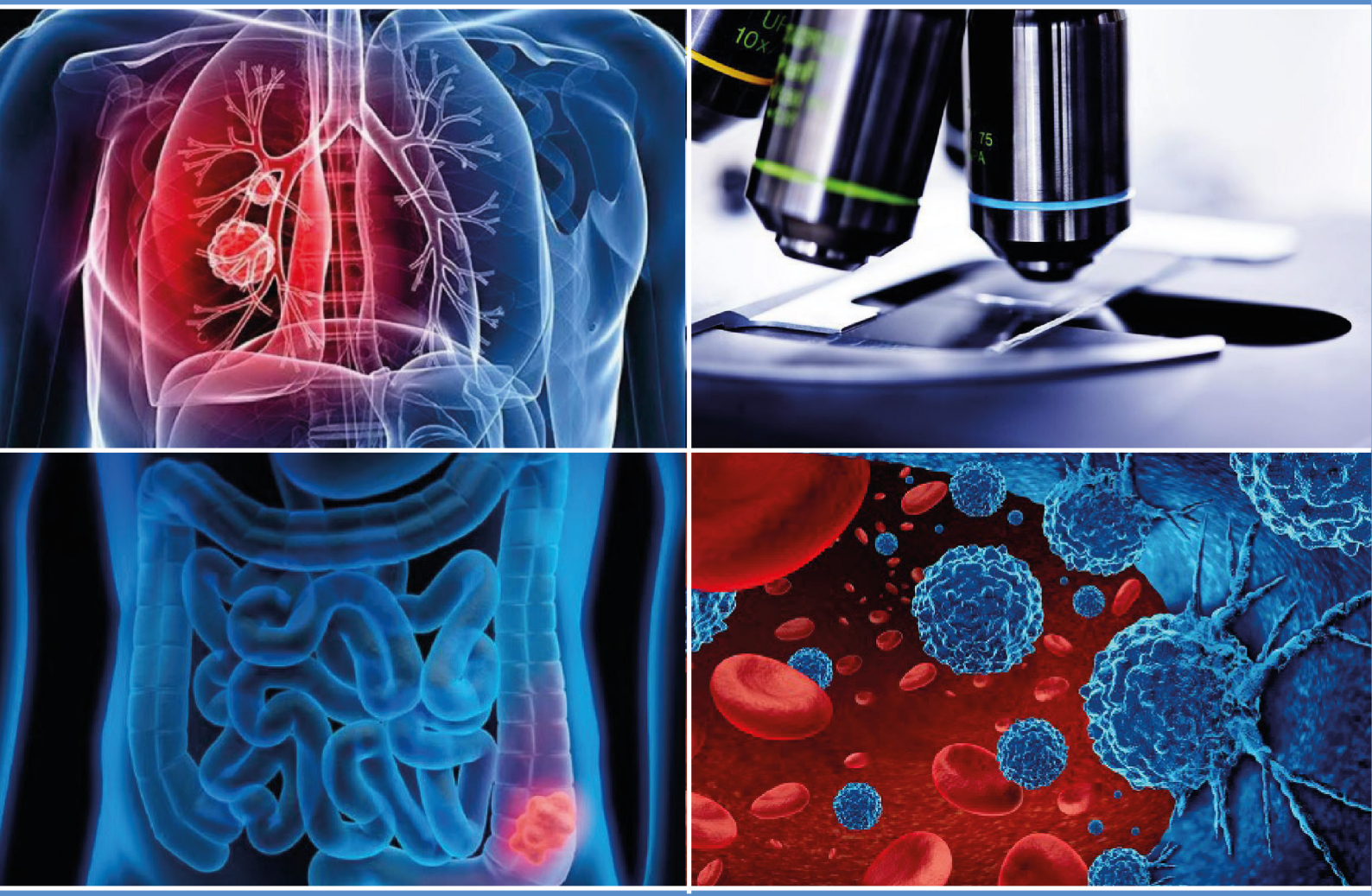
e-ISSN: 2980-0854

JCHOR

Journal of Current Hematology & Oncology Research



Volume: 3 Issue: 2 Year: 2025

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Original Article

DOI: 10.51271/JCHOR-0057

Hereditary thrombophilia and recurrent pregnancy loss: is it time to reassess routine genetic testing?

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Cite this article: Beyler Ö, Baş H, Balık B, et al. Hereditary thrombophilia and recurrent pregnancy loss: is it time to reassess routine genetic testing? *J Curr Hematol Oncol Res.* 2025;3(2):22-26.

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Received: 15/12/2024 ◆ **Accepted**: 16/01/2025 ◆ **Published**: 08/05/2025

ABSTRACT

Aims: Hereditary thrombophilias are genetic conditions that increase thromboembolic risk, with heightened thrombotic potential during pregnancy due to the associated hypercoagulable state. These conditions are recognized as significant risk factors for recurrent pregnancy loss (RPL), defined as the loss of two or more consecutive pregnancies before the 20th gestational week, affecting approximately 1-2% of women of reproductive age. RPL is multifactorial, influenced by genetic, environmental, and hormonal factors, with advanced maternal age and previous pregnancy loss being prominent risk factors. While the role of hereditary thrombophilias in adverse pregnancy outcomes remains controversial, studies have reported inconsistent findings regarding their association with RPL.

Methods: This retrospective cohort study included 736 women with a history of RPL and aimed to investigate the relationship between genetic thrombophilia variants and RPL, focusing on their impact on miscarriage risk. Genetic testing using PCR panels identified common mutations such as factor V Leiden, MTHFR, PAI-1, and prothrombin G20210A.

Results: Statistical analyses revealed no significant associations between these variants and RPL.

Conclusion: The findings suggest that, despite the prevalence of certain mutations, their contribution to miscarriage risk may be limited, underscoring the importance of selective genetic testing. This study highlights the need to optimize genetic screening practices to avoid unnecessary testing and reduce healthcare costs, supporting a more targeted approach in managing patients with RPL.

Keywords: Thrombophilia, miscarriage, FV Leiden, prothrombin G20210a

INTRODUCTION

Hereditary thrombophilias are genetic conditions that increase the risk of thromboembolic diseases, and their thrombotic potential further increases during pregnancy due to the hypercoagulable state associated with normal gestation.[1] Hereditary thrombophilia has been recognized as a significant risk factor for recurrent pregnancy loss (RPL), defined as two or more consecutive pregnancy losses before the 20th week of gestation.[2] RPL affects approximately 1-2% of women of reproductive age.[3] Early pregnancy loss occurs before the 12th week of gestation, while late pregnancy loss refers to losses occurring after this period.[4]

RPL is a multifactorial condition influenced by environmental, hormonal, and genetic factors. Common risk factors include advanced maternal age, a history of previous miscarriages, endocrine disorders, structural uterine abnormalities, chromosomal abnormalities in the parents, antiphospholipid syndrome, and hereditary thrombophilia. Among these, advanced maternal age and previous pregnancy losses are the most prevalent.[5]

The role of hereditary thrombophilias in adverse pregnancy outcomes is controversial. Studies investigating the association between hereditary thrombophilia and RPL have produced inconsistent findings. While prospective cohort studies have not demonstrated a significant association, meta-analyses and retrospective cohort studies have suggested potential links between specific genetic mutations and RPL. The prevalence of hereditary thrombophilia in women with recurrent first-trimester miscarriages has been

found to be similar to that in the general population, leading to recommendations that routine thrombophilia screening may not be necessary in these cases.[1,6-9]

This study aims to investigate the relationship between genetic variants associated with hereditary thrombophilia and RPL, with a particular focus on the impact of these variants on miscarriage risk. The findings aim to contribute to the literature on the potential role of thrombophilia in predicting or understanding recurrent miscarriages.

METHODS

The study was carried out with the permission of the Gazi Yaşargil Training and Research Hospital Scientific Researches Evaluation and Ethics Committee (Date:20.12.2022, Decision No: 295). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective cohort study included 736 women with a history of pregnancy loss who presented to our center between 2019 and 2023. These women were referred to us following gynecological evaluations in obstetrics clinics, where no other cause of abortion was identified, to determine mutations associated with hereditary thrombophilia. The exclusion criteria for the study included patients with known risk factors for RPL other than thrombophilia. RPL was defined as the occurrence of two or more consecutive miscarriages. Clinical assessments of patients included investigating the number of pregnancy losses, the trimester during which losses occurred, and family history of RPL. Additionally, patients with three or more consecutive miscarriages were grouped separately. The relationship between genetic thrombophilia mutations and RPL was examined based on the number of abortions.

High-quality genomic DNA was isolated from peripheral blood samples of all participants using standard extraction protocols. Genetic testing was conducted using a polymerase chain reaction (PCR) panel to screen for mutations commonly associated with thrombophilia. The PCR panels included the Prothrombin G20210A, Factor V Leiden (G1691A), MTHFR C677T, MTHFR A1298C variants, PAI-1 gene 4G/5G polymorphism, FXIII V34L variant, and FV H1299R variant.

Statistical Analysis

Data analysis was performed using IBM SPSS version 25. Summary statistics for quantitative data are presented as mean±standard deviation and median (minimum-maximum). Summary statistics for qualitative variables are presented as frequency and percentage. Relationships between categorical variables were evaluated using Chi-square tests (Pearson, Yates, Fisher Exact). A p-value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of the 736 women in our study was 30 years (range: 16-52). The average number of abortions was 2.43±1.15. The number of patients who miscarried at different trimesters and the details of recurrent miscarriages are presented in Table 1. The study included 510 women who had only first-trimester miscarriages, 54 who experienced only second-trimester miscarriages, and 9 who had only third-trimester miscarriages.

Table 1. Distribution of recurrent miscarriages according to trimesters

Trimester	Number of patients with abortion	Number of patients with recurrent miscarriage	Number of patients with recurrent miscarriage in only one trimester
1st trimester	660	462	458
2nd trimester	185	43	40
3rd trimester	58	11	10

A family history of RPL was assessed in 158 cases. Among patients with fewer than two miscarriages, 18.5% had a positive family history, while the rate was 22.9% in those with two or more miscarriages; however, this difference was not statistically significant (p=0.807).

The distribution of the MTHFR c.677C>T mutation was similar between groups with ≥2 abortions and <2 abortions, showing no statistically significant difference (p=0.438). In fact, the wild-type genotype was slightly more common in the group with ≥2 miscarriages (53.8% vs. 47.8%). Similarly, the MTHFR c.1298A>C mutation did not show a significant difference between groups (p=0.877). Results for patients with three or more miscarriages are shown in Table 2.

Table 2. Distribution of thrombophilia-related genetic variants in patients with less than three abortions versus three or more abortions

Mutation		Number of abortions		p
		<3	≥3	
PAI	5g5g	116 (26.7%)	89 (29.7%)	0.17
	4g5g	215 (49.5%)	157 (52.3%)	
	4g4g	103 (23.7%)	54 (18%)	
MTHFR c.677C>T	Normal	227 (52.1%)	161 (53.7%)	0.561
	Heterozigot	170 (39%)	107 (35.7%)	
	Homozigot	39 (8.9%)	32 (10.7%)	
MTHFR c.1298A>C	Normal	164 (37.6%)	111 (37%)	0.981
	Heterozigot	194 (44.5%)	134 (44.7%)	
	Homozigot	78 (17.9%)	55 (18.3%)	
FXIII p.V34L	Normal	191 (73.7%)	124 (77.5%)	0.657
	Heterozigot	60 (23.2%)	31 (19.4%)	
	Homozigot	8 (3.1%)	5 (3.1%)	
Protrombin G.20210G>A	Normal	423 (97%)	293 (97.7%)	0.34
	Heterozigot	13 (3%)	6 (2%)	
	Homozigot	0 (0%)	1 (0.3%)	
FV (Leiden) C.1691G>A	Normal	416 (95.4%)	285 (95%)	0.934
	Heterozigot	20 (4.6%)	15 (5%)	
	Homozigot	0	0	
FV H1299R	Normal	158 (89.3%)	120 (85.7%)	0.433
	Heterozigot	19 (10.7%)	20 (14.3%)	
	Homozigot	0	0	

For the PAI-1 mutation, the most common genotype observed in both groups was heterozygous 4G/5G. Its prevalence was higher in patients with two or more miscarriages (52.3%) compared to those with fewer than two (43.7%). Comparisons

of RPL for PAI 5G5G, 4G5G, and 4G4G genotypes in patients with ≥2 and ≥3 miscarriages are presented in Table 2.

Approximately 95% of patients showed the normal genotype for FV (Leiden) c.1691G>A. There was no significant difference in the distribution of the mutation between groups (p=1). The heterozygous mutation was slightly more common in the group with ≥2 miscarriages, though this difference was not statistically significant. In 317 cases, the FV H1299R variant was analyzed, while the FXIII V34L variant was evaluated in the remaining 419 cases. The Factor V H1299R mutation also showed no significant difference between groups (p=0.76).

The normal genotype of FXIII was observed in more than 70% of patients (Table 1, 3). The FXIII p.V34L mutation did not show a significant difference between the groups with ≥2 and <2 miscarriages (p = 0.583). Results for patients with three or more miscarriages are provided in Table 2.

Table 3. Comparison of thrombophilia-related genetic variants between patients with less than two abortions and those with two or more abortions

Mutation		Number of abortion		p
		<2	≥2	
PAI	5g5g	40 (29.6%)	165 (27.5%)	0.141
	4g5g	59 (43.7%)	313 (52.3%)	
	4g4g	36 (26.7%)	121 (20.2%)	
MTHFR c.677C>T	Normal	65 (47.8%)	323 (53.8%)	0.438
	Heterozigot	56 (41.2%)	221 (36.8%)	
	Homozigot	15 (11%)	56 (9.3%)	
MTHFR c.1298A>C	Normal	53 (39%)	222 (37%)	0.877
	Heterozigot	58 (42.6%)	270 (45%)	
	Homozigot	25 (18.4%)	108 (18%)	
FXIII p.V34L	Normal	62 (72.1%)	253 (76%)	0.583
	Heterozigot	22 (25.6%)	69 (20.7%)	
	Homozigot	2 (2.3%)	11 (3.3%)	
Protrombin G.20210G>A	Normal	130 (95.6%)	586 (97.7%)	0.369
	Heterozigot	6 (4.4%)	13 (2.2%)	
	Homozigot	0	1 (0.2%)	
FV (Leiden) C.1691G>A	Normal	130 (95.6%)	571 (95.2%)	1
	Heterozigot	6 (4.4%)	29 (4.8%)	
	Homozigot	0	0	
FV H1299R	Normal	45 (90%)	233 (87.3%)	0.76
	Heterozigot	5 (10%)	34 (12.7%)	
	Homozigot	0	0	

There was no significant difference in the prothrombin G.20210G>A polymorphism between patients with ≥2 miscarriages and those with only one miscarriage (p=0.369). Comparisons for patients with RPL of three or more miscarriages are presented in Table 2.

DISCUSSION

In our study, we assessed the potential association of specific genetic variants with the risk of recurrent miscarriage to determine their clinical significance.

In our study, no significant difference was found between individuals with and without a family history of thromboembolic events, consistent with the literature.[5] It is important to note that, in this context, thromboembolic events also include a family history of miscarriages, as these may be indicative of underlying thrombophilic conditions. A 2022 cohort study showed that the prevalence of hereditary thrombophilia in individuals with RPL was comparable to that of the general population.[5] The ALIFE2 study also supported this, finding that low molecular weight heparin (LMWH) had no effect on RPL. The European Society of Human Reproduction and Embryology recommends against routine hereditary thrombophilia screening, except in women with additional risk factors such as personal or family history of venous thromboembolism.[10]

Certain meta-analyses have shown that mutations such as MTHFR C677T, MTHFR A1298C, and PAI-1 4G/5G may increase the risk of RPL[11-14], though some studies have reported no increase in risk.[15,16] In the study by Barut et al.[17], no significant association was found between MTHFR A1298C polymorphism and RPL (p>0.05). The American College of Obstetricians and Gynecologists (ACOG) recommends screening for Prothrombin G20210A, protein C, protein S, and antithrombin III for hereditary thrombophilia.[18] Over 40% of physicians include MTHFR and homocysteine levels in thrombophilia screening, despite ACOG's recommendation against these tests. In our study, the MTHFR c.677C>T and MTHFR c.1298A>C mutations did not show significant differences between groups, suggesting that screening for these mutations in RPL may not be necessary.

According to the British Society for Haematology guidelines, PAI-1 plasma levels have no role in predicting thrombosis risk in women with pregnancy-related morbidities.[4] Although Wen et al.'s[11] meta-analysis initially indicated a strong association between PAI-1 mutation and RPL, subgroup analyses later revealed that this association was influenced by ethnicity and gestational age rather than the number of miscarriages. Consistent with the literature, our study did not find a significant association between PAI-1 mutation and recurrent miscarriage; thus, we do not recommend its inclusion in thrombophilia screening. According to UpToDate, both MTHFR polymorphism (C677T, A1298C) and PAI-1 polymorphism testing are not recommended in pregnancy.[19]

The factor V Leiden mutation is one of the most well-known genetic causes of thrombophilia, leading to resistance to activated protein C and an increased risk of venous thromboembolism.[20] Several meta-analyses have identified a significant association between factor V Leiden H1299R and RPL.[21] In the study by Barut et al.[17], a significant difference was found in the rate of heterozygous factor V Leiden H1299R mutation between patients with two miscarriages and those with three or more miscarriages. In our study, the mutation frequency was 2.4%, consistent with the literature. However, no significant difference was found between patients with fewer than three miscarriages and those with three or more miscarriages (p=0.934), suggesting that while factor V Leiden is a known risk factor for thrombosis, it may not contribute significantly to RPL in this cohort. We found no patients with the FV (Leiden) c.1691G>A or FV H1299R homozygous mutation, and no statistically significant difference was observed among those with heterozygous H1299R mutation.

The FXIII p.V34L mutation affects clot stability and has been studied for its potential role in RPL.[20] In our study, no significant difference was found between patients with two or more miscarriages and those with fewer miscarriages. However, the FXIII homozygous mutation was slightly more prevalent in patients with recurrent miscarriages, particularly among those with three or more miscarriages. Although this finding was not statistically significant, it suggests that FXIII mutation may contribute to RPL in certain patient groups; further studies with larger populations are warranted. Research has proposed that FXIII mutation may increase thrombotic risk during pregnancy by affecting clot stability, as seen in a study by Dossenbach-Glaninger et al.[22], which found that FXIII mutation in homozygous form could increase the risk of recurrent miscarriage. Conversely, other studies have not confirmed this association.[23]

Meta-analyses examining the Prothrombin gene mutation and RPL have generally shown no significant association.[7,8,24] Our findings align with these meta-analyses. However, in a study conducted on Turkish patients, Barut et al.[17] did report a relationship between this mutation and RPL. As hereditary thrombophilia may vary across ethnicities, the differing results in our study with a larger Turkish patient cohort may be of particular relevance.

Limitations

Differences in the prevalence and impact of genetic mutations across different ethnic groups could affect the applicability of our findings to other populations. Given that certain mutations are more prevalent in specific populations, the results may not be generalizable to other ethnic groups.

CONCLUSION

Our findings suggest that, despite the prevalence of certain thrombophilia mutations, their impact on pregnancy loss may be limited, prompting questions about the efficacy of routine screening in miscarriage prevention. This is important to prevent unnecessary genetic testing and optimize resource allocation. Considering the high cost and potential overuse of genetic testing, the results of this study emphasize the need for a more selective testing policy. Thus, our findings support a more targeted approach to risk assessment in pregnancy loss. The data presented here contribute to clinical practice and underscore the need for larger, prospective studies to further clarify the relationship between thrombophilia and pregnancy loss.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Gazi Yaşargil Training and Research Hospital Scientific Researches Evaluation and Ethics Committee (Date:20.12.2022, Decision No: 295).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0058

Evaluation of second-line treatment options in metastatic esophageal squamous cell carcinoma

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Cite this article: Yılmaz Ürün Y, Ürün M. Evaluation of second-line treatment options in metastatic esophageal squamous cell carcinoma. *J Curr Hematol Oncol Res.* 2025;3(2):27-31.

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Received: 30/12/2024 ◆ **Accepted**: 03/02/2025 ◆ **Published**: 08/05/2025

ABSTRACT

Aims: Esophageal cancer is the seventh most common cause of death worldwide and the survival rate of patients with metastatic esophageal cancer is very low. Although current guidelines recommend immunotherapy as a second-line treatment for esophageal squamous cell carcinoma (SCC), a significant proportion of patients have difficulty accessing this treatment. Therefore, conventional chemotherapy is used as second-line treatment. In this study, we aimed to compare the efficacy and tolerability of irinotecan- and taxane-containing chemotherapy regimens as second-line treatments for patients with disease progression after first-line cytotoxic chemotherapy.

Methods: This study included 43 patients with metastatic esophageal SCC at the time of diagnosis or relapse during follow-up. The patients were divided into two groups: irinotecan-based chemotherapy regimens (n=21) and taxane-based chemotherapy regimens (n=22). Demographic characteristics, treatment regimens, treatment responses, grade 3-4 toxicities, overall survival (OS), and progression-free survival (PFS) were documented and analyzed using appropriate statistical methods.

Results: Of the 43 patients who received second-line treatment, 25 (58.1%) were male and 18 (41.9%) were female. The mean age was 55.86±11.6 years. At the time of diagnosis, 72.1% of the patients had metastatic disease. The median OS was 5 months (95% CI, 2.5 to 7.4) for the irinotecan-based regimen and 10 months (95% CI, 2.6 to 17.3) for the taxane-based regimen (p=0.122). The median PFS was 4 months (95% CI, 2.9 to 5.0) in the irinotecan-based regimen group and 7 months (95% CI, 4.8 to 9.1) in the taxane-based regimen group (p=0.80). There were no significant differences in OS and PFS between the two groups. Grade 3-4 neutropenia (p=0.046) and grade 3-4 neuropathy (p=0.034) were higher in the group receiving taxane-based regimens, while grade 3-4 mucositis (p=0.027) was higher in the group receiving irinotecan-based regimens. There were no statistically significant differences in other side effects (p>0.05).

Conclusion: We found no statistically significant difference in the median PFS and median OS between the two chemotherapy groups used as second-line treatment for metastatic esophageal SCC. Grade 3-4 neutropenia and grade 3-4 neuropathy were higher in the group receiving taxane-based regimens, while grade 3-4 mucositis was higher in the group receiving irinotecan-based regimens. Although our study has limitations, such as its retrospective and single-center nature, it is one of the few studies performed in this patient group in recent years and is important because it reflects our clinical practice.

Keywords: Esophageal cancer, squamous cell carcinoma, second-line treatment

INTRODUCTION

Esophageal cancer is the seventh most common cause of death worldwide, accounting for >400.000 deaths annually.[1] There are two predominant subtypes of cancer, squamous cell carcinoma (SCC) and adenocarcinoma. These subtypes differ in several characteristics, including tumor location and predisposing factors. Smoking and alcohol use are the main risk factors for SCC, while Barrett's esophagus, obesity and smoking are risk factors for adenocarcinoma.[2] Although the adenocarcinoma subtype is more common in western countries, the predominant subtype is SCC.[3] More than one-third of the patients with esophageal cancer are diagnosed at the metastatic stage.[4] The prognosis of metastatic disease is extremely poor, with a 5-year survival rate of approximately 5%.[5]

Both Eastern and Western guidelines recommend endoscopic treatment or upfront surgery for early stage tumors, whereas surgery after neoadjuvant therapy is recommended for locally advanced diseases. Palliative chemotherapy, immunotherapy, and targeted therapies are recommended for the treatment of metastatic diseases. For second-line treatment, immunotherapy is recommended for patients with access to immunotherapy, while palliative chemotherapy is recommended for other patients.[6-8]

Phase-2 trials of paclitaxel[9], docetaxel[10] and irinotecan[11], chemotherapies in second-line treatment are available and have shown modest survival. Among immunotherapy agents, which are now an important part of oncologic treatment, there are four phase-3 studies with positive results. In the KEYNOTE-181 study, pembrolizumab was compared with conventional chemotherapy, and pembrolizumab improved overall survival (OS).[12] In the ATTRACTION-3 study, nivolumab was superior to taxanes (paclitaxel and docetaxel) in terms of OS.[13] The ESCORT study also showed a survival advantage of camrelizumab over chemotherapy.[14] Finally, the RATIONALE-302 study demonstrated the superiority of tislelizumab over taxanes and irinotecan.[15]

Although current guidelines recommend immunotherapy as second-line treatment for esophageal SCC in patients with access, a significant proportion of patients worldwide have problems accessing this treatment. Currently, there are no widely accepted chemotherapy regimens for patients who cannot receive immunotherapies. The aim of our study was to compare the efficacy and tolerability of irinotecan- and taxane-containing chemotherapy regimens, which are widely used worldwide and an important part of our clinical practice, as second-line treatments in patients who progress after first-line cytotoxic chemotherapy.

METHODS

Ethics

Ethical approval was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 18.09.2023, Decision No: 2023/09-01). The requirement for informed consent was waived owing to the retrospective nature of the study. All procedures were performed in accordance with. Ethical rules and principles of the Declaration of Helsinki.

Study Population

Esophageal SCCs treated and followed up at Van Yüzüncü Yıl University Medical Faculty Hospital between January 2011 and December 2023 were screened. The inclusion criteria were as follows: (1) age >18 years; (2) cytologically or histologically proven metastatic esophageal SCC; (3) treatment regimens including irinotecan, paclitaxel, or docetaxel; (4) previous treatment for recurrent metastatic disease and progression; and (5) at least two cycles of chemotherapy. Exclusion criteria were: (1) younger than 18 years of age; (2) no pathologic or cytologic diagnosis; (3) non-SCC subtypes; (4) no prior treatment for recurrent metastatic disease; (5) patients receiving treatment other than chemotherapy (such as targeted therapies and immunotherapies); (6) patients whose chemotherapy regimen did not include irinotecan or taxane group chemotherapy; and patients with missing data. Patients enrolled in the study received irinotecan-based regimens as second-line chemotherapy if they received taxane-based chemotherapy as first-line chemotherapy, and taxane-based chemotherapy as second-line chemotherapy if they did not receive taxane-based chemotherapy as first-line chemotherapy. Patients were screened prior to treatment by history and physical examination for the presence of potential side effects that may occur with second-line chemotherapy, and no findings related to potential side effects were noted in any of the patients.

Evaluation

The medical records of the patients were collected, including demographic characteristics, treatment regimens and responses to treatment, grade 3-4 toxicities, date of progression, date of the last follow-up, and date of death. Performance scores were assessed according to the Eastern Cooperative Oncology Group (ECOG) criteria. Progression-free survival (PFS) was calculated as the time from second-line treatment to the date of progression or death. OS was calculated as the time from the start of second-line treatment until death or last follow-up. Patients were divided into two groups: those receiving irinotecan-based chemotherapy regimens (irinotecan-folinic acid-fluorouracil (FOLFIRI) and irinotecan) and those receiving taxane-based chemotherapy regimens (paclitaxel and docetaxel). Radiological evaluations were performed every eight weeks if there was no clinical progression. The treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Toxicity was assessed by physical examination, medical history and biochemical tests on day 1 of each cycle. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3.0). Only grade 3-4 toxicities were observed.

Statistical Analysis

The data analyses were conducted using IBM SPSS Statistics for Windows Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as n and % for categorical variables, and as median (min–max) and mean±SD for continuous variables. Pearson's Chi-square test and Fisher's exact test were used to compare categorical variables. The Kaplan-Meier method was used to compare the OS and PFS durations between the various clinical parameter groups. Statistical significance was set at $p<0.05$.

RESULTS

In this study, 110 patients with metastatic disease at diagnosis or metastatic disease that recurred during the follow-up were screened. 91 the patients received first-line treatment. A total of 43 patients 25 (58.1%) males and 18 (41.9%) female received second-line treatment. The mean age was 55.86±11.6 years. Lung, liver, distant lymph node, and bone metastases were present in 69.8%, 34.8%, 30.2%, and 23.2% of patients, respectively. At the time of diagnosis, 72.1% of patients had metastatic disease. Among the patients who received second-line chemotherapy, 53.5% responded to first-line treatment. In contrast, 21% of the patients had a complete or partial response to second-line treatment and 32.6% had progressed. Grade 3-4 neutropenia developed in 18.6%, grade 3-4 thrombocytopenia in 14%, and neuropathy in 23.3%. The other demographic and clinical characteristics of the patients are summarized in **Table 1**. In the irinotecan-based chemotherapy regimen group, 15 and six patients received FOLFIRI and irinotecan, respectively. In the taxane-based chemotherapy regimen group, 17 and five patients received paclitaxel and docetaxel, respectively.

Considering all patients, the median PFS was 5 months (95% CI, 3.0 to 6.9) and the median OS was 7 months (95% CI, 4.5 to 9.5) (**Figure 1**). The median PFS was 4 months (95% CI, 2.9 to 5.0) in the irinotecan-based regimen group and 7 months (95%

Table 1. Demographic and clinical features of the patients

		Average±SD	Min-max (median)
Diagnosis age		55.86±11.6	26-83 (57)
		n	%
Gender	Male	25	58.1
	Female	18	41.9
Comorbidities			
Hypertension		8	18.6
Diabetes mellitus		4	9.3
Ischemic heart disease		5	11.6
Chronic obstructive lung disease		4	9.3
Smoking status		9	20.9
Dysphagia		42	97.7
Abdominal pain		6	14.0
Weight loss		21	48.8
Chemotherapy regimens	Irinotecan-based	21	48.8
	Taxane-based	22	51.2
ECOG	0	10	23.3
	1	29	67.4
	2	4	9.3
Localization of metastasis	Distant lymph node	13	30.2
	Lung	30	69.8
	Liver	15	34.8
	Bone	10	23.2
Diagnosis stage	Local/locally advanced	12	27.9
	Metastatic	31	72.1
Grade	1	2	4.7
	2	31	72.1
	3	10	23.2
Response to first-line treatment	Complete response	6	14
	Partial	17	39.5
	Stable	6	14
	Progression	14	32.6
Advers events			
Neutropenia		8	18.6
Anemia		7	16.3
Thrombocytopenia		6	14.0
Febrile neutropenia		5	18.6
Mucositis		15	34.9
Diarrhea		13	30.2
Neuropathy		10	23.3
Nausea and vomiting		12	27.9
Response to second-line treatment	Complete response	2	4.7
	Partial	7	16.3
	Stable	20	46.5
	Progression	14	32.6
Progression	No	35	81.4
	Yes	8	18.6
Latest situation	Exitus	35	81.4
	Alive	8	18.6

SD: Standard deviation, Min: Minimum, Max: Maximum, ECOG: Eastern Cooperative Oncology Group

CI, 4.8 to 9.1) in the taxane-based regimen group (p=0.80). The median OS was 5 months (95% CI, 2.5 to 7.4) in the irinotecan-based regimen group and 10 months (95% CI, 2.6 to 17.3) in the taxane-based regimen group (p=0.122) (**Figure 2**). Among the side effects between regimens, grade 3-4 neutropenia (p=0.046) and grade 3-4 neuropathy (p=0.034) were higher in the taxane-based regimen group, while grade 3-4 mucositis (p=0.027) was higher in the irinotecan-based regimen group. There were no statistically significant differences in the other side effects (**Table 2**).

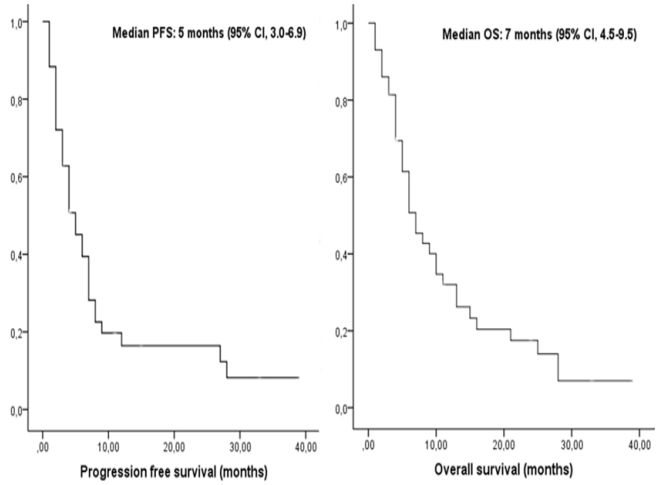

Figure 1. The overall survival and progression-free survival of the patients

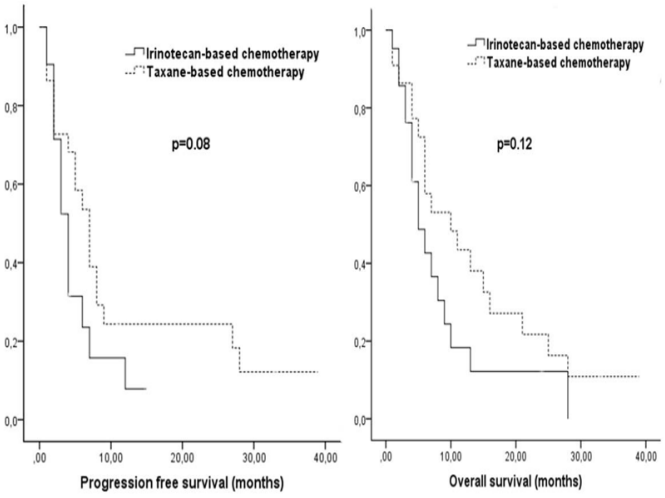

Figure 2. The overall survival and progression-free survival results according to the chemotherapy regimens

Table 2. Comparison of side effects of chemotherapy regimens

	Chemotherapy regimens				
	Irinotecan-based		Taxane-based		
	n (21)	%	n (22)	%	p
Grade 3-4 neutropenia	1	4.8	7	31.8	0.046
Grade 3-4 anemia	3	14.2	4	18.2	1.000
Grade 3-4 thrombocytopenia	2	9.5	4	18.2	0.664
Febrile neutropenia	2	9.5	6	27.2	0.240
Grade 3-4 mucositis	11	52.4	4	18.2	0.027
Grade 3-4 diarrhea	9	42.9	4	18.2	0.104
Grade 3-4 neuropathy	2	9.5	8	36.4	0.034
Grade 3-4 nausea and vomiting	8	12.1	4	18.2	0.185

DISCUSSION

In our study, we found no statistically significant differences in the median PFS and median OS between the two different chemotherapy groups used in the second-line treatment of patients with metastatic esophageal SCC. Among the side effects, grade 3-4 neutropenia and grade 3-4 neuropathy were higher in the group receiving taxane-based regimens, while grade 3-4 mucositis was higher in the group receiving irinotecan-based regimens.

A meta-analysis published in 2017 that investigated the efficacy of palliative treatment for metastatic esophageal cancer showed that second-line treatment contributed to OS.[16] Although the response of patients to second-line treatment varies, in a retrospective study evaluating paclitaxel and docetaxel regimens, docetaxel had a response rate of 5.3% and paclitaxel 19.4%.[17] In a phase-2 study evaluating 53 patients with progressive esophageal cancer who had previously received platinum-based chemotherapy and weekly paclitaxel, the response rate was 44.2%.[9] In a phase-3 study comparing camrelizumab with classical chemotherapy, the response rate was 7% in the classical chemotherapy arm.[14] In this study, the response rate was 21%.

In a meta-analysis of 29 studies evaluating second-line treatment for esophageal cancer published between 1996 and 2011, the time to progression was found to be between 1.4 and 6.2 months. Approximately 40% of patients with disease progression after first-line chemotherapy progress to second-line treatment.[18] Similarly, in our study, the median PFS was 5 months and 47.2% of patients who received first-line treatment were able to receive second-line treatment.

In a retrospective study evaluating patients using taxane and non-taxane chemotherapy regimens, the median OS was 7.4 months in the group receiving taxane-based regimens and 5.1 months in the group receiving non-taxane-based regimens and was found to be statistically significant.[19] In a study evaluating 124 patients who had previously received platinum-based chemotherapy and developed disease progression, the median OS was 6.1 months for those receiving docataxel and 7.2 months for those receiving paclitaxel.[20] In a retrospective study evaluating dual chemotherapy agents (FOLFIRI, carboplatin-paclitaxel and cisplatin-5-fluorouracil) as second-line treatments for metastatic esophageal SCC, the median OS was 14 months.[21] In a phase-3 study comparing nivolumab treatment with taxane agents, the median OS in the chemotherapy arm was 8.4 months.[13] In our study, the median OS was seven months for all patients, 10 months for the taxane-based regimen group, and five months for the irinotecan-based regimen group. Although the OS in the taxane group was twice that of the irinotecan group, the difference was not statistically significant owing to the limited number of patients.

In a retrospective study comparing docetaxel and paclitaxel after platinum-based therapy, grade 3-4 neutropenia was found in 40.3%, grade 3-4 anemia in 3.4% and grade 3-4 neuropathy in none.[20] In a study involving 163 patients evaluating taxane group chemotherapies as second-line treatment, grade 3-4 neutropenia was seen in 32.6%, grade 3-4 anemia in 9.1% and grade 3-4 thrombocytopenia in 2.3% in the docetaxel group, while grade 3-4 neutropenia was seen in 16.1% and grade 3-4 neuropathy in 6.5% in the paclitaxel group. Grade 3-4 anemia and grade 3-4 thrombocytopenia were not observed in the paclitaxel group.[17] In a study evaluating 53 patients who had previously received platinum-based chemotherapy and progressed, the most common grade 3-4 side effects were neutropenia (52.8%) and leukopenia (45.3%).[9] In a study comparing tislelizumab with classical chemotherapy, 55.8% of patients in the classical chemotherapy cohort developed grade 3 or higher side effects.[15]

In our study, 18.6% of patients developed grade 3-4 neutropenia, 14% grade 3-4 thrombocytopenia, and 23.3% developed neuropathy. As expected, grade 3-4 neutropenia and grade 3-4 neuropathy were higher in the group receiving the taxane-based regimen, while grade 3-4 mucositis was higher in the group receiving irinotecan-based regimens.

Limitations

Although our study has limitations, such as its retrospective and single-center nature, it is one of the few studies performed in this patient group in recent years and is important because it reflects our clinical practice. In the present study, the limited sample size may have impacted the frequency of adverse effects observed. However, the retrospective nature of the study also raises the possibility that the clinician may not have asked enough questions about side effects. Thus, it is suggested that a multicenter prospective cohort study with an expanded sample size might yield advantageous outcomes.

CONCLUSION

As a result, although taxane-group chemotherapeutic agents increased the frequency of neutropenia and neuropathy in the second-line treatment of patients with esophageal SCC, they increased OS compared to irinotecan-containing agents. For patients who do not receive taxane group agents as first-line treatment, we believe that taxane group chemotherapeutic agents should be used as second-line treatment, rather than irinotecan-based treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 18.09.2023, Decision No: 2023/09-01).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0059

The relationship between medical therapy and sarcopenia in advanced non-small cell lung cancer patients

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Cite this article: Erdem Keleş F, Yalçın S, Keleş AO, Erdem TE, Bozkurt Yavuz H, Ayçiçek GŞ. The relationship between medical therapy and sarcopenia in advanced non-small cell lung cancer patients. *J Curr Hematol Oncol Res.* 2025;3(2):32-41.

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Received: 22/05/2024 ◆ **Accepted**: 10/04/2025 ◆ **Published**: 08/05/2025

ABSTRACT

Aims: Sarcopenia, characterized by loss of skeletal muscle mass and function, is associated with worse clinical outcomes in patients with cancer. This study aims to determine the prevalence of sarcopenia before and after chemotherapy in advanced non-small cell lung cancer (NSCLC) patients and to evaluate its effect on treatment response.

Methods: Between October 13, 2022, and February 13, 2023, 38 patients over 18 years of age with advanced NSCLC who were admitted to the medical oncology department outpatient clinic were included in the study. Bioelectrical impedance analysis (BIA) and anthropometric measurements (hand grip strength and walking speed) were performed for all patients according to European Working Group on Sarcopenia in the Elderly (EWGSOP) criteria.

Results: Before treatment, 23.7% of patients had probable sarcopenia, 10.5% had sarcopenia, and 15.8% had severe sarcopenia. Sarcopenia developed in 21.1% of patients without sarcopenia before treatment, while 21.1% of patients with possible sarcopenia developed severe sarcopenia after treatment. Thirty percent of patients with pre-treatment sarcopenia died after treatment, and progression was detected in all remaining patients after treatment. Progression of sarcopenia was not significantly associated with BIA parameters but was associated with worse ECOG scores, lower oxygen saturation, decreased lean body mass and lower vitamin D levels. Adenocarcinoma subtype, stage 4, and platinum-based chemotherapy were associated with an increase in the post-treatment sarcopenia score.

Conclusion: The prevalence of sarcopenia in patients with NSCLC is approximately 50%, and disease stage, type, and treatment regimen play an important role in the development of sarcopenia. The presence of sarcopenia before treatment may have an impact on treatment response and increase the risk of chemotherapy-related toxicity and mortality.

Keywords: Lung cancer, bioelectrical impedance, advanced cancer, chemotherapy, sarcopenia

INTRODUCTION

Lung cancer originates from respiratory epithelial cells and is the leading cause of cancer incidence and mortality worldwide.[1] Malignant diseases cause significant loss of skeletal muscle mass, quality, and function.[2] This is associated with malnutrition, lipolysis, inflammation, and vicious metabolic cycles. Fat and muscle loss in cancer patients may be attributed to a "metabolic parasite" effect due to the tumor's appetite for glucose and glutamine. These relationships promote the occurrence of cachexia, which is an important cause of mortality in patients with advanced cancer and is observed in approximately 50% of patients.[3]

Cancer treatment can cause skeletal muscle changes in a variety of ways. Surgery radiotherapy, chemotherapy, and hormone therapy cause systemic loss of muscle mass.[4] Sarcopenia is associated with shorter disease-free survival and worse overall survival in advanced lung cancer.[5] Furthermore, skeletal muscle loss has been shown to negatively affect treatment outcomes in patients with cancer.[6] However sarcopenia before or after treatment is associated with decreased disease control.[7] Although it has been suggested that platinum-based chemotherapy drugs are distributed in lean body-mass, it is thought that sarcopenic

patients may be at a greater risk of toxicity.[8] However, although chemotherapy has been shown to improve quality of life and survival in patients with advanced cancer, there are limited data on the relationship between changes in muscle mass and function during chemotherapy and response to treatment and survival. Given the increasing incidence of cancer and an aging population, early detection of sarcopenia may play a prognostic role. The development of treatment strategies aimed at reversing or preventing metabolic changes that promote cancer progression or recurrence and improving quality of life is important for the early prevention of tissue loss.

The aim of this study was to determine the frequency of sarcopenia in patients with newly diagnosed advanced non-small cell lung cancer (NSCLC) patients according to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria, to detect new sarcopenia after standard chemotherapy protocol, and to determine the effect of sarcopenia on response to treatment. The aim of this study was to improve the survival and treatment complications of the disease with early detection of sarcopenia and to contribute to future studies.

METHODS

Ethics

This study was a prospective cross-sectional study and the protocol of the study was approved by the Kırıkkale University Clinical Researches Ethics Committee (Date: 13.10.2020, Decision No: 09/01). In 2013, the updated Declaration of Helsinki in Brazil was planned in accordance with the updated Declaration of Helsinki resolutions, patient rights regulations, and the Good Clinical Practice Rules.

Research Population

This prospective cross-sectional study was conducted in the outpatient clinic of the Department of Internal Medicine, Division of Medical Oncology, Kırıkkale University Faculty of Medicine. Between October 13, 2022, and February 13, 2023, 38 patients over 18 years of age with advanced NSCLC who were admitted to the medical oncology department outpatient clinic were included in the study. The sample size for the study was calculated as at least 28 patients with a 5% probability of error and 80% sampling power. Patients with advanced NSCLC who had no history of limb amputation that could interfere with bioelectrical impedance analysis (BIA), no cognitive impairment that might affect muscle measurement, and no signs of malnutrition were eligible for inclusion. Patients were excluded if they had acute decompensated heart failure, COPD exacerbation, malnutrition, or immobility, as well as those with implanted metal devices such as permanent pacemakers. Additionally, individuals with comorbidities that could affect the accuracy of muscle mass measurements using BIA, including prosthetic limbs, severe pretibial edema, mechanical heart valves, or pacemakers, were not included in the study.

Demographic characteristics, smoking history, cancer stage, chemotherapy regimen to be used, performance status, anthropometric measurements, biochemical parameters, and sarcopenia status were recorded on the patient follow-up form. Patients were categorized into three groups according to the presence or absence of sarcopenia: those without sarcopenia, those with possible sarcopenia, and those with sarcopenia.

Anthropometric Measurements

Anthropometric measurements included height, body weight, waist circumference, hip circumference, calf circumference, and upper middle arm circumference. BMI was calculated by dividing weight (kg) by the square of height (m^2). Waist circumference was measured at the midpoint of the distance between the iliac crest and the lower rib; hip circumference was measured at the widest part of the hip; calf circumference was measured at the thickest part of the calf when the knee joint was flexed 90 degrees in the sitting position; and upper mid-arm circumference was measured with a tape measure at the midpoint of the upper extremity between the humeral head and the olecranon process.

Evaluation of Sarcopenia

Sarcopenia was diagnosed based on the criteria of the EWGSOP working group. According to these criteria, sarcopenia is defined as a decrease in skeletal muscle mass accompanied by a decrease in muscle strength and/or muscle function. Skeletal muscle mass was assessed with a BIA device (Bodystat QuadScan4000, Appendix 5). After entering the patient's age, gender, height, and body weight into the device, measurement was performed at a frequency of 50 kHz. The resistance value measured during the analysis was used to calculate the skeletal muscle mass using the formula proposed by Jannsen et al.[9] The formula is as follows: [(height2/resistance value in BIA device measurement ×0.401)+(sex×3.825)+(age×0.071)]+5.102

For the variables used in the formula, height is calculated in meters, resistance is calculated in ohms, and sex is coded as 1 for males and 0 for females. The value obtained with this formula was divided by the square of the height of the patients in meters, and the absolute skeletal muscle mass was obtained. An absolute skeletal muscle mass value of <6.42 kg/m^2 in women and <8.87 kg/m^2 in men indicates decreased skeletal muscle mass.[10]

Muscle strength and hand squeeze strength were evaluated using an electronic hand dynomemeter, with results recorded in kilograms. Low muscle strength for men and women was determined according to the cut-off points given in the EWGSOP consensus based on body-mass index (BMI). Muscle performance was assessed based on walking speed, measured over a 4-meter track using an electronic stopwatch, and walking speed was calculated in m/sec using the formula 4 m/walking time (sec). Walking speed <0.8 m/sec was evaluated in favor of decreased muscle performance.[10]

Statistical Analysis

Statistical evaluation Statistical Package for Social Sciences (SPSS) for Windows 23 (IBM SPSS Inc., Chicago, IL) program was used. The normal distribution of the data was evaluated by the Kolmogorov-Smirnov test. Normally distributed numerical data were expressed as mean±standard deviation, and non-normally distributed numerical data were expressed as median (min-max). Qualitative data were expressed as numbers and percentages. The Chi-square test was used for the comparison of qualitative data, and the Fisher-exact

test was used if the expected frequencies were not met. Independent samples The T-test was used for comparison of normally distributed numerical data between two groups, and the Mann-Whitney U test was used for comparison of non-normally distributed numerical variables between groups. The ANOVA test (post hoc Bonferroni test) was used for comparison of numerical variables with a normal distribution between more than 2 groups, and the Kruskall-Wallis H test (post hoc Dunn's test) was used for comparison of numerical variables without a normal distribution. Changes before and after treatment were evaluated by paired samples T test or Wilcoxon sign test according to normality distribution. Post-treatment changes in categorical variables were evaluated by the McNemar test or the marginal homogeneity test. A value of $p<0.05$ was considered significant in statistical analyses.

RESULTS

The study included 38 patients, 32 (84.2%) males and 6 (15.8%) females, aged between 46 and 83 years (mean age: 66.4±8.6 years). Demographic data are shown in **Table 1**. Before treatment, 23.7% (n=9) had probable sarcopenia, 10.5% (n=4) had sarcopenia, and 15.8% (n=6) had severe sarcopenia. Anthropometric measurements and sarcopenia-related parameters of the patients are shown in the **Supplementary Table 1**. 63.2% (n=18) of the patients were stage 4 and had metastasis. When the post-treatment changes were analyzed, a significant decrease in mean walking speed (0.8±0.2 m/s vs. 0.7±0.4 m/s; p=0.031) was found after treatment. Of 19 patients without sarcopenia before treatment, 4 (21.1%) developed probable sarcopenia after treatment, and 4 (21.1%) developed severe sarcopenia after treatment (p<0.001).

Table 1. Demographic characteristics of patients

Variables	All patients n=38
Gender, n (%)	
Female	6 (15.8)
Male	32 (84.2)
Smoking, n (%)	
None	9 (23.7)
Active	12 (31.6)
Quit	17 (44.7)
Smoking, package/year	50 (7-120)
Profession, n (%)	
Worker	18 (47.4)
Public servant	8 (21.1)
Housewife	6 (15.8)
Self-employment	4 (10.5)
Farmer	2 (5.3)
Cancer type, n(%)	
Adenocarcinoma	18 (47.4)
SCC	15 (39.5)
NOS	5 (13.2)
Treatment, n (%)	
Platinum-based chemotherapy	30 (78.9)
Immunotherapy	8 (21.1)

Data were presented as mean±standard deviation, median (min-max) and number (%). Abbreviations: SCC: Squamous cell carcinoma, NOS: Non-small cell lung cancer unclassified type

Supplementary Table 1. Anthropometric measurements and distribution of parameters associated with sarcopenia

Variables	All patients n=38
Boy, cm	168.4±8.2
Weight , kg	75.0±18.2
Waist circumference, cm	102.0±12.6
Hip circumference, cm	104.9±11.2
Waist/hip ratio	0.9±0.1
Fat mass, %	32.6±8.6
Fat mass, kg	21.9 (8.6-62.1)
Fat-free weight, kg	48.9±13.5
Total body weight, kg	75.0±18.0
Dry fat-free weight, kg	11 (1.6-20.8)
Total body fluid, %	54.2±9.2
Total body fluid, kg	39.2±7.3
ECW, %	23.2±5.0
ECW, kg	17.0±3.8
ICW, %	32.0±9.7
ICW, kg	23.6±9.1
Body cell mass	31.4±6.9
Third cavity fluid	0.5 [(-0.5)-3.2]
Nutrition score	0.44 (0.17-0.70)
Disease score	0.8±0.3
BMR	1512.9±279.0
BMR/BW ratio	20.7±2.6
EAR	2301.3±513.2
VKI	26.4±6.2
BFMI	7.7 (2.9-25.8)
FFMI	17.5±3.3
Impedance 50	527 (384-1547)
Resistance 50	525 (383-1059)
Reactance 50	51.3 (16.2-11.27)
Phase Angle	5.3 (1.8-46.8)
Grip strength	23.4±10.1
Walking speed	0.8±0.2
Muscle mass	8.7±1.7
Sarcopenia, n (%)	
None	19 (50.0)
Possible	9 (23.7)
Sarcopenia	4 (10.5)
Severe	6 (15.8)

Data are presented as mean±standard deviation, median (min-max) and number (%). Abbreviations: BMR: Basal metabolic rate, BMR/BW: Basal metabolic rate/body weight, EAR: Average caloric requirement, ECW: Extracellular body fluid, ICW: Intracellular body fluid, BMI: Body-mass index, BFMI: Fat mass index, FFMI: Fat-free mass index

Mean lean, median dry lean weight, total body weight (kg), extracellular body fluid (ECW) (kg), mean disease score, mean basal metabolic rate (BMR), mean average caloric requirement (EAR), and mean BMI were lower, while median impedance 50, median resistance 50, and median reactance 50 levels were higher in patients with sarcopenia before treatment (**Table 2**).

There was a significant increase in saturation percentage after treatment in patients without sarcopenia before treatment

Table 2. Anthropometric measurements associated with sarcopenia

Variables	Sarcopenia			p
	None n=19	Possible n=9	Exist n=10	
Height, cm	170.3±9	164.7±7.5	168.3±6.3	0.235
Weight, kg	83.5±19.2	68.4±11.7	65.0±12.8	0.007*
Waist circumference, cm	103.8±14.7	103.9±8.3	96.8±11.1	0.328
Hip circumference, cm	106.3±10.6	107.7±10.5	100.0±12.4	0.260
Waist–hip ratio	1.0±0.1	1.0±0.1	0.9±0.2	0.309
Fat mass, %	32.4±8.2	29.5±7.9	35.7±9.9	0.304
Fat mass, kg	23.6 (8.6-62.1)	20.3 (11.1-27.6)	20.6 (10.6-47.1)	0.244
Fat-free weight, kg	55.7±9.9	49.2±10.1	35.5±13.0	<0.001*
Total body weight, kg	83.4±19	70.4±11.7	63.1±12.7	0.007*
Dry fat-free weight, kg	12.5 (0.8-20.8)	11 (1.3-17.3)	8.2 [(-1.6)-12.7]	0.021*
Total body fluid, %	53.0±10.3	56.7±7.9	54.1±8.7	0.618
Total body fluid, kg	42.8±6.4	39.5±5.9	32.0±4.4	<0.001*
ECW, %	23.7±5.6	24.8±3.1	20.8±4.7	0.194
ECW, kg	19.1±3.2	17.2±2.2	12.9±2.5	<0.001*
ICW, %	32.0±13.1	30.6±4.0	33.1±5.1	0.866
ICW, kg	26.2±8.1	21.4±3.8	20.4±2.0	0.190
Body cell mass	33.0±8.6	30.6±5.4	29.1±3.0	0.334
Third cavity fluid	0.4 [(-3.8)-3.2]	0.5 [(0.1)-2.4]	0.3 [(-5.0)-1.8]	0.094
Nutrition score	0.4±0.1	0.5±0.1	0.4±0.1	0.105
Disease score	0.8±0.3	0.8±0.1	0.6±0.2	0.027*
BMR	1655.1±245.0	1505.9±233.5	1249.1±177.5	<0.001*
BMR/BW ratio	20.4±2.8	22.0±2.4	20.1±2.4	0.246
EAR	2592.3±490.7	2226.1±262.3	1815.9±306.2	<0.001*
BMI	28.7±6.4	26.5±4.1	22.0±5.7	0.029*
BFMI	8.2 (2.9-25.8)	7.8 (4.0-11.5)	7.3 (5.0-19.6)	0.598
FFMI	19.1±2.3	18.2±3.0	13.7±2.6	<0.001*
Impedance 50	506 (384-1042)	508 (404-590)	675 (542-1547)	0.001*
Resistance 50	503 (383-903)	507 (402-589)	665.5 (541-1059)	<0.001*
Reactance 50	42.9 (16.2-678)	43 (28.5-169)	111.5 (33.1-1127)	0.210
Phase Angle	5 (1.8-29.9)	4.4 (2.4-8.3)	9.7 (3.2-46.8)	0.010*
Grip strength	31.5±6.5	14.0±3.6	16.6±6.9	<0.001*
Walking speed	0.9±0.1	0.7±0.2	0.7±0.3	<0.001*
Muscle mass	9.4±1.3	9.3±1.5	6.9±1.3	<0.001*

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, BMR/BW: Basal metabolic rate/body weight, EAR: Average caloric requirement, ECW: Extracellular body fluid, ICW: Intracellular body fluid, BMI: Body-mass index, BFMI: Fat mass index, FFMI: Fat-free mass index

(94.7±2.6 versus 92.5±5.2; p=0.035), whereas saturation level did not change after treatment in patients with possible sarcopenia or sarcopenia. In patients with sarcopenia, the median ECOG performance score decreased significantly after treatment (p<0.05).

Sarcopenia was observed after treatment in 11 patients without sarcopenia at baseline and in 11 patients with possible sarcopenia (Table 3). Those with an increased sarcopenia score had higher pre-treatment median fat mass (21 kg vs. 28 kg; p=0.050) and mean BMI (25.8±4.3 vs. 30.4±7.6; p=0.037), lower median impedance 50 (538 vs. 506; p=0.050), and lower median resistance 50 (534 vs. 503; p=0.041). Other anthropometric characteristics did not differ significantly between the groups.

Post-treatment saturation percentage decreased significantly in those with an increased sarcopenia score compared to pretreatment (92.7±2.6 versus 89.8±4.5; p=0.041), and the ECOG performance score increased (1 versus 1.5; p=0.003). In patients whose sarcopenia score did not change, saturation and ECOG performance score did not change significantly, but 25-OH vitamin D level increased significantly after treatment (20 versus 30; p=0.001). It was found to decrease significantly in those with an increased sarcopenia score (25 versus 12; p=0.020). There was no significant difference in other laboratory findings (Table 4).

Anthropometric characteristics did not differ significantly after treatment in patients with an unchanged sarcopenia score. In patients whose sarcopenia score increased, weight, waist circumference, BMI, lean weight, total body weight, dry lean weight, ECW, intracellular fluid content (ICW), body mass cell, BMR, mean caloric requirement, and lean mass index decreased significantly (Table 5).

Table 3. The relationship between the change in sarcopenia score and pretreatment anthropometric characteristics

Laboratory findings	Sarcopenia			p
	None n=19	Possible n=9	Exist n=10	
Hemoglobin, gr/dl	12.6±1.9	11.5±1.6	11.6±1.9	0.218
WBC, x10^9/L	7.6 (3.3-23.0)	7.1 (2.6-16.1)	11 (6.6-20.5)	0.137
Platelets, x10^9/L	239 (163-568)	351 (145-575)	310 (146-448)	0.505
Neutrophil, x10^9/L	4.7 (1.8-17.8)	5.9 (1.6-14.6)	8 (5.0-19.5)	0.074
ALT, u/l	22 (6-93)	11 (6-94)	13 (5-77)	0.849
AST, u/l	19 (9-31)	13 (9-25)	15.5 (14-33)	0.878
UREA, mg/dl	38 (19-61)	30 (16-73)	38.5 (12-78)	0.678
Creatinine, mg/dl	1±0.4	0.7±0.2	0.9±0.4	0.089
GFR, ml/dk	82.2±25.8	99±19.9	80.4±23.4	0.175
Sodium, mmol/l	138.6±4.3	137.4±2.5	139.3±2.2	0.505
Potassium, mmol/l	4.6±0.6	4.4±0.3	4.5±0.3	0.439
Magnesium, mg/dl	2.1±0.4	2±0.4	15.6±42.6	0.823
Calcium, mg/dl	9.6±1	9.1±0.4	9.2±0.7	0.371
Phosphorus, mg/dl	3.3±1.1	3.9±1	3.2±0.8	0.244
Total protein, gr/dl	7±0.7	6.8±1	7.1±0.5	0.669
Albumin, gr/dl	4±0.6	3.6±0.6	3.7±0.7	0.197
25-OH vitamin D, ng/dl	20 (11-46)	25 (15-49)	19 (15-25)	0.315
Sedimentation, mm/s	38 (5-120)	49 (17-88)	85.5 (1-135)	0.192
CRP, mg/dl	16.8 (0.1-99.0)	26.2 (0.2-132)	30.7 (2.0-195)	0.092

Data are shown as mean±standard deviation and median (min-max). Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, GFR: Glomerular filtration rate, WBC: White blood cells

Table 4. Changes in clinical findings according to the change in sarcopenia score

Variables	Sarcopenia score after treatment					
	Not changed		p	Increased		p
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
Saturation, %	93.6±3.7	94.8±3.3	0.298	92.7±2.6	89.8±4.5	0.041*
ECOG PS	1 (0-2)	0 (0-3)	0.649	1 (0-1)	1.5 (0-4)	0.003*
Hemoglobin, gr/dl	12.4±2.1	11.9±1.8	0.206	11.9±1.8	10.8±1.8	0.050*
WBC, x10^9/L	8.7 (2.6-23)	7.6 (2.1-19.6)	0.282	6.3 (4.6-15.1)	9.5 (3.8-12.9)	0.731
Platelets, x10^9/L	242 (145-575)	246 (144-487)	0.185	311 (167-536)	193 (1358-491)	0.056
Neutrophil, x10^9/L	6.2 (1.6-17.8)	5.2 (2.7-12.5)	0.242	3.9 (0.7-15.1)	6.3 (2.5-12.1)	0.748
ALT, u/l	16 (6-93)	16 (6-48)	0.162	20 (6-94)	12 (5-34)	0.056
AST, u/l	18 (8-98)	16 (9-30)	0.188	19 (8-57)	17 (9-31)	0.181
Ure, mg/dl	37 (17-60)	31 (10-49)	0.478	33 (16-61)	41 (20-75)	0.565
Creatinine, mg/dl	0.8±0.3	0.9±0.3	0.135	1.0±0.4	0.9±0.4	0.271
GFR, ml/dk	90.4±24.2	85.2±20.4	0.104	77.5±28.8	84.1±26	0.395
Sodium, mmol/l	138.4±3.2	138.7±3.9	0.692	138.7±4.4	139.8±1.5	0.483
Potassium, mmol/l	4.6±0.4	4.6±0.5	0.705	4.4±0.7	4.2±0.5	0.139
Magnesium, mg/dl	2.1±0.3	2.1±0.4	0.630	2±0.4	2.1±0.3	0.363
Calcium, mg/dl	9.3±0.6	9.5±0.5	0.413	9.6±1.2	8.7±1.1	0.111
Phosphorus, mg/dl	3.3±1.0	3.5±0.8	0.592	3.7±1.0	3.2±0.5	0.075
Total protein, gr/dl	7.1±0.6	7.1±0.6	0.466	6.9±0.7	6.6±1.1	0.241
Albumin, gr/dl	4.1±0.5	4.3±0.3	0.229	3.7±0.6	3.7±0.9	0.914
25-OH vitamin D, ng/dl	20 (12-40)	30 (15-53)	0.001*	25 (11-49)	12 (7-30)	0.020*
Sedimentation, mm/s	39 (5-135)	42 (15-117)	0.428	54 (9-117)	75 (10-127)	0.096
CRP, mg/dl	12.9 (0.1-154)	8.2 (0.1-84)	0.347	35.5 (3-99)	9 (2.2-185)	0.818

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: ECOG PS: Eastern cooperative oncology group performance score, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, GFR: Glomerular filtration rate, WBC: White blood cells

Table 5. Changes in anthropometric findings according to the change in sarcopenia score

Variables	Sarcopenia score after treatment					
	Not changed		p	Increased		p
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
Weight, kg	73.5±13.3	75.1±15.0	0.565	86.4±22.4	75.1±15.9	0.003*
Waist circumference, cm	101.4±10.3	100.8±13.1	0.930	106.5±15.8	104.7±16.1	0.043*
Hip circumference, cm	106.2±9.7	105.4±10.9	0.795	107.8±12	106.3±14.2	0.428
Waist/hip ratio	0.9±0.1	0.9±0.1	0.686	1.0±0.1	1.0±0.1	0.911
Fat mass, %	30.3±8.2	30.4±9.4	0.985	35.5±8.9	34.5±11.0	0.644
Fat mass, kg	21 (11-47)	20.5 (8-55)	0.844	28 (9-62)	23 (12-46)	0.169
Fat-free weight, kg	48.6±13.8	51.8±9.4	0.266	55.0±11.8	48.6±10.9	0.001*
Total body weight, kg	73.5±13.3	75±15	0.517	86.1±22.1	75.1±15.9	0.004*
Dry fat-free weight, kg	11.8 (1.3-19)	12 (1.1-20.3)	0.731	12.5 (0.8-20.8)	9 (1.5-21.5)	0.027*
Total body fluid, %	54.9±7.4	55±9.5	0.944	52.1±11.6	52.8±12.6	0.767
Total body fluid, kg	39.0±6.2	40.3±5.8	0.137	43.2±7.1	38.4±7.1	0.004*
ECW, %	23.7±5.0	23.5±4.2	0.800	22.8±4.8	22.7±5.9	0.919
ECW, kg	17.2±3.4	17.1±2	0.994	18.9±2.9	16.5±3.5	0.010*
ICW, %	32.7±12.3	30.6±3.9	0.444	28.9±5.0	30.2±4.6	0.196
ICW, kg	24.2±11.9	22.7±4.1	0.539	23.9±4.0	22.1±3.9	0.007*
Body cell mass	30.1±7.4	32.3±5.7	0.164	34.9±6.5	31.5±5.6	0.003*
Third cavity fluid	0.5 [(-3.4)-2.4]	0.9 [(-4.7)-3.8]	0.076	0.4 [(-3.8)-3.2]	1 [(-6.3)-2.8]	0.912
Nutrition score	0.4±0.1	0.7±0.3	0.322	0.4±0.01	0.4±0.1	0.436
Disease score	0.8±0.3	0.8±0.1	0.918	0.8±0.1	0.7±0.2	0.298
BMR	1526.7±225.2	1564.8±223.1	0.226	1648.8±286.5	1491.9±257.7	0.001*
BMR/BW	21.3±2.5	21.2±2.7	0.940	19.7±3.1	20.2±2.9	0.460
EAR	2392.8±439.8	2357.1±386.3	0.568	2453.4±518.1	2188.7±423.0	0.003*
BMI	25.8±4.3	26.3±4.9	0.497	30.4±7.6	26.5±5.6	0.003*
BFMI	7.2 (4-19.6)	6.7 (2.9-23.0)	0.909	10.3 (2.9-26.0)	7.3 (4.1-19.0)	0.163
FFMI	17.6±2.5	18±2.2	0.273	19.2±2.7	17.0±2.8	<0.01*
Impedance 50	538 (404-1042)	522 (386-734)	0.177	506 (384-560)	510 (386-711)	0.852
Resistance 50	534 (402-903)	514 (385-720)	0.195	503 (383-559)	523 (388-1899)	0.175
Reactance 50	58 (29-678)	41.6 (13-498)	0.059	37.8 (16-678)	33.1 (13-675)	0.340
Phase Angle	5.4 (3.2-30)	4.5 (2-17)	0.234	4.4 (1.8-7.4)	3.7 (1.8-37)	0.259
Grip strength	25.8±9.7	25.6±9.5	0.802	24.4±9.4	17.2±6.2	0.029*
Walking speed	0.8±0.3	0.8±0.4	0.933	0.9±0.1	0.6±0.3	0.004*
Muscle mass	8.7±1.6	9±1.6	0.164	9.4±1.1	7.8±1.9	0.017*

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, BMR/BW: Basal metabolic rate/body weight, EAR: Average caloric requirement, ECW: Extracellular body fluid, ICW: Intracellular body fluid, BMI: Body-mass index, BFMI: Fat mass index, FFMI: Fat-free mass index

In patients with the adenocarcinoma subtype, there was a significant decrease in mean handgrip strength and mean walking speed and an increase in the sarcopenia score after medical treatment. Patients with the SSC subtype had a significant decrease in mean walking speed and median phase angel score after medical treatment. In patients with the NOS subtype, there was a significant increase in vitamin D levels and a significant decrease in mean urea value after treatment. No significant change was observed in other measurements (**Supplementary Table 2**).

In patients with stage 3 at baseline, there were significant decreases in mean waist and hip circumference, mean fat mass, and mean fat mass index; increases in mean total body fluid and mean basal metabolic rate/body weight (BMR/BW) ratio; and no significant change in sarcopenia score after treatment. In patients with stage 4 NSCLC, an increase in sarcopenia score was observed after treatment, while a significant decrease was observed in walking speed, albumin level, platelet count, and ECW (%) (**Table 4**). Thrombocytopenia (platelet level below 150×109) was detected in 25% of patients with stage 4 NSCLC after treatment (**Supplementary Table 3**).

Patients who received platinum-based therapy at baseline showed a significant increase in sarcopenia score after treatment, while hip circumference, handgrip strength, walking speed, and platelet count decreased significantly (**Supplementary Table 4**). In patients receiving immunotherapy, no significant change was observed after treatment. Thrombocytopenia was detected in 25% of patients receiving platinum-based therapy.

A significant increase in sarcopenia score was observed in patients whose vitamin D level decreased after treatment, while a significant decrease was observed in muscle mass,

Supplementary Table 2. Symptoms associated with the type of disease

Variables		Findings	p
Adenocarcinoma			
Grip strength, kg	Pre-treatment	20.4±7.4	0.044 *
	Post-treatment	17.7±6.5	
Walking speed, m/s	Pre-treatment	0.7±0.3	0.043*
	Post-treatment	0.6±0.4	
Sarcopenia score	Pre-treatment	1 (0-3)	0.026 *
	Post-treatment	2 (0-3)	
SSC			
Walking speed, m/s	Pre-treatment	0.9±0.1	0.049*
	Post-treatment	0.7±0.3	
Sarcopenia score	Pre-treatment	0 (0-3)	0.301
	Post-treatment	1 (0-3)	
Fat mass, %	Pre-treatment	28.5±5.5	0.029
	Post-treatment	25.5±3.9	
Phase Angle	Pre-treatment	5.0 (3-8.7)	0.050*
	Post-treatment	4.4 (1.8-5.7)	
NOS			
Urea, mg/dl	Pre-treatment	40 (21-60)	0.043*
	Post-treatment	31 (10-43)	
Vitamin D, ng/dl	Pre-treatment	19 (15-25)	0.050*
	Post-treatment	30 (15-40)	
Sarcopenia score	Pre-treatment	0 (0-2)	0.999
	Post-treatment	0 (0-2)	

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. SCC: Squamous cell carcinoma, NOS: Non-small cell lung cancer unclassified type

Supplementary Table 3. Findings associated with the stage of the disease

Variables		Findings	p
Phase 3			
Waist circumference (cm)	Pre-treatment	101.9±13.5	0.046*
	Post-treatment	99.9±14.2	
Hip circumference (cm)	Pre-treatment	105.1±11	0.027*
	Post-treatment	103.5±10.8	
Sarcopenia score	Pre-treatment	0 (0-2)	0.194
	Post-treatment	0.5 (0-3)	
Fat mass, %	Pre-treatment	31.6±9.7	0.012*
	Post-treatment	27.9±7.5	
Fat mass, kg	Pre-treatment	21 (11-62)	0.013*
	Post-treatment	17 (8.3-46)	
Total body fluid, %	Pre-treatment	54.7±10.9	0.030*
	Post-treatment	58.9±9.0	
ECW, %	Pre-treatment	23.5±4.2	0.017*
	Post-treatment	25.6±3.4	
Third cavity fluid	Pre-treatment	0.8 [(-3.8)-2.4]	0.023*
	Post-treatment	1.0 [(-2.0)-3.8]	
BMR/BW ratio	Pre-treatment	20.7±3.1	0.007*
	Post-treatment	21.9±2.4	
BFMI	Pre-treatment	7.2 (4.0-25.8)	0.013*
	Post-treatment	6.2 (2.9-19.0)	
Phase 4			
Platelets	Pre-treatment	241 (145-457)	0.020*
	Post-treatment	188 (147-366)	
Albumin	Pre-treatment	3.8±0.5	0.038*
	Post-treatment	4.1±0.6	
Walking speed	Pre-treatment	0.8±0.3	0.009*
	Post-treatment	0.6±0.4	
Sarcopenia score	Pre-treatment	1 (0-3)	0.048*
	Post-treatment	1.5 (0-3)	
ECW, %	Pre-treatment	22.5±4.1	0.019*
	Post-treatment	21.3±5.2	
ECW, kg	Pre-treatment	17.4±3.3	0.049*
	Post-treatment	15.9±2.6	

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, BMR/BW: Basal metabolic rate/body weight ratio, ECW: Extracellular body fluid, BFMI: Fat mass index

Supplementary Table 4. Findings related to the treatment regimen

Variables		Findings	p
Platinum-based chemotherapy			
Hip circumference, cm	Pre-treatment	107.1±11.0	0.046*
	Post-treatment	105.0±11.5	
Platelets, x10^9/L	Pre-treatment	275 (145-575)	0.007*
	Post-treatment	217 (147-491)	
Grip strength, kg	Pre-treatment	25.2±10.3	0.052
	Post-treatment	22.0±9.0	
Walking speed, m/s	Pre-treatment	0.8±0.2	0.029*
	Post-treatment	0.7±0.3	
Sarcopenia score	Pre-treatment	0 (0-3)	0.046*
	Post-treatment	1 (0-3)	

Data are shown as mean±standard deviation and median (IQR). *p<0.05 indicates statistical significance

walking speed, the patient's performance level, and saturation measurement. Significant differences were also found in anthropometric findings (**Supplementary Table 5**). In patients who were found to have progression on thoracic tomography after medical treatment, significant differences were found in anthropometric measurements, but a significant decrease was observed in saturation measurements and walking speed, a worsening of performance status was detected, and an increase in the sarcopenia score was determined (**Table 6**).

DISCUSSION

Sarcopenia is defined as a loss in skeletal muscle mass, quality, and function associated with malnutrition, aging, a sedentary lifestyle, and chronic diseases, especially COPD and malignancies.[2] Sarcopenia in cancer patients is associated with malnutrition, lipolysis, inflammatory status, and vicious metabolic cycles. This relationship promotes the occurrence of cachexia, which is considered a major cause of mortality in advanced cancer patients. Cachexia is an exhaustion syndrome that affects approximately 50% of patients with lung cancer, occurring even in the presence of adequate caloric intake.[11,12] Therefore, the development of therapeutic strategies aimed at reversing or at least counteracting the metabolic changes that promote cancer progression or recurrence and improving quality of life is important for the early prevention of tissue loss.[13]

Skeletal muscle loss in NSCLC has been shown to negatively affect treatment outcomes.[6] In our study, approximately

Supplementary Table 5. Associated findings in patients with decreased vitamin D levels after treatment

Variables		Findings	p
Weight (kg)	Pre-treatment	76.6±18.5	0.019*
	Post-treatment	69.5±14.6	
Saturation	Pre-treatment	93.1±2.9	0.041*
	Post-treatment	90.1±5.2	
ECOG PS	Pre-treatment	1 (0-1)	0.023 *
	Post-treatment	1 (0-4)	
Sedimentation, mm/s	Pre-treatment	43 (14-86)	0.029*
	Post-treatment	75 (10-104)	
Grip strength, kg	Pre-treatment	23.0±9.2	0.197
	Post-treatment	18.7±9.8	
Walking speed, m/s	Pre-treatment	0.9±0.2	0.003*
	Post-treatment	0.6±0.3	
Muscle mass, kg	Pre-treatment	9.6±1.3	0.014*
	Post-treatment	8.5±1.6	
Sarcopenia score	Pre-treatment	0 (0-1)	0.011*
	Post-treatment	2 (0-3)	
Fat-free weight, kg	Pre-treatment	52.6±10.7	0.002*
	Post-treatment	48.0±11.7	
Total body weight, kg	Pre-treatment	76.6±18.5	0.019*
	Post-treatment	69.5±14.5	
Dry fat-free weight, kg	Pre-treatment	12.5 (0.8-17.8)	0.016*
	Post-treatment	7.9 (1.5-18.1)	
Total body fluid, kg	Pre-treatment	42.0±6.7	0.009*
	Post-treatment	39.1±7.3	
ECW, kg	Pre-treatment	18.1±2.8	0.032*
	Post-treatment	16.8±3.3	
ICW, kg	Pre-treatment	22.9±3.4	0.019*
	Post-treatment	21.5±3.4	
Body cell mass	Pre-treatment	33.4±5.9	0.010*
	Post-treatment	30.7±4.9	
BMR	Pre-treatment	1584.4±261.1	0.002*
	Post-treatment	1471.4±281.7	
EAR	Pre-treatment	2344.5±398.4	0.010*
	Post-treatment	2139.6±416.9	
BMI	Pre-treatment	27.3±5.4	0.014*
	Post-treatment	24.8±4.2	
FFMI	Pre-treatment	18.7±2.6	0.002*
	Post-treatment	17.0±2.9	
Resistance 50	Pre-treatment	519 (383-586)	0.050*
	Post-treatment	523 (388-710)	

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, EAR: Estimated average calorie requirement, ECW: Extracellular body fluid, ICW: Intracellular body fluid, BMI: Body-mass index, FFMI: Fat-free mass index

Table 6. Associated findings in patients with progression after medical treatment

Variables		Findings	p
Weight, kg	Pre-treatment	86.6±22.0	0.024*
	Post-treatment	76.3±16.2	
Waist circumference, cm	Pre-treatment	104.0±17.1	0.039*
	Post-treatment	101.3±17.7	
Saturation, %	Pre-treatment	94.1±2.8	0.005*
	Post-treatment	89.8±5.4	
ECOG PS	Pre-treatment	1 (0-1)	0.014*
	Post-treatment	3 (0-4)	
Hemoglobin, gr/dl	Pre-treatment	11.9±1.7	0.030*
	Post-treatment	10.6±1.8	
Sedimentation, mm/s	Pre-treatment	39 (15-117)	0.043*
	Post-treatment	73 (10-109)	
Walking speed, m/s	Pre-treatment	0.9±0.2	0.016*
	Post-treatment	0.5±0.3	
Muscle mass, kg	Pre-treatment	9.7±1.0	0.050*
	Post-treatment	8.1±2.2	
Sarcopenia score	Pre-treatment	0 (0-1)	0.023*
	Post-treatment	1 (0-3)	
Fat-free weight, kg	Pre-treatment	58.7±10.6	0.010*
	Post-treatment	52.6±11.0	
Total body weight, kg	Pre-treatment	86.2±21.6	0.029*
	Post-treatment	76.3±16.2	
Total body fluid, kg	Pre-treatment	45.3±6.2	0.037*
	Post-treatment	40.9±7.0	
ECW, kg	Pre-treatment	20.5±3.4	0.032*
	Post-treatment	17.3±3.3	
BMR	Pre-treatment	1734±265.7	0.010*
	Post-treatment	1583.3±267.7	
EAR	Pre-treatment	2631.3±500.6	0.003*
	Post-treatment	2327.4±437.0	
BMI	Pre-treatment	28.6±6.5	0.028*
	Post-treatment	25.3±4.6	
FFMI	Pre-treatment	19.5±2.6	0.001*
	Post-treatment	17.4±2.9	

Data are shown as mean±standard deviation and median (min-max) *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, EAR: Average calorie requirement, ECW: Extracellular body fluid, BMI: Body-mass index, FFMI: Fat-free mass index

80% of the patients received platinum-based chemotherapy, and the remaining patients received immunochemotherapy. Furthermore, the treatment distribution was similar in patients with and without sarcopenia at baseline, but sarcopenia developed after treatment in a large portion of patients who did not have sarcopenia or who had possible sarcopenia. On the other hand, 70% of the patients with pre-treatment sarcopenia showed regression in CT findings after treatment, while this rate was 42% in patients without pre-treatment sarcopenia. The disease control rate defines the proportion of patients with a reduced or stable disease burden during the study period.[14] In our study, we found that patients with sarcopenia exhibited a worse disease control rate. In a previous study, the presence of sarcopenia before treatment and worsening sarcopenic status after starting treatments were shown to be associated with a decreased disease control rate.[7]

The relationship between sarcopenia and stage in NSCLC may also play an important role in response to treatment. In the literature, the relationship between cancer stage and sarcopenia presents conflicting results. Some previous studies did not report a significant association between sarcopenia and cancer stage.[15,16] A study by Kinsey et al.[17] reported that patients with stage 4 NSCLC were more likely to experience a decrease in lean weight levels during treatment. Thrombocytopenia was also observed in 25% of patients with stage 4 NSCLC, which constituted the majority of our study,

while no significant difference was found in post-treatment platelet levels in stage 3 patients. However, a 0.5 increase in sarcopenia scores was observed in both stages. However, the sarcopenia score tended to be higher, and ECW levels significantly decreased in stage 4 patients both before and after treatment.

Weight loss has been shown to be a negative prognostic factor in patients with lung cancer.[18] While weight and BMI levels were significantly lower in patients with sarcopenia at baseline, there was no significant change in weight or BMI levels in these patients after treatment. On the other hand, patients without sarcopenia had higher weight and BMI levels at baseline, whereas a significant decrease in weight and BMI levels was observed after treatment. Although there was no post-treatment death in these patients, progression was detected on a post-treatment CT scan in 42% of them. Therefore, a loss in weight and BMI levels may lead to a worsening prognosis. In patients whose sarcopenia score increased after treatment, weight and BMI levels decreased, saturation levels decreased, and the ECOG performance score increased, while handshake strength, walking speed, and muscle mass decreased. The decrease in muscle mass is driven by a variable combination of reduced caloric/protein intake, metabolic changes, and inflammation.[19] This was consistent with decreased levels of LBM, BCM, and FFMI. A reduced lean mass index has been shown to be an independent predictor of reduced quality of life and mortality.[20,21] It has also been reported that low FFMI is more common in patients at risk of malnutrition and in patients with high levels of inflammatory biomarkers.[16] Among patients with weight loss, a higher incidence of mortality has been reported in those with low FFMI compared to those with a normal lean mass index.[18] A consequence of low lean mass may result in a low volume of distribution of cytotoxic chemotherapy drugs. In a previous study, low lean body weight was shown to be a significant predictor of toxicity in patients administered 5-FU using the dosing rule per unit of body surface area.[22]

It has been suggested that vitamin D deficiency may play an important role in the development of sarcopenia during chemotherapy, targeted therapy, and immunotherapy.[23] Increased levels of proinflammatory and anti-inflammatory cytokines (such as TNF-α, IFN-γ, and IL-6) due to vitamin D deficiency may result in increased muscle catabolism and decreased muscle protein synthesis.[24] In our study, no significant correlation was observed between pre-treatment sarcopenia and vitamin D levels. However, an increase in post-treatment vitamin D levels was observed in patients whose sarcopenia score did not change after treatment, while a decrease in post-treatment vitamin D levels was observed in patients whose sarcopenia score increased after treatment. Also, in patients whose vitamin D levels dropped after treatment, their saturation percentage and ECOG performance score got worse. There was also more inflammation and lower BMI measurements like walking speed, muscle mass, body cell mass, BMR, and lean mass index. These variables did not differ significantly in patients with unchanged or increased vitamin D levels after treatment compared to pretreatment. All these findings support the idea that decreased vitamin D levels, especially after treatment, increase the risk of sarcopenia, in accordance with the literature.

Limitations

This study has some important limitations. First, although this study had a prospective design, it was single-centered and had a small sample size. The small sample size may affect the statistical significance of differences in subgroup analyses. However, the large sample size could partially compensate for this limitation. Second, CT is considered the gold standard for measuring body composition, but we did not assess body composition by CT in our study. However, BIA measurement is a feasible, non-invasive, low-cost measurement and is widely used in clinical research settings. Finally, the limited number of patients receiving immunotherapy may have limited the significance of changes in BIA parameters.

CONCLUSION

Approximately half of NSCLC patients have sarcopenia before treatment, and this rate increases after treatment. In addition, it was observed that the risk of sarcopenia increased after treatment in patients without sarcopenia before treatment, and the severity of sarcopenia increased in patients with sarcopenia. Sarcopenia was found to be associated with body weight, BMI, waist circumference, and hip circumference. Therefore, anthropometric measurements and sarcopenia findings should be regularly screened in NSCLC patients before and after treatment.

Platinum-based chemotherapy may cause significant differences in the BIA parameters associated with sarcopenia. In addition, vitamin D deficiency may play an important role in the development of sarcopenia. Although a decrease in vitamin D levels is expected in patients with advanced NSCLC, vitamin D replacement may both reduce the risk of sarcopenia and improve the prognosis. Therefore, control of vitamin D levels may be important in the follow-up of NSCLC patients. The findings of this study will guide future research in the prevention and treatment of sarcopenia in patients suffering from NSCLC.

ETHICAL DECLARATIONS

Ethics Committee Approval

The protocol of the study was approved by the Kırıkkale University Clinical Research Ethics Committee (Date: 13.10.2020, Decision No: 09/01).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Case Report

DOI: 10.51271/JCHOR-0060

Familial hemophagocytic lymphohistiocytosis case in adult age: case report

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Cite this article: Fidan K, Çilek HG, Çelik S, et al. Familial hemophagocytic lymphohistiocytosis case in adult age: case report. *J Curr Hematol Oncol Res.* 2025;3(2):42-45.

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Received: 30/09/2024 ◆ **Accepted**: 19/11/2024 ◆ **Published**: 08/05/2025

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an immune disorder with high mortality due to uncontrolled activation of T lymphocytes and macrophages and excessive proliferation of inflammatory cytokines. A 37-year-old female patient diagnosed with primary HLH is presented here. The patient was hospitalized with complaints of fever, weakness, and joint pain. The patient was pancytopenic, had high ferritin and low fibrinogen. She had hepatosplenomegaly. The bone marrow biopsy pathology result was consistent with hemophagocytosis. The patient's NK cytotoxicity was low. As a result of the genetic whole exon sequencing performed upon the presence of a family history; PRF1/NM-001083116/Ezxone 3, C.560C> G p (Pro187Arg) came as homozygous. HLH 2004 protocol was started with the diagnosis of familial hemophagocytic syndrome. Allogeneic bone marrow transplant was planned for the patient. Pulse steroid was initiated and plasma exchange was performed due to diffuse alveolar hemorrhage in thoracic tomography performed upon the development of dyspnea, tachypnea and tachycardia at the 7th week of the treatment. The patient died at the 8th week of treatment. In adult patients, primary hemophagocytic syndrome should be considered in differential diagnosis, treatment should be initiated after diagnosis and bone marrow transplantation should be performed as soon as possible.

Keywords: Familial hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, hemophagocytic lymphohistiocytosis

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by cytopenia and tissue infiltration due to excessive proliferation of inflammatory cytokines. It is an immune disorder resulting from uncontrolled activation of T lymphocytes and macrophages. Its characteristic clinical features are fever, pancytopenia, hepatosplenomegaly (HSM), and hemophagocytosis in bone marrow, liver, spleen, and lymph tissue. It is of two types as primary and secondary. Familial hemophagocytic lymphohistiocytosis (FHL) is also called primary and shows autosomal recessive inheritance. Secondary HLH is caused by infection, malignancy, collagen tissue diseases, tissue damage, metabolites and immunosuppression.[1]

A 37-year-old female patient who applied to our clinic with the complaints of fever, fatigue, and joint pain and was diagnosed with primary HLH with pancytopenia, HSM, lymphadenopathy (LAP), hyperferritinemia, hypertriglyceridemia, and hypofibronogenemia, is presented here.

CASE

The 37-year-old female patient was admitted to our hospital with complaints of fever, fatigue, and joint pain. Steroid treatment was started with the diagnosis of sarcoidosis by the pulmonology clinic about 1.5 years ago. The patient, who showed a stable course while under steroid treatment, discontinued her steroid treatment byherself about 1.5-2 months ago and applied to our hospital when her fever, weakness, and joint pain persisted. In laboratory tests the results were as follows; hemoglobin: 6.8 g/dl, leucocyte:1.06x10^3/µL, platelet:8x10^3/µL, neutrophil:0.73x10^3/µL, lymphocyte:0.18x10^3/µL, fibrinogen:160.18 mg/dl, AST: 55 U/L, ALT: 118 U/L, lactate dehydrogenase:302 U/L, total bilirubin: 1.72 mg/dl, direct bilirubin: 1.14 mg/dl, albumin:

2.76 g/dl, BUN: 15 mg/dl, serum creatinine: 0.73 mg/dl, CRP: 32.81 mg/L, triglyceride:405 mg/dl, ferritin:2820 mg/dl. She had HSM. The pathology result of the bone marrow aspiration/biopsy performed to determine the etiology of pancytopenia was found as normocellular bone marrow biopsy showing histiocytes with hemophocytic activity and increased lymphoid cells (**Figure 1**). Current findings were "compatible with hemophagocytosis, no concomitant lymphoproliferative disease and EBV infection". As a result of bone marrow flow cytometry, the CD4/CD8 ratio was 72/25 in CD3+ T cells. As a result of flow cytometry studied in terms of immune deficiency, although B cells were within the reference values, loss of CD3 expression was found in T cells. In B cells, the rate of cells capable of transitioning to the memory phase with CD19+IgM+ CD27+ character was <1%. The patient had low natural killer (NK) cytotoxicity (**Figure 2**). In the brain MRI taken for brain involvement, a 20x12 mm signal change in the central part of the pons that did not show pathological contrast enhancement was observed (central pontin myelinosis?). The patient underwent a control lumbar puncture. The result of cerebrospinal fluid pathology was found to be class 1. Genetic analyzes were performed for the whole sequence analysis in the patient with a positive FHL history, in terms of familial hemophagocytic syndrome. Whole exon sequencing resulted in homozygous PRF1/NM-000183116/EXON 3, C.560C>G p(Pro187Arg) (classified as likely pathogenic variant). Since the patient had clinical, laboratory, genetic, bone marrow pathology and family history, familial (primary) hemophagocytic syndrome was considered according to HLH 2009 criteria (**Table**). The patient was started on the HLH 2004 treatment protocol (**Figure 3**). Allogeneic hematopoietic stem cell transplantation (AHSCT) plan was made for the patient after the treatment. Due to tachypnea of shortness of breath at the 7th week of HLH 2004 protocol treatment, consolidation in both lungs and bilateral ground-glass images (vasculitis? alveolar hemorrhage?) were evaluated in the thorax tomography (**Figure 4**). The COVID-19 PCR sample taken from the patient came back negative. A 1 mg/kg/dose prednisolone treatment was started for the patient in terms of diffuse alveolar hemorrhage. In the control thorax tomography of the patient with persistent respiratory distress, the existing lesions showed progression (diffuse alveolar hemorrhage?) (**Figure 5**). As the general condition of the patient worsened and tachypnea and hypoxia deepened, she was followed up in the intensive care unit. A 1 gr methylprednisolone and 1 gr/kg intravenous immunoglobulin (IVIG) treatment was given, plasmapheresis was applied. She was intubated on the 2nd day of her hospitalization in the intensive care unit due to the deepening of respiratory failure. The patient died on the 8th day of her intensive care hospitalization.

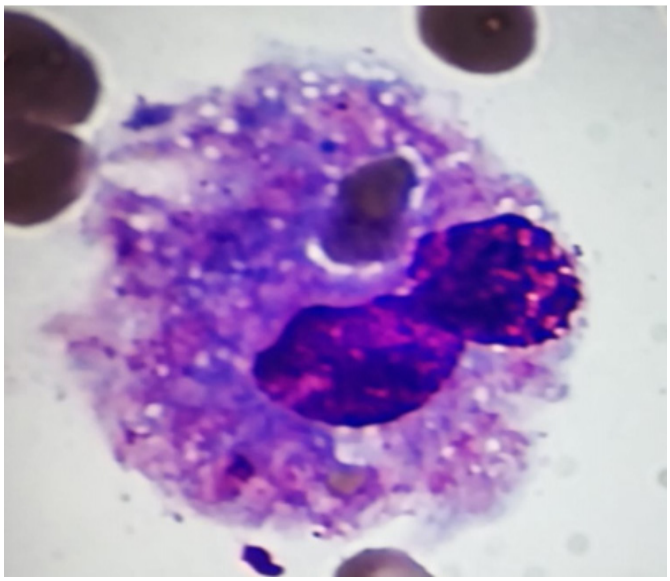

Figure 1. Bone marrow biopsy. Showing histiocytes with hemophocytic activity and increased lymphoid cells

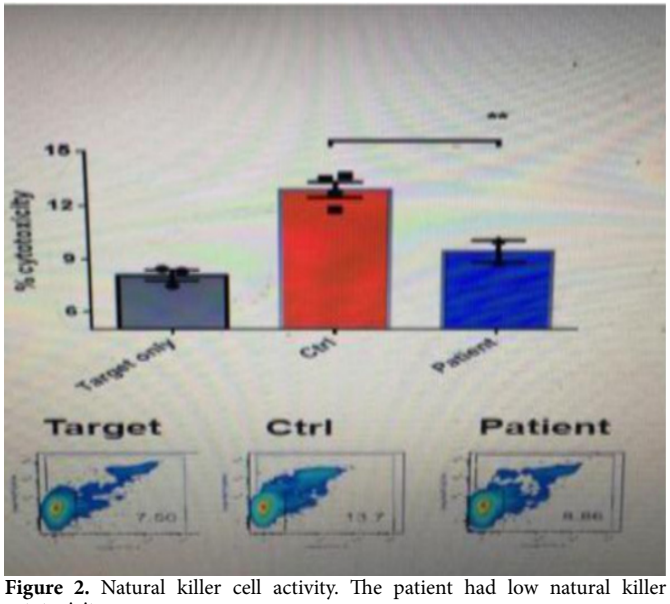

Figure 2. Natural killer cell activity. The patient had low natural killer cytotoxicity

Table. Diagnostic criteria for hemophagocytic histiocytosis (2009)

Molecular diagnosis compatible with hemophagocytic lymphohistiocytosis or x-linked a lenphoproliferative disease
Or at least 3 criteria from the 4 major criteria+at least 1 criterion from the minor criteria below
Major criteria:
1-Fever (over 38.5 °C for 7 days or more) 2-Splenomegaly 3-Bicytopenia(hemoglobin<9 g/dl, neutrophil<1x10^9/L, platelet<100x10^9/L 4-Hepatitis
Minor criteria:
1-Hemophagocytosis 2-Hyperferritinemia (ferritin>500 µg/L) 3-High sIL-2Ralpha 4-Low or undetectable natural killer cell activity 5-Other supporting findings -Hypertriglycerdaemia (fasting TG>265 mg/dl) -Hypofibrinogenemia (fibrinogen level <1.5 g/L -Hyponatremia

DISCUSSION

Being a rare and highly fatal disease, HLH is characterized by phagocytosis of shaped blood elements by macrophages as a result of abnormally increased T lymphocyte and macrophage activation and overproduction of inflammatory cytokines. Primary (familial) HLH demonstrates autosomal recessive inheritance. Despite the fact that the highly fatal

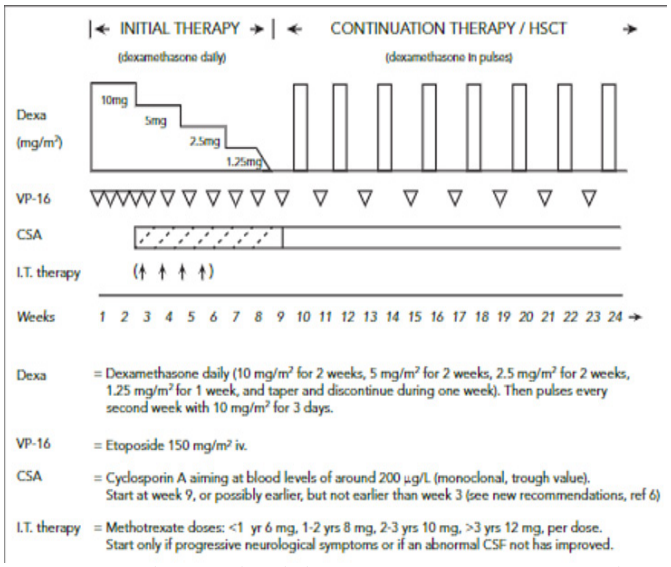

Figure 3. Hemophagocytic lymphohistiocytosis 2004 treatment protocole

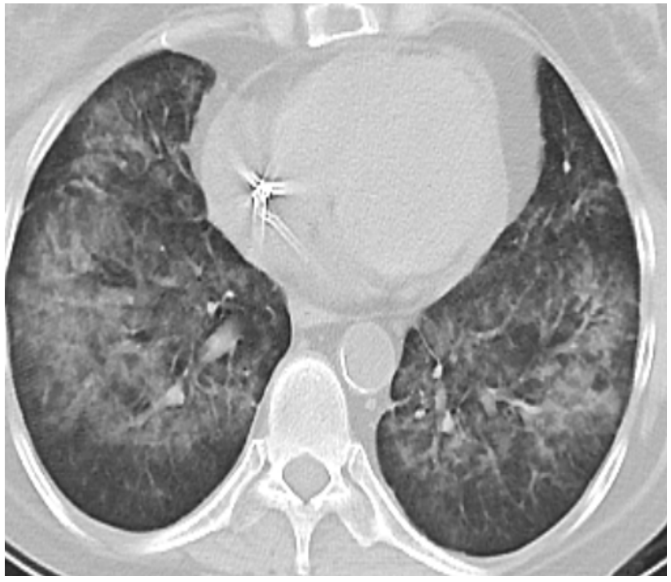

Figure 4. Thorax tomography (consolidation in both lungs and bilateral ground-glass images (vasculitis? alveolar hemorrhage?)

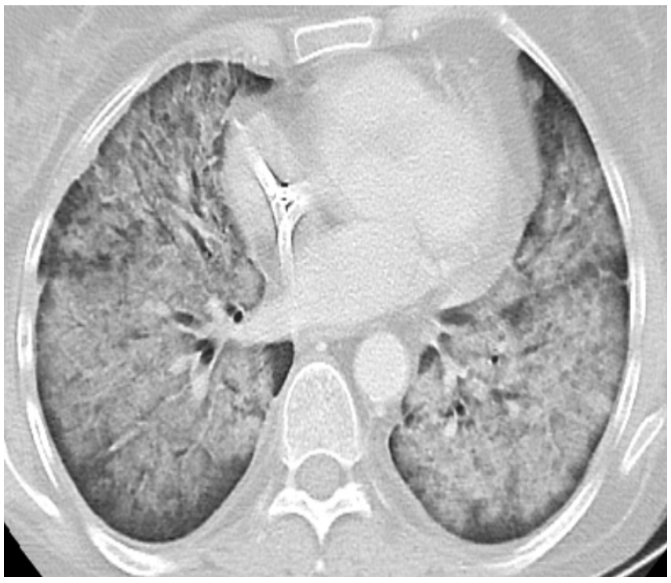

Figure 5. Control thorax tomography (The existing lesions showed progression (diffuse alveolar hemorrhage?)

disease can occur at any age, it most commonly affects infants, but it also occurs in children and adults of all ages. The oldest case was reported to be 65 years old.[1] NK cell and cytotoxic T lymphocyte functions, which are thought to be due to defects in the perforin/granzyme-mediated cytotoxic pathway, decrease in FHL.[2-4] There is usually a positive family history or an identified genetic cause for FHL. There are five different forms of FHL with different genetic mutations identified as chromosome 9q (FHL1), PRF1 (FHL2), UNC13D (MUNC13-4) (FHL3), STX11 (FHL4) and STXBP2 (MUNC18- 2) (FHL5).[5-9] First, Stepp et al.[8] confirmed the relationship between FHL2' and PRF1 in 1999, and it was reported that this mutation in the PRF1 gene causes cytokine storm, which is responsible for the pathogenesis of FHL2. Perforin plays a critical role in the cytolytic process. Impaired cytotoxicity is crucial in the pathophysiology of FHL2. Approximately seventy mutations of PRF1 have been observed in the exon 2 and exon 3 coding region. PRF1 mutation is found in 15-50% of patients with FHL.[10] PRF1 is located on chromosome 10q21-22. PRF1 mutations lead to decreased or lost expression of perforin proteins in cytotoxic T lymphocytes. The most common mutation, c.1122G> A, (which can cause 374 tryptophan codon stagnation) causes nonfunctional PRF proteins to be produced. As a result of perforin gene mutation, the activation of NK cells decreases, and as a result of T cell activation and expansion, excessive cytokine production occurs. Interferon gamma, IL-1, IL-6, TNF alpha and GM-CSF increase, macrophage activation and inflammatory reaction resulting from hemophagocytosis cause clinical findings. This mutation is found at a high rate in patients in Turkiye. In our patient, PRF1 exon 3 c.560C>G p(pro187arg) was found to be homozygous and this mutation has not been observed in any case before.

The diagnostic criteria for hemophagocytosis were determined by the "Histiocyte society" working group in 1994, revised in 2004, and presented again in 2009 (**Figure 3**). Accordingly, for diagnosis, at least three of the major diagnostic criteria (fever, splenomegaly, bicytopenia, hepatitis) and at least one of the minor diagnostic criteria (hemophagocytosis, hyperferritinemia, elevated sIL-2Rα for age, low or undetectable NK activity) are required. Hypertriglyceridemia and hypofibrinogenemia, which were included in the 2004 diagnostic criteria, were accepted as supportive criteria in the 2009 diagnostic criteria.[2,9] FHL is diagnosed in the presence of concomitant gene mutations; however, for the diagnosis of FHL, even in the absence of these mutations, a positive family history is sufficient.[3,9] Our case met the diagnostic criteria for hemophagocytic syndrome with clinical, laboratory, genetic and bone marrow findings. If left untreated, primary HLH is 100% fatal with an average life of two months. If the secondary form is not treated, it is 50% fatal. The HLH-2004 protocol, which consists of dexamethasone, etoposide, cyclosporine, and intrathecal methotrexate, is widely used in treatment.[2,9] The applied treatment protocol is continued for 52 weeks. In our case, the HLH-2004 protocol was started. Erythrocyte, thrombocyte, fresh frozen plasma and fibrinogen support were given. Broad spectrum multiple antibiotics, G-CSF and IVIG were given.

When a suitable donor for bone marrow transplantation is found in patients with FHL, the treatment is terminated.

Neurodevelopmental disorders and mortality are reduced with appropriate early treatment and timely bone marrow transplantation.[9] As for our patient, her sister had 10/10 HLA tissue compatibility. But the patient worsened at the 7th week of treatment and followed up in the intensive care unit with the diagnosis of diffuse pulmonary hemorrhage, died on the 8th day of the treatment.

CONCLUSION

For patients presenting with fever, pancytopenia, HSM, LAP, coagulopathy and a suspected positive family history, Primary Hemophagocytic Syndrome should be considered in the differential diagnosis and tests should be performed for it; and after diagnosis, bone marrow transplantation should be performed as soon as possible.

ETHICAL DECLARATIONS

Informed Consent
The patient signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Case Report

DOI: 10.51271/JCHOR-0061

Secondary cutaneous diffuse large B-cell lymphomas: bad scenario

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Cite this article: Demircioğlu S, Çiftçi MG, Baysal S, Merter M, Tekinalp A. Secondary cutaneous diffuse large B-cell lymphomas: bad scenario. *J Curr Hematol Oncol Res.* 2025;3(2):46-48.

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Received: 07/02/2025 ◆ **Accepted**: 23/02/2025 ◆ **Published**: 08/05/2025

ABSTRACT

Primary or secondary cutaneous involvement may occur in common diffuse large B-cell lymphomas. The secondary cutaneous involvement of diffuse large B-cell lymphoma is a condition that develops during the course of the disease and is associated with an aggressive course and shorter survival. The development of secondary cutaneous involvement shortly after the initial diagnosis of the primary disease predicts more aggressive clinical outcomes and is more likely to present with multiple skin lesions.

Keywords: Premature, sepsis, thrombocytopenia

INTRODUCTION

Primary cutaneous lymphomas (PCL) are composed of approximately 25% B-cell origin lymphomas. B-cell cutaneous lymphomas (B-PCL) are classified into three main categories: primary cutaneous follicle-center lymphoma (pcFCL), primary cutaneous diffuse large B-cell lymphoma, leg type (pcDLBCL-LT), and primary cutaneous marginal zone lymphoma (pcMZL).[1,2] While pcMZL and pcFCL are clinically indolent, pcDLBCL-LT is an aggressive lymphoma. Secondary cutaneous DLBCL (scDLBCL) is defined as lymphoma that demonstrates secondary spread to the skin after systemic involvement. Patients with both pcDLBCL and scDLBCL are older than those with pcFCL and pcMZL.[3] In scDLBCL, skin lesions emerge as a result of disease progression, leading to a significantly lower survival rate. Additionally, this may indicate an increase in tumor burden and/or the ability of the disease to spread through blood or lymphatic vessels.[4] We present this case to emphasize the appearance of secondary skin involvement and the poor prognosis associated with diffuse large B-cell lymphomas.

CASE

A 49-year-old male patient presented with complaints of cough, abdominal pain, sweating, and weight loss. Abdominal computed tomography (CT) revealed splenomegaly and a heterogeneous, lobulated mass in the left upper quadrant of the abdomen, approximately 20×17×16 cm in size, with central necrotic areas and heterogeneous contrast enhancement. A biopsy of the splenic mass confirmed the diagnosis of diffuse large B-cell lymphoma of the germinal center type (CD19 (+), C-MYC (+) BCL-6 (+), BCL2 (-)). The patient was staged as stage 2 bulky, with an International Prognostic Index (IPI) of high-intermediate risk and a high Central Nervous System International Prognostic Index (CNS IPI). The patient underwent 4 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy and 3 intrathecal methotrexate treatments. A follow-up positron emission tomography-computed tomography (PET-CT) scan showed stable disease. Due to an inadequate response to first-line therapy, salvage treatment with 3 cycles of rituximab plus gemcitabine and dexamethasone (R-GDP) was administered. However, progression was observed after 3 cycles of R-GDP. Subsequently, the patient received 2 cycles of rituximab plus dexamethasone, cytarabine, and cisplatin (R-DHAP) chemotherapy, but progression was again detected on PET-CT. On physical examination, erythematous, indurated, papular lesions were observed in a large area of the skin over the left abdominal quadrant (**Figure**). Punch biopsy of these lesions was performed, and the biopsy was evaluated as germinal center type diffuse large B-cell lymphoma. The patient was started on bendamustine, rituximab, and ibrutinib therapy. However, the patient passed away on the 3rd day of the new treatment, 9 months after the diagnosis.

DISCUSSION

The most common primary extranodal sites of diffuse large B-cell lymphoma (DLBCL) are the gastrointestinal system,

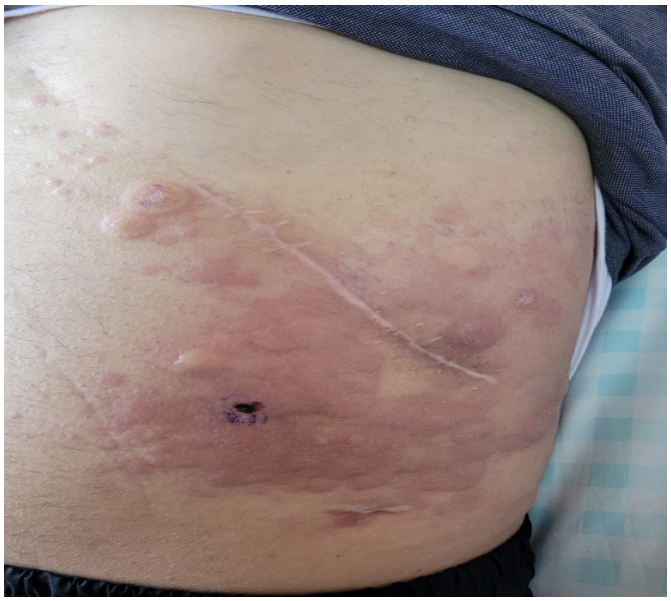

Figure. Erythematous, indurated, papular lesions spread over a large area on the left abdominal skin

head and neck, and skin/soft tissues. In a large cohort of 25.992 patients with DLBCL, primary skin/soft tissue involvement accounted for 3.3% of all cases.[5] Cutaneous involvement in DLBCL can be divided into two distinct subsets based on the primary site of involvement: primary cutaneous DLBCL, which initially presents in the skin, and DLBCL with secondary spread to the skin. While primary cutaneous DLBCL, leg type, has been extensively studied, there is limited data available regarding the clinical features or survival analysis of patients with secondary cutaneous DLBCL.[6]

A retrospective review identified that 44 out of 2.067 DLBCL cases (2.1%) had cutaneous involvement. Among these cases, 14 were diagnosed with pcDLBCL-LT and 30 with scDLBCL. Advanced stage, high (>2) IPI score, B symptoms, and elevated LDH levels were significantly more common in scDLBCL compared to pcDLBCL-LT. Patients with pcDLBCL-LT demonstrated significantly better survival outcomes than those with scDLBCL (5-year survival: pcDLBCL-LT: 65%, scDLBCL: 31%).[6]

In a study regarding the anatomical region of secondary cutaneous lymphoma involvement, it was found that extremities were more likely to be affected by T/NK SCL, while B-cell lineage SCL predominantly involved the trunk.[7] Another study has shown that pcDLBCL most commonly affects the legs (28.7%) and face (21.9%), while scDLBCL similarly affects the legs (32.3%), head (27.2%), and trunk (15.7%).[3] In our patient, trunk involvement was observed. The clinical presentation of SCL is highly heterogeneous, and the literature reports the presence of papules, plaques, tumors, and even erythroderma.[7-14] However, Lee and colleagues[7] observed that T/NK SCL is more likely to present as a maculopapular rash, while B-cell SCL is more likely to present with plaques or nodules. It has been described that some cases of angioimmunoblastic lymphoma (AIL) or otherwise unspecified peripheral T-cell lymphoma (PTNL) mimic reactive dermatoses or erythroderma.[14-16] HL is typically seen as reddish-brown papules, patches, or even nodules, sometimes accompanied by ulceration.[12,13,17]

In DLBCL, skin biopsies typically show infiltration by large and transformed B cells with prominent nucleoli and basophilic cytoplasm in the dermis and subcutaneous tissue; small lymphocytes (CD3+) may also be present in the samples. Immunohistochemistry reveals the general expression of all B-cell markers (CD19, CD20, CD22, CD79a), CD45, Bcl-2, Bcl-6, CD10, and MUM1, as well as possible variants such as the strongly expressed PAX-5 and CD30 in the polymorphic EBV+DLBCL variant, and weak CD20 and CD79a positivity in a background with mild inflammation.[13,18]

Cutaneous involvement associated with systemic DLBCL indicates disease progression and leads to worse outcomes compared to conventional DLBCL. The survival rates for secondary cutaneous DLBCL are lower than those for primary cases. The prognosis of secondary cutaneous DLBCL is related to the interval between the initial diagnosis and the development of skin lesions. The development of secondary cutaneous involvement shortly after the initial diagnosis of the primary disease predicts more aggressive clinical outcomes and is more likely to present with multiple skin lesions. In contrast, secondary cutaneous involvement that develops later after the initial diagnosis tends to have a less aggressive course.[19,20] It has been observed that other conventional prognostic factors such as stage, age, sex, and the IPI have a minimal effect on the prognosis of SCL.[7]

CONCLUSION

In conclusion, although secondary cutaneous involvement in DLBCL is rare, the presence of extensive skin lesions and skin involvement shortly after the initial diagnosis are associated with worse overall survival outcomes. There is no recommendation for treatment different from conventional DLBCL therapy. New therapeutic agents are needed to improve survival in the treatment of secondary cutaneous involvement.

ETHICAL DECLARATIONS

Informed Consent
The patient signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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