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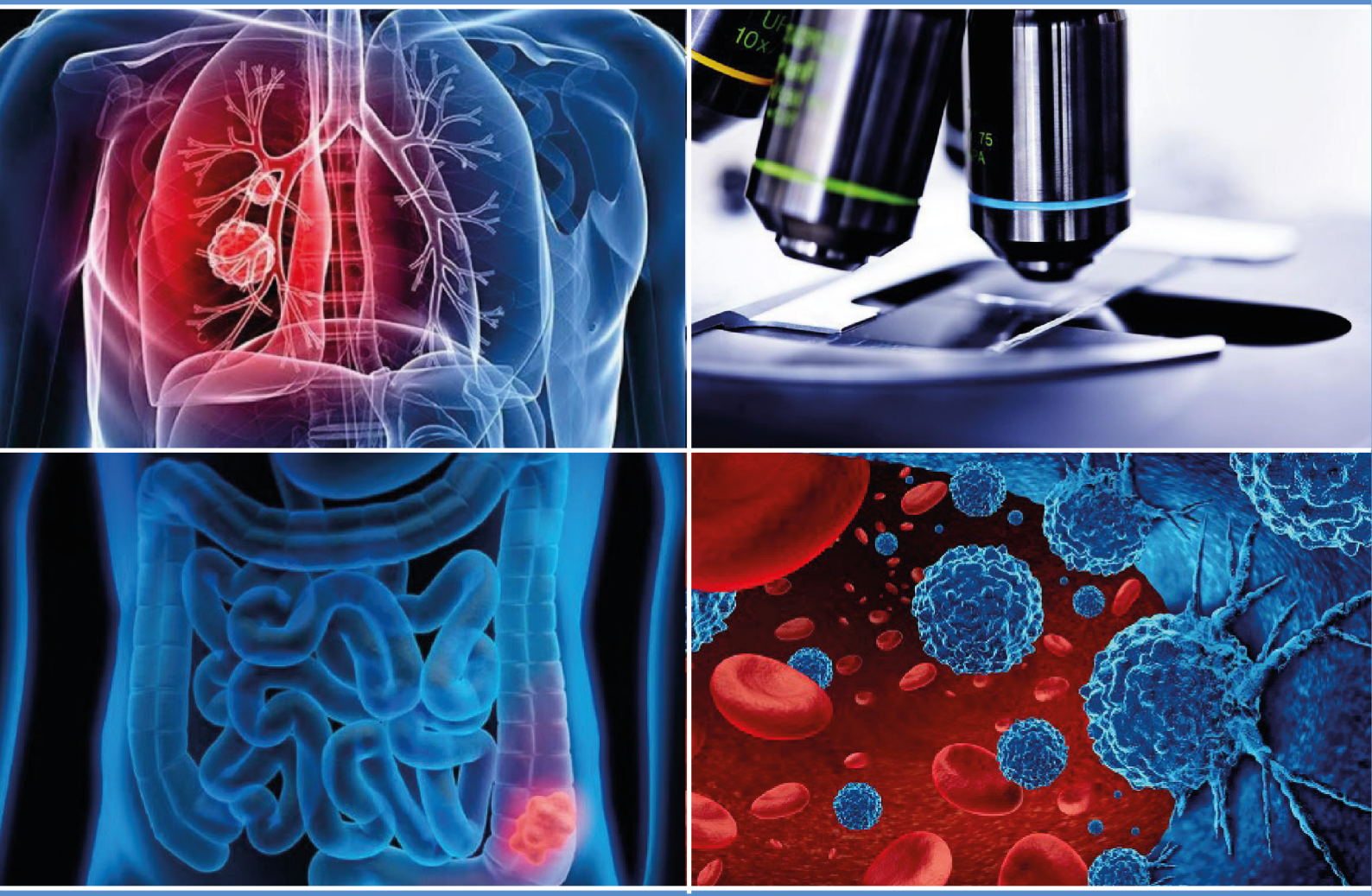

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EDITORIAL

Dear Colleagues,

I am delighted to say that our journal has successfully completed its third year of publication, continuing to grow with strength and academic rigor. In the past year, we have published a total of 12 original articles, seven case reports, two review articles, and one letter to the editor, all of which have contributed meaningfully to the expanding body of knowledge in hematology-oncology.

One of the most notable milestones of this year has been the internationalization of our journal. For the first time since our establishment, we have received and published submissions from authors based outside our country. This development represents an important step forward in enhancing the global visibility, diversity, and scientific impact of our publication. We believe this progress reflects the growing recognition of our journal within the international academic community. In addition, we are proud to announce that our journal has recently been indexed in ULAKBİM TR Dizin, marking another significant achievement in our ongoing efforts to strengthen the scientific standing and accessibility of our publication.

Our editors, editorial board members, reviewers, publishing team, and, of course, our contributing authors all worked hard to make these successes possible. I also want to thank our readers and supporters from the bottom of my heart. Your continued interest and trust drive us to raise our standards even higher.

As we start the new year of publishing, we are still dedicated to improving the quality of our science and our editorial work. We want to grow our pool of international authors, have more citations, and get into more well-known indexing databases. We are sure that, with your continued support and helpful contributions, our journal will continue to have a bigger impact on academics.

Thank you for being a part of this journey and for helping us reach yet another important milestone. We look forward to your continued contributions and to publishing high-quality work that advances the field of hematology-oncology.

Best regards,

Assoc. Prof. Serhat ÇELİK, MD
Editor in Chief

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ORIGINAL ARTICLES

CASE REPORTS

Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0073

Are decreased serum Maresin 1 levels predictive of cholangiocarcinoma?

Salih Karatlı*[1], Özlem Gül[2], Üçler Kısa[3], Ercan Tekin[3], Bilal Ergül[2]

[1]Department of Medical Oncology, Ankara Etlik City Hospital, Ankara, Turkiye
[2]Department of Gastroenterology and Hepatology, Faculty of Medicine, Lokman Hekim University, Ankara, Turkiye
[3]Department of Medical Biochemistry, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkiye

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***Corresponding Author:** Salih Karatlı, karatlisalih@hotmail.com

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ABSTRACT

Aims: Cholangiocarcinoma (CC) is a rare form of adenocarcinoma originating from the epithelial cells of the biliary tract. Chronic inflammation is known to be a risk factor for this tumor. The present study aimed to investigate whether serum levels of Maresin 1 (MaR1) (a macrophage-derived anti-inflammatory lipid mediator) were associated with the presence of benign biliary disease (BBD) or CC.

Methods: The study was conducted with 104 participants, including 42 patients with CC, 32 patients with BBD, and 30 volunteers without any hepatobiliary pathology. Blood samples were taken from each participant, and serum MaR1 levels were measured with enzyme-linked immunosorbent assay kits.

Results: Serum MaR1 levels were significantly lower in the CC and BBD groups compared to controls ($p<0.001$, for both); however, there was no significant difference between the CC and BBD groups in terms of MaR1 level ($p>0.05$). The cancer antigen (CA) 19-9 and carcinoembryonic antigen (CEA) values of the CC group were found to be significantly higher than the BBD and control groups ($p<0.001$, for both). Although MaR1 was found to have diagnostic value in differentiating patients with CC or BBD from controls, it had no value in distinguishing CC from BBD; whereas CA19-9 and CEA had significant discriminatory power.

Conclusion: Decreased serum MaR1 level may predict inflammation in hepatobiliary pathologies such as CC and BBD; however, it cannot be used to discriminate CC from BBD, and classical cancer markers such as CA19-9 and CEA appear to retain superiority in this respect.

Keywords: Cholangiocarcinoma, benign biliary disease, Maresin 1

INTRODUCTION

Cholangiocarcinoma (CC) is an aggressive malignancy from any part of the biliary tract. It has become the second most frequent primary liver cancer in the last decades.[1] CC generally has a poor prognosis, with 5-year survival rates of 30–40% after surgical treatment.[2] Diseases that cause chronic biliary inflammation, such as *Clonorchis sinensis* infections or primary sclerosing cholangitis, are known to be predisposing factors and predict poor prognosis.[3] Inflammation is a necessary process for survival, but repetitive cycles of inflammatory insult or chronic inflammation may lead to tissue fibrosis and DNA mutations which are early steps for carcinogenesis. Various mediators play a role in the resolution of inflammation, and some of these specific mediators are called specialized pro-resolving mediators (SPMs). Decreased levels of such mediators are thought to give rise to unresolved and chronic inflammation, thereby triggering the formation of carcinogenesis with the increase of pro-inflammatory cytokines.[4] Furthermore, since tumorigenesis is closely related to chronic inflammatory processes, the antitumor activity of SPMs has become a focus of interest in recent studies.[5-7]

Maresin 1 (MaR1) is a macrophage-derived SPM synthesized from docosahexaenoic acid, a form of polyunsaturated fatty acid (PUFA), which exerts anti-inflammatory and cytoprotective effects by stimulating anti-inflammatory macrophages selectively and by inhibiting neutrophil infiltration, generation of reactive oxygen species and expression of inflammatory cytokines.[5,8,9] Previous studies indicate that maresins have a vital role in reversing carcinogenesis in the early stages, and other researchers have shown that tumor cells have decreased amounts of PUFA-related compounds including maresins.[10,11] Based on these data, we hypothesized that serum levels of MaR1 may be associated with the risk of diseases demonstrating chronic inflammation, including cancer, and also may be used as a

marker for the early diagnosis of some types of cancer that are difficult to diagnose. To the best of our knowledge, there are currently no studies that have investigated the relationship between MaR1 and CC.

In the present study, we investigated the serum MaR1 levels in patients with CC, patients with benign biliary disease (BBD), and healthy volunteers to identify the role of MaR1 in the pathogenesis of CC and its potential to be used as a marker for CC diagnosis.

METHODS

Ethics

Study participation was approved by the Clinical Researches Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 24.04.2021, Decision No: 05/05). All procedures were conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

Study Design and Population

This study was conducted with 42 patients with CC and 32 patients with BBD who applied to the Gastroenterology Outpatient Clinic of Kırıkkale University Faculty of Medicine. The BBD group included patients with choledocholithiasis, benign biliary stricture, gallbladder stone, and Mirizzi syndrome, and no cases with acute inflammatory conditions such as acute cholangitis were present. This minimizes the likelihood of acute inflammation acting as a confounding factor on MaR1 levels. Also, 30 healthy volunteers who were admitted to internal medicine outpatient clinics for routine controls between May and December 2021 were included in the study. The study was observational and prospective in design and was not registered as a clinical trial. Patients younger than 18 years of age, those with any systemic or metabolic disease (diabetes mellitus, chronic renal disease, collagen tissue disease, etc.), other malignancies, patients under chronic immunosuppressive or steroid treatment, those with chronic inflammatory diseases or a history of organ transplantation, and subjects who refused participation were excluded from the study. The healthy volunteer group comprised individuals aged 18 years or older who did not have any acute or chronic diseases.

Serum levels of MaR1 and other laboratory outcomes were evaluated comparatively between the two study groups (42 patients with CC and 32 patients with BBD) and one control group (30 healthy volunteers).

Laboratory Analysis

After at least 12 hours of fasting, 2 ml venous blood samples were drawn from all participants. Serum samples were separated by centrifugation at 5000 rpm for 5 minutes and were transferred to sterile Eppendorf tubes and stored in a deep freezer at -80°C.

C-reactive protein (CRP), aspartate transaminase, alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), fasting plasma glucose, total bilirubin, albumin, and creatinine were studied using Roche Cobas® c501 brand device with original Roche diagnostic kits.[12] Hemogram parameters (hemoglobin, white blood cell, platelet, neutrophil, lymphocyte, etc.) were studied by flow cytometric impedance method in an automatic complete blood count device (Mindray BC 6800, Shenzhen, China). Cancer antigen (CA) 19-9 and carcinoembryonic antigen (CEA) levels were studied by chemiluminescence using Cobas® e601 brand device. Serum Maresin 1 levels were measured using a Human MaR1 enzyme-linked immunosorbent assay (ELISA) kit (Sunred Biotechnology Company, Shanghai, China) in accordance with the manufacturer's instructions. The optical density at 450 nm was quantified spectrophotometrically with a CLARIOstar PLUS device (BMG Labtech, Germany). Test results were expressed in pg/ml. The measurement range of the kit was 7.5–2000 pg/ml, with a sensitivity of 7.247 pg/ml. The intra-assay coefficient of variation (CV) was <10%, and the inter-assay CV was <12% as reported by the manufacturer.

Statistical Analysis

The IBM SPSS 23.0 package program (IBM Corp., Armonk, NY) was used for all analyses, and a significance threshold of 0.05 (p-value) was set. The normality of data distribution was assessed using the Shapiro–Wilk test. Depending on the distribution pattern, parametric or non-parametric tests were applied. Descriptive statistics were presented as frequency (n) and percentage (%) for categorical variables, and, for normally distributed continuous variables, descriptive data were given with mean±standard deviation (SD) values, while median (min-max) values were used for continuous variables without normal distribution. Categorical variable distributions were compared with Fisher's Exact or Pearson's Chi-square tests. The Kruskal-Wallis's test was used in the non-parametric comparison of the continuous variables between groups, and the Bonferroni correction was used as the post hoc test for significance. One-way ANOVA was used to compare three groups when the assumption of normal distribution was met, and for pairwise analyses, the Tukey HSD test was used when homogeneity of variance was met, while the Dunnett T3 test was used when it was not met. Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic performance of biochemical parameters and to determine cut-off values. The results were presented with the area under curve (AUC), cut-off points, sensitivity, and specificity values, with 95% confidence intervals (CIs).

Sample Size and Power Analysis

A priori sample size estimation was performed using G*Power version 3.1. Assuming an expected AUC of 0.75 and a significance level of $\alpha=0.05$, a minimum of 50 participants in total (CC and BBD groups combined) was required to achieve 80% statistical power. In our study, with 42 patients in the CC group and 32 in the BBD group (n=74 in total), the achieved power was calculated as 97.9%, indicating that the study was adequately powered.

RESULTS

The mean age of the participants was 71.48±11.14 years in the CC group, 64.81±13.45 years in the BBD group, and 61.47±8.74 years in the control group. The mean ages of the CC and BBD groups were significantly higher than the control group (p=0.001). The frequency of male patients in the CC and BBD groups (54.8% and 59.4%; respectively) was higher than the control group (26.7%) (p=0.019). When biochemical and hemogram parameters were evaluated relative to control

values, we found that fasting blood glucose, CRP, AST, ALT, ALP, GGT, and total bilirubin levels were significantly higher, while platelet and MaR1 levels were significantly lower in the CC and BBD groups (p<0.05 for all). In addition, in the CC group, ALT and hemoglobin levels were significantly lower, and ALP, CEA, and CA19-9 levels were significantly higher compared to patients in the BBD group (p<0.05 for all) (**Table 1**).

ROC analysis was performed to determine the discriminative performance of MaR1 to distinguish CC and BBD patients from controls, while MaR1, CEA, and CA19-9 values were assessed for their role in distinguishing CC patients from those with BBD (**Table 2**).

The discriminative performance of MaR1 values was found to be high in identifying CC patients from controls (AUC=0.880, 95% CI: 0.782-0.945; p<0.001) (**Figure 1a**) and BBD patients from controls (AUC=0.826, 95% CI: 0.708-0.910; p<0.001) (**Figure 1b**). For discrimination of CC from controls, the optimal cut-off value was ≤467.94, with 90.48% sensitivity and 73.33% specificity. For discrimination of BBD from controls, the optimal cut-off value was ≤415.19, with 75% sensitivity and 76,67 specificity. MaR1 values were not found to have significant value in distinguishing patients with CC from those with BBD (p>0.05) (**Figure 1c**).

The discriminative performance of CEA and CA19-9 values were found to be high in terms of distinguishing CC patients from those with BBD (AUC=0.807, 95% CI: 0.698-0.889; p<0.001 for CEA (**Figure 2a**), and AUC=0.922, 95% CI: 0.836-0.971; p<0.001 for CA19-9 (**Figure 2b**).

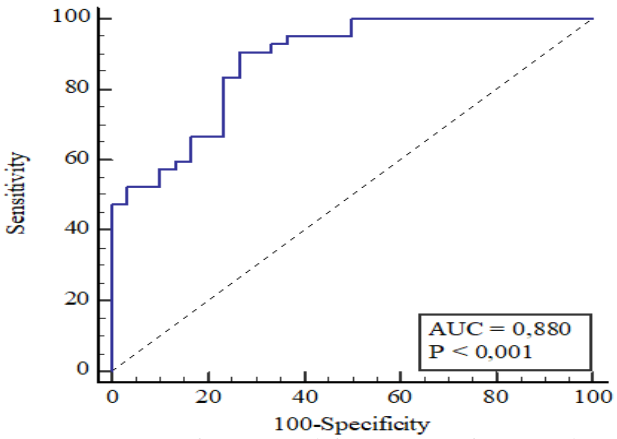

Figure 1a. ROC curve for MaR-1 in differentiating CC from control
ROC: Receiver operating characteristic, MaR1: Maresin 1, CC: Cholangiocarcinoma, AUC: Area under the curve

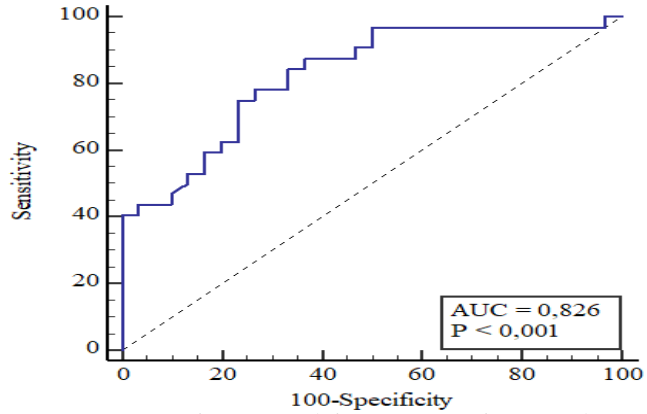

Figure 1b. ROC curve for MaR-1 in differentiating BBD from control
ROC: Receiver operating characteristic, BBD: Benign biliary disease, AUC: Area under the curve

Table 1. Demographic and clinical characteristics of patients according to study groups

	CC (n:42)	BBD (n:32)	Control (n:30)	p
FBG, mg/dl	119.5 (91-132) [a]	121 (104-158) [a]	98 (92-112) [b]	0.001
CRP, mg/L	36 (14-69) [a]	14.25 (3.95–59.05) [a]	4.06 (2.5-8) [b]	0.001
AST, IU/L	73.5 (34-130) [a]	108 (44.5–201.5) [a]	18 (15-22) [b]	0.001
ALT, IU/L	53 (30-135) [a]	122.5 (49.5–297.5) [b]	16 (13-26) [c]	0.001
ALP, IU/L	384 (203-610) [a]	227.5 (104-336) [b]	75.5 (55-93) [c]	0.001
GGT, IU/L	434.5 (157-738) [a]	257.5 (99.5-539) [a]	47 (26-65) [b]	0.001
HGB, g/dl	11.76±1.54 [a]	13.27±2.45 [b]	14.16±1.21 [b]	0.001
WBC, x10^9/L	8.25 (6.87-10.1)	7.95 (6.55–12.4)	7.56 (5.93–8.5)	0.257
Platelet, x10^9/L	236 (196-280) [a]	233.5 (181-282) [a]	270.5 (235-297) [b]	0.039
CEA, ng/ml	5 (2.57-15)	2 (1–3.38)	-	0.001
CA19-9, U/ml	230.65 (102-539)	10.3 (5.38–22.8)	-	0.001
T.bil, µmol/L	6 (1-12) [a]	2.6 (1.15–5.75) [a]	0.65 (0.51–0.9) [b]	0.001
MaR1, pg/ml	326.52 (243.02–423.88) [a]	343.24 (256.25–426.56) [a]	551.66 (437.48–746.53) [b]	0.001

Data are given as mean±standard deviation or median (min-max) for continuous variables according to the normality of distribution. [a,b,c]: Different exponential letters in the same row indicate statistically significant differences between groups. ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate transaminase, BBD: Benign biliary disease, CC: Cholangiocarcinoma, CEA: Carcinoembryonic antigen, CRP: C-reactive protein, FBG: Fasting blood glucose, GGT: Gama-glutamyl transferase, HGB: Hemoglobin, MaR1: Maresin 1, T.bil: Total bilirubin, WBC: White blood cell

Table 2. ROC analysis for MaR1, CEA and CA19-9

	AUC (95% CI)	p	Cut-off	Sensitivity	Specificity
MaR1 (CC/control)	0.880 (0.782-0.945)	<0.001	≤467.94	90.48%	73.33%
MaR1 (BBD/control)	0.826 (0.708-0.910)	<0.001	≤415.19	75.00%	76.67%
MaR1 (CC/BBD)	0.540 (0.420-0.657)	0.564	-	-	-
CEA (CC/BBD)	0.807 (0.698-0.889)	<0.001	>4.22	57.14%	93.75%
CA19-9 (CC/BBD)	0.922 (0.836-0.971)	<0.001	>80.20	76.19%	100.00%

ROC: Receiver operating characteristic, AUC: Area under the curve, BBD: Benign biliary disease, CA: Cancer antigen, CC: Cholangiocarcinoma, CEA: Carcinoembryonic antigen, MaR1: Maresin 1

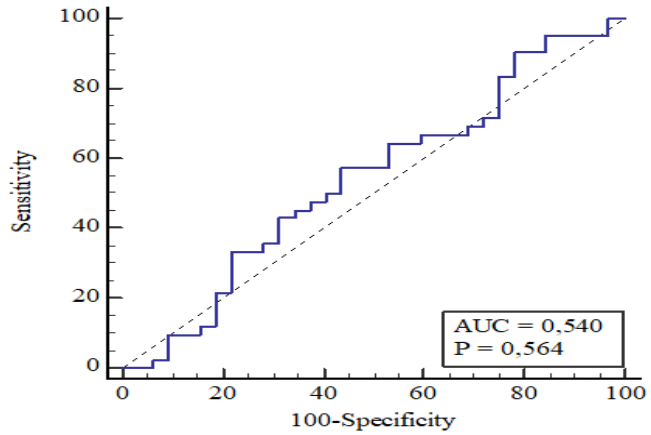

Figure 1c. ROC curve for MaR-1 in differentiating CC from BBD
ROC: Receiver operating characteristic, MaR1: Maresin 1, CC: Cholangiocarcinoma, AUC: Area under the curve, BBD: Benign biliary disease

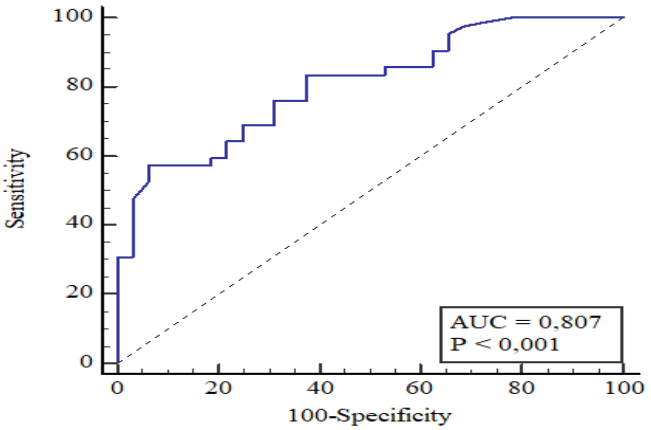

Figure 2a. ROC curve for CEA in differentiating CC from BBD
ROC: Receiver operating characteristic, CC: Cholangiocarcinoma, AUC: Area under the curve, BBD: Benign biliary disease, CEA: Carcinoembryonic antigen

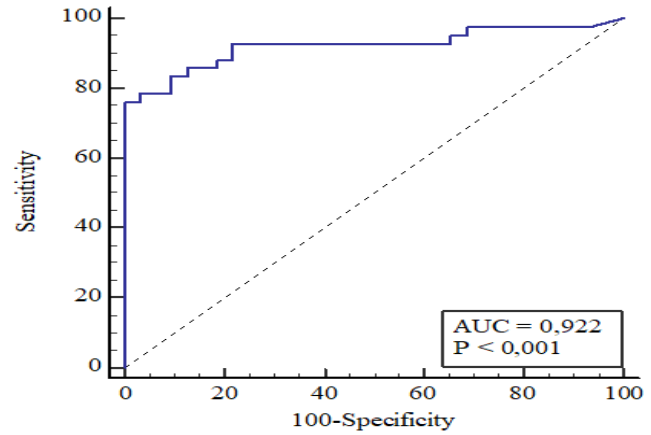

Figure 2b. ROC curve for CA19-9 in differentiating CC from BBD
ROC: Receiver operating characteristic, CC: Cholangiocarcinoma, AUC: Area under the curve, BBD: Benign biliary disease, CA: Cancer antigen

DISCUSSION

Although rare, CC is a malignancy with a poor prognosis partly because diagnosis is often delayed with current diagnostic methods. Definitive diagnosis is usually based on imaging techniques and tissue biopsy. Some tumor markers, especially CEA and CA19-9, have been used for tumor screening –especially in risk groups– and for the follow-up of the disease.[13] However these markers were shown to have variable sensitivity and specificity in different studies, and therefore, their usefulness for this purpose cannot always be generalized.[14] New sensitive and specific algorithms are needed to enable early diagnosis and to improve treatment success. In the present study, serum MaR1 levels in patients with CC and BBD were investigated for the first time, and levels were found to be significantly lower compared to healthy subjects. However, it was determined that CEA and CA19-9 levels were relatively better in the differential diagnosis of CC patients compared to MaR1–which does not appear to have the potential to distinguish CC from BBD.

It is known that prolonged or recurrent low-grade inflammation plays an important role in the pathophysiology of various malignancies and other diseases via mechanisms of oxidative stress, necrosis, fibrosis, and DNA damage, indicating the criticality of the balance between the development and resolution of inflammation which unanimously remains as a topic of interest.[15-21] As mentioned previously, endogen chemicals that contribute to a swift resolution of acute inflammation are called SPMs.[22] MaR1 is a member of the SPM family and has been suggested to inhibit proinflammatory cytokines, thereby limiting chronic inflammation and potentially preventing inflammation-induced proliferation of cancer cells. For instance, in a study conducted by Li et al.,[23] the effects of MaR1 on liver damage (induced by intraperitoneal carbon tetrachloride injection) were investigated in an experimental mice model. MaR1 was shown to alleviate liver damage, decrease inflammatory mediators, and increase the antioxidative mediators. In a similar study by Fang et al.,[24] serum MaR1 levels in patients with non-alcoholic fatty liver disease were found to be significantly lower than in healthy individuals. In another study, conducted with a mice model of ulcerative colitis (induced by dextran sulfate sodium), the disease activity index, macrophage infiltration, and oxidative enzyme activity were found to have decreased after MaR1 treatment.[25] Vatnick et al.[26] demonstrated that maresins inhibit the growth of primary breast cancer cells by stimulating the apoptotic effect of macrophages and increasing endogenous anti-inflammatory cytokines. Also, it has been reported that omega-3 PUFA treatment causes tumor regression by stimulating apoptosis in gastric cancer cells, which may show an underlying relationship with MaR1 since this mediator is synthesized from PUFAs.[27] Consistently, the study by Varol et al.[28] was the one that demonstrated the role of MaR1 alterations in the pathogenesis of chronic pancreatitis, further supporting the relevance of MaR1 in inflammation-driven diseases. Based on these data, we hypothesized that low serum MaR1 levels could serve as a marker for the early detection of CC. However, the findings of our study only partially supported this hypothesis. While serum MaR1 levels clearly distinguished CC patients from healthy individuals, they failed to differentiate CC patients from those with BBD. Although we excluded acute cholangitis and infectious conditions from the BBD group, non-infectious factors such as gallstone-related obstruction, bile stasis, and chronic mucosal irritation may have triggered persistent inflammatory responses in these patients. This underlying non-infectious inflammatory background likely contributed to the similarities observed between the CC and BBD groups. Therefore, our results suggest that serum MaR1 levels alone may be insufficient to discriminate between diseases that share overlapping chronic inflammation–driven pathological mechanisms.

In our study, some other related biochemical parameters were also examined, including AST, ALT, ALP, and GGT (which can mirror hepatobiliary damage), CRP and WBC (markers of inflammation), total bilirubin (associated with anabolic liver functions), CEA and CA19-9. The levels of many of these parameters were found to be significantly elevated in patients with CC compared to the other two groups. Similarly, previous studies have reported that these parameters increase to a level that has diagnostic value in CC patients. Gül et al.[29] compared CA19-9 levels in CC patients, BBD patients, and healthy participants, and showed significantly higher levels of the CA19-9 tumor marker in CC patients. Conversely, in another study, the CA19-9 and CEA levels were measured to be considerably elevated in patients with obstructive jaundice and hepatolithiasis; therefore, they concluded that the 'tumor marker' utility of these parameters was questionable in several conditions.[21] Although many different results have been presented in various studies, CEA and CA19-9 are reported to have sensitivity and specificity values around 70% and 90% for the identification of CC based on BBD.[30] In an earlier study by Ramage et al.,[31] an index score derived from serum CEA and CA19-9 levels was reported to detect CC development with an accuracy of 86% among a group of patients with BBD. We also found similar sensitivity and specificity for CEA and CA19-9 in the discrimination of CC from BBD. Therefore, taken together, these results further support our notion that MaR1 levels provide unsatisfactory results in this context.

Limitations

One of the main limitations of our study is that it was conducted in a single center with a relatively limited number of patients. In addition, homogeneity in terms of age and sex could not be achieved between the control and patient groups, which may have introduced potential confounding effects in the interpretation of MaR1 levels. The possible effects of age and sex on MaR1 levels were not specifically analyzed in our study, and this should be considered as a potential limitation. MaR1 measurements were performed at a single time point only, and therefore intra-individual variability of biomarker levels could not be assessed. Moreover, CEA and CA19-9 levels were not measured in the healthy control group due to ethical reasons, which precluded direct comparison with the patient groups. Finally, the potential additional diagnostic value of MaR1 in combination with CA19-9 or CEA was not evaluated. Furthermore, the statistical analyses were limited by the sample size, and therefore the generalizability of the findings may be restricted. These limitations should be taken into account when interpreting the results.

CONCLUSION

As a result, serum MaR1 levels were found to be significantly lower in the CC and BBD groups compared to the control group. MaR1 levels appear to be incapable of distinguishing between CC and BBD, possibly due to the considerable levels of inflammation in patients with BBD. On the other hand, classical cancer markers, CEA and CA19-9, were significantly elevated in the CC group and demonstrated reliability in distinguishing CC from BBD. Accordingly, MaR1 may be a marker to predict inflammation in CC and BBD; however, it does not appear to have a tumor marker value in the differential diagnosis for CC.

ETHICAL DECLARATIONS

Ethics Committee Approval

Study participation was approved by the Clinical Researches Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 24.04.2021, Decision No: 05/05).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: S.K., B.E., Ö.G.; Design: B.E., S.K.; Control: S.K., B.E., Ö.G.; Resources: S.K.; Ü.K., E.T.; Materials: S.K.; Ü.K., E.T.; Data Collection and/or Processing: S.K., B.E., E.T.; Analysis and/or Interpretation: B.E., Ü.K., Ö.G.; Literature Review: S.K., B.E., Ö.G.; Article Writing: S.K., B.E., Ü.K.; Critical review: S.K., B.E., Ö.G.

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Original Article

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Evaluation of the response and adverse effects of intravenous iron therapy in patients with iron deficiency anemia: a single-center experience

Gökhan Aydeniz[1], Ramazan Esen[2], Ali Doğan*[2]

[1]Department of Internal Medicine, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye
[2]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye

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***Corresponding Author:** Ali Doğan, dr.alidogan44@gmail.com

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ABSTRACT

Aims: The present study evaluates the treatment responses and adverse effect profile of intravenous (IV) iron (ferric carboxymaltose) therapy in patients diagnosed with iron deficiency anemia (IDA).

Methods: The medical records of 65 patients diagnosed with IDA and treated with IV iron therapy after presenting to various clinics in our center between 2014 and 2023 were retrospectively reviewed. Pre- and post-treatment hemoglobin (Hb), serum iron, total iron-binding capacity (TIBC), ferritin, and transferrin saturation levels were compared, treatment-related adverse effects were recorded, and improvements in symptoms were noted.

Results: The patients were aged 18–90 years, and 89.2% (n=58) were female. Significant improvements were observed in all laboratory parameters following IV iron therapy. The mean Hb increased from 9.8 g/dl before treatment to 12.7 g/dl after treatment ($p<0.001$); while the median serum ferritin increased from 4.6 µg/L before treatment to 231 µg/L after treatment, indicating a replenishment of iron stores ($p<0.001$). All patients experienced an improvement in clinical symptoms, while six (9.2%) developed an allergic reaction to the IV iron therapy.

Conclusion: The present study demonstrated that IV iron therapy rapidly and significantly increases Hb levels and replenishes iron stores, alleviates symptoms, and exhibits an acceptable safety profile in patients with IDA. The incidence of serious adverse effects from IV iron therapy is low, and it can thus be considered an effective treatment approach, particularly in patients who are unresponsive to or intolerant of oral iron therapy.

Keywords: Anemia, ferric carboxymaltose, ferritin, iron-deficiency

INTRODUCTION

According to the World Health Organization (WHO), anemia is defined as a Hb level below 13 g/dl in men, below 12 g/dl in nonpregnant women and below 11 g/dl in pregnant women aged ≥15 years.[1] Globally, approximately 30% of people are affected by anemia, and the underlying cause is iron deficiency anemia (IDA) in half of the cases.[2] Iron deficiency can lead to clinical problems even in the absence of anemia, including restless leg syndrome and fatigue.[3,4] Iron replacement therapy is recommended in symptomatic patients with low iron stores, regardless of the presence of anemia.[3,5]

Oral iron formulations are the first-line treatment for IDA. Oral iron therapy is readily accessible, inexpensive, and efficacious, but is often associated with gastrointestinal adverse effects, particularly at high doses. It has been reported in the literature that approximately 70% of patients receiving oral iron therapy exhibit poor treatment compliance due to such gastrointestinal adverse effects as nausea, constipation, and abdominal pain.[6,7] This may adversely affect treatment outcomes by leading many patients to discontinue oral iron therapy or to take inadequate doses. IV iron therapy can be considered an effective alternative for patients who are unresponsive to or cannot tolerate oral iron therapy.[8] Although anaphylaxis and fatal reactions have been reported with iron dextran in the past, the risk of serious allergic reactions with newer iron formulations is considerably low.[9] Another advantage of parenteral iron is that the total iron replacement dose can usually be administered in one or two infusions. IV Iron administration thus serves as a practical and effective solution in cases requiring rapid iron replacement or in which oral treatment is ineffective.[10]

The present study assesses treatment response and adverse effects in patients diagnosed with IDA who received IV iron therapy. Specifically, it evaluates the efficacy of this

therapeutic approach by analyzing the changes in Hb and iron parameters following IV iron administration. The study further assesses the safety of the treatment by determining the frequency of adverse effects.

METHODS

Ethics

The study was approved by the Non-interventional Clinical Researches Ethics Committee of Van Yüzüncü Yıl University (Date: 20.01.2023, Decision No: 2023/01-13). The study was conducted in accordance with the principles of the Declaration of Helsinki. The identities of the participants were kept confidential.

The medical records of patients diagnosed with IDA and treated with IV iron at Van Yüzüncü Yıl University Faculty of Medicine Hospital between January 2014 and December 2023 were analyzed retrospectively.

Data Collection

The demographic characteristics of the patients, existing comorbidities, presence of malignancy, and potential underlying etiological factors, such as gastrointestinal system pathologies, were retrieved from patient files and the hospital information system. Complete blood count (Hb, hematocrit) and iron panel parameters (serum iron, total iron-binding capacity (TIBC), ferritin, and transferrin saturation) measured prior to IV iron therapy were recorded as baseline values, and the same parameters were re-evaluated in laboratory tests during treatment follow-up. Additionally, patient follow-up notes were reviewed to identify any improvements in symptoms (e.g., fatigue, palpitations, exercise capacity) after treatment and any adverse effects that may have occurred during or after the infusion (e.g., allergic reaction, hypotension).

Study Inclusion Criteria

The study included patients aged 18 years and older who had been diagnosed with IDA according to WHO criteria and who had received intravenous iron therapy with ferric carboxymaltose. Patients with complete laboratory data on hemoglobin (Hb) and iron parameters before and after treatment were included in the evaluation.

Study Exclusion Criteria

Patients under 18 years of age, pregnant women, those with anemia causes other than iron deficiency, those with active infection or acute bleeding, those without sufficient clinical or laboratory data, and patients who did not consent to participate in the study were excluded from the study.

Statistical Analysis

The study data were analyzed using IBM SPSS Statistics, Version 28.0 (IBM Corp., 2011). Descriptive statistics for continuous variables were presented as mean±standard deviation for normally distributed date; and as median and minimum–maximum values for non-normally distributed data. Categorical data were summarized as numbers and percentages. The distribution of quantitative data was evaluated using the Kolmogorov-Smirnov test. Pre-treatment and post-treatment values were compared using a paired t-test for variables meeting the parametric test assumption, and with a Wilcoxon signed-rank test for non-normally distributed variables. Comparisons of two independent groups (e.g., by sex) were performed using either an Independent samples t-test or the Mann-Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. In all analyses, a p value of less than 0.05 was considered statistically significant.

RESULTS

Among the 65 patients included in the study, 58 were female (89.2%) and seven were male (10.8%). The median age of the female and male patient groups was 38 and 68 years, respectively. The laboratory and clinical parameters (e.g., symptoms, development of allergies) of the patients before and after treatment were compared. The clinical and demographic characteristics of the patients are presented in Table 1.

Table 1. Distribution of patients according to clinical characteristics and demographic features

Clinical parameters	n (%) or median (min-max)
Age (years)	
18-44	33 (50.8)
45-64	24 (36.9)
≥65	8 (12.3)
Sex	
Male	58 (89.2)
Female	7 (10.8)
Hemoglobin, g/dl	9.7 (5.8-16.1)
Ferritin, ng/ml	4.6 (1–198)
Serum iron, µg/dl	23 (9–150)
Total iron-binding capacity, µg/dl	358 (142–527)
Transferrin saturation, %	6.7 (2.6–77)
Intravenous iron dose	
500 mg	3 (4.6)
1000 mg	45 (69.2)
2000 mg	17 (26.2)
Development of allergy	
Yes	6 (9.2)
No	59 (90.8)
Malignancy	
Present	1 (1.5)
Absent	64 (98.5)
Abnormal radiological finding	
Present	13 (20)
Absent	52 (80)
Regression of symptoms	
Present	65 (100)
Absent	0 (0)

Min: Minimum, Max: Maximum

The hematological and biochemical profiles of the patients before starting IV iron therapy exhibited a typical profile for IDA. Following IV iron therapy, significant improvements were observed in the Hb levels and iron values of all patients (Table 2). An average increase of 2.9 g/dl in Hb levels was observed after treatment. Notably, patients with baseline ferritin levels below 5 ng/ml experienced a pronounced increase in ferritin values following treatment. A comparison of pre- and post-treatment Hb levels and iron parameters is presented in Table 2.

The total IV elemental iron dose administered to the majority of patients was 1000 mg in a single session, and the approximately one-quarter of the patients with a greater iron

Table 2. Comparison of hemoglobin and iron parameters before and after treatment

Laboratory parameters	Pre-treatment value (mean)	Post-treatment value (mean)	p-value
Hemoglobin, g/dl	9.7	12.9	<0.001
Serum iron, µg/dl	23	91	<0.001
Total iron-binding capacity, µg/dl	358	175	<0.001
Transferrin saturation, %	6.7	52.3	<0.001
Ferritin, ng/ml	4.6	231	<0.001

deficit in the study received total doses of 2000 mg of IV iron. Table 3 presents the relationship between the administered IV iron doses and the age and sex of the patients, as well as allergic reactions. In the assessment of adverse effects, it was found that six patients (9.2%) developed acute allergic reactions during IV iron infusion. When the etiology of iron deficiency was examined in the study, it was determined that the most common cause, as presented in Table 4, was menstrual bleeding in premenopausal women.

Table 3. Comparison of applied parenteral iron treatment doses

Clinical parameters	IV iron dose <2000 mg	IV iron dose ≤2000 mg	p-value
	n (%)	n (%)	
Age (years)			
18-44	20 (41.7)	13 (76.5)	0.048
45-64	21 (43.8)	3 (17.6)	
≥65	7 (14.6)	1 (5.9)	
Sex			
Female	43 (89.6)	15 (88.2)	1.000
Male	5 (10.4)	2 (11.8)	
Development of allergy			
Yes	5 (10.4)	1 (5.9)	1.000
No	43 (89.6)	16 (94.1)	
Malignancy			
Present	1 (2.1)	0 (0)	1.000
Absent	47 (97.9)	17 (100)	
Abnormal radiological finding			
Present	9 (18.8)	4 (23.5)	0.672
Absent	39 (81.2)	13 (76.5)	

Table 4. Distribution of the etiology of iron deficiency in patients

Etiology	n (%)	Sex
Premenopausal (menstrual bleeding)	42 (64.61)	Female
Postmenopausal (nutritional causes)	16 (24.61)	Female
Advanced age (nutritional causes)	4 (6.14)	Male
Young age (nutritional causes)	2 (3.07)	Male
Malignancy (stomach cancer)	1 (1.53)	Male

DISCUSSION

In this study, the treatment response and adverse effect profile in patients diagnosed with IDA and treated with IV iron using ferric carboxymaltose were retrospectively evaluated using real-world data. WHO defines IDA as the presence of low Hb levels accompanied by low serum ferritin levels (<15 ng/ml, or <50 ng/ml in patients with chronic conditions).[11] The present study assessed the treatment outcomes and adverse effect profiles of 65 patients who received IV iron therapy for IDA. The study findings suggest that IV iron therapy is highly effective and well tolerated in patients with IDA, with an acceptable safety profile. A 3 g/dl increase in Hb levels was noted following treatment, as was expected. Previous studies in the literature suggest that effective iron replacement can be expected to increase Hb levels by 2 g/dl within 2–3 weeks and to restore them to normal levels within 6–8 weeks.[12] In the present study, Hb levels increased by 3 g/dl within 4–6 weeks, noted during the first control visit, achieving the target range. The marked improvement in serum ferritin and iron parameters indicates that IV iron therapy rapidly replenishes iron stores. The increase in mean transferrin saturation from 10% to 70% indicates a substantial rise in functional iron levels. Consequently, all patients showed improvement in clinical symptoms, with a corresponding enhancement in quality of life. Notably, some patients who were asymptomatic at baseline reported improvement after treatment, highlighting that iron deficiency can impair functional capacity even at a subclinical level and emphasizing the benefits of therapy. In a study by Sharma et al.,[4] IV iron therapy was found to significantly alleviate fatigue in young women with iron deficiency, even when Hb levels were within the normal range. In the present study, restoring iron stores was associated with symptomatic improvement and enhanced overall well-being in patients.

There have been several studies to date reporting IDA to be particularly prevalent among women of reproductive age and those who are pregnant.[13,14] Consistent with the literature, the majority of patients in the present study were female. In our country (Turkiye), the prevalence of anemia is low among healthy adult males who do not donate blood, whereas higher rates have been reported in women, attributable to such factors as menstruation and pregnancy.[14,15] Furthermore, studies have shown that ferric carboxymaltose is an effective and safe treatment for patients with IDA associated with hypermenorrhea, menorrhagia, and menometrorrhagia.[16] Although the number of male patients in our study was small, it is worthy of note that the mean age of the male patients was considerably higher than that of female patients, indicating that iron deficiency is particularly prevalent among young women and in older men, likely associated with other comorbid conditions. Half of the male patients in the present study were aged 65 or older, representing an age group in which anemia may be associated with gastrointestinal bleeding or the presence of chronic conditions. The identification of gastric cancer in one male patient in our study underlines the need to thoroughly investigate the underlying pathology in cases of iron deficiency involving older men. When examined alongside the findings of previous studies in the literature, it can be concluded from the present study that all patients diagnosed with IDA, particularly men and postmenopausal women, should be evaluated for sources of gastrointestinal bleeding and underlying malignancy.[17] Although the malignancy rate in our study was low (1.5%), a comprehensive evaluation is advisable to investigate potential sources of occult bleeding that could be detected at an early stage.

In the present study, the adverse effects associated with IV iron therapy were found to be at a tolerable level. Among the observed adverse reactions, none of those related to the IV treatment progressed to anaphylactic shock, and most reactions were managed through such measures as slowing the infusion rate, and the administration of antihistamines and corticosteroids, when necessary. A

review of the literature confirms the low incidence of serious adverse events associated with newer-generation IV iron formulations reported in the present study. In a meta-analysis by Avni et al.[14] involving more than 10,000 patients, IV iron therapy was found not to increase the risk of life-threatening complications, including death, although minor infusion reactions were reported slightly more frequently when compared to a placebo or oral iron treatments.

In this context, the 9% rate of minor reactions observed in our study is consistent with the literature, and no patients experienced any permanent sequelae. The severe reactions historically associated with iron dextran have prompted clinicians to exercise caution; however, the introduction of ferric carboxymaltose has substantially reduced these concerns. In the present study, none of the patients had a known history of allergy to IV iron, and so no test doses were administered for prophylactic purposes.

Although the initial cost of IV iron therapy is higher than that of oral treatment, it may contribute to health economics by rapidly reducing work loss, alleviating symptoms, and decreasing the need for transfusions. Oral therapy should be prioritized as the first-line treatment for patients with mild or uncomplicated anemia who demonstrate good treatment adherence, while IV iron should be considered early in patients with malabsorption (e.g. gastrointestinal intolerance, celiac disease, history of bariatric surgery) or in patients requiring rapid correction, such as those with severe symptomatic anemia or as a preoperative preparation.[8]

Based on studies in the literature, there is consensus that correcting Hb levels with IV iron therapy in patients diagnosed with IDA is associated with better outcomes in terms of reduced hospital admissions and improved quality of life. Achieving target Hb levels plays an important role in reducing anemia-related morbidity and ultimately improving patient-centered outcomes in these various clinical settings.[19]

Limitations

The retrospective design of the study may lead to gaps in the data, and some measurements may not have been performed at the defined time points. Furthermore, there may have been variations in the timing of the post-treatment laboratory follow-up, introducing heterogeneity to the assessment of treatment response. Finally, the data on symptoms and adverse effects came from patient records, and assessments may have been influenced by subjective reporting.

The study is based on real-world data, and so provides insight into the outcomes of IV iron therapy in routine clinical practice. The administration of ferric carboxymaltose to all patients in the study has ensured homogeneity in treatment response and safety assessments, thereby enhancing the reliability of the results.

CONCLUSION

The findings of the present study indicate that patients should receive appropriate replacement therapy upon the detection of iron deficiency, regardless of whether or not symptoms are present. It can further be concluded that IV iron therapy is an effective and reliable option in patients who cannot tolerate oral iron therapy or whose response to oral treatment is inadequate. The patients in the present study experienced a rapid increase in laboratory parameters following IV iron therapy, including Hb and ferritin levels, and the treatment was noted to have a well-tolerated safety profile and to spur a rapid improvement in symptoms.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Non-interventional Clinical Researches Ethics Committee of Van Yüzüncü Yıl University (Date: 20.01.2023, Decision No: 2023/01-13).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: G.A., R.E.; Design: G.A., A.D.; Control: G.A., R.E.; Data Collection and/or Processing: G.A., R.E., A.D.; Analysis and/or Interpretation: G.A., A.D.; Literature Review: G.A., A.D.; Article Writing: G.A., R.E., A.D.; Critical Review: All authors.

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Original Article

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Evaluation of demographic and clinical data of patients diagnosed with lung cancer: a single-center experience

Mehmet Maruf Kayran[1], Mehmet Naci Aldemir[1], Ozan Aydemir[2], Mehmet Erdem[2], Şerafettin Erzen[2], Senar Ebinç*[1]

[1]Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye
[2]Department of Internal Medicine, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye

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***Corresponding Author:** Senar Ebinç, senarebinc@gmail.com

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ABSTRACT

Aims: To retrospectively evaluate the demographic, epidemiological, and clinical characteristics of patients diagnosed with lung cancer.

Methods: Patients diagnosed and treated for lung cancer in our medical oncology clinic were included in the study. Patient records were obtained retrospectively from the electronic databases of the hospital. Demographic and clinical characteristics were recorded for each patient.

Results: A total of 313 patients diagnosed with lung cancer were included in the study. Mean age was 62.7±10.3 years. Of the patients, 83.4% were male and 16.6% were female. Most common presenting complaints were dyspnea (40.9%) and chest pain (32.2%). Smoking history was present in 66.5% of patients, and 15.3% had a history of tandoori smoke exposure. Radiologically, the most frequent tumor localization was the right upper lobe (38%). Most common histopathological types were squamous cell carcinoma (39.3%), adenocarcinoma (27.2%), and small cell carcinoma (20.1%). Most common disease stage at the time of diagnosis was stage IV (48.9%), followed by stage III (39%), II (10.9%), and I (1.3%). Mean OS was 14±1.4 (range, 11.2–16.8) months. Higher ECOG performance scores and advanced stage were associated with poorer survival. Mean OS was 31 months for females and 13 months for males.

Conclusion: The findings obtained in our study were found to be consistent with those of previous research. In Turkiye, the high prevalence of smoking, the asymptomatic nature of the disease, and the tendency of patients to attribute existing symptoms to smoking appear to contribute to delayed presentation to healthcare facilities, which likely plays a role in the high proportion of advanced-stage diagnoses. Additionally, unlike in other studies, the higher proportion of female patients diagnosed in our cohort was considered to be related to the widespread use of tandoori ovens in our region.

Keywords: Lung cancer, smoking, demographic

INTRODUCTION

Lung cancer is the most common cause of cancer-related mortality worldwide. Each year, 1.8 million individuals are diagnosed with lung cancer, and 1.6 million die from the disease. Five-year survival rates vary between 4% and 17%, depending on stage and regional differences.[1] Although the incidence and mortality of lung cancer are declining in developed countries, they continue to increase in developing countries. Lung cancer is the second most common malignancy after breast cancer among women and ranks second after prostate cancer among men.[2]

Lung cancer is generally classified into two types, including small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). NSCLC accounts for 80–85% of all lung cancers. Less than 50% of NSCLC cases are resectable at the time of diagnosis, while approximately 25% present with locally advanced disease. In SCLC, about 30% of patients are diagnosed at the limited stage.[3] Surgical resection is the most effective treatment modality, particularly for early-stage lung cancer; however, it can be performed in only 20-25% of patients. For locally advanced disease, chemoradiotherapy and radiotherapy constitute the primary treatment approach.[4] This study aimed to evaluate the distribution of lung cancer subtypes, stages at presentation, and survival outcomes of patients who were admitted to and treated at our center.

METHODS

The study included patients that were diagnosed with lung cancer and followed up and treated at Yüzüncü Yıl University Dursun Odabaş Medical School Medical Oncology Department between January 2011 and June 2020. Patient data were obtained retrospectively from databases of the hospital. A data collection form was created to obtain clinical data of the patients. The study was initiated after obtaining an approval from Van Yüzüncü Yıl University Ethics Committee for Non-interventional Clinical Researches (Date: 16.10.2020, Decision No: 2020/07-17). The study was conducted in accordance with the principles of the Declaration of Helsinki. Age, gender, pathological subtype, comorbidities, presenting symptoms, date of hospital admission, smoking history, and demographic and clinical data at initial admission were recorded for each patient.

Histological classification was performed using the World Health Organization (WHO) classification. Patients with benign lung tumors, pleural tumors, or lung metastases were excluded from the study. Histological staging was carried out at the time of diagnosis based on the tumor, node, metastasis (TNM) classification system for lung cancer. Clinical staging was achieved according to the results of chest radiography, thoracic computed tomography (CT), bone scintigraphy, abdominal CT, brain CT, positron emission tomography CT (PET/CT), and other imaging modalities when available.

Statistical Analysis

Data were analyzed using SPSS for Windows version 22.0 (Armonk NY, IBM Corp. 2013). Descriptives were expressed as mean±standard deviation (SD), and minimum and maximum values for continuous variables and as frequencies (n) and percentages (%) for categorical variables. Continuous variables were analyzed with the Student's t-test for normally distributed data and with the Mann-Whitney U test for non-normal data. Proportions were compared between groups using the Chi-square test. When test assumptions were violated, Monte Carlo simulation was applied. Survival analyses were conducted using the Kaplan-Meier method. A p value of <0.05 was considered significant.

RESULTS

A total of 313 patients were evaluated, comprising 261 (83.4%) male and 52 (16.6%) female patients with a mean age of 62.7±10.3 years. Of the patients, 33 (10.5%) had never smoked and 208 (66.5%) had a history of smoking; smoking data were unavailable for 72 patients (23%). Among smokers, mean smoking exposure was 49.12±29.62 pack-years. A history of tandoori smoke exposure was present in 48 (15.3%) patients, predominantly female (93.7%), which was statistically significant (p<0.01). Nineteen (6%) patients had a history of both tandoori smoke exposure and cigarette smoking, all of whom were female. Mean body height, weight, BMI, and BSA were 167.99±8.41 cm, 68.94±15.25 kg, 24.23±4.87 kg/m², and 1.77±0.19 m², respectively. According to the ECOG Performance Status Scale, most patients were ECOG 1 or 2 (40.9% each). Comorbidities were present in 138 (44.6%) patients, with coronary artery disease being the most common. The most frequent presenting symptom was shortness of breath (40.9%). At diagnosis, most patients were in stage IV (48.9%), followed by stage III (39%). Poorly differentiated tumors were the most common (56.9%). Tumor localization was most frequently in the right upper lobe (38%) (**Table**).

Tablo. Demographic and clinical characteristics of the patients

		n	%
Gender	Yes	261	83.4
	No	52	16.6
Smoking	Yes	208	86.3
	No	33	13.7
Tandoor exposure	Yes	48	15.3
	No	265	84.7
Performance status	ECOG 0	31	9.9
	ECOG 1	128	40.9
	ECOG 2	128	40.9
	ECOG 3	23	7.3
	ECOG 4	2	1.0
Comorbidity	No	175	55.4
	Coronary artery disease	48	44.6
	Hypertension	43	
	Chronic obstructive pulmonary disease	33	
	Other	14	
Symptoms	Dyspnea	128	40.9
	Chest pain	101	32.2
	Other	81	27.9
Diagnostic method	Bronchoscopy	209	66.5
	Surgery	39	12.5
	Transthoracic biopsy	28	8.9
	Metastasis	25	8.0
	Pleural fluid	12	3.8
Histopathological diagnosis	Squamous cell carcinoma	123	39.3
	Adenocarcinoma	85	27.2
	Small cell carcinoma	63	20.1
	Other	42	13.4
Stage	4	153	48.9
	3	122	39.0
	2	32	10.2
	1	4	1.3
Grade	Well differentiated	6	3.1
	Moderately differentiated	78	40.0
	Poorly differentiated	111	56.9
Tumor location	Right upper lobe	115	38.0
	Left upper lobe	86	28.4
	Right lower lobe	48	15.8
	Left lower lobe	37	12.2
	Right middle lobe	17	5.6

The table continues

Tablo. Demographic and clinical characteristics of the patients (The table continues)

	Gender	Mean±SD	p
Age (years)	Female	58.25±10.33	0.054
	Male	61.33±10.42	
	Overall	62.7±10.3	
Body surface area (m^2)	Female	1.72±0.20	0.08
	Male	1.78±0.18	
	Overall	1.77±0.19	
Body-mass index (kg/m^2)	Female	27.79±6.14	0.01
	Male	23.67±4.29	
	Overall	24.23±4.87	

SD: Standard deviation

Bronchoscopy was the most commonly used diagnostic method (66.5%), and squamous cell carcinoma was the most frequent histopathological subtype (39.3%). Squamous cell carcinoma was more common in men, whereas adenocarcinoma was more common in women, with a statistically significant difference (p=0.003) (**Figure 1**).

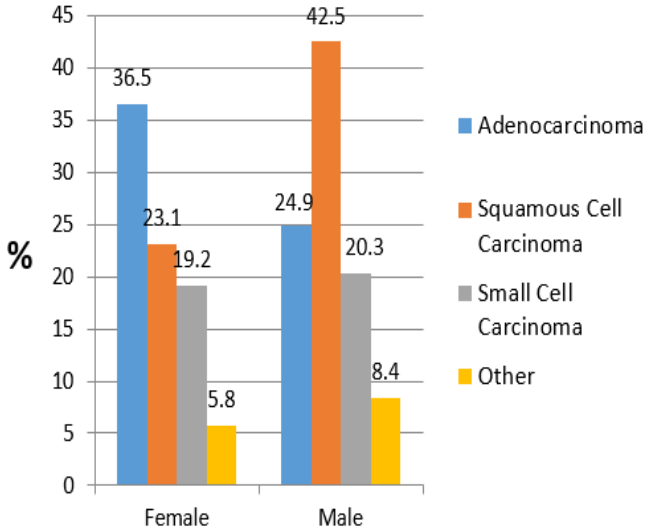

Figure 1. Histopathological frequency of lung cancer according to gender

A significant association was found between histopathological subtype and disease stage (p<0.001); squamous cell carcinoma was more commonly diagnosed at stage III, while adenocarcinoma and small cell lung carcinoma were mostly diagnosed at stage IV (**Figure 2**). During follow-up, 242 (77.8%) patients died, with a mean overall survival (OS) of 14±1.48 months. Mean OS decreased with worsening ECOG score and advanced disease stage (p<0.001) (**Figure 3**). Mean OS was 46, 17, and 8 months for patients with stage II, III, and IV, respectively (p<0.001) (**Figure 4**). Mean OS for squamous cell carcinoma, adenocarcinoma, and small cell carcinoma was 17, 13, and 11 months, respectively. Women had significantly longer mean OS compared to men (31 vs. 13 months, p<0.001) (**Figure 5**).

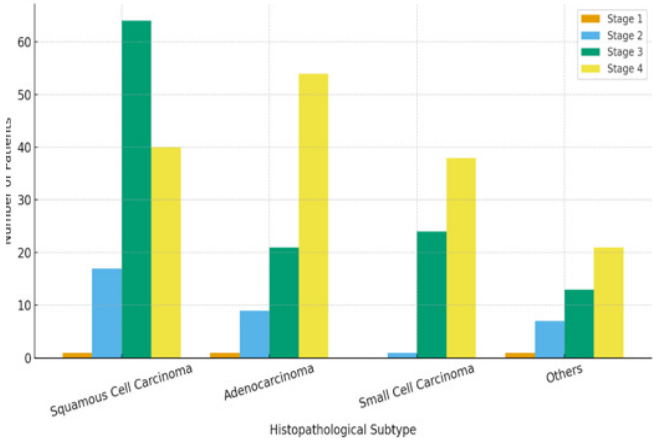

Figure 2. Histopathological type-stage relationship

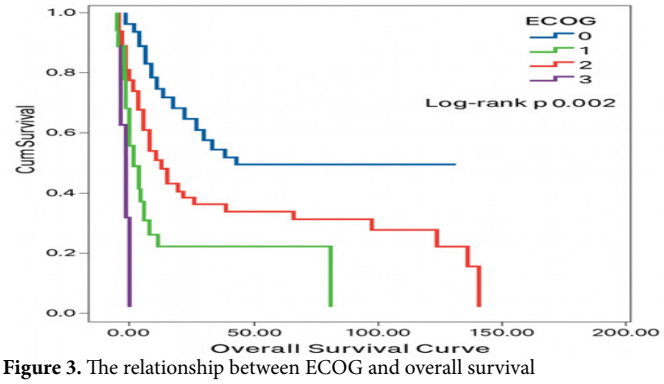

Figure 3. The relationship between ECOG and overall survival

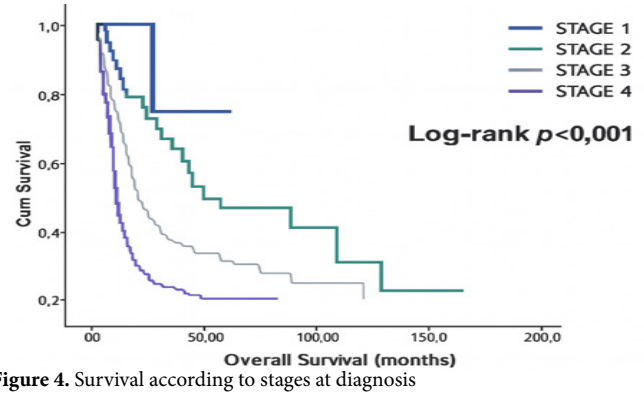

Figure 4. Survival according to stages at diagnosis

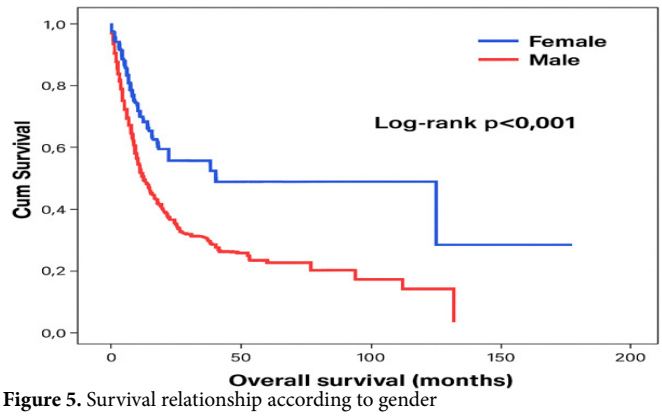

Figure 5. Survival relationship according to gender

DISCUSSION

Lung cancer was a rare disease in the early 20th century and has recently increased in incidence due to a surge in tobacco product consumption. Moreover, it has become the most commonly diagnosed cancer worldwide.[5] According to data from the International Agency for Research on Cancer (IARC), a total of 1,352,132 people are diagnosed with lung cancer each year, including 965,241 men and 386,891 women, and 1,180,000 people die from lung cancer annually.[6] In a study involving 5,628 cases of primary lung cancer, mean age at diagnosis was found to be 65.4±11.0 years for all patients, 64.2±11.4 years for women, and 66.3±10.7 years for men.[7] In our study, 313 patients were aged between 20 and 90 years and had a mean age of 62.7±10.3 years. Additionally, mean age at diagnosis was 61.3±10.4 years for men and 58.2±10.3 years for women.

A study conducted in Poland involving 20,561 lung cancer patients reported a male-to-female ratio of 6:1.[8] Likewise, a study conducted in Turkiye in 2011, which included 9,504 patients, found a male-to-female ratio of 6.2:1.[9] In our study, 83.4% of the patients were male and 16.6% were female, resulting in a male-to-female ratio of 5:1.

The WHO World Cancer Report showed that the risk of developing lung cancer is 20 times higher in smokers compared to non-smokers. Additionally, it was also reported that squamous cell carcinoma and SCLC are more commonly seen in smokers, while adenocarcinoma is more frequent in non-smokers.[10] In our study, 10.5% of patients had never smoked, while 66.5% of them had a history of smoking. Nevertheless, smoking history data was not available for 23% of the patients. Among smokers, mean smoking exposure was 49.12±29.62 pack-years. Among all smoking patients, 92.1% of men and 56.4% of women were smokers. Additionally, a history of tandoori smoke exposure was present in 15.3% of the patients.

In patients with chronic obstructive pulmonary disease (COPD), the risk of developing lung cancer is 3-4 times higher compared to smokers with normal respiratory function. In a study involving 5,887 patients, lung cancer was reported as the most common cause of death in patients with COPD, accounting for 33% of deaths.[11] In our study, most common comorbidities were coronary artery disease and hypertension, and COPD was observed in only 33 patients.

In patients with lung cancer, 75% present with one or more symptoms at the time of diagnosis. Symptoms vary depending on the primary tumor, pattern of intrathoracic metastasis, distant metastases, and paraneoplastic syndromes. In a study involving 3,547 patients, most commonly observed symptoms included cough (51.6%), chest pain (44.2%), shortness of breath (34.8%), sputum production (21%), weight loss (19%), hemoptysis (14.19%), fatigue (12.7%), and loss of appetite (10.7%). It was also found that 0.65% of patients were asymptomatic.[12] In our study, however, most frequent symptom was shortness of breath (40.9%) and chest pain was the second most common symptom (32.2%).

It is well established that lung cancer localizes more frequently in the right lung than in the left and that it mostly involves the upper lobes.[13] Consistently, in our study, most common localization was the right upper lobe (38%).

Sputum cytology is the most non-invasive technique used in the diagnosis of lung cancer. Fiberoptic bronchoscopy is the key diagnostic method for lung cancer. During diagnostic bronchoscopy, various techniques may be employed, including forceps biopsy, bronchial brushing and aspiration, transbronchial fine needle aspiration, transbronchial lung biopsy, bronchoalveolar lavage, and post-bronchoscopy sputum examination.[10] In our study, bronchoscopy was the most frequently used diagnostic method (66.5%), followed by surgical intervention (12.5%).

In a study conducted with 5,628 patients diagnosed with lung cancer, adenocarcinoma was identified in 45.3% of cases, squamous cell carcinoma in 23.7%, NSCLC of unspecified subtype in 12.1%, SCLC in 11.3%, large-cell carcinoma in 2.8%, and mixed histology in 1.1%.[7] According to data from the Lung Cancer Mapping Project in Turkiye (LCMPT), the most common subtype was reported to be squamous cell carcinoma (29.2%), followed by NSCLC of unspecified subtype (23.3%), adenocarcinoma (16.9%), and SCLC (15.4%). Of these, adenocarcinoma was the most common subtype in women (55.9%) as opposed to squamous cell carcinoma in men (49.3%).[14] In our study, the most common subtype was squamous cell carcinoma (39.3%), followed by adenocarcinoma (26.8%) and SCLC (20.1%). As consistent with the literature, the most frequent subtype was squamous cell carcinoma in men (42.5%) and adenocarcinoma in women (36.5%), and this difference was statistically significant. This difference was considered to be related to gender-specific variations in smoking history.

The literature indicates that there is no clear evidence explaining the higher survival in females compared with males.[15] Adenocarcinoma is more common in females compared to males. Women also demonstrate better treatment response regardless of stage, treatment modality, or histopathology.[16] In a previous study conducted in Turkiye, mean OS was reported as 23.4 months for men and 18.1 months for women.[17] Likewise, in our study, mean OS was 31 months in women and only 13 months in men.

In a study conducted by Kefeli et al.,[18] mean OS was reported as 12 months for squamous cell carcinoma, 11.9 months for adenocarcinoma, 15.2 months for SCLC, and 10.9 months for unspecified subtypes, with no significant difference observed. In another study involving 80 patients, although there was no significant difference at the time of initial diagnosis, patients with adenocarcinoma were observed to live longer than those in the other NSCLC group (13.6 months vs. 9.5 months). This difference was attributed to the longer doubling time of adenocarcinoma.[19] In our study, the mean OS calculated for the three most common histopathological subtypes (squamous cell carcinoma, adenocarcinoma, and small cell carcinoma) was found to be 17, 13, and 11 months, respectively, and no significant difference was observed.

In a study conducted at the Mayo Clinic involving 5,628 patients diagnosed with lung cancer, it was reported that among NSCLC patients, 34.9% were diagnosed at stage IV, 30.3% at stage III, 8.4% at stage II, and 26.4% at stage I.

Among SCLC patients, 53% were diagnosed at an advanced disease stage.[7] In a study conducted in Turkiye including 11,849 lung cancer cases, 40.4% of NSCLC patients were diagnosed at stage IV, while 62.1% of SCLC patients were diagnosed at an advanced disease stage.[14] In our study, 49% of the patients were diagnosed at stage IV.

Among all types of lung cancer, approximately 80% of patients have an OS of about one year, and the 5-year survival rate is 5-15%. Patients with NSCLC have a better prognosis than those with SCLC. Prognosis worsens with advancing stage; the 5-year survival rate is about 70% in stage I, 30-50% in stage II, 10% in stage III, and even lower in the presence of metastasis.[20] In our study, mean OS according to disease stage at diagnosis was consistent with the literature: 46, 17, and 8 months for stage II, III, and IV, respectively. Nevertheless, OS could not be calculated for stage I.

Prognostic factors influencing survival in lung cancer have been examined in numerous studies. In a study involving 172 patients with stage IV NSCLC, an ECOG performance score of >2 was identified as a poor prognostic factor.[21] In our study, mean OS for patients with ECOG 0, 1, 2, and 3 scores was 33, 14, 14, and 5 months, respectively. There were only two patients with ECOG 4, and their OS was found to be less than one month. Consistent with previous studies, higher ECOG performance scores were shown to have a negative effect on survival.

Limitations

Our study has several limitations, including a single-center, retrospective design, a small number of patients, heterogeneous study groups, and the lack of molecular subgroup analysis.

CONCLUSION

As a result, lung cancer, which is most often diagnosed at an advanced stage, represents a major public health problem. Although advances in diagnostic and therapeutic methods have provided positive effects, a rapid decline in mortality rates has not been achieved. The findings obtained in our study were found to be largely consistent with those of previous research. Based on our findings, we consider that in Turkey, where smoking is highly prevalent, the tendency of patients to attribute their symptoms to smoking as well as the lack of symptoms leads to delayed hospital admission and contributes to the high proportion of advanced-stage diagnoses. As recommended in the National Comprehensive Cancer Network (NCCN) guidelines, we believe that annual low-dose CT for early lung cancer detection is of vital importance in high-risk individuals, regardless of the presence of symptoms. In addition, unlike in other studies, the higher proportion of female patients diagnosed in our cohort was considered to be related to the widespread use of traditional tandoori ovens in our region. Further etiological studies, particularly in our region, are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated after obtaining an approval from Van Yüzüncü Yıl University Ethics Committee for Non-interventional Clinical Researches (Date: 16.10.2020, Decision No: 2020/07-17).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: M.M.K., M.N.A.; Design: M.M.K., M.N.A., M.E., S.E.; Control: M.M.K., M.N.A., M.E., S.E., O.A., Ş.E.; Resources: M.M.K., M.N.A., M.E.; Materials: M.M.K., M.N.A.; Data Collection and/or Processing: M.M.K., M.N.A.; Analysis and/or Interpretation: M.M.K., M.N.A., M.E., S.E.; Literature Review: M.M.K., M.N.A., M.E., S.E.; Writing the Article: M.M.K., M.N.A., M.E., S.E.; Critical Review: M.M.K., M.N.A., M.E., S.E., O.A., Ş.E.

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SMARCA2 and SMARCA4 expression in epithelioid pleural mesothelioma: association with inflammatory microenvironment

Neslihan Akanıl Fener

Department of Medical Pathology, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkiye

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Corresponding Author: Neslihan Akanil Fener, neslihanakanilfener@gmail.com

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ABSTRACT

Aims: To investigate the frequency of SMARCA2 and SMARCA4 loss in epithelioid pleural mesothelioma (pleural mesothelioma) and to evaluate their clinicopathologic correlates, with particular attention to the inflammatory tumor microenvironment.

Methods: This retrospective study included 64 patients who underwent surgery for epithelioid pleural mesothelioma between January 2007 and October 2019. Cases with biphasic histology, unavailable clinical data or tissue blocks, and early postoperative mortality were excluded. Clinicopathologic parameters (age, sex, stage, histologic pattern, necrosis, inflammation) were reviewed. Immunohistochemistry for SMARCA2 and SMARCA4 was performed using tissue microarrays using anti-SMARCA4 (clone EPNCIR111A, 1:100) and anti-SMARCA2 (clone D9E8B, 1:100). Loss of expression was defined as complete absence of nuclear staining in tumor cells in the presence of an internal stromal positive control. Statistical analyses were conducted using R (version 3.5.1). Associations between categorical variables were assessed using Chi-square or Fisher's exact tests; continuous variables were compared using Student's t-test or one-way ANOVA. Vendor and catalog number (SMARCA4): Abcam (Cambridge, UK), cat. no. orb513921. Vendor and catalog number (SMARCA2): Abcam (Cambridge, UK), cat. no. orb575109.

Results: The cohort comprised 51 men (79%) and 13 women (21%), with a mean age of 57.1±12 years (range, 30–91). Fifty-three patients (82.8%) underwent decortication and 11 (17.2%) extrapleural pneumonectomy. Most tumors were stage I (n=60, 94%), with 4 (6%) at stage II. Histologic patterns were tubulopapillary (n=33, 50%), trabecular (n=2, 3%), adenomatoid (n=11, 18%), solid (n=3, 6%), and micropapillary (n=15, 23%). Inflammation was mild in 58 cases (91%) and severe in 6 (9%); necrosis was present in 8 cases (12.6%). Loss of SMARCA2 and SMARCA4 expression was detected in 4 patients each (6% for both markers). SMARCA2 loss was significantly associated with severe inflammation (p=0.02), whereas no significant relationships were observed between SMARCA4 loss and age, sex, stage, histologic pattern, necrosis, or inflammation. Mean overall survival was 22 months; 2-year and 5-year overall survival rates were 35% and 6%, respectively. Neither SMARCA4 loss (p=0.33) nor SMARCA2 loss (p=0.88) had a significant impact on survival.

Conclusion: SMARCA2 and SMARCA4 loss are uncommon events in epithelioid pleural mesothelioma. However, in this small surgical cohort, SMARCA2 deficiency was associated with a more pronounced lymphocytic/inflammatory infiltrate; this observation should be considered exploratory and hypothesis-generating, and its clinical/biomarker relevance requires confirmation in larger, multi-institutional cohorts with survival and immune profiling.

Keywords: Mesothelioma, pleural neoplasms, chromatin remodeling, SMARC A2, SMARC A4, tumor microenvironment

INTRODUCTION

The mammalian SWI/SNF (BAF) chromatin-remodeling complex is a multi-subunit assembly that uses ATP-dependent nucleosome mobilization to regulate chromatin accessibility and gene transcription, thereby playing key roles in cell differentiation, DNA repair, and tumor suppression.[1,2] Two mutually exclusive ATPase subunits, SMARCA4 (BRG1) and SMARCA2 (BRM), together with accessory subunits such as SMARCB1 and ARID1A, define distinct complex variants and confer tissue-specific functions.[1,2] Recurrent alterations in SWI/SNF components have been documented across a broad spectrum of human malignancies and collectively account for a substantial fraction of cancers.[1,2]

Within the thorax, inactivating alterations of SMARCA4, frequently accompanied by SMARCA2 co-loss, define a group of highly aggressive neoplasms now termed SMARCA4-deficient undifferentiated thoracic tumors (SMARCA4-DUT), previously described as SMARCA4-deficient thoracic sarcomas.[3,4] The 5th edition of the World

Health Organization (WHO) Classification of Thoracic Tumours recognizes SMARCA4-DUT as a distinct entity separate from SMARCA4-deficient non-small cell lung carcinoma (NSCLC).[5] These tumors typically present as bulky intrathoracic masses with undifferentiated or rhabdoid morphology and carry a dismal prognosis despite multimodal therapy.[3,5]

Although SMARCA4-deficient thoracic tumors are an important differential diagnosis, our cases showed a mesothelial immunophenotype and lacked clinicopathologic features typical of SMARCA4-DUT sarcoma.

Malignant pleural mesothelioma (MPM) is an aggressive malignancy of mesothelial origin, strongly associated with asbestos exposure and characterized by limited therapeutic options and poor survival.[6,7] Genomic profiling studies indicate that MPM is driven predominantly by loss-of-function alterations in tumor suppressor genes such as BAP1, NF2, and CDKN2A, with less frequent involvement of SWI/SNF components including ARID1A and SMARCA4.[6,8] Standard diagnosis relies on morphology supported by immunohistochemistry, typically using mesothelial markers (calretinin, WT-1, cytokeratin 5/6, D2-40) together with carcinoma-associated exclusion markers (CEA, Ber-EP4, TTF-1).[6,7]

Data on SMARCA2 and SMARCA4 expression specifically in pleural mesothelioma are limited and somewhat conflicting. Perret et al.[4] reported SMARCA4 loss in a subset of epithelioid mesotheliomas in a series enriched for SMARCA4-deficient thoracic tumors, suggesting potential diagnostic overlap with SMARCA4-DUT. In contrast, Ahadi and Gill[9] found SMARCA4 loss to be very rare in thoracic mesothelioma, and Ren et al.[10] concluded that pleural malignant mesotheliomas generally do not show SWI/SNF complex deficiency.

In parallel, increasing evidence in other tumor types suggests that SWI/SNF deficiency may be associated with an inflamed or "hot" tumor microenvironment, characterized by increased tumor-infiltrating lymphocytes and, in some settings, enhanced sensitivity to immunotherapy.[11,12] In mesothelioma, chronic inflammation driven by asbestos fibers and the resulting immune dysregulation are central to pathogenesis and may influence response to treatment.[6,7,12]

In this context, we aimed to (i) determine the frequency of SMARCA2 and SMARCA4 loss in a single-institution cohort of epithelioid pleural mesotheliomas; and (ii) explore associations between SMARCA2/4 expression status and clinicopathologic features, with particular emphasis on the inflammatory infiltrate.

METHODS

Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Researches Ethics Committee of İstanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 01.07.2021, Decision No: 2021-130). Due to the retrospective design, informed consent was waived according to local regulations.

Study Design and Patient Selection

This retrospective study included patients who underwent surgery for pleural mesothelioma at our institution between January 2007 and October 2019. A total of 107 patients with a diagnosis of pleural mesothelioma were initially identified from pathology archives.

Exclusion criteria were:

- biphasic mesothelioma (n=18);
- unavailable clinical data (n=2);
- unavailable histological material (slides or paraffin blocks) (n=20);
- death because of postoperative complications within the first 2 weeks after surgery (n=3).

After applying these criteria, 64 patients with epithelioid pleural mesothelioma and adequate clinical and pathologic data were included in the final analysis.

Histopathologic Evaluation and Diagnosis

All cases were reviewed by thoracic pathologists. Diagnoses were established using standard histological criteria and immunohistochemistry. Calretinin, WT-1, cytokeratin 5/6, and D2-40 were used as positive markers supportive of pleural mesothelioma, whereas thyroid transcription factor-1 (TTF-1), carcinoembryonic antigen (CEA), and Ber-EP4 were used as negative markers to exclude metastatic carcinoma.

Histologic patterns in epithelioid mesothelioma were categorized as tubulopapillary, trabecular, adenomatoid, solid, or micropapillary. The presence and severity of inflammation (mild vs severe) and the presence of tumor necrosis (yes vs no) were recorded. Inflammation was assessed on hematoxylin-eosin sections as lymphoplasmacytic infiltrates within and/or surrounding tumor nests; mild inflammation was defined as scant to moderate, patchy infiltrates without dense aggregates, whereas severe inflammation was defined as brisk, diffuse or band-like infiltrates and/or prominent lymphoid aggregates. Scoring was performed by two pathologists blinded to SMARCA2/4 status; discrepancies were resolved by consensus.

Mitoses were counted per 2 mm^2, and cases were stratified into three groups according to the mitotic count–based scoring system. A score of 1 was assigned to low mitotic activity, a score of 2 to intermediate mitotic activity, and a score of 3 to high mitotic activity. Specifically, the presence of a single mitosis was assigned a score of 1; two to four mitoses were assigned a score of 2; and five or more mitoses were assigned a score of 3.

TNM staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.

Tissue Microarrays and Immunohistochemistry

Two 1 mm cores of representative tumor were taken from each case to construct tissue microarrays (TMAs). SMARCA4 and SMARCA2 immunohistochemistry was performed using a Ventana Benchmark platform using standardized protocols

provided by the manufacturer, with appropriate positive controls on each slide. Given the known heterogeneity of mesothelioma, representative regions were selected on review of whole sections prior to TMA construction, and cases showing loss on TMA were re-checked on whole-tissue sections when available to minimize sampling bias.

The following primary antibodies were used:

- anti-SMARCA4 (clone EPNCIR111A, 1:100 dilution);
- anti-SMARCA2 (clone D9E8B, 1:100 dilution).

Interpretation of SMARCA2 and SMARCA4 Staining

Nuclear staining in tumor cells of any intensity was considered retained expression (positive) (**Figure 1**). Complete loss of expression was defined as total absence of nuclear staining in tumor cells in the presence of positive nuclear staining in adjacent non-neoplastic stromal or inflammatory cells, serving as an internal positive control (**Figure 2**).

Cases in which both tumor and internal control elements lacked nuclear staining were considered non-interpretable and were excluded from marker-specific analyses.

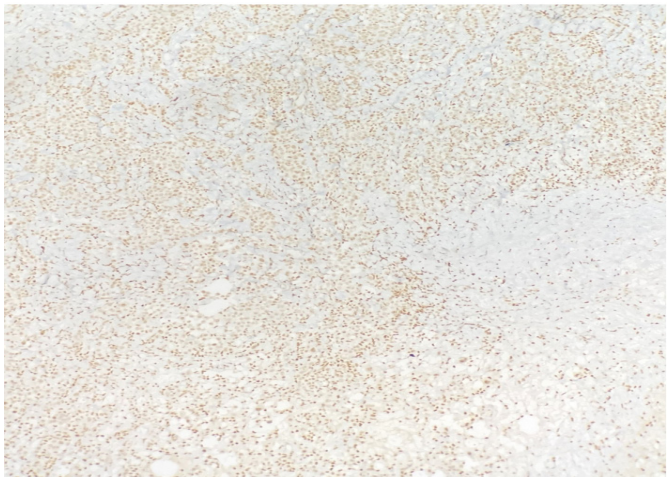

Figure 1. SMARCA4-positive nuclear staining in tumor cells of epithelioid pleural mesothelioma (immunohistochemistry, 20×)

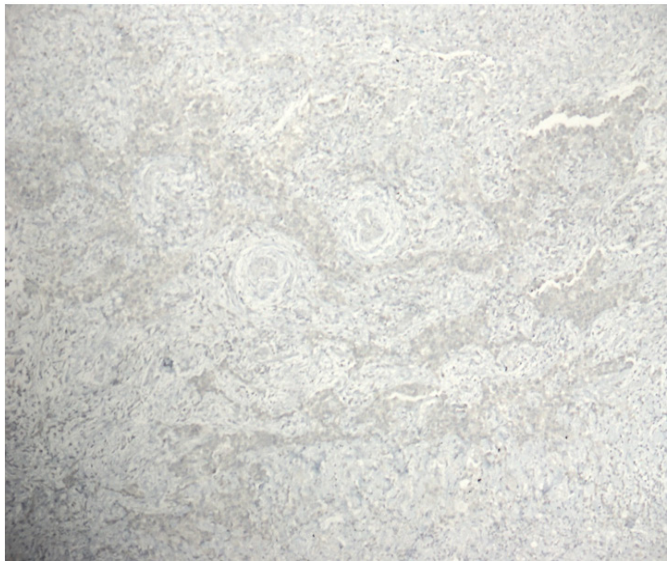

Figure 2. Complete loss of SMARCA2 nuclear staining in tumor cells, with severe inflammatory infiltrate in the stroma (immunohistochemistry, 20×).

Clinicopathologic Parameters

Demographic data (age, sex), type of surgery [decortication (DC) vs extrapleural pneumonectomy (EPP)], and pathologic stage were retrieved from patient records. Histologic growth patterns, grade (where applicable), presence of necrosis, and inflammation (mild vs severe) were documented.

Statistical Analysis

All analyses were performed using R software (version 3.5.1; Bell Laboratories, Lucent Technologies, New Jersey, USA). Categorical variables were compared using Chi-square or Fisher's exact test, as appropriate. Continuous variables were analyzed using Student's t-test or one-way ANOVA. A p value <0.05 was considered statistically significant.

Survival Analysis

Overall survival (OS) was defined as the interval from the date of surgery to death from any cause or last follow-up. Progression-free survival (PFS) was defined as the interval from surgery to documented recurrence/progression or death, whichever occurred first. OS and PFS were estimated using the Kaplan–Meier method and compared using the log-rank test; because of the small number of SMARCA2-/SMARCA4-loss cases, subgroup comparisons were considered exploratory.

RESULTS

Clinicopathologic Characteristics

Among the 64 patients included, 51 (79%) were male and 13 (21%) female. The mean age at diagnosis was 57.1±12 years (range, 30–91). Fifty-three patients (82.8%) underwent pleural decortication, and 11 patients (17.2%) had extrapleural pneumonectomy.

Forty-four patients (68.7%) were 65 years of age or younger, and 20 (31.3%) were older than 65 years. Most tumors were stage I (n=60, 94%), while 4 (6%) were stage II. Neither T category nor overall TNM stage was significantly associated with overall survival in univariate analysis, likely because of the highly homogeneous stage distribution of the cohort, in which 94% of patients had stage I disease.

Histologically, the predominant pattern was tubulopapillary in 33 cases (50%). Other patterns included trabecular in 2 (3%), adenomatoid in 11 (18%), solid in 3 (6%), and micropapillary in 15 (23%).

Inflammatory infiltrates were present in all cases and graded as mild in 60 patients (94%) and severe in 4 (6%). Tumor necrosis was identified in 8 cases (12.6%).

SMARCA2 and SMARCA4 Expression

Loss of SMARCA2 nuclear expression was observed in 4 of 64 cases (6%), while loss of SMARCA4 nuclear expression was also observed in 4 cases (6%) (**Table 1**). No case showed combined complete loss of both SMARCA2 and SMARCA4 in interpretable cores. Non-interpretable cases for a given marker were excluded only from that specific analysis.

Association with Clinicopathologic Parameters

There was no significant association between SMARCA2 loss and age, sex, follow-up time, tumor grade, type of surgery, or

Table 1. Demographic and clinicopathological details of the study population (n=64)

Variables	Value
Age, years[a]	57.1±12
<65	44 (67)
Gender, (male), n (%)	51(79)
Histopathologic subtype, n (%)	
Tubulopapillary	33 (50)
Trabecular	2 (3)
Adenomatoid	11 (18)
Solid	3 (6)
Micropapillary	15 (23)
The presence of necrosis, n (%)	8 (12)
The presence of SMARC A2, n (%)	60 (94)
The presence of SMARC A4, n (%)	60 (94)
The presence of nuclear atypia, n (%)	
Mild	14 (22)
Moderate	27 (42)
Severe	23 (36)
The presence of mitosis, n (%)	
Low	29 (45)
Intermediate	18 (28)
High	17 (27)
The presence of inflammation	
Mild	58 (91)
Severe	6 (9)
The grade of mesotheliomas	
Low	49 (76)
High	15 (24)
Stage, n (%)	
I	60 (94)
II	4 (6)
Surgical procedure, n (%)	
EPP	11 (17)
PD	53 (83)

a: Results given as mean±SD; n: Number of cases, SMARC A4, A2; EPP: Extrapleural pneumonectomy, PD: Pleurectomy/decortication

Table 2. Univariate analysis of variables in patients with mesetolioma between SMARCA 2 positive and SMARCA 2 negative group

Variables	SMARCA2-positive (n=60)	SMARCA2-negative (n=4)	p value
Age, years[a]	57.5±12.8	52.1±9.4	0.35
Male sex, n (%)	47 (78)	4 (100)	0.39
Presence of necrosis, n (%)	8 (16)	0 (0)	0.90
Nuclear atypia, n (%)			0.079[+]
– Mild	11 (18)	3 (75)	
– Moderate	27 (45)	0 (0)	
– Severe	22 (37)	1 (25)	
Mitotic index, n (%)			0.165[+]
– Low	26 (44)	3 (75)	
– Intermediate	17 (33)	1 (25)	
– High	17 (33)	0 (0)	
Inflammation, n (%)			0.02
– Mild	57 (95)	3 (75)	
– Severe	3 (5)	1 (25)	
Tumor grade, n (%)			0.56
– Low	45 (75)	4 (100)	
– High	15 (25)	0 (0)	
Stage, n (%)			0.23
– I	57 (95)	3 (75)	
– II	3 (5)	1 (25)	
Surgical procedure, n (%)			0.13
– Pleurectomy/ decortication (PD)	51 (85)	2 (50)	
– Extrapleural pneumonectomy (EPP)	9 (15)	2 (50)	
Follow-up time, months[b]	18.5 (9.0–31.7)	10.0 (4.5–56.7)	0.49

a: Results given as mean±SD, b: Results given as median (interquartile rage (IQR)), n: Nnumber of cases, +one-way ANOVA tests,
SMARC A2, -; EPP: Extrapleural pneumonectomy, PD: Pleurectomy/decortication

stage. However, SMARCA2 loss was significantly associated with severe inflammation, with SMARCA2-deficient cases more frequently displaying marked lymphocytic infiltrates compared with SMARCA2-retained tumors (p=0.02) (**Table 2**).

SMARCA4 loss showed no statistically significant relationships with age, sex, follow-up duration, tumor grade, type of surgery, stage, necrosis, or inflammation intensity (**Table 3**).

Survival Analysis

At the time of analysis, all patients had died. The mean overall survival (OS) was 22 months, with 2-year and 5-year OS rates of 35% and 6%, respectively. Stage-specific 5-year OS was 10% for stage I, whereas no 5-year survivors were observed in stage II.

In the SMARCA2-deficient group, the median OS was 24 months and the 5-year OS rate was 17%, while no 5-year survivors were observed among SMARCA2-retained cases; however, SMARCA2 loss was not significantly associated with OS (log-rank p=0.88) (**Figure 3**).

In the SMARCA4-deficient group, the median OS was 23 months and the 5-year OS rate was 13%, whereas no 5-year survivors were observed among SMARCA4-retained cases; SMARCA4 loss was not significantly associated with OS (log-rank p=0.33) (**Figure 4**).

Survival outcomes: Given the low number of SMARCA2-/SMARCA4-loss cases and limited events, subgroup comparisons should be interpreted as descriptive/exploratory.

DISCUSSION

In this single-institution cohort of epithelioid pleural mesothelioma, we found that SMARCA2 and SMARCA4 loss were relatively rare events (6% each). Importantly, SMARCA2 loss, but not SMARCA4 loss, was associated with a marked inflammatory infiltrate in the tumor microenvironment.

Frequency of SMARCA2/SMARCA4 Loss

Our findings are broadly consistent with prior work suggesting that SWI/SNF deficiency is uncommon in conventional pleural mesothelioma. Perret et al.[4] described SMARCA4-deficient thoracic sarcomas and reported SMARCA4 loss in a subset of mesotheliomas in a series that also included SMARCA4-DUT, raising diagnostic considerations at the interface of these entities. Ahadi and Gill,[9] in a larger series of 296 mesotheliomas, identified SMARCA4 loss in only two epithelioid cases (0.7%) and did not observe SMARCA2 loss. Ren et al.[10] subsequently reported that pleural malignant mesotheliomas generally do not demonstrate SWI/SNF complex deficiency, arguing against a major role of core SWI/SNF subunit loss in typical mesothelioma biology.

Table 3. Univariate analysis of variables in patients with mesetolioma between SMARCA 4 positive and SMARCA 4 negative group

	Patients with SMARCA 4 (+) (n=60)	Patients with SMARCA 4 (-) (n=4)	p value
Age, years [a]	56.8±12	62.5±10	0.31
Gender (Male), n, (%)	47 (78)	4 (100)	0.39
The presence of necrosis, n (%)	8 (16)	0 (0)	0.57
The presence of nuclear atypia, n (%)			
Mild	13 (22)	1 (25)	0.76+
Moderate	26 (42)	1 (25)	
Severe	21 (36	2 (50)	
The presence of mitosis, n (%)			
Low	28 (46)	1 (25)	0.64+
Intermediate	16 (31)	2 (50)	
High	16 (31)	1 (25)	
The presence of inflammation, n (%)			
Mild	55 (91)	3(75)	0.33
Severe	3 (9)	1 (25)	
The grade of mesotheliomas, n (%)			
Low	45 (75)	4 (100)	0.33
High	15 (25)	0	
Stage, n (%)			
I	57 (95)	3 (75)	0.23
II	3 (5)	1 (25)	
Surgical procedure, n (%)			
EPP	51 (85)	2 (50)	0.13
PD	9 (15)	2 (50)	
Follow-up period(mounth) [b]	17 (9-31.7)	27 (23-61)	0.09

a: Results given as mean±SD, b: Results given as median (interquartile rage (IQR)), n: Number of cases, +: One-way ANOVA tests,
SMARC A4,; EPP: Extrapleural pneumonectomy, PD: Pleurectomy/decortication

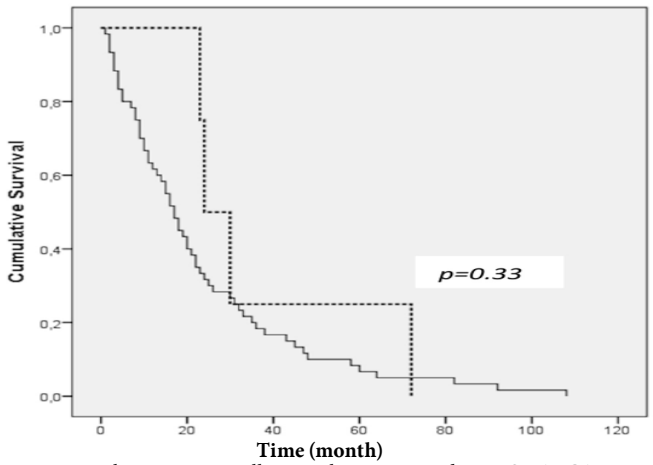

Figure 3. Kaplan–Meier overall survival curves according to SMARCA2 status in epithelioid pleural mesothelioma (log-rank test).

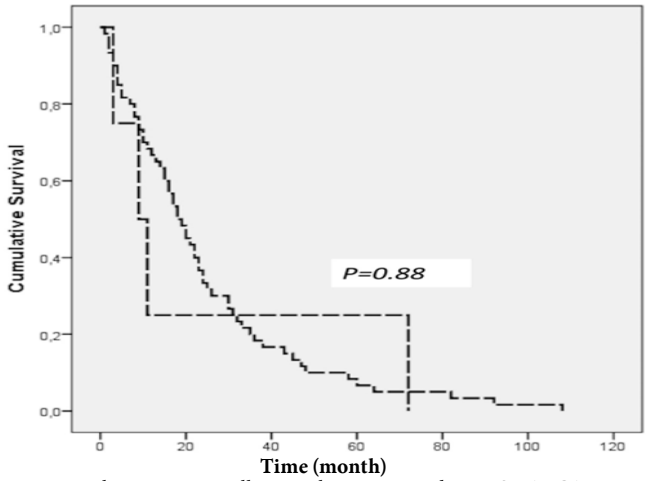

Figure 4. Kaplan–Meier overall survival curves according to SMARCA4 status in epithelioid pleural mesothelioma (log-rank test).

In our series, the frequency of SMARCA4 loss (6%) is higher than that reported by Ahadi[9] and Ren[10] but still indicates that complete SMARCA4 deficiency is uncommon in epithelioid pleural mesothelioma. Differences in detection rates may reflect cohort size, selection criteria, technical factors (antibody clones, cut-offs, tissue microarray vs whole sections), or tumor sampling. Importantly, none of our SMARCA4-deficient cases showed the classic clinicoradiologic or morphological features of SMARCA4-DUT, supporting their interpretation as bona fide mesotheliomas rather than misclassified SMARCA4-DUT.

SMARCA2 Loss and Inflammatory Microenvironment

A novel observation of this study is the significant association between SMARCA2 loss and severe inflammatory infiltrates. Although patient numbers are small, this finding aligns with emerging evidence that SWI/SNF alterations can shape tumor–immune interactions. Experimental and translational studies have linked SWI/SNF deficiency to increased immunogenicity, enhanced tumor-infiltrating lymphocytes, and in some settings improved responses to immune checkpoint blockade.[11,12]

In mesothelioma, chronic inflammation caused by asbestos and other mineral fibers is a key pathogenic driver, and the crosstalk between genetic alterations and the immune microenvironment is increasingly recognized as a therapeutic target.[6,8,12] Our data raise the possibility that SMARCA2-deficient epithelioid mesotheliomas may represent a biologically distinct subgroup with heightened immune activation. Whether this translates into differential sensitivity to immunotherapy or other targeted approaches warrants further investigation in larger, multi-institutional cohorts with detailed immune profiling.

Diagnostic Implications

Because SMARCA4-deficient thoracic tumors and mesotheliomas may share some clinical and morphologic features, SMARCA4 immunohistochemistry has been proposed as a potential ancillary marker in the differential diagnosis of pleural tumors.[4,9,10] The low frequency of SMARCA4 loss in our cohort supports the notion that sustained SMARCA4 expression is typical of epithelioid pleural mesothelioma. If future multi-center series confirm that SMARCA4 loss remains rare in mesothelioma, SMARCA4 status—interpreted in combination with morphology and mesothelial and epithelial markers—could be useful in distinguishing mesothelioma from SMARCA4-DUT and SMARCA4-deficient lung carcinomas in challenging thoracic biopsies.

Biological and Clinical Relevance

The SWI/SNF complex acts as a tumor suppressor through context-dependent transcriptional regulation and chromatin remodeling.[1,2,8] Although truncal SWI/SNF mutations appear to be relatively infrequent in mesothelioma compared with other tumors, subtle alterations in complex composition or function may still contribute to disease heterogeneity and treatment response.[6,8] Our observation that SMARCA2 loss is associated with a robust inflammatory infiltrate suggests that even low-frequency SWI/SNF alterations may have disproportionate effects on the tumor microenvironment.

Future studies integrating next-generation sequencing, immunohistochemical panels for multiple SWI/SNF subunits, and comprehensive immune profiling (including CD8+ T-cell density, PD-L1 expression, and T-cell receptor clonality) are needed to clarify the prognostic and predictive significance of SMARCA2/4 loss in mesothelioma.

Limitations

Adjuvant chemotherapy and/or radiotherapy was planned for all patients; however, actual treatment delivery and completion could not be reliably ascertained because of the retrospective design and incomplete treatment documentation.

Immune cell subtyping (e.g., CD3/CD8/CD68) was not performed; therefore, the cellular composition of the inflammatory infiltrate could not be characterized.

This study has several limitations. First, its retrospective, single-center design may introduce selection bias. Second, the sample size is relatively small, particularly for the subgroup with SMARCA2 and SMARCA4 loss, limiting the statistical power to detect subtle associations and precluding robust survival analysis. Third, we relied on TMA cores, which may not fully capture intratumoral heterogeneity of SMARCA2/4 expression. Fourth, molecular analyses (e.g., sequencing of SMARCA2/4 and other SWI/SNF genes) and detailed immune profiling were not available, preventing association of immunohistochemical findings with underlying genetic alterations and immune signatures. Finally, only epithelioid mesotheliomas were included; sarcomatoid and biphasic subtypes were not evaluated. Tumors were staged according to the AJCC 8th edition TNM system, in which T3 tumors may fall into stage II or III depending on nodal status; thus, the scarcity of higher-stage cases reflects surgical selection and institutional referral patterns rather than misclassification. Finally, the association between SMARCA2 loss and severe inflammation is based on very small numbers (n=4) and should be viewed as hypothesis-generating.

CONCLUSION

In summary, SMARCA2 and SMARCA4 expression loss is rare in epithelioid pleural mesothelioma, occurring in only a small subset of cases. While SMARCA4 status did not correlate with clinicopathologic or inflammatory parameters, SMARCA2 deficiency was associated with a marked lymphocytic (inflammatory) response in this cohort; given the small number of SMARCA2-loss cases (n=4), this finding should be interpreted cautiously as exploratory. These data support the notion that alterations in SWI/SNF subunits may contribute to shaping an immunogenic tumor microenvironment and suggest that SMARCA2/SMARCA4 assessment may provide both diagnostic and potential biomarker information in pleural malignancies. Confirmation of these findings in larger, multi-institutional cohorts with integrated genomic and immune profiling will be essential to clarify the true prevalence, biological impact, and therapeutic relevance of SMARCA2 and SMARCA4 alterations in pleural mesothelioma.

ETHICAL DECLARATIONS

Ethics Committee Approval

Was approved by the Clinical Researches Ethics Committee of İstanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 01.07.2021, Decision No: 2021-130).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The author declare no conflicts of interest related to this study.

Financial Disclosure

The author received no financial support for the conduct or publication of this research.

Author Contributions

The preparation of the article, the analysis of the data, and the writing process were carried out entirely by the author.

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Case Report

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Development of common variable immunodeficiency in a patient with severe aplastic anemia: a case report

İzel Özgören*[1], İrfan Yavaşoğlu[2]

[1]Department of Internal Medicine, Faculty of Medicine, Aydın Adnan Menderes University, Aydın, Turkiye
[2]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Aydın Adnan Menderes University, Aydın, Turkiye

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***Corresponding Author:** İzel Özgören, izelzgren@gmail.com

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ABSTRACT

Severe aplastic anemia (AA) and common variable immunodeficiency (CVID) are distinct clinical entities that may rarely coexist due to shared molecular mechanisms. This report describes a 43-year-old male patient diagnosed with severe AA who subsequently developed CVID associated with an IKZF1 gene variant. Bone marrow examination confirmed severe hypocellularity. Although initial immunosuppressive therapy failed to achieve transfusion independence, hematologic recovery was obtained with eltrombopag. Approximately one year later, immunologic evaluation demonstrated hypogammaglobulinemia (IgA 0,7 g/L, IgM 0,63 g/L, IgG 4,78 g/L) and marked B-cell lymphopenia (total lymphocytes 1,990/mm³; B cells 100/mm³) with preserved T-cell counts. Genetic analysis revealed a heterozygous IKZF1 (c.115A>G, p.Thr39Ala) variant, supporting the diagnosis of CVID. This case highlights the importance of integrating genetic evaluation into the diagnostic work-up of patients presenting with combined hematologic and immunologic abnormalities, enabling accurate classification, appropriate management, and long-term follow-up.

Keywords: Aplastic anemia, common variable immunodeficiency, IKZF1 gene

INTRODUCTION

Aplastic anemia (AA) is a bone marrow failure syndrome characterized by marked hypocellularity of the bone marrow and peripheral pancytopenia.[1] Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder resulting from defective B-cell differentiation and impaired immunoglobulin production.[2]

Although these conditions are traditionally considered distinct, recent genetic studies suggest that shared molecular pathways, particularly involving transcription factors regulating hematopoiesis and lymphopoiesis, may link bone marrow failure and immune deficiency. Herein, we report a rare case of severe AA followed by CVID associated with an IKZF1 gene variant, highlighting the importance of genetic evaluation in patients presenting with combined hematologic and immunologic features.

CASE

A 43-year-old male with no significant past medical history presented with gingival bleeding, ecchymosis, and purpura. Initial laboratory evaluation revealed hemoglobin 8.7 g/dl, mean corpuscular volume 62.4 fL, leukocytes 1,370/mm³, neutrophils 350/mm³, lymphocytes 880/mm³, platelets 2,000/mm³, lactate dehydrogenase 238 U/L (reference range: 125–243 U/L), and a reticulocyte count of 12,500/mm³.

Viral and autoimmune markers, including hepatitis B surface antigen, anti-hepatitis C virus, anti-human immunodeficiency virus, Epstein–Barr virus viral capsid antigen IgM, cytomegalovirus polymerase chain reaction, and antinuclear antibody, were negative. Paroxysmal nocturnal hemoglobinuria and Fanconi anemia were excluded using flow cytometric fluorescent aerolysin (FLAER) analysis and diepoxybutane testing, respectively.

Bone marrow aspiration and biopsy demonstrated approximately 15% cellularity with mild reticulin fibrosis (+1), consistent with severe AA. The patient received cyclosporine combined with horse anti-thymocyte globulin as first-line immunosuppressive therapy; however, he remained transfusion-dependent and lacked a human leukocyte antigen–matched donor. Eltrombopag (150 mg/day) was subsequently initiated, leading to progressive hematologic recovery and transfusion independence within three months.

Approximately one year later, the patient developed a carbuncle on the anterior thoracic wall. Immunologic evaluation revealed hypogammaglobulinemia, with immunoglobulin A 0.7 g/L (0.5–4 g/L), immunoglobulin M 0.63 g/L (0.5–2.5 g/L), and immunoglobulin G 4.78 g/L (6–15 g/L). Lymphocyte subset analysis showed 1,990 lymphocytes/mm³, including only 100 B cells/mm³, while

T-cell counts were preserved. These findings could not be fully explained by prior immunosuppressive therapy. Molecular genetic testing identified a heterozygous IKZF1 (c.115A>G, p.Thr39Ala) variant, supporting the diagnosis of CVID. Notably, the patient had no prior history of recurrent infections and demonstrated a normal serologic response to hepatitis B vaccination (anti-HBs seroconversion) before this presentation.

Given the absence of recurrent or severe infections at the time of evaluation, the patient was not started on regular intravenous immunoglobulin replacement therapy. Preventive counseling regarding infection control was provided, and close clinical and laboratory follow-up was recommended.

DISCUSSION

The IKZF1 gene encodes Ikaros, a zinc-finger transcription factor essential for lymphoid lineage commitment and immune homeostasis. Pathogenic variants in IKZF1 have been associated with a spectrum of immune dysregulation disorders, including CVID, combined immunodeficiency, and bone marrow failure syndromes such as AA.[2-6]

In this patient, CVID was considered more likely to represent a shared immune dysregulation spectrum related to the IKZF1 variant rather than a treatment-related complication or a coincidental association, since there is no established evidence that equine anti-thymocyte globulin (ATG) or eltrombopag induces CVID.

This case illustrates a rare but clinically relevant overlap between severe AA and CVID, suggesting a shared genetic background. While IKZF1-associated disorders have been reported to present with CVID/dysgammaglobulinemia and various cytopenias, a distinctive aspect of our case is the clinical predominance of severe AA at onset, followed by the delayed emergence of hypogammaglobulinemia and profound B-cell lymphopenia approximately one year after the initial presentation, with preserved T-cell counts after hematologic recovery with eltrombopag. This temporal dissociation supports a shared IKZF1-related immune dysregulation that may evolve along hematologic and immunologic axes over time. Recognition of such associations is crucial, as immune deficiency may evolve after apparent hematologic recovery. Comprehensive genetic analysis should therefore be considered in patients with bone marrow failure who later develop immunologic abnormalities, enabling timely diagnosis, appropriate surveillance, and individualized management strategies.

CONCLUSION

Clinicians should remain vigilant for the development of immune deficiency in patients with AA, particularly when pathogenic variants such as IKZF1 are identified. Early molecular diagnosis facilitates accurate disease classification, guides follow-up strategies, and improves long-term patient care.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

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Case Report

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Early-stage cervical leiomyosarcoma and carcinosarcoma with long-term disease-free survival after surgery alone: a dual case report

Bengü Mutlu Sütcüoğlu*[1], Hatice Kansu Çelik[2], Emre Akarsu[3]

[1]Department of Obstetrics and Gynaecology, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

[2]Department of Obstetrics and Gynaecology, Faculty of Medicine, Lokman Hekim University, Ankara, Turkiye

[3]Department of Medical Pathology, Faculty of Medicine, Lokman Hekim University, Ankara, Turkiye

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***Corresponding Author:** Bengü Mutlu Sütcüoğlu, drbengumutlu@gmail.com

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ABSTRACT

Cervical leiomyosarcoma and cervical carcinosarcoma are extremely rare malignancies, and optimal management strategies remain undefined. In early-stage disease, the benefit of adjuvant therapy is controversial, raising concerns about potential overtreatment. We report two patients with early-stage primary cervical sarcomas who presented with similar clinical findings but were diagnosed with different histopathological subtypes. A 47-year-old woman presented with abnormal vaginal bleeding and a polypoid cervical mass and was diagnosed with cervical leiomyosarcoma following complete excision. A 66-year-old postmenopausal woman presented with postmenopausal bleeding and was diagnosed with cervical carcinosarcoma after comprehensive surgical staging. In both cases, preoperative imaging demonstrated disease confined to the cervix, and final pathology confirmed FIGO stage IB2 tumors with negative surgical margins and no lymph node or distant metastases. Multidisciplinary tumor board evaluation was performed, and adjuvant chemotherapy or radiotherapy was not administered in either patient. Despite the aggressive histological features traditionally associated with these tumor types, both patients achieved sustained long-term disease-free survival at 2 and 4 years of follow-up, respectively. These cases suggest that selected patients with early-stage cervical sarcomas may achieve favorable outcomes with surgery alone and support a risk-adapted, individualized approach to adjuvant treatment decisions to avoid potential overtreatment.

Keywords: Cervical sarcoma, leiomyosarcoma, carcinosarcoma, surgery alone, overtreatment, risk-adapted treatment, case report

INTRODUCTION

Sarcomas of the uterine cervix are extremely rare, accounting for less than 1% of all cervical malignancies.[1] Among these, cervical leiomyosarcoma (CLMS) and cervical carcinosarcoma (CCS) represent particularly uncommon histological subtypes and pose significant diagnostic and therapeutic challenges. Due to their rarity, available evidence is limited to case reports and small case series, and no standardized management guidelines exist.

Leiomyosarcoma commonly arises in soft tissue and visceral organs; however, primary involvement of the uterine cervix is extremely uncommon. A 2020 literature review identified only 40 reported cases of primary CLMS worldwide.[2] Patients typically present with vaginal bleeding and a cervical mass, and the disease predominantly affects peri- and postmenopausal women.[3] Carcinosarcoma is a biphasic malignancy composed of both epithelial and mesenchymal components and most frequently arises in the uterine corpus.[4] Primary CCS is exceedingly rare, accounting for approximately 0.005% of cervical cancers, with only 70 cases reported in the English literature by 2013.[5] Similar to CLMS, the most common clinical findings are vaginal bleeding and a protruding cervical mass, and most patients are postmenopausal.[6] There is no established consensus regarding the optimal management of CLMS, including the roles of lymphadenectomy and adjuvant therapy. Likewise, treatment strategies for CCS remain unclear and are largely extrapolated from data on uterine carcinosarcoma.[6]

Despite distinct histopathological features, CLMS and CCS may present with similar clinical findings, making accurate pathological diagnosis essential for appropriate management. In early-stage disease, the role of adjuvant therapy remains controversial, and concerns regarding potential overtreatment have emerged. In this report, we present two cases of early-stage cervical sarcoma with similar clinical presentations but different histological diagnoses, both achieving favorable long-term outcomes following surgical management alone.

CASE 1

A 47-year-old woman (G4P2) presented with persistent vaginal bleeding for two months. Her medical and family histories were unremarkable. Cervical smear tests performed during the previous year were normal. On gynecological examination, a hemorrhagic polypoid mass approximately 3 cm in diameter was observed protruding from the cervix (**Figure 1**).

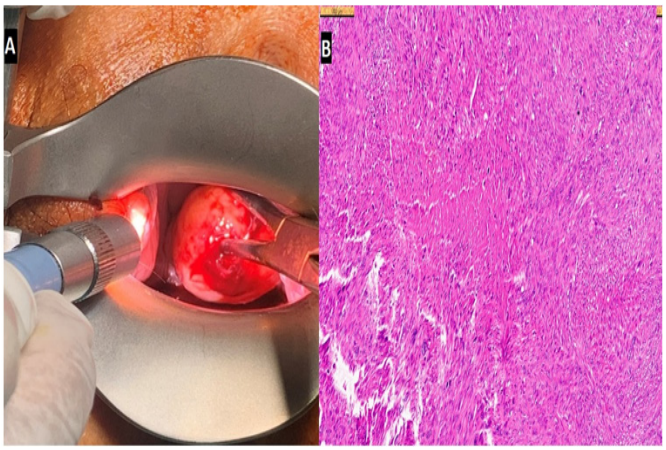

Figure 1. Tumor appearence of the case 1. (**A**) Macroscopic view of the tumor (**B**) Tumor necrosis and mitotic figures in smoth muscle bundles with atypical, spinde-shaped morphology

A cervical punch biopsy was attempted before surgery; however, the specimen was nondiagnostic due to extensive necrosis and hemorrhage. Therefore, complete surgical excision of the cervical mass was performed together with endometrial curettage. The excised mass measured 4×3×3 cm. Histopathological examination revealed moderate cellular atypia, tumor necrosis and a mitotic activity of 9 per 10 high-power fields, consistent with a diagnosis of leiomyosarcoma. Immunohistochemical staining demonstrated positivity for smooth muscle markers including SMA and desmin and negativity for cytokeratin markers, supporting the diagnosis of leiomyosarcoma. No additional molecular or genetic analyses were performed in these cases, which represents a limitation of the present report. No malignant cells were detected in the endometrial curettage specimen. Preoperative imaging with contrast-enhanced computed tomography of the chest, abdomen and pelvis showed no evidence of metastatic disease. Pelvic magnetic resonance imaging demonstrated a lesion confined to the cervix, with no evidence of parametrial, uterine or extra-cervical extension.

The patient subsequently underwent comprehensive surgical staging, including total hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic and para-aortic lymph node dissection. Although routine lymphadenectomy is not universally recommended in leiomyosarcoma, comprehensive staging including pelvic and para-aortic lymph node dissection was performed in this case due to the initial diagnostic uncertainty and to exclude occult metastasis as part of institutional staging practice. Final pathological examination showed no residual tumor in the surgical specimen. All surgical margins were negative and no lymph node or distant metastases were identified. The final stage was determined as FIGO stage IB2.

The case was discussed in a multidisciplinary tumor board including gynecologic oncology, pathology and medical oncology specialists. Given that the tumor was confined to the cervical polyp, completely excised, with negative margins and no evidence of residual or metastatic disease, adjuvant chemotherapy or radiotherapy was not recommended. The patient has remained disease-free for two years and is followed regularly every three months with pelvic examination and imaging.

CASE 2

A 66-year-old postmenopausal woman (G2P2) presented with a two-month history of postmenopausal spotting. Her medical and family histories were unremarkable. Previous cervical cytology and HPV test results were not available in the electronic medical records. On gynecological examination, a necrotic and bleeding mass approximately 3 cm in diameter was observed arising from the cervical canal. Bimanual examination revealed no parametrial involvement. Transvaginal ultrasonography demonstrated that the lesion was confined to the cervix and was independent of the uterus and adnexal structures.

A cervical punch biopsy performed prior to surgery revealed atypical epithelial proliferation with spindle cell components, raising suspicion for a mixed malignant tumor. Preoperative imaging with contrast-enhanced computed tomography of the chest, abdomen, and pelvis showed no evidence of distant disease. Pelvic magnetic resonance imaging demonstrated a cervical lesion without extension to the parametrium, uterus, or adjacent pelvic structures. The patient subsequently underwent comprehensive surgical treatment, including radical hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic and para-aortic lymph node dissection. The excised tumor measured 3.5×2×2 cm. Final histopathological examination confirmed the diagnosis of CCS. The tumor was confined to the cervix, did not extend to the vagina, and showed no lymphovascular invasion. Surgical margins were negative. The omentum was benign, and no lymph node metastases were identified. The final stage was determined as FIGO stage IB2. Immunohistochemical analysis demonstrated strong positivity for p16, pan-cytokeratin, CAM5.2, and PAX8, with desmin positivity in the sarcomatoid component. p53 was positive in both epithelial and mesenchymal components, while p40 was negative (**Figure 2**).

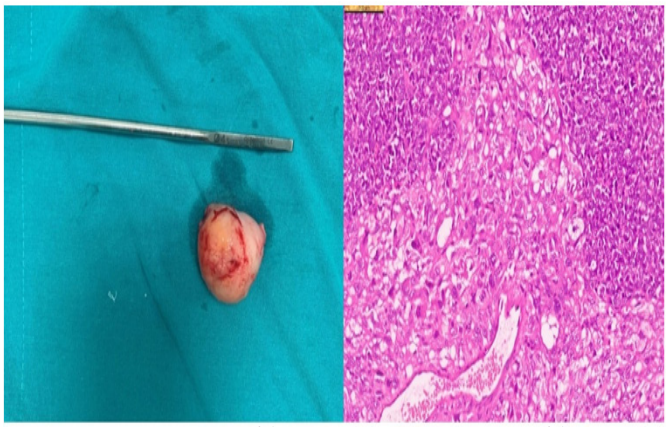

Figure 2. Tumor appearance of the case 2. (**A**) Macroscopic view of the tumor (**B**) Showing a high-grade malignant tumor with biphasic morphology (H&E, 40x)

The case was discussed at a multidisciplinary tumor board. Given the aggressive biological behavior of carcinosarcoma, adjuvant treatment with four cycles of carboplatin–paclitaxel chemotherapy and external beam radiotherapy was recommended. However, the patient declined further treatment. She has remained disease-free for four years and is followed regularly with pelvic examination and imaging every three months for the first two years and every six months thereafter.

DISCUSSION

Primary sarcomas of the uterine cervix, including CLMS and CCS, are exceedingly rare and account for less than 1% of all cervical malignancies. Because of this rarity, available evidence is largely derived from case reports and small case series, which leads to heterogeneous treatment approaches and a lack of consensus guidelines. In the present report, we describe two early-stage cervical sarcomas with distinct histopathological subtypes: one CLMS and one CCS. Both patients were treated with comprehensive surgical staging alone without adjuvant therapy and remain disease-free at two and four years of follow-up. These outcomes provide meaningful clinical evidence regarding the ongoing debate on the necessity of adjuvant treatment in selected early-stage cases.

Surgery remains the cornerstone of treatment for both CLMS and CCS. In the largest systematic review and meta-analysis of CLMS, Kılıç et al.[2] demonstrated that hysterectomy was an independent prognostic factor for disease-specific survival, whereas the extent of surgery did not significantly influence recurrence. Similarly, Bansal et al.[7] reported no lymph node metastases among patients who underwent lymphadenectomy, and Kılıç et al.[2] observed no nodal involvement in most patients who had lymph node dissection. These findings suggest that routine lymphadenectomy may not be necessary in CLMS and should be reserved for patients with bulky or radiologically suspicious lymph nodes. In localized CCS, surgical management typically includes radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection. Radical surgery is strongly recommended for stage IB disease, which accounts for nearly half of reported cases, whereas cytoreductive surgery is generally reserved for advanced disease or for patients who are not candidates for radical surgery.[8]

To date, no studies have defined an optimal adjuvant treatment strategy for cervical sarcomas. In CLMS, reported adjuvant approaches include chemotherapy alone or combined chemoradiotherapy, yet available data have failed to demonstrate a clear survival benefit. Given the substantial toxicity associated with systemic therapy, the role of adjuvant treatment in early-stage CLMS remains uncertain.[9] In CCS, some authors advocate aggressive adjuvant treatment. A meta-analysis by Comert et al.[10] recommended adjuvant radiotherapy with or without chemotherapy for locally advanced disease and reported improved disease-free survival in early-stage cases treated with multimodal therapy. However, these recommendations are largely extrapolated from uterine carcinosarcoma data. In the review by Shu et al.,[6] most reported patients received radiotherapy, but the absence of randomized or well-designed comparative studies limits any definitive conclusions regarding its impact on survival. Similarly, although platinum-based chemotherapy regimens are frequently used, their true efficacy remains difficult to assess.

Despite the frequent use of adjuvant therapy in published reports, favorable outcomes have also been observed in selected early-stage patients treated with surgery alone. In CLMS, Doshi et al.[11] reported recurrence-free survival in a patient managed without adjuvant therapy, whereas Khosla et al.[12] described early mortality in an older untreated patient, supporting evidence that age may be an independent prognostic factor. In CCS, Sharma et al.[13] reported long-term disease-free survival in two patients with stage IB disease managed without adjuvant therapy, and Lin et al.[14] described a similar outcome in a patient with stage IB1 disease treated with surgery alone. These observations suggest that disease stage and patient-related factors may be more relevant determinants of outcome than routine adjuvant therapy and that surveillance after surgery may be appropriate in carefully selected early-stage cases.

CONCLUSION

Primary sarcomas of the uterine cervix, including CLMS and CCS, are exceedingly rare malignancies with overlapping clinical presentations. Due to limited evidence derived mainly from case reports, standardized treatment algorithms are lacking. While surgery remains the cornerstone of management in early-stage disease, the role of adjuvant therapy is undefined. These observations may contribute to the limited existing literature suggesting that surgery alone could be considered in carefully selected early-stage cases; however, definitive recommendations require larger collaborative studies. Multicenter collaborative studies are needed to refine evidence-based management strategies.

ETHICAL DECLARATIONS

Informed Consent
Written informed consent was obtained from the patient(s) included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process
This report underwent external peer review.

Conflict of Interest
The authors declare no conflicts of interest.

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Author Contributions
Concept: B.M.S.; Design: B.M.S., H.K.Ç., E.A.; Materials: B.M.S., H.K.Ç., E.A.; Data Collection and/or Processing: B.M.S., H.K.Ç., E.A.; Writing the Article: B.M.S.; Critical Review: B.M.S., H.K.Ç., E.A.; Final Approval: B.M.S., H.K.Ç., E.A.

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