radiological response
HER2: Human epidermal growth factor receptor 2, MRI: Magnetic resonance imaging

DNA-damaging agent. The clinical benefit observed aligns with growing evidence supporting the combined use of platinum agents and targeted therapy in biologically aggressive tumors [3]. Furthermore, the substantial increases in pathological complete response (pCR) observed with neoadjuvant trastuzumab highlight that the therapeutic efficacy of HER2-directed treatments can vary markedly depending on the underlying molecular architecture of HER2-driven tumors [4]. The phase III TRAIN-2 trial demonstrated that anthracycline-free, carboplatin-containing regimens achieved pCR rates equivalent to those achieved with anthracycline-based therapy while providing a more favorable toxicity profile, thereby supporting the use of TCHP as a potent but safer alternative in patients with high-risk disease [5]. Similarly, the KRISTINE trial showed significantly higher pCR rates with TCHP than with the antibody-drug conjugate trastuzumab emtansine plus pertuzumab, underscoring the robust early efficacy of taxane- and platinum-based anti-HER2 therapy in tumors with aggressive biology [6]. Taken together, these data highlight TCHP as a highly effective neoadjuvant option that offers strong cytoreduction, an improved safety profile over anthracycline-containing regimens, and the advantage of introducing full anti-HER2 therapy from the outset of treatment.

Divergent Therapeutic Outcomes as a Manifestation of Genomic Complexity

The marked difference between disease progression observed under AC therapy and the near-complete clinical and radiologic response achieved with TCHP reflects distinct therapeutic sensitivities arising from underlying biological diversity. Even among tumors with similar histologic features and receptor expression profiles, considerable genomic heterogeneity may be present, resulting in variable responsiveness to sequential treatment modalities [2]. In this context, TCHP therapy resulted in substantial tumor regression and produced meaningful clinical and radiologic downstaging. Although a pCR was not achieved and postoperative assessment demonstrated ypT1aN2a disease—with micrometastatic involvement in five lymph nodes, the largest metastatic focus measuring 5 mm—the conversion of an initially bulky nodal burden into microscopic disease strongly suggests a favorable biological sensitivity to intensified treatment. Accordingly, the presence of residual disease should not be interpreted as diminishing the therapeutic impact of TCHP, but rather as a complementary pathological finding underscoring the extent to which early progression under AC was effectively reversed through treatment intensification. The magnitude of tumor regression observed with TCHP is further supported by preclinical and clinical evidence demonstrating enhanced activity of platinum-containing anti-HER2 combinations in HER2-positive tumors that are biologically heterogeneous, genomically unstable, or TP53-mutated [7]. Taken together, this case highlights the genomic complexity of HER2-positive disease and emphasizes the crucial influence of timely, biology-guided therapeutic modification on clinical outcomes.

Conclusion

This case illustrates the necessity of reevaluating therapeutic strategies in real time when clinical expectations are not met and reinforces the role of the neoadjuvant period as a biological assay. The observed discrepancy in response, despite favorable prognostic markers, highlights the importance of integrated molecular profiling in clinical decision-making. In carefully selected patients, early therapeutic intensification may yield significant benefits and may represent a key component of personalized oncologic care.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.T., S.T., Concept: G.Ö., S.T., Design: G.Ö., S.T., Data Collection or Processing: N.T., B.K., Analysis or Interpretation: G.Ö., B.K., Writing: G.Ö., N.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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Erratum

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Published on page 416;

A total of 774 ERCP procedures performed on 574 patients between January 2013 and December 2015 in Endoscopy Unit of Gastroenterology Clinic of [Hidden for Blind Review] University Faculty of Medicine Department of Internal Medicine were included in our study. The demographic characteristics of patients; outcomes, procedural interventions, complications and relations between procedural interventions and complications of ERCP procedures were investigated. This study was approved by the Clinical Research Ethics Committee of [Hidden for Blind Review] University Faculty of Medicine (No: 2016/6-21) and complies with research and publication ethics.

Corrected page 416;

A total of 774 ERCP procedures performed on 574 patients between January 2013 and December 2015 in Endoscopy Unit of Gastroenterology Clinic of **Atatürk** University Faculty of Medicine Department of Internal Medicine were included in our study. The demographic characteristics of patients; outcomes, procedural interventions, complications and relations between procedural interventions and complications of ERCP procedures were investigated. This study was approved by the Clinical Research Ethics Committee of **Atatürk** University Faculty of Medicine (No: 2016/6-21) and complies with research and publication ethics.