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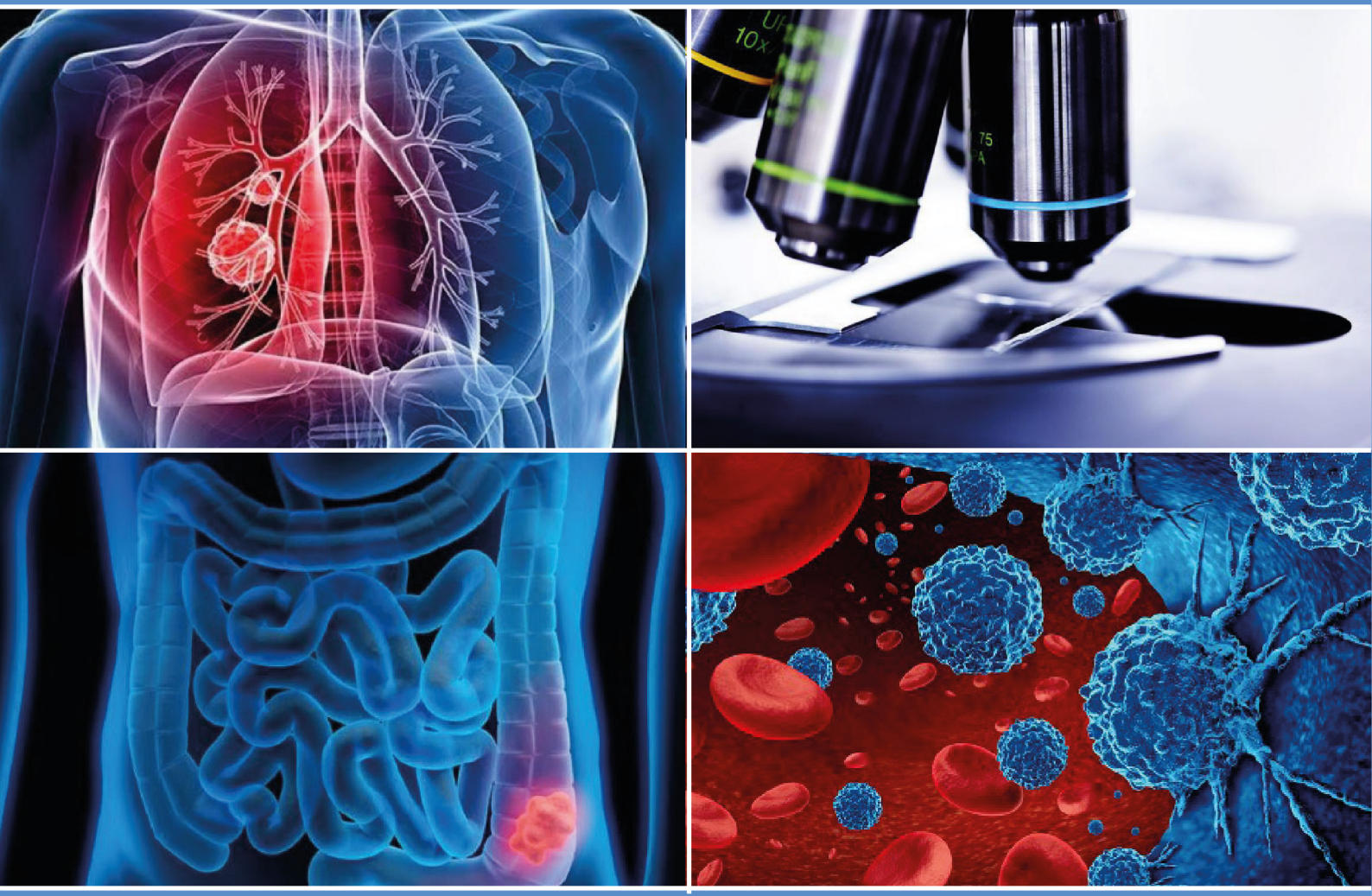

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EDITORIAL

Dear Colleagues,

I am delighted to announce that our journal has completed its second year with great success. Over the past year, we have published a total of 15 original articles, 6 case reports, 2 reviews, and 2 letters to the editor. These contributions have made significant advancements in the field of hematology-oncology. At the conclusion of our first year, we achieved our short-term goal of being included in international indexes. Building on this momentum, during our second year, we successfully gained inclusion in additional international indexes, reflecting the growing impact and recognition of our journal.

This success would not have been possible without the hard work and dedication of our editors, editorial team, and authors, as well as the unwavering support of our readers and supporters. I extend my heartfelt gratitude to all of you who have contributed to this journey.

As we enter the new year, I am pleased to share that the first issue of this year has been published, featuring 3 original articles, 2 case reports, and 1 letter to the editor. However, it is with profound and heartfelt sadness that we acknowledge the loss of 78 lives in the devastating fire disaster that shook our country to its core this year. This tragedy has left an indelible mark on all of us, and we grieve deeply for the lives lost and the families affected. As a tribute to their memory, we dedicate the first issue of the year to them, with the hope of honoring their legacy through our unwavering commitment to excellence in the field of hematology-oncology.

Looking ahead, our primary goal is to further expand our reach and enhance our contributions to the scientific community. We aspire to be included in additional indexes and to continue making a significant impact in hematology-oncology research and practice. I firmly believe that with your continued support and contributions, we can achieve these objectives and establish our journal as a valuable resource for researchers and practitioners in the field.

Once again, I extend my sincere thanks to everyone who has been part of this journey and helped us reach this milestone. Let us move forward together, contributing even more to the advancement of hematology-oncology with new and impactful publications.

Best regards,

Assoc. Prof. Serhat ÇELİK

Editor in Chief

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Journal of Current Hematology & Oncology Research

Original Article

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Can platelet and leukocyte counts guide the early prediction of neonatal sepsis?

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ABSTRACT

Aims: Early recognition of neonatal sepsis, which is an important cause of neonatal mortality and morbidity, contributes positively to clinical outcomes. Although culture methods are the gold standard for diagnosis, they take time and can delay critical treatment decisions. Therefore, there is a need for validation of easily accessible, cost-effective practical approaches in the diagnosis of neonatal sepsis. Our study aimed to evaluate the leukocyte and platelet counts as diagnostic markers in early neonatal sepsis.

Methods: In our prospective study, the contribution of platelet and leukocyte counts to the diagnostic accuracy of two groups of patients diagnosed with sepsis (group I) and without sepsis (group II) in the neonatal intensive care unit (NICU) were evaluated on days 1, 3, 5, and 7.

Results: The group diagnosed with sepsis showed a significant difference in terms of low platelet count and platelet reduction rates. The specificity and sensitivity of thrombocytopenia in the diagnosis of sepsis were 88.8% and 81.3%, respectively. In addition, thrombocytopenia in the early period was informative about the unfavorable prognosis.

Conclusion: Our findings suggest that thrombocytopenia can be used as a red flag for early sepsis diagnosis.

Keywords: Premature, sepsis, thrombocytopenia

INTRODUCTION

Mortality and morbidity due to sepsis in premature infants are still high.[1] Because of the rapid course, multiorgan involvement, and high mortality in sepsis, prompt diagnosis and initiation of treatment are extremely important to improve the prognosis. However, making the correct diagnosis is difficult work for the clinician, and diagnostic tests are needed to predict neonatal sepsis early and accurately.[2,3] One of the most important of these tests is complete blood count (CBC). It is performed on consecutive days in every infant hospitalized in the neonatal intensive care unit (NICU). Changes in leukocyte and platelet counts have also been used in the diagnosis of sepsis in many studies.[2,3]

In this study, we aimed to evaluate the role of leukocyte and platelet counts, which are cost-effective and easily accessible CBC parameters, in the early prediction of sepsis in premature infants.

METHODS

The study was carried out with the permission of the Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 22.12.2005, Decision No: 2005/159). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This prospective study included a total of 207 premature infants with a gestational age between 24-37 weeks who were followed up in the NICU of Kırıkkale University Medical Faculty Hospital between September 2005-November 2005.

Demographic data and sepsis risk factors of premature and their mothers were recorded. Töllner scoring system was used to diagnose sepsis.[3] Physical examinations were performed by the same physician every day, and findings consistent with those of the sepsis clinic were evaluated. CBC and C-reactive protein (CRP) were measured in premature newborns on postnatal days 1, 3, 5 and 7. Blood and urine cultures were obtained from those with a prediagnosis of sepsis, and tracheal aspirate cultures were obtained from those who were intubated. Indications for cesarean section in both groups were placental abruption, placenta previa, fetal distress, breech presentation, eclampsia, preeclampsia, prolonged premature rupture of membranes, oligohydramnios, multiple pregnancies, repeated C/S, HELLP syndrome, non-progressive labor, cord presentation, pregnancy by invitro fertilization and chorioamnionitis.

The study group was divided into two groups. Premature with suspected sepsis (Töllner score 5-10), clinical (Töllner score >10), and definite sepsis (bacterial and fungal growth in blood culture) were included in group I. Premature without a diagnosis of sepsis (Töllner score <5 and no culture growth) were included in group II. Clinical signs of sepsis (cyanosis, skin color changes, hypotonia, respiratory problems, feeding intolerance, decreased sucking, hypo-hyperthermia, bradycardia, distension, irritability, convulsions, vomiting, petechiae) were recorded daily in the patient file.

CBCs in premature infants were performed on days 1, 3, 5, and 7 in groups I and II. Leukocyte and platelet values were also recorded.

Statistical Analysis

The data obtained as a result of the study were analyzed in the SPSS program, and p<0.005 was accepted as the significance limit. Values other than the number of pregnancies were given as mean±SD and number of pregnancies as median. Chi-Square, Mann-Whitney-U test, and Wilcoxon test were used to compare variables. ROC analysis and the Cox regression model were tested.

RESULTS

The study included 207 premature infants. Of these, 29 (14%) were in group I and 178 (86%) were in group II. **Table 1** shows the demographic characteristics of both groups and the comparison of these characteristics.

Table 1 also shows the comparison of the groups in terms of maternal and neonatal risk factors. The maternal history of foul-smelling vaginal discharge and urinary tract infection were more prominent in the sepsis group, and the difference between the groups was significant (p=0.003, p=0.001, respectively). The rates of resuscitation were 72.4% in group I and 16.8% in group II, and the difference between them was significant (p<0.001).

Blood cultures grew in 31% of patients with sepsis. Of the microorganisms, 33.3% were gram-positive (*Staphylococcus aureus, Enterococcus faecium*), 55.6% were gram-negative (*Klebsiella ozanea, Enterobacter aeroginoza, Enterobacter sakazakii*) and 11.1% were fungal (*Candida sp.*). There was no significant difference in clinical and laboratory values of the microorganisms.

While there was no significant difference between the groups in terms of leukocyte counts, a statistically significant difference was found in terms of the decrease in platelet counts on days 1, 3, 5, and 7 (p=0.02, pCRP, p<0.001, p<0.001, **Tables 2, 3**, respectively). The mean platelet counts of group I showed a decrease of 5.8% on day 3, 17.69% on day 5, and 17.94% on day 7 compared to the value obtained on the first day (**Table 3**). It was observed that the early reduction started on day three and markedly decreased later. The lowest platelet values on day 1 were 15.000, 19.000 on day 3, 25.000 on day 5, and 11.000/mm^3 on day 7.

Cyanosis (100%), changes in skin color (96.6%), hypotonia (96.6%), respiratory problems (75.9%), and non-suction (62.1%) were the most common clinical findings in infants with sepsis (group I). The onset of clinical findings in patients with sepsis was usually on days 3-4, whereas thrombocytopenia usually started on day 3. It took an average of 16 days for the patients to completely recover clinically and 13 days for thrombocytopenia to resolve.

It was observed that the sensitivity and specificity of the decrease in platelet count detected on the first day and the following days increased concerning sepsis. **Table 4** shows the specificity and sensitivity rates of thrombocytopenia for the diagnosis of sepsis on days 1, 3, 5, and 7.

To show the effect of platelet count on prognosis in patients who developed sepsis, the presence of early sepsis was included as a categorical variable, and platelet count on the first day was included as a continuous variable in the Cox regression model.

Table 1. Demographic characteristics and comparison of group I and group II

	Group I (n=29)		Group II (n= 178)		p value
Gestational age (weeks)	29.4±4.2		33.3±2.9		0.000
Birth weight (kg)	1438.79±687.8		2026.19±561.56		0.000
Gender (M/F)	19/10		111/67		0.74
Mode of delivery (NSVD-C/S)	15/14		67/111		0.15
APGAR Scores (1st/5th min)	5±2/9±1		7±1/10		0.000
Comparison of maternal and neonatal sepsis risk factors of the groups					
Maternal factors	n	%	n	%	
Hypertension	3	10.3	19	10.6	0.90
DM	2	6.9	12	6.7	0.97
UTI	2	6.9	0	0	0.001
Foul-smelling vaginal discharge	3	10.3	2	1.12	0.003
Preeclampsia	1	3.4	6	3.3	0.97
Cigarette smoking	5	17.2	26	14.6	0.65
EMR (24 hours a day)	4	13.8	20	11.2	0.74
Factors related to the baby					
Multiple pregnancy	4	13.8	21	11.7	0.70
Resuscitation practice	21	72.4	29	16.2	0.000
Congenital malformation	3	10.3	7	3.9	0.15
Mechanical ventilation therapy	21	72.4	21	11.7	0.000
Umbilical catheter insertion	2	6.9	1	0.56	0.010
Surfactant therapy	12	41.4	12	6.7	0.000

DM: Diabetes mellitus, EMR: Early membrane rupture, UTI: Urinary tract infection

Table 2. Platelet (mean±SD) and leukocyte (median-value range) counts on days 1, 3, 5 and 7 in groups I and II

	Day 1		Day 3		Day 5		Day 7	
	Platelets (/mm³)	Leukocytes (/mm³)	Platelets (/mm³)	Leukocytes (/mm³)	Platelets (/mm³)	Leukocytes (/mm³)	Platelets (/mm³)	Leukocytes (/mm³)
Group I	185000±60	14200 (6480-86000)	174107±75	11750 (2890-43190)	152269±84	9930 (2160-42200)	151800±104	8210 (2010-51900)
Group II	207309±66	14100 (5670-87350)	249928±65	11690 (5240-39580)	292263±68	9860 (6300-20100)	319117±74	9443 (4610-16400)
p value	0.02	0.61	0.000	0.71	0.000	0.67	0.000	0.66

SD: Standart deviation

Table 3. Comparison of both groups according to changes in platelet counts

	Group I		Group II	
	Mean±SD	Reduction rates (%)	Mean±SD	Increase rates (%)
Day 1	185000±60	-	207309±66	-
Day 3	174107±75	5.8	249928±65	20.5
Day 5	152269±84	17.6	292263±68	40.9
Day 7	151800±104	17.9	319117±74	53.9

SD: Standart deviation

Table 4. Sensitivity and specificity rates of thrombocytopenia in the diagnosis of sepsis according to days in group I

	Day 1	Day 3	Day 5	Day 7
Sensitivity (Sensitivity) (%)	23.8	66.7	81.3	81.3
Specificity (%)	88.5	88.8	88.2	85.2

The odds ratio for platelet count on the first day was 0.990, 95% confidence interval (0.983-0.997) (p=0.008).

DISCUSSION

Despite advances in neonatal intensive care management, difficulties in the diagnosis and treatment of neonatal sepsis still pose a severe problem for neonatologists. Despite increasing precautions against infections, the incidence of neonatal sepsis is reported to be 1-20% in different studies,[4-9] with mortality rates between 19.4% and 26.7%.[1,4,6,7,10-12] Mortality is more than 30% in early-onset, late-diagnosed and fulminant sepsis.[10-12] In our study, the incidence of sepsis in our NICU unit was 14%, and the mortality rate was 6.2%, consistent with the literature.

Clinical findings constitute the first step in the diagnosis of sepsis, and laboratory investigations support the diagnosis. Clinical findings are not specific and vary in a wide spectrum. Sepsis is a diagnosis that should be considered in almost every newborn with a sick appearance. Clinical findings may be subtle, and it is an important problem that the picture may be aggravated when sepsis clinic occurs.[2,4,7,13-22]

The definitive diagnosis of neonatal sepsis is made by bacterial growth in blood cultures. However, the time lost until the results of blood cultures are obtained will negatively affect morbidity and mortality.[18]

Easy, inexpensive tests with high specificity and sensitivity are needed for early recognition of sepsis in the NICU. CBC is an accessible and cost-effective test. Leukocyte and platelet counts have been previously used in different studies to diagnose and follow up on infection.[14,16,19,23]

In our study, we investigated the efficacy of the changes in leukocyte and platelet counts in CBCs on days 1, 3, 5, and 7 in the early recognition of sepsis in the follow-up of premature infants in our NICUs. When platelet and leukocyte counts were compared between group I, which was followed up with a diagnosis of sepsis, and group II, which was not diagnosed with sepsis, it was found that platelet counts decreased in group I on days 1, 3, 5 and 7 (p=0.02, p<0.001, p<0.001, p<0.001, p<0.001, respectively), whereas leukocyte count variability was not significantly different (p>0.05).

We found that platelet count decreased during the early sepsis period in the groups at risk for sepsis. No significant change was seen in platelet values in group II, which included non-sepsis individuals. In the sepsis prediction score developed by Sofouli et al.[13] in 2023, it was stated that thrombocytopenia as a laboratory marker was as strong in predicting sepsis as other findings. In a study conducted in patients with proven sepsis, it was reported that platelet indices (platelet count, MPV, PCT, and immature platelet fraction) act as acute phase reactants and change with inflammation and may be both predictive and prognostic biomarkers in neonatal sepsis.[14,23,24] Many studies in the literature have reported that thrombocytopenia is frequently observed in neonates with sepsis. It has been suggested that bacteria and their endotoxins cause thrombocytopenia in sepsis by increasing platelet adhesion to the vascular endothelium, suppressing megakaryocytes, decreasing platelet production, and accelerating their consumption.[19,21,25] In the study by Worku et al.[19] the role of CBC parameters in the diagnosis of neonatal sepsis was evaluated, and total leukocyte count and platelet count showed a significant association with neonatal sepsis. It was also reported that these parameters had high sensitivity and specificity in the diagnosis of neonatal sepsis.[19] In our study, the specificity of thrombocytopenia in the diagnosis of sepsis reached its highest value on day 3 (88.8%), and the sensitivity (81.3%) reached its highest value on day 5. This suggests that thrombocytopenia can be used to rule out the diagnosis of sepsis in the early period and may help confirm the diagnosis in late sepsis.

In group I, the effectiveness of the number of platelets obtained from the babies on the first day of diagnosis and prognosis was studied in the Cox regression model, and the odds ratio was

0.990, 95% confidence interval (0.983-0.997) (p=0.008). It was also found that premature infants with thrombocytopenia on the first day had high mortality rates due to sepsis.

In our study, no significant difference was found when leukocyte counts were compared between the groups. Although leukocyte count is one of the most commonly used biomarkers for the diagnosis of infection, it may be affected by many factors, such as stress, trauma, drugs, hemolysis, and hypoxia, its use in newborns is limited, and its sensitivity and specificity are low.[26] However, contrary to our data, there are studies in the literature reporting that an increase in leukocyte count is significant in sepsis.[19,27,28]

Limitations

Intrauterine growth retardation and hypoxic delivery affect platelet counts in newborns. The fact that patients with growth retardation and low APGAR scores were not excluded and that subgroup evaluation for gestational age could not be performed due to the small number of patients in the groups may be limitations of our study. Large-scale multicenter studies are needed to confirm our findings.

CONCLUSION

In conclusion, consecutive CBC assessments performed within the first week of life can be used as a screening test for the early diagnosis of sepsis in premature infants. Monitoring platelet count variability starting from the first day of life will save time in the diagnosis of sepsis and help the neonatologist in sepsis follow-up as a simple, easily accessible, and cost-effective test. However, validation with different prospective studies on CBC parameters and sepsis is needed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 22.12.2005, Decision No: 2005/159).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Journal of Current Hematology & Oncology Research

Original Article

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The importance of acidic microenvironment in urothelial carcinomas of the bladder: relationship with carbonic anhydrase IX expression and prognostic factors

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ABSTRACT

Aims: Bladder urothelial carcinoma (BUC) is a prevalent malignancy worldwide, ranking 13th in terms of mortality. Several prognostic factors affecting survival have been identified, including histologic grade, invasion of the muscularis propria, tumor diameter, and lymphovascular invasion. However, new markers that will be helpful in diagnosis, treatment and prognosis are still needed. Carbonic anhydrase IX (CA IX) is a tumor-associated cell surface glycoprotein that aids in adaptation to acidosis induced by hypoxia and plays a role in cancer progression.There are few studies on the prognostic impact of CA IX on BUCs. This study aimed to investigate whether CA IX is a promising diagnostic and prognostic biomarker in BUC.

Methods: A retrospective analysis was conducted on 117 cases diagnosed with BUC whithout muscularis propria invasion between September 1995 and January 2023. Transurethral resection (TUR) specimens were examined histological grade, lymphovascular invasion, tumor diameter by a single pathologist. CAIX was performed by immunohistochemical (IHC) method.

Results: Among the 117 patients included in the study, 61 had low-grade tumors, while the remaining 56 had high-grade tumors. CA IX expression exhibited a significant positive correlation with histological grade ($p<0.01$), lymphovascular invasion ($p<0.01$). and tumor diameter ($p<0.01$). Low CA IX staining was observed in three normal tissues and it was found to be a biomarker in the distinction between malignant and benign cases.

Conclusion: CA IX expression is associated with poor prognosis in BUCs as in some other tumors. Evaluation of CA IX staining may be important for patient follow-up and treatment strategies. Adding carbonic anhydrase enzyme inhibitors to chemotherapy regimens could potentially create new treatment options.

Keywords: Bladder, carcinoma, CAIX, prognostic factor

INTRODUCTION

Bladder urothelial carcinoma (BUC) is a disease that is common worldwide and ranks 13th in terms of mortality.[1] According to 2022 GLOBOCAN data, 614.298 people are diagnosed with bladder cancer worldwide each year.[2] Each year, 220.596 people lose their lives to bladder cancer. The majority of patients with BUC are men, and the incidence in men is three times higher than in women. The average age at diagnosis is 73 years. Imaging examinations and cystoscopy are the basic clinical diagnostic methods, and the primary treatment is surgery. Early diagnosis significantly increases treatment results and recovery rates.[3] Therefore, it is important to identify tumor markers for BUC.[4,5] Several prognostic factors affecting survival have been identified, including histologic grade, invasion of the muscularis propria, tumor diameter, and lymphovascular invasion.[6-10] However, new markers that will be helpful in diagnosis and treatment are still needed.

Hypoxia poses a life-threatening condition for all aerobic organisms, and they develop various adaptation mechanisms to survive in such conditions.[11-13] The rapid proliferation of cancer cells increases the oxygen demand, but the vessels supplying oxygen-carrying blood cannot keep up. Consequently, hypoxia occurs in rapidly growing tumor tissues, and tumor cells develop adaptive responses to cope with this stress.[14] Hypoxia can be moderate or severe, acute or chronic, and intermittent or persistent, leading to various cellular responses that promote aggressive tumor phenotypes.[5] At the molecular level, these changes are primarily determined through the remodeling of hypoxia-inducible factor (HIF)-mediated transcriptional

profiles. HIF targets genes that encode angiogenesis mediators such as vascular endothelial growth factor (VEGF) and VEGF receptors, as well as enzymes involved in the glycolytic pathway such as hexokinase 2, lactate dehydrogenase, and glucose transporters (GLUT-1 and GLUT-3). Additionally, it affects erythropoiesis, vascular remodeling, cell proliferation and viability, cell adhesion, cell-matrix metabolism, and pH regulation.[15,16]

Due to the development of hypoxia and increased energy demand, glycolysis is enhanced, leading to the production of excess acidic metabolic end products such as lactic acid, protons, and carbon dioxide. This activation triggers pH regulatory mechanisms. Intracellular acidosis is usually eliminated by CO_2 diffusion, removal of lactate and protons from the cell, and intake of bicarbonate ions. However, because tumor vessels cannot effectively remove acidic metabolic waste, pericellular acidosis often persists in the tumor microenvironment.[17]

Carbonic anhydrase IX (CA IX) is a tumor-associated cell surface glycoprotein that aids in adaptation to acidosis induced by hypoxia and plays a role in cancer progression. The active site of the CA IX enzyme in the catalytic domain is positioned towards the extracellular space, contributing to pH regulation across the plasma membrane by facilitating CO_2 hydration. This, in turn, enhances CO_2 diffusion and proton mobility in the tumor tissue. Simultaneously, CA IX exacerbates extracellular acidosis, which can activate proteases to degrade the extracellular matrix, promote epithelial-mesenchymal transition and invasion, reprogram metabolism, affect cell adhesion, and stimulate inflammation and angiogenesis. CA IX is more abundant in tumor tissues than in normal tissues.[18,19]

Numerous studies have found that CA IX is a new type of tumor antigen involved in tumor formation and invasion, enabling tumors to maintain high viability under hypoxic conditions. Hypoxia and low-pH environments promote the invasion and metastasis of cancer cells. Several studies have shown that CA IX can be highly expressed in various malignant tumors.[20-22]

There is an increasing focus in the literature on the role of CA IX in cancer development and its prognostic impact. Urothelial carcinomas are one of the common malignancies. Identifying prognostic markers for this aggressive type of cancer is vital to improving patient outcomes and tailoring treatment strategies. In this study, we investigated whether CA IX, an enzyme involved in the regulation of pH balance in cells, was a promising prognostic biomarker in BUC and its prognostic effects.

METHODS

This retrospective study was initiated after obtaining approval from the Ethics Committee of Fırat University (Date: 09.03.2023, Decision No: 2023/04-34). All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or ethical standards. The study focused on patients who were diagnosed as having BUC and were referred to the pathology laboratory of our hospital between September 2018 and January 2023. All samples were obtained through transurethral resection (TUR). The tissues of some cases were not available in the pathology archive. In some cases, there was not enough tissue left for re-evaluation. Therefore, these cases were excluded from the study. Cases with smooth muscle invasion were also excluded from the study.

A single pathologist examined hematoxylin-eosin sections of patient samples and archival materials using a Leica DM 2000 light microscope. The pathologist confirmed tumor type, histologic grade, muscularis propria invasion, and lymphovascular invasion. 117 patients without muscularis propria invasion were included in the study. The diagnosis was made according to World Health organization (WHO) 2016 histopathologic type criteria.[6] Additionally, tumors were classified as low-grade or high-grade according to WHO histologic grading criteria.[7]

Fifty benign bladder biopsies taken for various non-tumor reasons were also determined as a control group to determine the diagnostic effectiveness of CA IX. It was desired to investigate whether CA IX was expressed in benign tissues. Three-micron-thick sections were taken from the paraffin blocks of both the tumor tissues and the control group and placed on the slides. An immunohistochemical (IHC) method was applied to determine CA IX expression. After deparaffinization and treatment with 3% H_2O_2 for 5 minutes, tissue samples were blocked with 10% serum in a blocking solution for 1 hour. They were then incubated overnight at 4°C with anti-CA IX antibodies at a 1/400 dilution in antibody diluent (Leica Prodact code: NCL-L-CAIX-U Clon:TH22).

CA IX exhibits cytoplasmic membrane staining because it is a transmembrane protein. Immunohistochemically positive cells were graded as follows: negative if <10%, low stain if 10-50%, intermediate stain if 51-75%, and high stain if 76-100%.[8]

Demographic, laboratory, and clinical variables of the patients were obtained from the Hospital Information System (HIS) database. Tumor diameter information was collected from radiologic imaging reports and categorized as follows: 0-1 cm, 1.1-2 cm, 2.1-3 cm, and >3 cm.

Statistical Analysis

The data analysis was conducted using the SPSS version 22 software (IBM Corp., Armonk, NY, USA). All analyses were based on the assumption of normality. Descriptive data are expressed as median and mean values for normally distributed variables due to the approximate values of the calculated mode. The Chi-square test and regression analyze were used. A p-value of <0.01 was considered statistically significant.

RESULTS

Of the 117 patients included in the study, 61 had low-grade tumors and the remaining 56 had high-grade tumors. Among the patients, 21 were female and 96 were male, with a mean age of 68 years. Among the women, nine were classified as having low-grade tumors, and 12 had high-grade tumors. Fifty-two men had low-grade tumors and 44 had high-grade tumors.

Negative staining for CA IX was seen in 53 of 61 (88%) low-grade cases. Six cases (10%) showed low staining and two cases (2%) showed intermediate staining. In high-grade cases, 13 (23.2%) showed negative staining, 17 (30.3%) showed low staining, 12 (21.4%) showed intermediate staining, and 14 (25.1%) showed high staining. Regression analysis was performed. Based on the results of the regression analysis conducted to predict the effect of CA IX expression on histologic grade, it was observed that CA IX expression levels have a statistically significant positive

impact on histologic grade. The R-squared value, representing the explanatory power of the model, was calculated as 0.406 (R=0.637, R^2=0.406, p=0.001). This indicates that the intensity of CA IX expression accounts for 40.6% of the variance in histologic grade. In other words, it was observed that as the level of CA IX expression increases, the histologic grade of the tumor also increases (**Table 1**, **Figure**).

Lymphovascular invasion was observed in 11 patients, all of which were classified as high histologic grade. There was no lymphovascular invasion in 89 patients. No lymphovascular invasion was observed in any low-grade cases. Negative CA IX staining was observed in two of the lymphovascular invasion-positive cases, intermediate staining was observed in two cases, and high staining was observed in seven cases. Regression analysis was performed. It was observed that CA IX expression levels have a statistically significant positive impact on lymphovascular invasion. The R-squared value, representing the explanatory power of the model, was calculated as 0.479 (R=0.479, R^2=0.229, p=0.001). This indicates that the intensity of CA IX expression accounts for 22,9% of the variance in lymphovascular invasion. This suggests that as CA IX expression increases, so does the lymphovascular invasion of the tumor (**Table 1**).

In the examination of 53 cases of CAIX-negative low-grade tumors, the tumor diameter was found to be between 0-1 cm in 7 cases, between 1.1-2 cm in 44 cases, and between 2.1-3 cm in 2 cases. In 6 low-grade urothelial carcinoma cases showing low staining, the tumor diameter was found to be between 1.1-2 cm in 4 cases and between 2.1-3 cm in 2 cases. In both cases showing intermediate staining, the tumor diameter was measured to be between 2.1-3 cm. Among the 13 high-grade urothelial carcinoma cases showing negative staining, one had a tumor diameter of 0-1 cm, eight had diameters of 1.1-2 cm, and four had diameters of 2.1-3 cm. In the 17 cases with low staining, one had a tumor diameter of 0-1 cm, 11 had diameters of 1.1-2 cm, three had diameters of 2.1-3 cm and two had greater than 3 cm. In 12 cases with intermediate staining, the tumor size was 1.1-2 cm in 4 cases, 2.1-3 cm in 4 cases, and greater than 3 cm in 4 cases. In 14 cases with high staining, 6 cases had a tumor size of 2.1-3 cm, and in 8 cases, the tumor size was greater than 3 cm. In the regression analysis, a weak but statistically significant positive effect of CA IX expression on lymphovascular invasion was identified (R=0.335, R^2=0.112, p=0.01) (**Table 2**).

Table 1. Relationship between CA IX expression and histologic grade, lymphovascular invasion

	Low grade UC	High grade UC	p
Female Male	9 52	12 44	
CA IX staining Negative Grade 1 Grade 2 Grade 3	 53 6 2 -	 13 17 11 14	**p<0.01**
Lymphovascular invasion	-	11 2 cases; CA IX negative 2 cases; CA IX intermediate staining 7 cases; CA IX high staining	**p<0.01**

CA IX: Carbonic anhydrase IX, UC: Urothelial carcinoma

Table 2. Relationship between CA IX expression and tumor diameter

Staining grade	Low grade UC Tumor diameter			High grade UC Tumor diameter			
	0-1 cm	1.1-2 cm	2.1-3 cm	0-1 cm	1.1-2 cm	2.1-3 cm	>3 cm
Negative	7	44	2	1	8	4	0
Grade 1	0	4	2	1	11	3	2
Grade 2	0	0	2	0	4	4	4
Grade 3	0	0	0	0	0	6	8

UC: Urothelial carcinoma

In CA IX staining applied to fifty normal tissues, low staining was observed in three cases. When compared with tumor tissues, a statistically significant difference was observed in the CA IX staining of tumor tissue and normal tissues (p<0.01).

DISCUSSION

CA IX is a tumor-associated cell surface glycoprotein and its expression is primarily induced by the transcription factor HIF-1α during hypoxia. The key features of CA IX are : a) the absence of healthy, nonhypoxic, nontumor tissues (except for some areas of the gastrointestinal tract); b) overexpression in a wide variety of tumors with a hypoxic phenotype;

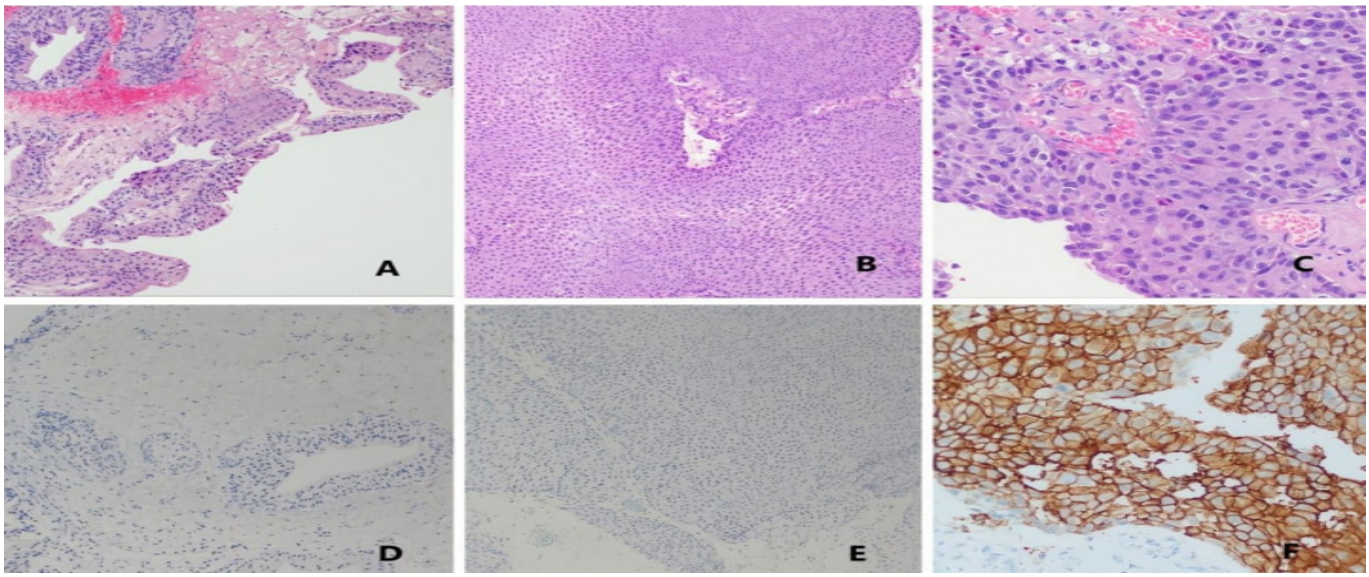

Figure. A. Normal bladder epithelium, **B.** Low grade urothelial carcinoma, **C.** High grade urothelial carcinoma, **D.** Negative staining of CA IX in normal bladder epithelium, **E.** Low grade staining of CA IX in low grade urothelial carcinoma, **F.** High grade staining of CA IX in High grade urothelial carcinoma

c) maintenance of a neutral pH within tumor cells and contribution to the acidosis of the tumor microenvironment; d) it facilitates cell migration and invasion with its ability to regulate pH; e) participation of its proteoglycan (PG)-like domain in tumor cell adhesion and proliferation processes. In summary, CA IX promotes tumor cell survival in hypoxia/acidosis and contributes to the increased ability of tumor cells to migrate, invade, and cure. It metastasizes as reviewed in the literature.[19]

High expression of CA IX is observed in various cancer tissues because it confers resistance to hypoxia and promotes proliferation of cancer cells. Previous studies demonstrated elevated CA IX expression in kidney clear cell carcinoma, prostate cancers, and breast carcinomas. Furthermore, a significant association has been observed between CA IX expression, advanced disease stage, and poor prognosis in certain cancers.[23] A comprehensive meta-analysis of clinical studies results confirmed the significant prognostic importance of IHC diagnostics of CA IX in solid tumors.[24] Patients with high CA IX expression have a higher risk of local failure, disease progression, and a higher risk of metastases developing, independently of tumor type or site. It has been found that the presence of CA IX in tumor tissue may also serve as a predictive marker for radiotherapy and chemotherapy resistance.[25]

In this study, CA IX expression was evaluated in bladder carcinomas without muscularis propria invasion. In our studies including 117 patients, a positive correlation was found between CA IX expression and histologic grade, lymphovascular invasion, and tumor size. Consistent with the literature, as the degree of CA IX expression increased, so did histologic grade and lymphovascular invasion. In the study by Xiang et al.[8] no significant relationship was found between tumor diameter and CA IX expression. These factors have prognostic importance for BUC. When CA IX expression increases, poor prognostic factors increase. CA IX expression has been identified as a diagnostic marker for malignancy.[8] In our study, a statistically significant difference was observed in the CA IX staining of tumor tissue and normal tissues. We think that these data can be used as a diagnostic marker in cases where it is difficult to distinguish malignant from benign.

When studies on CA IX expression in BUCs began to be conducted, Hoskin et al.[26] investigated 64 patients and found that the survival rate in CA IX-positive patients was 35%. In the study conducted by Klatte et al.[27] in 2009, the authors said that the study by Hoskin et al. was the most comprehensive study on this subject. In Klatte et al.'s study, it was shown that there was more CA IX expression in invasive carcinomas than in non-invasive tumors. Additionally, it was observed that CA IX expression increased as histologic grade increased. Also, it was observed that there was no staining in the normal bladder epithelium, as in our study.[27]

In the study conducted by Xiang et al.[8] CA IX expression was detected in 68.1% of 194 patients with urothelial carcinoma. Among the 76 patients who experienced recurrence during their 5-year follow-up, 59 expressed CA IX. In our study, we were unable to access recurrence outcomes because the hospital's information system data did not extend beyond 5 years. In their study on 180 patients, Todenhöfer et al.[28] found that there was more staining in tumor tissue than in normal tissue and that CA IX expression was only associated with molecular subtypes, not with other prognostic parameters. In addition, it was determined that its use in the diagnosis of malignant/benign tumors was limited because staining was also observed in normal tissues in their studies.

In addition to the diagnostic and prognostic importance of CA IX, studies investigating its importance in treatment attract attention. According to the current clinical research results, the therapeutic strategy of CAIX has two directions. The first is to inhibit the enzyme activity at the active site of CAIX, including sulfonamides and their thioesters. The second is to use specific monoclonal antibodies to selectively kill tumors with CAIX expression, such as G250/girentuximab and M75.[19,29] In the study conducted by Chen et al.[30] on rats with breast carcinoma, CA IX was found to be quite high in cancer tissues. It was found that tumor diameter decreased and invasion decreased when CA IX inhibitors were used and that the treatment increased apoptosis.[30] There are contradictory reports regarding the response to treatment in BUCs. Some studies reported a positive response to treatment, but other studies observed that bladder tumors were insensitive to the inhibition of CA IX.[31,32]

Limitations

It is worth noting that our study has some limitations, such as the small sample size and the lack of long-term patient follow-up. It is important to conduct further research with larger study groups in order to apply these findings to routine clinical practice.

CONCLUSION

We conclude that CA IX expression is associated with poor prognosis in urothelial carcinomas of the bladder. Evaluating the degree of CA IX staining in TUR-M materials and biopsies is important in terms of prognosis prediction, patient follow-up, and treatment. Therefore, we predict that the addition of carbonic anhydrase enzyme inhibitors to chemotherapy regimens will affect the prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Fırat University Non-interventional Researches Ethics Committee (Date: 09.03.2023, Decision No: 2023/04-34).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Etiologic evaluation of male patients diagnosed with anemia in the first consultation of the hematology department

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ABSTRACT

Aims: Anemia is a decrease in hemoglobin (Hb) levels below the normal values determined by gender. Since anemia is a laboratory finding, its etiology must be investigated. The present study aimed to investigate the etiologic spectrum of male patients diagnosed with anemia in the first consultation of a tertiary hospital hematology department.

Methods: This study was conducted with male patients who were consulted at İnönü University, Turgut Özal Medical Center, Adult Hematology Department between the dates of 2010-2015. Adult male patients aged 18 years and older, who were diagnosed with anemia in the first consultation were included in the study. Hb levels under 13 g/dl in the complete blood count were accepted as anemia criteria. The study was carried out retrospectively by examining the records of the hospital automation system.

Results: The records of a total number of 7840 adult male patients were examined and 473 (6%) of them were found to have anemia when they first consulted in the hematology department. Iron deficiency was the most common etiological cause with the number of 97 patients (20.5%). In the first consultation; malign diseases were found in 50.3% (238), and benign diseases were found in 49.7% (235) of the patients, as the etiologic causes of the anemia. Multiple myeloma (MM) was found to be the most common malignant disease with a rate of 26.5% (63 patients), and isolated iron deficiency was found to be the most common benign disease with a rate of 41.3 % (97 patients); among the etiologic factors or anemia.

Conclusion: In our study, malignant diseases were detected as the etiological cause in more than half of the adult male patients with anemia in their first consultation. We think that it is important to keep this situation in mind in the etiology of anemias, especially considering the profile of patients referred to tertiary hospitals.

Keywords: Anemia, etiology, male

INTRODUCTION

Anemia is defined as a decrease in hemoglobin (Hb) levels below the normal values determined considering age and gender. According to World Health Organization (WHO)'s criteria; Hb levels, less than 12 g/dl in women, less than 13 g/dl in men, and less than 11 g/dl in pregnant women are defined as anemia.[1] Anemia is a laboratory finding that is seen in the diagnosis and/or follow-up of many diseases. Therefore, the etiological cause must be investigated in patients with anemia in clinical practice. There are two general approaches; (I) kinetic and (II) morphological in defining the causes of anemia. Classification is made according to the mechanisms causing anemia in the kinetic approach (erythrocyte production deficiency, increase in erythrocyte destruction and blood loss), and according to the mean erythrocyte volume (microcytic, normocytic, macrocytic) in the morphological approach.[2] Iron deficiency anemia (IDA) due to iron deficiency is the most common type of anemia worldwide and is estimated to be approximately 50% of all anemia.[3] Especially children and women of childbearing age are more at risk for RIA. However, the differential diagnosis of anemia due to many etiological causes besides iron deficiency in adult men and postmenopausal women may be an important problem.

Anemia may be the first laboratory finding in some malignancies. The incidence of anemia varies on the histological type and stage of the malignancy, as well as the duration of diagnosis and treatment procedures. The etiology of anemia that occurs due to malignancies, is often multifactorial. As known; the frequency of IDA is lower in adult men than in children and women of childbearing age. For this reason, in adult males with anemia, many other etiological causes, including malignant diseases, should be considered besides iron deficiency. The number of studies investigating the etiological causes of anemia in our country is relatively small and data on the prevalence of anemia is limited. This study;

it was aimed to investigate the etiological spectrum of male patients diagnosed with anemia in the first consultation of the hematology department.

METHODS

The study was conducted with the permission of İnönü University Scientific Researches and Publication Ethics Committee (Date: 26.10.2016, Decision No: 2016/15-1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted with adult male patients diagnosed with anemia at the first admission to the adult hematology outpatient clinic. A total of 7840 adult male patients who applied to the adult hematology outpatient clinic of İnönü University, Turgut Özal Medical Center between January 2010 and December 2015 were included in the study. The Hb values below 13 g/dl in the complete blood count were considered as anemia, and patients at the age of 18 and above were considered as adults. In this retrospective study, anemia was detected in the first admission, in 473 (6%) of 7840 adult male patients whose medical records were examined. In our study, the etiological causes of anemia that were detected at the first admission of 473 patients, were evaluated from the hospital automation system records. Patients with compatible peripheral smear data and ferritin levels below 15 ng/ml were diagnosed with RIA, and patients with vitamin B12 levels below 200 pg/ml were diagnosed with megaloblastic anemia due to vitamin B12 deficiency. Increased Hb A2 levels (≥3.5%) in Hb electrophoresis with anemia were accepted as beta thalassemia minor. The presence of pancytopenia in complete blood count and hypocellular bone marrow without abnormal infiltration and reticulin fiber increase were aplastic anemia (AA) criteria. Patients with low thrombocyte levels accompanying anemia were diagnosed with primer immune thrombocytopenia (ITP) after eliminating external factors that can cause thrombocytopenia. Spherocytic and polychromatic erythrocytes in the peripheral smear, increased serum indirect bilirubin/lactate dehydrogenase levels and direct Coombs test positivity were criteria for autoimmune hemolytic anemia (OIHA) diagnosis. Increased schistocyte (≥1%) rates in peripheral smear and Coombs test negativity with anemia were criteria for microangiopathic hemolytic anemia (MAHA) diagnosis.

Among the malign diseases, patients with increased clonal plasmacytoma (≥10%) in bone marrow were diagnosed with multiple myeloma (MM). Patients with the presence of blasts in peripheral smear and/or bone marrow inspection were diagnosed with acute myeloblastic leukemia (AML) and/or acute lymphoblastic leukemia (ALL) as a result of flow cytometry and cytogenetic research. Increased leukocyte count in complete blood count, specific peripheral smear findings and Philadelphia chromosome presence in cytogenetic analysis were accepted as chronic myeloid leukemia (CML) criteria. Chronic lymphocytic leukemia (CLL) was diagnosed with an increase of monoclonal B lymphocytes in peripheral blood (≥5.000%/microL) that have special phenotypic characteristics for KLL in flow cytometry. Non-Hodgkin lymphoma and Hodgkin lymphoma (HL) diagnoses were given histopathologically after lymph node and/or organ biopsy. Myelodysplastic syndrome (MDS) and primer myelofibrosis (PMF) diagnoses were given according to the diagnostic criteria of the World Health Organization.[4,5] Diagnosis of solid tumors was made by the relevant organ/tissue biopsy. Patients; who did not continue their follow-ups for advanced examination, did not approve interventional procedures were diagnosed with anemia and received medical treatment before the study, were excluded from the study. In addition, anemias due to non-hematological diseases (infection, rheumatological, kidney diseases, etc.) were not included in the study.

Statistical Analysis

Statistical evaluation of data was done using SPSS for Windows Version 17.0 software. Identification of quantitative data of the variants was presented as mean±standard deviation (SD); identification of qualitative data was presented as number and percent (%). With the Kolmogorov-Smirnov test; Hb, WBC and trombocyte levels were not normally distributed according to benign and malign causes ($p>0.05$). So comparison of benign and malign causes was made by using the Whitney-U test. Values of $p<0.05$ were considered statistically significant.

RESULTS

A total of 473 adult male patients diagnosed with anemia at the first visit were included in to study. The etiological causes of anemias were evaluated under two main titles benign and malignant diseases. It was detected that anemia was developed in 238 (50.3%) of 473 patients due to malignant etiological causes and 235 (49.7%) due to benign etiological causes. MM was the most common etiological cause with 63 (26.5%) patients, while AML was the second with 39 (16.4%) patients and CLL was the third with 32 patients (13.4%). IDA was the most common cause of anemia with 97 (41.3%) patients with benign etiologies. The second common benign cause was IDA+vitamine B12 deficiency with 60 (25.5%) patients and the third common benign cause was isolated vitamine B12 deficiency with 37 (15.8%) patients. IDA was also the most common cause among the total of benign and malign etiologies with 97 (20.5%) patients.

Table shows all etiological causes of anemia and their percentages in 473 patients who participated in this study:

Table. Etiologic causes of anemies

Etiology	n of p	%
Iron deficiency anemia	97	20.5
Multiple myeloma	63	13.3
Iron deficiency+vitamine B12 deficiency	60	12.7
Acute myeloid leukemia	39	8.2
Vitamine B12 deficiency	37	7.9
Chronic lymphocytic leukemia	32	6.8
Chronic myeloid leukemia	28	5.9
Beta thalessemia minor	26	5.5
Non-Hodgkin lymphoma	25	5.3
Myelodysplastic syndrome	18	3.8
Acute lymphoblastic leukemia	16	3.4
Aplastic anemia	8	1.7
Hodgkin lymphoma	7	1.5
Primer myelofibrosis	6	1.3
Solid tumor	4	0.8
Primer immune thrombocytopenia	3	0.6
Hemolytic anemia	3	0.6
Thrombotic thrombocytopenic purpura	1	0.2
Total	**473**	**100.0**

The average age of the patients included in the study was 59.9 (20-90) years. While the average age in patients with benign etiologies was 55.6 years, the average age in patients with malign etiologies was 64.3 years. The mean Hb value of 235 patients with benign etiology was 9.57±2.109 g/dl, the mean white blood cell (WBC) was 6.490±2.842/µL and the mean platelet count was 260.430±129.069/µL, while the mean Hb value of 238 patients with malignant etiology was 9.66±2.195g/dl, the mean WBC was 26.652±43.146/µL and the mean platelet count was 218.160±273.276/µL. While there was no statistical difference in Hb values between benign and malignant causes (p=0.492), there was a significant difference in terms of leukocyte and platelet counts (p=0.0001).

DISCUSSION

Anemia is a global health problem due to its high prevalence and the associated significant morbidity and mortality in the adult population. Anemia can be seen in all periods of life, it is more common in pregnant women and young children. In a WHO report published in 2011, the global anemia prevalence was estimated to be 38% in pregnant women, 29% in non-pregnant women and 43% in children.[6] Data on the prevalence of anemia in our country is relatively limited. Çoban et al.[7] investigated the frequency of anemia in 2100 patients aged 65 years or older who applied to the internal medicine outpatient clinic. The frequency of anemia was reported as 30.5% in this study population in which anemia frequency was not reported by gender. Şahin et al.[8] studied a total of 521 (48% male and 52% female) patients 65 years and older, they reported that 63% of the patients were anemic, and the frequency of anemia in male (69.1%) patients was significantly higher than female (57.7%) patients. In a larger study conducted by Memişoğulları et al.[9] including 2187 adults (18-92 years of age) and involving the etiology and prevalence of anemias in the Turkish population, it was reported that 565 (25.8%) patients were anemic, and the prevalence of anemia was 30.0% in women and 18.2% in men. The prevalence of anemia was observed as 16% in another study of 66 male patients over the age of 65.[10]

In the present study, anemia rates were determined as 6.0% among adult male patients at the first consultation in the hematology department. In these studies reported by different centers in our country, it seems that the results of the prevalence of anemia are contradictory. This may be due to the different parameters such as the number of patients, gender, socio-economic conditions, geographical regions and age in these studies. In addition, besides anemia due to non-hematological diseases (infection, rheumatological, kidney diseases, etc.) were not included in the study, we think that such factors may play a role in the lower prevalence of anemia in our study, compared to other studies; (I) only male patients were included in our study, (II) and the study was conducted in the tertiary health institution. However, Çetin et al.[11] investigated the prevalence of anemia in a total of 1095 adults over 18 years of age in the Tokat region, they reported the frequency of anemia as 15.9% in women, whereas 6.1 % in men, at a rate similar to our results.

The most common type of anemia worldwide is IDA, with a rate of 50% among all anemia types.[11] IDA is also the most common cause of anemia due to nutritional deficiencies. Although our study was conducted in a tertiary hospital, we found iron deficiency as the most common cause of anemia in male patients who applied to the adult hematology outpatient clinic in the literature. The incidence of IDA varies depending on different age groups, gender and socio-economic conditions. Although IDA occurs in all age groups, it is most common in children, pregnant women and women of childbearing age. The incidence of IDA in developed countries is reported as 2-5% in adult men and postmenopausal women, 10% in women aged between 15-59, and 23% in pregnant women.[12] In our study we investigated the etiologies of anemia, we detected anemia due to isolated iron deficiency in 97 of 473 male patients (20.5%). Sezer et al.[14] studied 546 anemia patients aged 65 and over in Izmir, they reported that 29.9% (163 patients) of patients were diagnosed with IDA and 79 of them (48.5%) were male. In another study, Dilek et al.[15] investigated IDA prevalence among 642 (168 male, 474 female) adults in Van region, they reported IDA rates as 15.9% (17.3% among females and 11.9% among males). In these reported studies, the inconsistency in IDA rates with our results may be related to the characteristics of the groups in which the study was conducted, as well as the number and age of samples. As it is known, chronic gastrointestinal system hemorrhages due to various diseases in elderly patients are the main cause of IDA.

Megaloblastic anemia caused by vitamin B12 deficiency is one of the most important nutritional anemias. In our study, 37 (7.9%) of the patients diagnosed with anemia in their first admission were categorized as megaloblastic anemia due to isolated vitamin B12 deficiency. An important study conducted in the USA that examined the etiological causes of anemia among 60-year-old and older patients reported that vitamin B12 deficiency was the cause of 17.2% of nutritional anemia and 5.9% of all anemia types.[15] Also in this study, iron deficiency+folate deficiency and vitamin B12 deficiency+iron deficiency are reported to constitute 9.9% of nutritional anemia and 3.4% of all anemia types. Memişoğulları et al.[9] reported a 29.3 % prevalence of vitamin B12 deficiency, among 565 adult patients with anemia. In another study, Karakuş et al.[17] investigated the etiology of 561 anemia patients at the university hospital adult hematology department, they determined the frequency of vitamin B12 deficiency-related anemia as 7.6%. In addition, in this study, the researchers reported iron and vitamin B12 deficiency as an etiological cause in 43.8% of patients with anemia. In this study, we found vitamin B12 deficiency anemia together with DEA in 12.7% (60 patients) of our patients with anemia. In these types of anemias called combined nutritional anemias, sometimes more causes of anemia (DEA and vitamin B12 deficiency and folate deficiency) can be detected simultaneously. In another study reported from abroad that included a total of 424 hospitalized patients aged 65 and over, vitamin B12 deficiency anemia was reported to be much lower (3.8%).[18]

Anemia may be the first and/or only sign of malignancies such as MDS, hairy cell leukemia and GIS adenocarcinoma. Anemias are one of the most important hematological findings in malignant patients. It was reported that more than 30% of malignant patients had anemia associated with malignancy at the time of diagnosis, and in a large series, more than half (63%) of the patients were anemic at the time of diagnosis.[19,20] The pathogenesis of anemias associated with hematological malignancies or solid tumors is multifactorial. In patients with malignancies; anemia occurs due to one or more of the disorders including; functional iron deficiency, bone marrow infiltration, pure erythroid array aplasia, hemolysis, malnutrition, microangiopathy, hemophagocytosis, cytokine-

induced erythropoiesis inhibition, and trombocytopenic hemorrhage (mucocutaneous and/or GIS bleeding). In our study, we demonstrated that anemia was due to malignant diseases in 50.3% (238 patients) of the 473 male patients diagnosed with anemia on their first admission to adult hematology outpatient clinic. MM was the most common etiologic cause with a rate of 26.5% (63 patients) among these 238 patients. MM patients were followed by AML (16.4%) and CLL (13.4%) patients, respectively. We think that the main reason for the rate of malignant patients to be more than 50% in the etiology of anemia is related to our patient population who applied to our hematology outpatient clinic. The majority of these patients were referred to our clinics because of hematological anomalies detected in primary or secondary health institutions.

CONCLUSION

As a result; studies investigating the causes of anemia in the adult age group in our country are still insufficient. In this study, we aimed to investigate the etiological causes of male patients diagnosed with anemia for the first time in the adult hematology outpatient clinic. 474 male patients we included in our study, we detected malignant diseases in 50.3% and benign diseases in 49.7% of them as the etiological cause of anemia. The relatively low number of patients, exclusion of chronic disease anemia and the inclusion of only adult male patients limit the value of our study. Further studies are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of İnönü University Scientific Researches and Publication Ethics Committee (Date: 26.10.2016, Decision No: 2016/15-1).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Case Report

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Pituitary extramedullary plasmacytoma without any systemic involvement: a rare case report

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ABSTRACT

Extramedullary plasmacytoma (EMP) is a rare soft tissue plasma cell disorder without systemic involvement like multiple myeloma (MM). It develops outside of the bone marrow. It happens seldom for a plasma cell neoplasm to manifest as an intracranial or cranial tumor, and it is much less common for it to resemble a pituitary adenoma. In patients with sellar area plasmacytomas, headaches, cranial nerve deficits, visual abnormalities, bloody nasal discharge, and discomfort in the eyes and craniofacial regions are common presentations. A biopsy is required to make the diagnosis. For parasellar plasmacytomas to be successfully managed, an accurate diagnosis is essential. Overall, patient survival is excellent, although it might be lowered if they go on to develop overt MM. Suppose there is no known history of MM. In that case, it is advised to do a thorough workup to identify any underlying MM or to closely monitor any MM development in the future. In this study, we aimed to report a rare case who presented with loss of vision without systemic involvement of MM and whose pituitary biopsy was a plasmacytoma.

Keywords: Pituitary plasmacytoma, multiple myeloma, radiotherapy, monoclonal gammopathy

INTRODUCTION

Extramedullary plasmacytoma (EMP) is a rare soft tissue plasma cell disorder without systemic involvement like multiple myeloma (MM). EMP usually affects the upper respiratory system, which includes the larynx, nasopharynx, sinuses, and nasal cavity.[1] In a few number of instances, the brain has been implicated. Approximately 4% of all plasma cell tumors are EMP.[2] It is less common for myelomatous illness to cause involvement of the central nervous system (CNS), and most of these individuals exhibited normal systemic symptoms of MM before developing brain involvement.[3] In patients with sellar area plasmacytomas, headaches, cranial nerve deficits, visual abnormalities, bloody nasal discharge, and discomfort in the eyes and craniofacial regions are common presentations.[4] A biopsy is required to make the diagnosis. It is necessary to follow up on these patients later. As per research, 25-45% of individuals receive a subsequent diagnosis of MM; hence, it is important to seek assessment for systemic disease upon diagnosis to further guide therapy.[5,6] In this study, we aimed to report a rare case who presented with loss of vision without systemic involvement of MM and whose pituitary mass biopsy was a plasmacytoma.

CASE

A 45-year-old female patient was admitted to the emergency department with acute loss of vision. There were no neurological or endocrinological clinical findings other than acute vision loss in the patient's history. In the physical examination performed in the emergency room, no pathological findings were found in the systemic and neurological examination, except for vision loss. In the patient's cranial magnetic resonance imaging (MRI), a 32x47 mm contrast-enhanced mass was detected in the pituitary gland, expanding the sella and extending to the clivus. The suprasellar cistern was narrowed, and there was slight pressure on the optic chiasm (**Figure 1 a-d**). The patient underwent microscopic transsphenoidal surgery via an endonasal approach. The tumor was gross-total resected. Histopathologically, the surgical specimen showed a monotonous plasmacytoid cell population with eccentric nuclei and abundant cytoplasm (**Figure 2a**). Immunohistochemical staining was positive for CD138, MUM1, (**Figure 2b, 2c**), and the kappa light chain, but not the lambda light chain (**Figure 2d, 2e**). Based on these findings, the tumor was diagnosed as a plasmacytoma.

The patient had no complaints other than acute vision loss. Neurological examination was normal except for visual impairment. After the excision of the pituitary mass, vision loss resolved. There was no comorbidity in the patient's history and no medications. There was no history of malignancy in his family history. Laboratory tests revealed a hemoglobin level of 11.5 g/dl, leukocyte 10.8x10^9/L, and platelet 391x10^9/L. No endocrinological anomaly was detected in the patient's

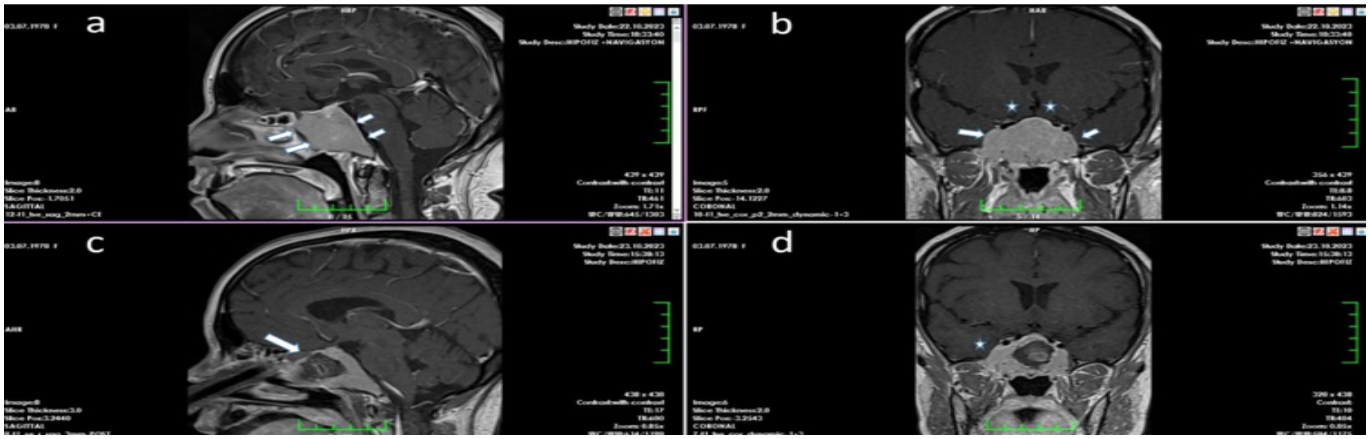

Figure 1. (**a,b**): Preoperative sagittal and coronal sections contrast-enhanced MRI, (**c,d**): postoperative sagittal and coronal sections contrast-enhanced MRI

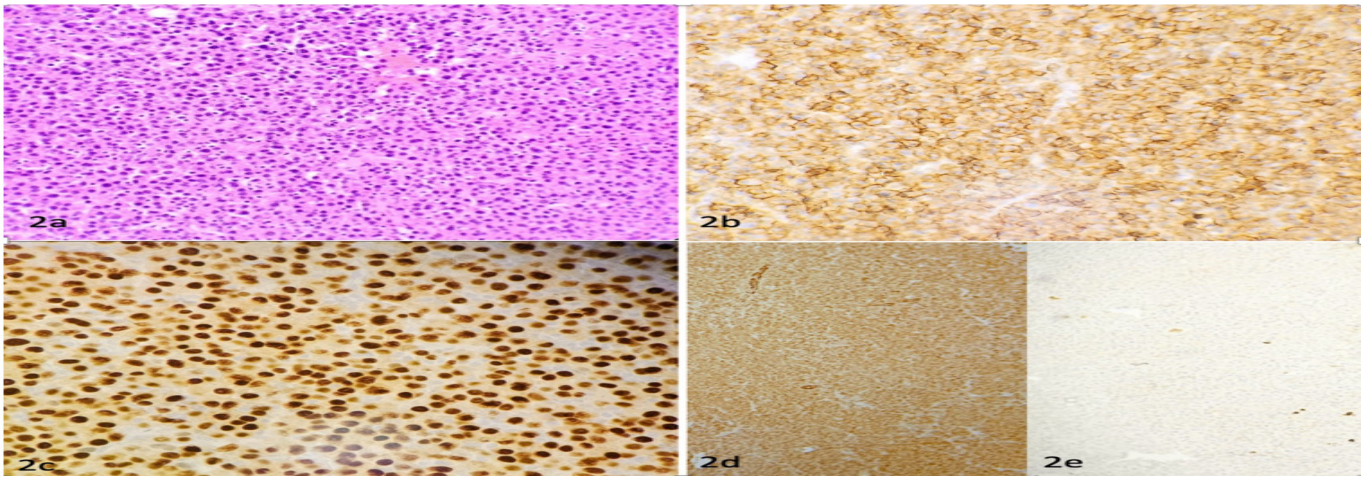

Figure 2. (**a**) Neoplastic plasmacytoid cells in diffuse sheets (HEX200), (**b**) Neoplastic cells with diffuse CD138 positivity (X200), (**c**) Neoplastic cells with diffuse MUM 1 positivity (X200), (**d**) monoclonal kappa light chain positivity (X100), (**e**) Lambda light chain immunonegative (X100)

laboratory findings. There was no evidence of renal dysfunction or hypercalcemia. No monoclonal gammopathy was detected in protein electrophoresis and serum, urine immunofixation. Serum immunoglobulin levels and serum-free light chains were found to be within the normal range. Serum beta-2 microglobulin was normal. The patient underwent bone marrow aspiration and biopsy. The plasma cell rate was observed to be around 8%. No increase in monoclonal plasma cells was detected in bone marrow biopsy. The patient was evaluated with positron emission tomography (PET). There was no involvement or any lytic lesion in the patient's PET findings. The EMP that was diagnosed was found to be a mass in the pituitary region with no systemic symptoms. The patient was consulted with radiation oncology for residual disease in the pituitary. The patient was given 46 Gy/23 FX radiotherapy to the pituitary region. The patient's vision loss was completely resolved. The patient, who had no active complaints, was kept under close clinical follow-up.

DISCUSSION

MM, solitary plasmacytoma of bone, and EMP single lesions with a microscopic appearance of plasma cell neoplasms without any clinical or radiological evidence of MM are among the clinicopathologic entities that are classified as plasma cell neoplasms.[7] It happens seldom for a plasma cell neoplasm to manifest as an intracranial or cranial tumor, it is much less common for it to resemble a pituitary adenoma.[8] Through a careful endocrine workup, neurological, radiological assessment, and sellar biopsy, most reported cases had no known diagnosis of plasma cell tumor until the sellar biopsy. This is because a plasmacytoma is one of many intrasellar masses that can mimic a pituitary adenoma.[9,10] The management of plasmacytoma and MM necessitates cooperation between subspecialists in hematology with a focus on stem cell transplants, radiation oncologists, and surgeons. Radiotherapy or surgery is usually recommended when a single plasmacytoma is detected, or both may be used together. There was no systemic involvement in the case we presented. There is a solitary plasmacytoma. She had the maximum safe excision of the plasmacytoma, which helped with debulking and alleviated her symptoms. Then, she got a total of 46 Gy/23 FX radiotherapy. Before a surgical pathologic evaluation, the tumor's rarity, clinical presentation, and imaging results that resemble those of other regional cancers sometimes lead to a misdiagnosis as pituitary adenomas, chordomas, or meningiomas. A misdiagnosis can postpone systemic therapy for the underlying MM and result in an incorrect surgical strategy. Lee et al.[11] reported a healthy 65-year-old male patient with no previous medical illness. Neurological examinations reported normal functioning of the cranial nerves, except for the patient's complaint of diplopia that occurred 2 weeks before presentation, similar to our case. Blood tests and pituitary hormone evaluations showed normal results, as in our case. It was reported that the patient developed MM 15 months later.[11] Another patient, a healthy 54-year-old male with no previous medical illness, was admitted to the hospital with intermittent headaches. Neurological examinations, including cranial

nerves, and ophthalmological tests showed normal results. Pituitary hormones were evaluated as normal. However, it was reported that the patient was given chemotherapy and radiotherapy because of pituitary plasmacytoma and involvement in the bone marrow biopsy.[11] Ferreira et al.[12] reported a 68-year-old male patient who first applied to the endocrinology clinic due to gynecomastia, decreased libido, and sexual impotence. Histological examination revealed plasmacytoma and MM was excluded. The patient was treated unsuccessfully with radiation therapy (no tumor shrinkage). Myeloma eventually developed and several similar lesions occurred in different locations. The patient was started on chemotherapy and underwent bone marrow transplantation.[12] Sidlo et al.[1] reported an extremely rare case of sudden death due to intrasellar EMP in a 24-year-old female patient with no previous clinical findings. The cause of death was determined to be CNS failure. Jin et al.[13] reported 5 cases of parasellar plasmacytoma. All patients underwent endonasal endoscopic surgery with adjuvant therapy. They reported complete remission after postoperative radiotherapy at a median follow-up of 41 months (range, 15–120).[13]

CONCLUSION

In conclusion, for parasellar plasmacytomas to be successfully managed, an accurate diagnosis is essential. Overall, patient survival is excellent, although it might be lowered if they go on to develop overt MM. Suppose there is no known history of MM. In that case, it is advised to do a thorough workup to identify any underlying MM or to closely monitor any MM development in the future. Because of all these, we followed our patient closely.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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Journal of Current Hematology & Oncology Research

Case Report

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Comprehensive management of concurrent chronic lymphocytic leukemia and Evans syndrome: combinating rituximab, venetoclax and eltrombopag

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ABSTRACT

Chronic lymphocytic leukemia (CLL) and Evans syndrome represent complex hematologic disorders characterized by distinct yet interconnected pathophysiologies. This case report explores the diagnostic and therapeutic intricacies of managing concurrent CLL and Evans syndrome in a 59-year-old male patient presenting with fatigue and petechiae. Laboratory findings revealed severe hematologic derangements indicative of advanced CLL and autoimmune hemolytic anemia (AIHA). The diagnostic journey encompassed bone marrow analysis confirming CLL and Coombs positivity suggesting Evans syndrome, with careful exclusion of immune thrombocytopenia. Initial therapeutic interventions included steroids and intravenous immunoglobulin for AIHA, alongside eltrombopag for persistent thrombocytopenia. Subsequently, rituximab and venetoclax were initiated for CLL, leading to complete remission. The successful outcome underscores the importance of an integrated therapeutic approach in managing concurrent CLL and Evans syndrome, offering insights for future clinical management of complex hematologic disorders.

Keywords: Eltrombopag, CLL, Evans, ITP

INTRODUCTION

Chronic lymphocytic leukemia (CLL) and Evans syndrome represent two distinctive yet interconnected challenges in the realm of hematologic disorders, encompassing a spectrum of complexities in diagnosis and management. CLL, characterized by the gradual proliferation of mature B lymphocytes, predominantly affects the elderly population and underscores the delicate balance between indolent progression and the potential for transformation into a more aggressive form.[1] On the other hand, Evans syndrome, a rare autoimmune disorder, presents an intricate interplay of immune dysregulation, manifesting as the simultaneous occurrence of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). The coexistence of these conditions in a single patient poses unique clinical considerations, demanding a nuanced understanding of their individual pathophysiologies and the synergistic impact on the patient's health.[2]

As we embark on the exploration of this complex case, it is imperative to delve into the intricate molecular and immunological mechanisms underlying CLL and Evans syndrome. This case report not only serves as a documentation of a compelling clinical scenario but also contributes to the broader discourse on the evolving landscape of hematologic malignancies and autoimmune phenomena.[2] By examining the synergistic effects of CLL and Evans syndrome within the framework of a single patient's journey, we strive to provide insights that may inform future clinical approaches and therapeutic strategies for similar complex hematological presentations.

CASE

A 59-year-old male diagnosed with CLL presented with complaints of fatigue. The clinical picture was further complicated by the presence of petechiae. Laboratory findings provided quantitative insights into the severity of the patient's hematologic derangement. Hemoglobin levels were recorded at 4.7 g/dl, platelet counts at 15,000/µL, and lymphocyte counts at 125,000/µL. It has been observed that the spleen size is 16 cm, the Rai stage is 4, and there are widespread lymphadenopathies.

The diagnostic journey unfolded with a comprehensive assessment, including a bone marrow analysis revealing the characteristic features of CLL. Additionally, Coombs positivity and hemolytic anemia were observed, prompting the concurrent consideration of AIHA and the diagnosis of Evans syndrome. This dual diagnosis exemplifies the intricate nature of hematologic disorders and the need for a holistic approach

in patient management. Notably, the diagnostic process included the evaluation of ITP as a potential component of Evans syndrome. The diagnosis of ITP was confirmed through bone marrow biopsy, which demonstrated normal or increased megakaryocytes, consistent with peripheral platelet destruction. Additionally, the bone marrow analysis showed lymphocytic infiltration characteristic of CLL. CLL is recognized as an important secondary cause of ITP, further emphasizing the link between the two conditions. Thorough exclusion criteria were applied to rule out other potential causes of thrombocytopenia.

The initial therapeutic interventions included standard doses of steroids (1 mg/kg/day) to address the autoimmune hemolysis component of Evans syndrome. During the initial phases of treatment, intravenous immunoglobulin (IVIG 1 gr/kg/day for 2 days) and steroids were employed for thrombocytopenia without achieving a satisfactory response. Consequently, eltrombopag (50 mg/day) was initiated. However, with the successful treatment of bone marrow involvement and CLL through the rituximab-venetoclax combination (rituximab 375 mg/m^2/day once for 28 days, venetoclax 400 mg/day everyday), Eltrombopag became unnecessary in the ensuing months following the reduction of lymphocytic infiltration observed in the bone marrow aspiration and the successful completion of rituximab-venetoclax therapy. This led to the complete resolution of thrombocytopenia, eliminating the need for eltrombopag in the management of secondary ITP.

Four months into treatment, the patient exhibited a positive therapeutic response. AIHA resolved, as evidenced by the achievement of Coombs negativity. Furthermore, a complete remission of lymphocytic infiltration in the bone marrow was observed, validating the effectiveness of the standardized therapeutic regimen (**Figure**).

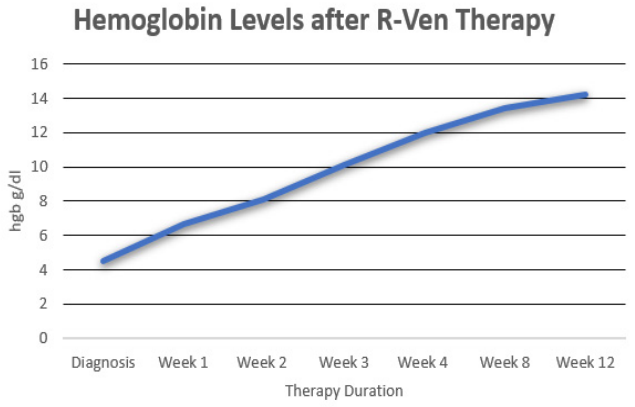

Figure. Hemoglobin levels after R-ven therapy

DISCUSSION

The presented case of a 59-year-old male with coexisting CLL and Evans syndrome encapsulates the intricate diagnostic and therapeutic challenges inherent in managing complex hematologic disorders. The initial presentation of fatigue, accompanied by night sweats, weight loss, and petechiae, prompted a thorough diagnostic investigation. The subsequent identification of severe hematologic derangement, marked by profound anemia, thrombocytopenia, and lymphocytosis, underscored the complexity of the case. The advanced Rai stage, enlarged spleen, and widespread lymphadenopathies indicated an aggressive form of CLL, further complicated by the presence of Evans syndrome.

This case exemplifies the need for a meticulous diagnostic evaluation and a tailored therapeutic strategy in managing the rare concurrence of CLL and Evans syndrome, considering potential ITP involvement.[2] The integrated therapeutic approach, incorporating eltrombopag, rituximab, and venetoclax at standard dosages, proved effective in achieving a favorable hematologic response. The successful outcome underscores the importance of a comprehensive understanding of concurrent hematologic disorders and the significance of an integrated therapeutic approach.[3]

CONCLUSION

In conclusion, our case highlights the importance of recognizing the diverse manifestations of CLL and the challenges presented by concurrent Evans syndrome, with careful consideration of ITP in the diagnostic process. The application of standardized therapeutic interventions offers a promising avenue for navigating the complexities of these hematologic disorders, providing valuable insights for future clinical management.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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Journal of Current Hematology & Oncology Research

Letter to the Editor

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Letter: Evaluation of the frequency of hepatitis B virus reactivation and the importance of hepatitis B prophylaxis in hematology patients receiving immunosuppressive therapy: a single-center study

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Dear Editor,

We are writing to express our appreciation for the recent publication in the Journal of Current Hematology & Oncology Research titled "Evaluation of the frequency of hepatitis B virus reactivation and the importance of hepatitis B prophylaxis in hematology patients receiving immunosuppressive therapy: a single-center study" by Doğan et al.[1] As gastroenterologists, we find this work particularly valuable as it highlights the importance of hepatitis B virus (HBV) prophylaxis in patients undergoing immunosuppressive therapy, which is a vital concern in gastroenterology practice as well.

This study underscores the significant reduction in HBV reactivation rates through consistent prophylactic antiviral treatment in hematology patients. Notably, HBV reactivation rates in patients receiving immunosuppressive agents, including chemotherapy and Rituximab, can vary from 4% to 86%, depending on HBV status and treatment intensity.[2] Such variability underscores the necessity of routine HBV screening and prophylaxis before starting immunosuppressive therapy, particularly for patients who are at increased risk.

However, as reported in the literature, the risk of HBV reactivation extends beyond hematology and affects patients across specialties including oncology, dermatology, rheumatology, and gastroenterology, where immunosuppressive agents are increasingly utilized. Immunosuppressive therapy, particularly with agents such as anti-TNF and other biologics, has been associated with HBV reactivation rates of up to 16% in patients with previously resolved HBV infection in these fields.[3] This emphasizes the broader applicability of prophylactic measures across diverse clinical practice areas to mitigate the complications associated with HBV reactivation.

Moreover, atypical serological profiles should be considered in high-risk patients. These profiles could be found as dual positivity for HBV surface antigen and antibody, dual positivity for HBV "e" antigen and antibody, isolated surface antigen or core antibody (IgG) positivity.[4] As carefully taken into consideration in the study by Doğan et al.[1] we would like to emphasize the importance of broader serological workup in order not to overlook such patients.

While the findings of this study are promising, the limited patient population from a single center suggests that further research with larger, multicenter cohorts would provide more robust and generalizable data. Such multicenter research would also offer a clearer understanding of HBV reactivation risks across diverse healthcare settings, enhancing the reliability of these findings for broader clinical practice.

In conclusion, we commend the authors for their contribution to advancing knowledge on HBV prophylaxis in immunosuppressed patients and hope that these findings encourage proactive screening and prevention measures across medical practice areas.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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

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