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EDITORIAL

Dear Colleagues,

As it is known, a short time ago, we had a major earthquake disaster affecting approximately 11 cities in our country. I wish God's mercy on those who died in this disaster, in which we lost approximately 40,000 people, and a speedy recovery to the injured.

I am proud of publishing the first issue of the **Journal of Current Hematology Oncology Research (JCHOR)** in these difficult days. The journal focuses on all aspects of cancer, hematology and related researchs, including original or experimental researchs, case reports, editorial letters and review articles This first issue includes two original researches, one review article and two case reports. In addition to all researchers, referees and editorial board who contributed to the preparation of the journal; we would like to thank the printing team for their effort in preparing it for publication. In the upcoming period, with your support, our goal is for the **JCHOR** to be indexed in nationally and internationally accepted scientific indexes.

I would like to thank you in advance for your contribution.

Kind Regards

İlhami BERBER. MD
Editor in Chief

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Original Article

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Effect of tyrosine kinase inhibitor and conventional chemotherapy on COVID-19 antibody level in hematological patients

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ABSTRACT

Aims: In this study, we aim to discover if there is a difference between COVID-19 antibody level in hematological patients taking conventional chemotherapy and tyrosin kinase inhibitors.

Methods: COVID-19 IgG levels were measured using the QuantiCOR anti-SARS-CoV-2 IgG ELISA test kit on 74 patients who received chemotherapy and used tyrosine kinase inhibitors in the adult hematology clinic of Turgut Özal Medical Center between May 2019 and January 2022. Age, height, weight, badimeks index of the patients were measured, the doses and durations of vaccine use, the time between the first vaccine and the second vaccine, how long after the first vaccine antibodies were checked, and vaccine-related side effects were recorded. Collected data statistical analysis was performed using Python 3.9 and IBM SPSS Statistics for Windows version 26.0 (New York; USA).

Results: Antibody levels of the patients were significantly higher in the healthy control group than in the groups that received chemotherapy and tyrosine kinase inhibitors. Antibody levels of female patients in the control group were higher than male patients. Antibody levels of the patient groups receiving chemotherapy and tyrosine kinase inhibitor were not found to differ between the two groups. When the patients receiving B lymphocyte suppressing chemotherapy in the chemotherapy group were compared with the control group, antibody levels were found to be higher in the control group.

Conclusion: COVID-19 vaccination in hematological cancers did not produce adequate antibody response, especially in patients receiving chemotherapy or tyrosine kinase inhibitors.

Keywords: COVID-19 vaccine, tyrosine kinase inhibitor, chemotherapy, anti-SARS-CoV-2 IgG

INTRODUCTION

In February 2020, the World Health Organization designated the virus that caused the epidemic as the disease COVID-19.[1] During the pandemic providing medical care for patients with cancer or suspected cancer, managing the risks of death from cancer against serious complications arising from it has been very difficult given the possible higher lethality of COVID-19 in immunocompromised cancer patients.[2] In order to control the current pandemic, vaccination studies have been started in many centers.

Surface spike protein is the antigenic target for COVID-19 vaccines. Binds to host cells and induces membrane fusion.[3-7] It is recommended that all individuals with cancer be uptodate on their vaccination to prevent COVID-19 Infection. Patients with cancer may have attenuated response to vaccines, but vaccination is recommended in populations with cancer.[8] In patients with cancer, the COVID-19 vaccine reduces the risk of infection and can be administered safely.[9-11] However, studies also show that vaccine efficacy is reduced in those with active cancer compared to those without cancer, particularly those with hematological malignancies, and those receiving anti-CD20 antibody therapy in particular.[12] Immunogenicity studies also show reduced immune response in cancer patients, particularly those with hematological malignancies.[12] Cancer patients receiving immunosuppressive therapy should receive the third dose at least 28 days later. The third dose has been shown to be effective against the Omicron variety in cancer patients receiving treatment, but the response is poor in hematological cancers.[13,14] Current data support booster vaccination in cancer patients receiving immunosuppressive therapy.[15] The most current approach is to vaccinate between treatment regimens.[16-18]

The aim of this study is to examine the effects of the use of tyrosine kinase inhibitor (TKI) and conventional chemotherapy (CT) on the levels of COVID-19 antibodies in patients diagnosed with hematological cancer.

METHODS

COVID-19 IgG levels were measured using the QuantiCOR anti-SARS-CoV-2 IgG ELISA test kit on 74 patients who received chemotherapy and used TKIs in the adult hematology clinic of Turgut Özal Medical Center between May 2019 and January 2022. Age, height, weight, body mass index (BMI) of the patients were measured, the doses and durations of vaccine use, the time between the first vaccine and the second vaccine, how long after the first vaccine antibodies were checked, and vaccine-related side effects were recorded. Collected data Statistical analysis was performed using Python 3.9 and IBM SPSS statistics for Windows version 26.0 (New York; USA). This study was approved by Inönü University Clinical Research Ethics Committee 2021/151 protocol code. All ethical procedures and standards were carried out in accordance with the 1975 Helsinki Declaration.

Antibody Determination

Specific IgG antibodies against SARS-CoV-2 were measured in human sera by a commercial enzyme-linked immunosorbent assay (QuantiCOR anti-SARS-CoV-2 IgG ELISA test kit, Y Immunotek A.Ş., Malatya, Türkiye). This test kit was independently tested and approved by the Ministry of Health of Türkiye, General Directorate of Public Health, Department of Microbiology Reference Laboratories and Biological Products (MRLBP) by applying the World Health Organization (WHO) criteria. MRLBP is the single official authority for the endorsement of all Covid-19 test materials before commercialization. Data was presented as relative unit per milliliters (RU/mL) and the cut-off value for positive sera was 10 RU/mL.

Statistical Analysis

Qualitative data were summarized by number and percentage, and quantitative data by median and interquartile range. The Kruskal-Wallis test was used to examine the difference between groups. Since the multivariate analysis assumptions could not be provided (Multivariate normal distribution and homogeneity of variances assumptions) for the antibody level, two-way PERMANOVA (Permutational Analysis of Variance) analysis was performed using the Bray-Curtis distance (Permutation N=9999) as the similarity matrix to examine the difference between the groups and the interaction effect. $p<0.05$ was considered significant. Analyzes were performed using Python 3.9 and IBM SPSS Statistics for Windows version 26.0

RESULTS

Data of 74 patients, 27 (36.5%) female and 47 (63.5%) male, were used in the study. Descriptive statistics data regarding the demographic information of the patients are presented in Table 1. There was a significant difference between the groups in terms of antibody level. Antibody levels of the patients were significantly higher in the control group than in the patient groups receiving CT and TKI in Table 2. In the research data, a statistically significant difference was found in terms of antibody levels in male and female healthy control groups (p1=0.04). There was a statistically significant difference between the patient groups (TKI-CT-Control) in terms of antibody levels (p2<0.001). While there was a statistically significant difference in antibody level between TKI-Control (p3=0.001) and CT-Control (p3<0.001) groups, there was no statistically significant difference between TKI and CT (p3=0.12) groups. According to the data obtained in the study, the interaction effect (Gender * Group) was statistically significant (p=0.035). As a result, in addition to affecting the antibody levels of the patients separately according to gender and groups, the gender-group interaction was found to be statistically significant especially for the antibody level.

Table 1. Descriptive statistics

Variable **	Group *			p value
	CT	TKI	Control	
Age	70[a] (18)	53[b] (20.25)	35c (8.5)	<0.001
Height (cm)	170[a] (17.5)	170[a] (8.5)	168[a] (11.5)	0.66
Weight (kg)	76[a] (16)	81[a] (14.5)	73[a] (24.5)	0.11
BMI (kg/m2)	26.28[a] (5.685)	28.415[a] (3.55)	26[a] (4.4)	0.13

*: There is a statistically significant difference in group categories that do not contain the same letter. **: Variables are summarized as 'median (interquartile range)'. BMI: body mass index

Table 2. Group comparison results

Variable**	Group*			p value
	CT	TKI	Control	
Antibody level	1.67[a] (10.405)	7.105[a] (14.588)	54[b] (150.75)	<0.001
How many days between the first vaccination and the 2nd	28[a] (0)	28[a] (3)	28[a] (0)	0.98
How many days after the 2nd vaccine, antibodies were tested	90[a] (60)	90[a] (15)	172.5[a] (356.25)	0.44

*: There is a statistically significant difference in group categories that do not contain the same letter. **: Variables are summarized as 'median (interquartile range)'.

The antibody levels of the female patients in the control group were found to be higher than the antibody levels. male patients and other groups of the study (Table 3). The antibody level in the control group was statistically significantly superior than in the patient group receiving R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) - R-BENDA (rituximab, bendamustine) chemotherapy. There was no statistical difference when the patient group receiving R-CHOP - R-BENDA conventional chemotherapy was compared among themselves. (Table 4). Post vaccination joint pain in 4 patients, skin allergy in 1 patient, dizziness in 1 patient, tachycardia in 1 patient were observed as vaccine-related side effects (Table 5).

Table 3. Two-way PERMANOVA results for antibody level

Groups	Median (IQR)	Sex Main Effect	Group Main Effect	Interaction
		p1 Value	p2 Value	
Antibody level-TKI-Female	26.4 (48.55)	p1=0.04	p2<0.001 TKI-CT p3=0.12 TKI-Control p3=0.001 CT-Control p3<0.001	p=0.035
Antibody level-TKI-Male	4.42 (10.78)			
Antibody level-CT-Female	1.67 (13.55)			
Antibody level-CT-Male	1.48 (7.48)			
Antibody level-Control-Female	78 (184.62)			
Antibody level-Control-Male	53.3 (142)			

CT: chemotherapy, TKI: tyrosine kinase inhibitor. IQR: interquartile range, p1 Value; significance test result between women and men, p2 value; intergroup PERMANOVA significance test result, p3: the results of the in-group comparison significance test., Interaction: Sex * Group

Table 4. Comparison results between control, R-chop and R-benda

	Group		p value
	R-CHOP and R-BENDA	CONTROL	
	Median (IQR)	Median (IQR)	
Antibody level	1 (2.64)	54 (162.4)	<0.001
Number of days between the first and the second vaccine	28 (0)	28 (0)	0.62
How many days after 2nd vaccine, antibody tested	90 (60)	165 (360)	0.42

IQR: interquartile range, R-CHOP; Rituksimab-siklofosfamid-doksorubisin-vinkristin-prednizon, R-BENDA; Bendamustine +Rituximab

Table 5. Descriptive statistics of patients related to Covid-19 and vaccine for groups

Variable	Category	Group		
		CT	TKI	Control
		n (%)	n (%)	n (%)
Has he/she had Covid-19 illness?				
	No	21 (77.78)	22 (91.67)	6 (26.09)
	Yes	6 (22.22)	2 (8.33)	17 (73.91)
Vaccine				
	2 doses of sinovac	12 (60.00)	24 (100.00)	6 (27.27)
	2 doses of biontech	2 (10.00)	0 (0.00)	2 (9.09)
	3 doses of sinovac	2 (10.00)	0 (0.00)	1 (4.55)
	3 doses of sinovac + 1 dose of biontech	1 (5.00)	0 (0.00)	1 (4.55)
	2 doses of sinovac + 1 biontech	1 (5.00)	0 (0.00)	5 (22.73)
	2 doses of sinovac + 2 biontech	2 (10.00)	0 (0.00)	5 (22.73)
	3 doses of biontech	0 (0.00)	0 (0.00)	2 (9.09)
Post-vaccine side effect?				
	No	24 (88.89)	21 (87.50)	16 (69.57)
	Yes	3 (11.11)	3 (12.50)	7 (30.43)

Table 6. Chemotherapy received by patients receiving chemotherapy (CT)

Variable	n (%)
Brentiksumab	2 (7.4)
Desitabine	1 (3.7)
DRC	1 (3.7)
DRD	1 (3.7)
Ixazomibe + Lenalidomide	1 (3.7)
Mini CHOP	1 (3.7)
R-BENDA	4 (14.81)
R-CHOP	6 (22.22)
Lenalidomide	6 (22.21)
VCD	2 (7.4)
Azasitidine	2 (7.4)

DRC; Cyclophosphamide - Dexamethasone – Rituximab, DRD; Daratumumab, lenalidomide, and dexamethasone , R-CHOP; Rituksimab-siklofosfamid-doksorubisin-vinkristin-prednizon, R-BENDA; Bendamustine +Rituximab, VCD; cyclophosphamide+ bortezomib+ dexamethasone

Table 7. Tyrosine kinase inhibitors used by patients (TKI)

Variable	n (%)
Bosutinib	2 (8.32)
Dasatinib	4 (16.67)
Imatinib	14 (58.33)
Nilotinib	4 (16.67)

DISCUSSION

During the pandemic, viral antibody level has an important place in isolating the population. There are many questions clinicians need to answer regarding COVID-19 diagnostic testing.[19] Since COVID-19 is fatal in cancer patients, prophylaxis for the disease is needed. In the study of Thakkar A et al.[20] a high antibody response rate (94%) was observed in 200 patients treated for cancer in New York and immunized with vaccines that act on COVID-19 surface protein. Solid tumors (98%), patients with hematological cancer (85%), especially patients who received CD 20 monoclonal antibodies with high immunosuppressive properties, had a lower rate of antibody responses (70, 73%). High antibody response was seen after vaccination in patients receiving immune checkpoint inhibitors (97%) or patients receiving hormonal therapy.

Patients with COVID-19 infection had higher seroconversion titers after vaccination. Relatively lower IgG titers were seen after vaccination with vaccines developed against the surface protein than with mRNA based vaccines.[20] In this study, hematological malignancies were compared and the antibody level of the patients who received TKI and CT was found to be lower than the control group. This decrease was found to be statistically significant. However, in the study, no significant difference was found between the patients who received TKI and those who received CT in terms of antibody levels. (CT-Control p3<0.001, TKI-Control p3<0.001, TKI-CT p3<0.12). In particular, female patients in the Control group had higher antibody levels compared to male patients and other groups of the study (p1<0.04). In the study of Ollila TA et al.[21] 160 patients with cancer were examined for response to COVID-19 vaccines. In the study, 105 (66%) patients received B-cell-reducing monoclonal antibodies, most commonly.

Patients with active disease have a higher antibody response than patients in remission or waiting without any cancer treatment. The time from the last chemotherapy administration to vaccination was associated with increased antibody response rates. While 69% of patients who completed their chemotherapy more than 12 months ago had an antibody response, this rate was found to be 24% in those who were vaccinated within 12 months. It has been observed that the antibody response to the COVID-19 vaccine is lower in patients using B cell destroying antibodies.[21] In the study, ten patients who received CT used B cell reducing monoclonal antibody. When the patient group receiving R-CHOP - R-BENDA conventional chemotherapy was compared among themselves, no statistical difference was observed, but when compared with the control group, the antibody level was found to be significantly higher in the control group. In the study of Mair MJ et al.[12] after the first vaccination, anti-S antibody levels were found to be lower in patients with hematological cancer who received B cell targeting agents than those who received other treatments. After the first vaccination, anti S levels were found to differ according to the ongoing antineoplastic treatment modalities. Antibody levels after full immunization have been found to be higher in healthcare workers than in patients with cancer or in patients continuing treatment in combination with immunotherapy. In the study, the antibody response of the patients who received TKI and conventional chemotherapy was found to be statistically significantly lower than the healthy control group. (CT-Control p3<0.001, TKI-Control p3<0.001, TKI-CT p3<0.12).

CONCLUSION

COVID-19 vaccination in hematological cancers does not produce adequate antibody response, especially in patients receiving CT or TKIs. However, vaccination is recommended in immunocompromised patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Malatya Clinical Researches Ethics Committee (Decision No: 2021/151).

Informed Consent: All patients signed the free and informed consent form.

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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Original Article

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The evaluation of presepsin level and bacterial infection in neutropenic patients

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ABSTRACT

Aim: Neutropenia is a life-threatening complication of chemotherapy, especially in cancer patients, when the patient has an infection. Early treatment of the infection has an important effect on mortality. This study aimed to investigate the usability of presepsin for diagnosing bacterial infection in patients with neutropenia after chemotherapy.

Method: In this study, presepsin, erythrocyte sedimentation rate (ESR), CRP (C-reactive protein), and procalcitonin were measured in 25 neutropenic patients, and comparisons were made between those who were culture positive and negative and those who had a fever and those who did not. In addition, presepsin and CRP values were compared with the control group of 22 people.

Results: Presepsin, CRP, ESR, and procalcitonin were significantly higher in those who did not reproduce in each culture ($p<0.001$, $p=0.003$, $p=0.026$, $p<0.01$, respectively) compared to those who did not have fever ($p<0.001$, $p<0.001$, $p < 0.001$, $p=0.019$, respectively).

Conclusion: Presepsin has the potential to be used in the early evaluation of bacterial infections in neutropenic patients. However, more work should be done on this issue.

Keywords: Presepsin, neutropenic fever, C-reactive protein, procalcitonin, cancer

INTRODUCTION

Chemotherapy has an effective role in the treatment of cancer.[1] Especially in advanced-stage cancers, there is a high probability of disseminating microscopic cancer. Therefore, adjuvant chemotherapy given after surgery has a great place in cancer treatment.[2] Neutropenia is when the number of neutrophils circulating in the blood is less than 1500/microL and is one of the most important side effects of chemotherapy.[3] Mortality is 10% in hospitalized patients, and in patients with multiple or severe morbidities, this rate increases to 20%. In the long term, increased mortality may be observed due to reduction of treatment dose, delay or change of treatment.[4]

The first dose of antibiotic must be without delay in neutropenic fever. Early intervention greatly affects the patient's mortality.[5-7]

In recent years, a wide range of serum (or plasma) sepsis biomarkers have been commercialized. These typically include C-reactive protein (CRP), procalcitonin, presepsin, interleukin 6 (IL6), lipopolysaccharide-binding protein (LBP), neutrophil CD64 (nCD64), myeloid cells-1 (which contains the soluble trigger receptor expressed on sTREM-1), a serum-soluble urokinase-type plasminogen activator receptor (suPAR), and others.[7,8] Although none of these biomarkers fulfil all of the ideal characteristics of a sepsis biomarker, many published studies and meta-analyses have revealed stronger clinical evidence for procalcitonin, presepsin, and CRP.[9,10]

Presepsin is a subtype of the soluble component of CD14. CD14 is a receptor consisting of glycoprotein located on the surface of monocytes/macrophages with a lipopolysaccharides. It has membranous and soluble components.[5-7,11]

Marker detection may be useful for early diagnosis and treatment of neutropenic fever, which is an oncological emergency and also to reduce mortality. This study aimed to investigate the usability of presepsin for early recognition of bacterial infection in patients who are neutropenic after chemotherapy.

METHODS

The study included 25 patients with solid malignant neoplasm and neutrophils <1500/mm³ who applied to Kırıkkale University Faculty of Medicine Hospital between November 2019 and April 2020, and 22 people without any known chronic disease and active infection

who applied for any reason as the control group. The study was initiated with the approval of the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 31/10/2019, Decision No: 25/01). All procedures were carried out following the ethical rules and the principles of the Declaration of Helsinki.

Those younger than 18 years of age, pregnant women, those with active infection, those with renal or hepatic failure, patients who were neutropenic for reasons other than malignancy, those who did not approve the study were not included in the study.

Anamnesis was taken from all individuals included in the study, physical examinations were performed, their temperatures were measured. Complete blood count, biochemistry, CRP, erythrocyte sedimentation rate (ESR), procalcitonin, blood and urine culture, and lung film examinations were routinely performed in the patient group, whereas complete blood count, biochemistry, CRP and ESR values were selected from the control group for any reason. A venous blood sample was taken into an 8-10 ml biochemistry tube from each patient in the patient and control groups, and their serums were separated by centrifugation at 3000 rpm for 20 minutes under sterile conditions. Serums were stored in clean and dry Eppendorf tubes at -24°C in the freezer until their analysis. After the serums were dissolved at room temperature, the Sunred Biotechnology Human Presepsin ELISA kit was used.

Statistical Analysis

Shapiro-Wilk normality test was performed to determine whether the parameters were normally distributed in the statistical evaluation. While mean and standard deviation were used in normally distributed parameters, median and minimum-maximum values were used for non-normally distributed parameters. Correlation analysis was performed with Spearmen's rho test in normally distributed groups, and those that were not normally distributed with the Pearson test.

The Mann-Whithney U test was used to compare two continuous groups that were not normally distributed independently. SPSS 24.0 program was used in the statistical evaluation and $p<0.005$ was considered significant.

RESULTS

While there were 12 women and 13 men in the patient group, there were 14 women and 8 men in the control group. While the mean age of the patient group was 57.76, the mean age of the control group was 57.64. While 10 of the patients had fever, 15 had no fever. At least one culture result of 4 of the patients was positive.

In the study, while the presepsin level of the patients was higher than the control group ($p<0.001$), there was no significant difference between women and men in terms of presepsin level in all groups ($p=0.614$). In the evaluation of neutropenic patients within themselves, the presepsin levels in those with fever were found to be statistically significantly higher than those without, and those with positive culture were found to be statistically significantly higher than those with negative culture.

Table 1. Demographic Results

	Neutropenic (n=25)	Control (N=22)	p
Age (years)	57.76±8.44	57.64±11.46	0.966
Gender			
Female	12 (48%)	14 (64%)	0.292
Male	13 (52%)	8 (36%)	
Body temperature ≥38°C			
Yes	10 (40%)	0 (0%)	
No	15 (60%)	22 (100%)	
Culture			
Positive	4 (16%)	None	
Negative	21 (84%)	None	
Cancers.			
Lung	9 (36%)		
Breast	5 (20%)		
Ovary	3 (12%)		
Neuroendocrine	2 (8%)		
Urinary bladder	2 (8%)		
Cervical	2 (8%)		
Peritoneal	1(4%)		
Gastric	1 (4%)		

Table 2. Presepsin levels in neutropenic patients

	Presepsin level (mg/L)	p-value
Body temperature ≥38 °C		<0.001
Yes	0.695 (0.16-1.82)	
No	0.19 (0.09-1)	
Culture		<0.001
Positive	0.755 (0.62-1.82)	
Negative	0.2 (0.09-1)	

While the CRP level was found to be higher in the patient group than in the control group ($p<0.001$), it was found to be statistically significantly higher in those with positive culture than in those with negative culture and in those with fever than in those without fever.

Table 3. CRP levels in the patient group

	CRP level (mg/L)	p-value
Fever ≥38°C		
Yes	213.6±70.819	<0.001
No	24.935±46.867	
Culture		
Positive	202±58.737	0.003
Negative	52.34±86.204	

Procalcitonin levels were found to be statistically significantly higher in those with positive culture compared to those with negative culture and in those with fever compared to those without.

Table 4. Procalcitonin levels in the patient group

	Procalcitonin level (ng/mL)	p-value
Body temperature≥38 °C		
Yes	0.546 (0.05-21)	0.019
No	0.65 (0.02-0.84)	
Culture		
Positive	0.754 (0.05-21)	<0.001
Negative	0.081 (0.02-4.98)	

ESR levels were found to be statistically significantly higher in those with positive culture compared to those with negative culture and in those with fever compared to those without.

Table 5. ESR levels in the patient group		
	ESR (mm/h)	p-value
Body temperature≥38 °C		<0.001
Yes	93.6±21.077	
No	45.4±28.147	
Culture		0.026
Positive	87.25±14.127	
Negative	60.429±36.038	

There was a significant positive correlation between presepsin levels and ESR (**Figure 1**), CRP (**Figure 2**) and procalcitonin (**Figure 3**) values (p=0.027 r=0.443, p<0.001, r=0.594, p=0.02 r=0.462, respectively).).

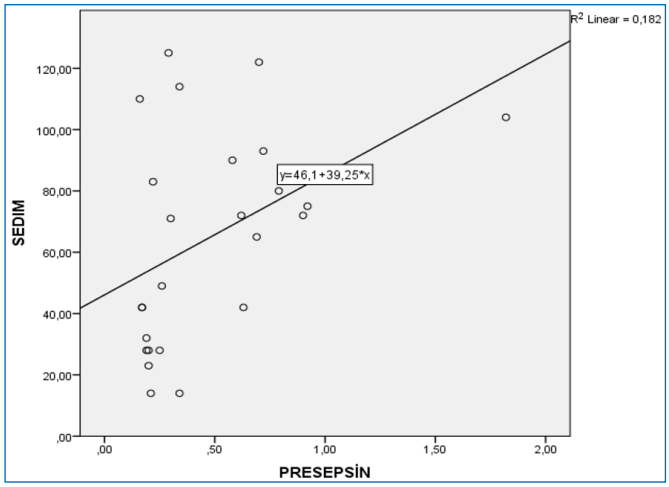

Figure 1. ESR relationship of presepsin in neutropenic patients

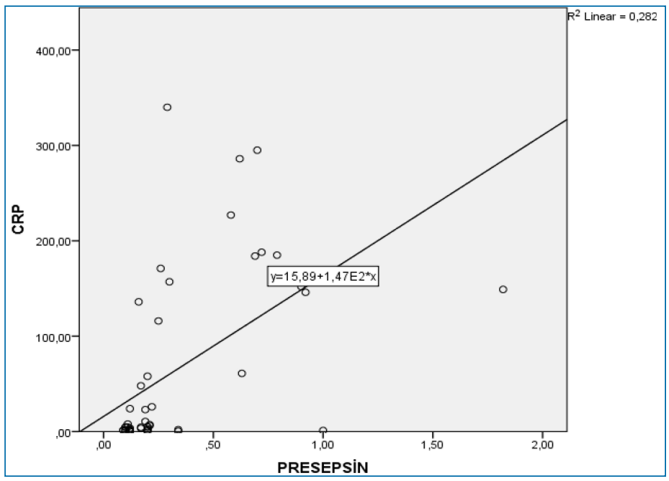

Figure 2. CRP relationship of presepsin in neutropenic patients

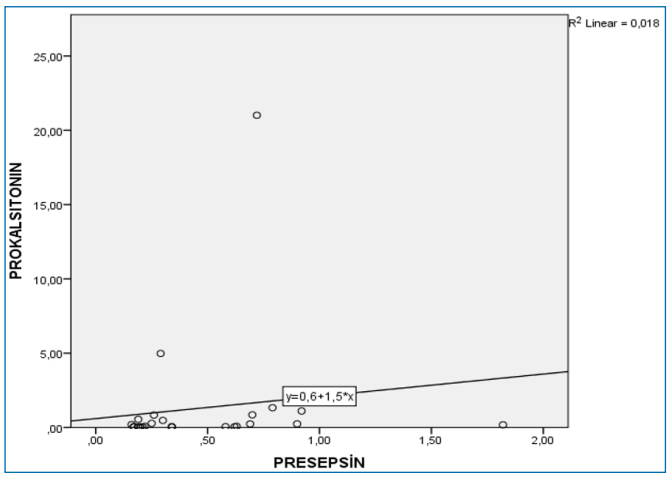

Figure 3. Relationship between presepsin and procalcitonin in neutropenic patients

DISCUSSION

The importance of current study is to show that serum presepsin measurement in the neutropenic patients' group can be detected at an earlier stage of infection. In this study, serum presepsin levels were found to be higher in patients compared to the control group. In addition, it was higher in patients with fever than those without, and those with positive cultures than those with negative cultures. Procalcitonin, CRP, and ESR were all found to be higher in those with fever than in those without, and in those with positive culture than in those with negative. Presepsin values were positively correlated with procalcitonin, CRP, and ESR values.

In a study conducted on children with neutropenic fever, CRP and procalcitonin values were found to be higher in culture-positive patients, while there was no difference in presepsin values. In the same study, it was observed that although the patients were neutropenic, the presepsin values could still increase in the patient group.[12] These findings are in line with our results.

A study by Olad et al.[13] on paediatric patients with chemotherapy-induced neutropenia, presepsin levels were found to be higher in culture-positive patients than in negative patients, and in patients with fever compared to those without fever. In our study, we found that presepsin levels were high in chemotherapy-induced neutropenic patients.

In another study by Maurice et al.[14] they compared the presepsin values in healthy, SIRS (systemic inflammatory response syndrome) positive patients with sepsis, severe sepsis, and septic shock, and found that the presepsin value increased as the patient's condition worsened. In our study results, we found an increase in both presepsin and CRP, ESR, and procalcitonin levels as the general condition of the patients worsened.

In a study conducted to demonstrate the effectiveness of presepsin in recognizing fungal infection, procalcitonin, and presepsin levels were measured in 11 patients with fungaemia, and the SOFA (sequential organ failure assessment) score was calculated. As a result, both presepsin value and procalcitonin values were found to be positively correlated with the SOFA score. It was observed that presepsin decreased in patients whose fungaemia improved and whose general condition improved.[15]

In a study conducted in Japan, serial presepsin measurements were performed in patients with hematological malignancy receiving chemotherapy. While individual monocyte, neutrophil, and white blood cell counts were monitored, the number of white blood cells and presepsin levels were not found to be correlated. The reason for this has been interpreted as the release of presepsin mostly from monocytes and the macrophages in the tissues reaching a certain level of presepsin. Presepsin levels increased early in most of the patients with bacteraemia and in all of the patients with growth.[16]

In a study conducted to measure the usability of presepsin in sepsis in Slovenia, sepsis was decided with two different culture results and procalcitonin values, and accordingly, the presepsin value was compared with patients with sepsis and patients with aseptic meningitis. As a result, the presepsin value was higher in patients with sepsis. There was no difference between Gram negative and positive.[17]

In the study of Mihajlovic et al.[18] blood culture, and SeptiFast test were performed on patients with suspected sepsis and compared with presepsin and procalcitonin levels. SeptiFast is a test that measures bacteraemia and fungaemia in the blood. As a result, procalcitonin and presepsin were significantly higher in those who were positive for SeptiFast, while no significant difference was found in those with positive and negative blood cultures. In our study, the higher presepsin in patients with positive cultures and the increase in presepsin in in neutropenic patients with bacterial infection are consistent with the results of most studies in the literature.

In some studies, the absence of a significant difference in those with positive cultures, may have been due to reasons such as the amount and quality of the sample, the severity of the infection, and the inadequacy of the laboratory.[6]

According to the results of the systematic meta-analysis conducted by Guarino et al.[19] a significant correlation was found between the severity of COVID-19 and presepsin level. Similarly, Kim et al.[20] found a significant correlation between the severity of COVID-19 and presepsin level.

Limitations of the study: The most important limitation was the small number of patients. The limited duration of the study, the fact that it was a single-center study, and the prophylactic administration of GC-SF to some of the patients receiving chemotherapy were the factors that cause of the low number of patients. Another limitation of the study was that bacteria with growth in culture are not specified separately as Gram-positive or negative, since the number was very small. The patients were not homogeneous; there were patients from different cancer groups within the patient group, and many of these patients had additional diseases.

CONCLUSION

Our results are generally consistent with the data in the literature. In the diagnosis of many diseases, the search for early diagnosis continues. Presepsin is a parameter that is examined in serum, gets quick results and is easy to look at. It gives parallel results with ESR and CRP. Therefore, according to the results of our study, presepsin can be used as a guide in the early diagnosis of bacterial infection and in monitoring the response to treatment. However, large-scale studies should be conducted while ensuring the homogeneity of the patient group with a larger patient population with presepsin in patients with adult solid malignant tumours.

ETHICAL DECLARATIONS

Ethics Committee Approval: This thesis study was carried out with the permission of Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 31/10/2019, Decision No: 25/01).

Informed Consent: All patients signed the free and informed consent form.

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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Review

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Tumor markers: when, whom?

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ABSTRACT

Cancer is a leading health problem with its prevalence, clinical course and deaths all over the world. It is known that cancer is the second leading cause of death in Turkey after cardiovascular diseases. Therefore, intensive research is carried out on the early diagnosis and treatment of cancer. The most important of these are tumor markers that are still used in clinical practice. Based on this definition, it is theoretically possible to obtain information about the presence of the tumor and the character of the tumor by investigating tumor markers in body fluids. A tumor marker is a molecule that is present in the structure of the tumor cell, secreted by the tumor cell or produced in response to the tumor and can be measured or demonstrated in body fluids. However, its use is limited due to its low sensitivity and specificity to cancer type in the early period. Therefore, it is important to select the appropriate test at the appropriate time for the appropriate patient. In this review, general principles regarding the use of tumor markers were tried to be explained.

Keywords: Tumor markers, cancer, early diagnosis

INTRODUCTION

Each cell has its own unique molecules that it produces due to its structure or physiological function. With the measurement of these molecules from blood or body fluids, it is possible to obtain information about the presence and functionality of that cell or tissue. Basically, a tumor marker is a molecule that is present in the structure of a tumor cell, secreted by the tumor cell or produced in response to the tumor, and can be measured or demonstrated in body fluids. Based on this definition, it is theoretically possible to obtain information about the presence of the tumor and the character of the tumor by investigating tumor markers in body fluids.[1-3]

With its prevalence and difficulties in diagnosis and treatment, cancer is a challenging disease for clinicians and a popular field for researchers. Every day, new advances in cancer are announced and new techniques against cancer are discussed. Which molecule is the tumor marker and its place in cancer treatment is now indispensable for research and guidelines.[2-5]

Cancer is a leading health problem with its prevalence, clinical course and deaths all over the world. According to GLOBOCAN, there was an incidence of 19.3 million new cancer cases and almost 10.4 million cancer-related deaths worldwide in 2020. According to the records of the Ministry of Health of the Republic of Turkey, in 2017, approximately 180,000 people were diagnosed with cancer in our country, one in every five deaths was caused by cancer and the second most common cause of death in our country was cancer.[6,7]

AREAS OF USE AND PURPOSES OF TUMOR MARKERS

Tumor markers are used for various purposes in the clinical diagnosis and treatment phase. For our clinical purposes, a tumor marker should be detected in those with that disease, it should not be present in those who do not have that disease, it should be detected in the early and silent period of the disease, it should be specific to a particular organ or cancer type, it should provide information about its quantitative value and the size and metastases of the tumor, and it should act in correlation with cancer progression and regression. However, current tumor markers are far from these expectations. Tumor markers in routine use can be measured at high values in non-cancerous and benign conditions, result in normal results in the early stages, and cannot be detected in every patient with that cancer, even though it is defined as particular to a specific cancer. The mismatch between expectations and facts greatly restricts the use of tumor markers.[1,2,4,8]

Screening programs are applications such as examination, imaging, sample examinations for the early diagnosis and early treatment of a particular disease in the society. Diseases that frequently appear in the society, have an asymptomatic period in their course, are easy to treat or save lives when recognized early; diseases that are very difficult to treat or result in death when recognized late are candidates for screening programs. From this point of view, cancers are excellent candidates for screening programs. Cancer screening programs are carried out with various methods and the use of tumor markers for screening is a popular field of study. However, its use is limited due to its low sensitivity and specificity to cancer type in the early period.[1,3,8-11]

The low sensitivity and specificity of tumor markers limit their use for screening purposes as well as their use in diagnosis. Tumor markers have a limited and helpful role in diagnosing cancer today, and biopsy and histopathological examinations are still the priority for definitive diagnosis. They can help with whether a tumor in a particular organ is benign or malignant. They can guide the determination of histopathological diagnosis. They are frequently used in the diagnosis of metastatic cancers of unknown primary origin.[3,12,13]

One of the main elements in the planning of cancer treatment is prognosis. Although tumor stage, tumor size and metastasis are generally evaluated when determining the prognosis, tumor markers may contribute to the prognosis. One of the important problems in the follow-up of cancer treatment is the response to the treatment applied. Although radiological methods stand out in this regard, it is thought that tumor markers can be used. Recurrence and metastasis are another issue that should be followed up as well as the treatment response. Routine follow-up of tumor markers in post-treatment follow-up can alert the clinician about new metastasis and recurrence in patients.[3,4,14-16]

PROMINENT TUMOR MARKERS IN CLINICAL PRACTICE

Although new molecules are proposed as tumor marker candidates every day and new application potentials are attributed to them, tumor markers in routine use within the current guidelines and laboratory facilities are limited in number.

The beta unit of human chorionic gonadotropin, also known as B-hCG, is produced by the placenta and is in routine use as a pregnancy test. However, germ cell tumors can be pathologically detected in the presence of trophoblastic tumors. When used together with other tumor markers, it can give an idea in terms of histological diagnosis at the diagnosis stage and can be used in follow-up.[14,17]

Alpha-fetoprotein (AFP) is often used in the follow-up of chronic liver patients and in the diagnosis of hepatocellular cancer. Although it has low sensitivity in the early period, it is used for screening in people at risk (cirrhosis and chronic hepatitis patients). In addition, its quantitative value can provide information about prognosis and can be a guide for treatment planning. AFP can also be detected in stomach and germ cell tumors. Other causes of AFP elevation include hepatitis, cirrhosis, and pregnancy.[18-20]

Carcinoid tumors cause carcinoid syndrome with the mediators they secrete. Serotonin is the molecule primarily responsible for carcinoid syndrome and is very difficult to measure and interpret. For this reason, the measurement of 5-Hydroxyindoleacetic acid (5-HIAA), a breakdown product of serotonin, is very valuable in terms of diagnosis in the suspicion of carcinoid syndrome and can also be used in the follow-up of treatment. Apart from carcinoid syndrome, it can also be seen in lung cancer, pancreatic islet tumors and non-malignant diseases of the intestine.[18,21,22]

Carcinoembryonic antigen (CEA) is frequently detected in gastrointestinal tract (GI) cancers, primarily colorectal cancers. Apart from cancer, it can be seen in GI diseases such as gastritis, pancreatitis, pancreatitis, colitis. It can give high results in patients who smoke. Due to its low sensitivity and specificity, it is not used for screening purposes. CEA can provide valuable information on prognosis in colorectal cancers. Treatment planning can be followed up in terms of monitoring the treatment response and recurrences.[18]

The prominent tumor markers in breast cancer are CA 15-3 and CA 27.29. Tumor markers are prominent in breast cancer screening and diagnosis in examination and imaging, but are also used in monitoring, especially for metastasis and recurrence. CA 15.3 can cause adenocarcinomas of various organs and liver diseases, high levels of sarcoidosis and hypothyroidism.[18-21]

CA-125 is frequently detected in advanced ovarian cancers and is measured at normal values in half of the early-stage cases. In addition, it may increase in the presence of pelvic inflammatory disease (PID), endometriosis, hepatitis and non-ovarian cancers. Due to these limitations, although the use of CA-125 alone or together with ultrasonography for screening purposes has been studied, it has not been included in current guidelines. CA-125 is a valuable marker in monitoring whether ovarian masses known to be present are benign or malignant and treatment response.[18,19,21]

Although CA 19.9 has been associated with colorectal cancers, it is a tumor marker of pancreatic cancer with its frequent detection in pancreatic cancers. CA 19.9 can be detected in GI malignancies and used for follow-up.[18,22-24]

Prostate-specific antigen (PSA) is the most important marker of prostate cancer. Although PSA elevation raises the suspicion of cancer and the need for a biopsy, PSA is a prostate-specific molecule and can be high in many prostate-related conditions. These conditions can be pathological (benign prostatic hyperplasia (BPH), prostatitis), physiological (ejaculation), even medical interventions (rectal

Table. Intended use of tumor markers and other pathologies with high detection[4,5,9-13]

Organ/tumor	Tumor marker	Intended use	Other pathologies in which the marker can be detected
Liver	AFP	Screening, diagnosis, follow-up	Hepatitis, cirrhosis, pregnancy, other malignancies
Carcinoid tumor	5-HIAA	Diagnosis, follow-up	Pancreatic islet tumor, lung cancer, intestinal diseases
Colon and rectum	• CEA • CA-19.9	Follow-up	• GI malignancies, GI benign diseases, Thyroid medullary cancer • GI malignancies
Choriocarcinoma	B-hCG	Diagnosis, follow-up	Testicular cancer, trophoblastic tumor
Breast	CA-15.3	Follow-up	Liver diseases, sarcoidosis, hypothyroidism, other malignancies
Ovarian	CA-125	Diagnosis, follow-up	PIH, endometriosis, hepatitis, peritoneal irritation, other malignancies
Pancreas	CA-19.9	Follow-up	GI malignancies
Prostate	PSA	Screening, diagnosis, follow-up	BPH, prostatitis, iatrogenic interventions
Thyroid (well differentiated)	Thyroglobulin	Follow-up	Surgical and invasive interventions, benign diseases of the thyroid, pregnancy
Thyroid (medullary carcinoma)	Calcitonin	Follow-up	Liver and kidney malignancies

examination, cystoscopy and biopsy). It should be kept in mind that BPH is the most common cause of PSA elevation. Despite the difficulties in differential diagnosis, PSA is the first test evaluated in social screenings, in the diagnosis of prostate cancer and other benign prostate diseases, and in determining the need for biopsy. It can be monitored for response and recurrence.[25-27]

Thyroglobulin is specific to thyroid tissue and is involved in thyroid hormone metabolism. Thyroglobulin is used to evaluate the success of treatment of well-differentiated thyroid cancers after treatment and to investigate the presence of recurrence in follow-ups. Invasive procedures against the thyroid gland, inflammation of the thyroid gland and autoimmune diseases, disorders in iodine metabolism, pregnancy may cause an increase in thyroglobulin. Among thyroid cancers, medullary thyroid carcinoma is in a different position from other thyroid cancers due to its origin from parafollicular C cells, and calcitonin is used instead of thyroglobulin in its follow-up. Calcitonin may also be high in liver and kidney-related malignancies.[2-4,28,29]

CONCLUSION

There is a bias and expectation in society, and even in clinical routine, that tumor markers give a definitive view of whether a person has cancer. Clinicians, patients, and healthy people who are worried about cancer hope that there is a technique that works with a simple blood test and tells the patient if they have cancer, but that expectation is far from over right now.

- Tumor markers do not give precise information about whether a person has cancer.
- Tumor markers are more valuable in monitoring patients diagnosed with cancer than in cancer research in healthy people.
- A tumor marker can be detected in many different cancers.
- Even if it has been identified for a specific cancer, it may not be detectable in all patients with that cancer.
- Tumor markers may indicate non-cancerous diseases.
- Inappropriate use of tumor markers causes loss of resources and time, and may lead the patient to troublesome, dangerous or even fatal examination and research processes.
- Tumor markers should only be used in certain patients for specific purposes.

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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Journal of Current Hematology & Oncology Research

Case Report

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A case of malignant melanoma presented with lumbar vertebra fracture

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ABSTRACT

Malignant melanoma is a type of skin cancer with a very poor prognosis. It is the most common skin cancer. Metastases are frequently observed in malignant melanoma, which can have a very aggressive course, even without skin findings. Here, we aimed to report a malignant melanoma case presenting with lumbar vertebra fracture, which is a unique form of presentation. A 31-year-old male patient was admitted to the internal medicine outpatient clinic with complaints of low back pain and inability to walk 15 days ago. After the first hour sedimentation value was found to be 101 in the examinations of the patient who came with the complaint of low back pain, he was referred to the hematology department with the preliminary diagnosis of multiple myeloma. Bone marrow aspiration and biopsy was performed. Non-hematopoietic cells were observed in bone marrow aspiration. L2 vertebra fracture was detected in lumbar MRI of the patient with bilateral limitation of movement in the lower extremities. The patient with L2 vertebral fracture was transferred to the neurosurgery service for operation. The patient was diagnosed with malignant melanoma after the frozen biopsy sent after the operation and the previous bone marrow biopsy. Bone marrow infiltration can be seen in malignant melanoma patients. However, a malignant melanoma patient presented with lumbar vertebra fracture has not been reported before in the literature.

Keywords: Malignant melanoma, metastasis, vertebral fracture, bone marrow aspiration, atypical presentation

INTRODUCTION

Malignant melanoma is a type of skin cancer with a very poor prognosis. It is the most common skin cancer. It is the fifth most common cancer in men and women in the United States.[1] In 2015 worldwide, the number of malignant melanoma cases was 351,880, with an age-standardized incidence rate of 5 per 100,000 people per year. And even it is one of the cancer types with the fastest increasing incidence in the world.[2] Malignant melanoma incidence rates remained low and stable in children 0 to 9 years old, while in those aged 10 to 29, the incidence peaked in 2004-2005 and then began to decline.[3]

Metastases are frequently observed in malignant melanoma, which can have a very aggressive course, even without skin findings.[4] Malignant melanoma metastases mainly occur to regional lymph nodes, skeleton and central nervous system. Malignant melanoma can also metastasize to the bone marrow. It has been reported long ago in case series that malignant melanoma can cause bone marrow infiltration with bone marrow aspiration.[5-7] However, a case of malignant melanoma presenting with vertebral fracture has not been reported in the literature so far.

In our case, a patient who was diagnosed with malignant melanoma with bone marrow aspiration and vertebral fracture was presented in our patient who presented with the complaint of weakness in both lower extremities and inability to walk.

CASE

A 31-year-old male patient was admitted to the internal medicine outpatient clinic with complaints of low back pain and inability to walk 15 days ago. After the first hour sedimentation value was found to be 101 in the examinations of the patient who came with the complaint of low back pain, he was referred to the hematology department with the preliminary diagnosis of multiple myeloma.

The patient had no history of chronic disease. Physical examination revealed weakness, limited range of motion, and pain in both lower extremities. Brucella agglutination tests were negative. HSV, EBV, CMV were negative. Rheumatological markers were found to be negative. IgA, IgG, IgM levels and immune electrophoresis tests in serum and 24-hour urine were within normal limits. The patient's hemoglobin, calcium and kidney function tests were normal. Bone marrow aspiration/biopsy was performed for diagnostic purposes in the patient with low back pain and increased

sedimentation. Bone marrow aspiration/biopsy evaluation revealed cells that were considered to be of non-bone marrow origin. Non-hematopoietic cells were observed in bone marrow aspiration (**Image 1**). Human melanoma black 45 was positive and, S100 and kappa/lambda staining were negative.

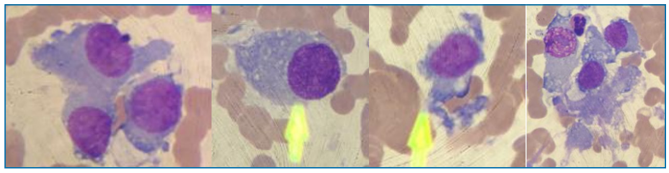

Image 1: Non-hematopoietic cells in the bone marrow aspiration

L2 vertebra fracture was detected in lumbar MRI of the patient with bilateral limitation of movement in the lower extremities (Sagittal T1-weighted images are shown in **Image 2**).

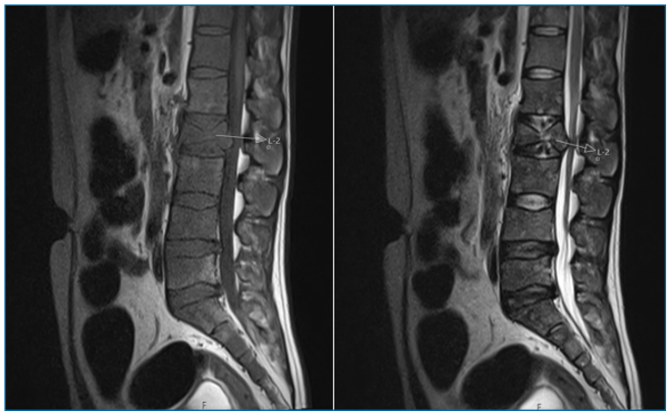

Image 2: Lumbar MRI showing lumbar fracture

Coronal CT is shown in **Image 3**.

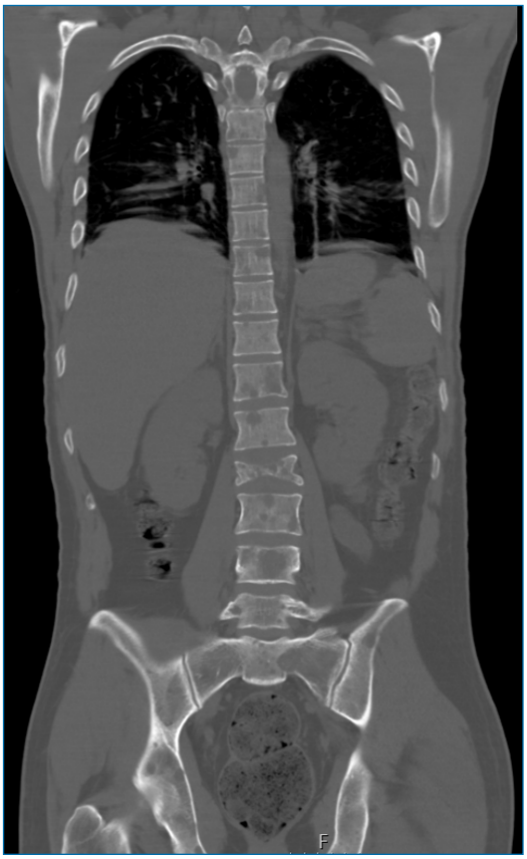

Image 3: Coronal CT

The patient with vertebral fracture was consulted with neurosurgery. The operation was planned. The patient with L2 vertebral fracture was transferred to the neurosurgery. He was diagnosed with malignant melanoma after the frozen biopsy sent after the operation and the previous bone marrow biopsy.

DISCUSSION

The most important localization of malignant melanoma, which is a malignant tumor of melanocytes and nevus cells, is the skin. Rarely, it may originate from the mucous membranes, meninges, eyes, and internal organs. Although malignant melanoma accounts for approximately 2% of all skin cancers, it is the leading cause of death due to skin cancer.[8]

When malignant melanoma is left untreated, it often metastasizes, resulting in death. On the other hand, if skin melanoma reaches the physician by attracting the patient's early attention, it is mostly eliminated at an early stage and the patient can lead a normal life. Since a significant part of the deaths due to malignant melanoma can be prevented, the correct approach of the relevant branch physicians is important.

Malignant melanoma can usually be eliminated at an early stage if the patient receives the attention of the patient and reaches the physician. In case of delay in diagnosis, it may cause diagnosis at the metastatic stage. malignant melanoma is a tumor with a frequent metastatic tendency. Especially lymph nodes, lung and brain metastases have been reported frequently. Metastases to other organs including the bone, pancreas, adrenal and small intestine have also been reported.

Bone marrow aspiration/biopsy is indicated for the evaluation of unexplained anemia, leukopenia, thrombocytopenia or pancytopenia, diagnosis and staging of lymphoma or solid tumors, fever of unknown origin, suspected mycobacterial, fungal or parasitic infections or granulomatous diseases. The diagnostic importance of bone marrow aspiration/biopsy in malignancies has been reported many times since its introduction as a routine hematological procedure. Neoplastic cells may be found in the aspirated bone marrow with various malignant cells.

In the literature, some rare cases in which malignant melanoma was diagnosed by bone marrow aspiration/biopsy have been reported previously. Basu et al.[6] reported the presence of bone marrow infiltration in 2 malignant melanoma patients. While the first of the cases was diagnosed as primary anal malignant melanoma, the second was diagnosed as tonsillar malignant melanoma. Both cases had their initial diagnosis from bone marrow aspiration/biopsy.

Savage et al.[9] evaluated 112 bone marrow aspirations/biopsies performed for staging purposes in 97 patients with malignant melanoma between 1975-1980. They reported that infiltration was seen in the bone marrow aspiration/biopsy of 5 of the patients.

Rubinstein[6] reported a case where the diagnosis of malignant melanoma was made by bone marrow aspiration.

CONCLUSION

The peculiarity of the case we have reported is that there are no previous cases of malignant melanoma presenting with vertebral fractures in the literature. In this respect, our case is the first and unique.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

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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Case Report

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A case of dapsone-induced hemolytic anemia related to G6PD enzyme deficiency

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ABSTRACT

Hemolytic anemia is characterized by a decrease in the number of circulating erythrocytes due to an increase in their hemolysis. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common erythrocyte enzyme defects related to hemolysis. The G6PD enzyme abrogates the hemolysis of erythrocytes by protecting them against oxidative stress due to its involvement in the glutathione metabolism. G6PD enzyme deficiency-related hemolytic anemia may present as neonatal jaundice or become manifest due to exposure to infections, favism and medications later in life. Dapsone is a medication that is preferred by doctors in the treatment of many dermatological disorders such as pemphigus vulgaris, and leads to hemolysis in the presence of G6PD enzyme deficiency. In this type of non-immune hemolysis, haptoglobulin is low and Coombs' tests are negative. Hemolytic anemia, a serious complication that may appear subsequent to dapsone use, can be prevented by testing G6PD enzyme levels prior to dapsone therapy. In this case, we emphasized that the hemolytic anemia in the patient using dapsone may be due to G6PD enzyme deficiency.

Keywords: Dapsone, glucose-6-phosphate dehydrogenase, hemolytic, anemia

INTRODUCTION

Hemolytic anemia defines a group of anemias occurring due to the shortening of normal red blood cell (RBC) lifespan due to factors extrinsic to RBCs or structural changes in RBCs (1). As a result of the increase in RBC hemolysis, anemia and associated clinical symptoms become manifest. Hemolytic anemias can be categorized under two broad titles: hereditary and acquired. Here, we present a case diagnosed with pemphigus vulgaris who was determined to have Glucose-6-phosphate dehydrogenase (G6PD) deficiency based on the tests performed subsequent to hemolytic anemia that occurred during dapsone therapy.

CASE

66 year-old female patient presented to the dermatology polyclinic with raised erythema and bullous lesions in a butterfly distribution on the face involving the eyelids (**Figure 1**). The patient was diagnosed with pemphigus vulgaris based on punch biopsy and, as treatment, was started on 2x50 mg dapsone (PO), 1x16 mg methylprednisolone (PO) and corticosteroid pomades. Blood parameters at diagnosis were as follows: leukocyte, 8.1×10^9/L (4.4-11); hemoglobin (Hgb), 12.3 gr/dl (12-16); thrombocyte, 270×10^9/L (142-424); MCV, 86 fl (80-100); LDH, 210 U/L (135-214); ALT, 22 U/L (0-33); AST, 16 U/L (0-32); direct bilirubin, 0.5 mg/dl (0-0.3); indirect bilirubin, 0.8 mg/dl (0.1-0.9); creatinine, 0.59 mg/dl (0.5-0.9); folate, 10 ng/ml (5.4-24); vitamin B12, 310 ng/ml (210-910). The patient presented to the dermatology polyclinic 6 days after the onset of treatment due to fatigue, pallor, icterus of the sclerae. The patient was referred to the hematology polyclinic based on the following test results: Hgb, 3.8 gr/dl; leukocyte, 11×10^9/L; thrombocyte, 222×10^9/L; MCV, 108 fl; creatinine, 0.8 gr/dl; LDH, 810 U/L; indirect bilirubin, 6.4 mg/dl; direct bilirubin, 0.8 mg/dl.

The patient's history and anamnesis did not include a similar condition that followed medication use or an operation. On physical examination; sclerae were icteric, skin was pale, and there was no organomegaly or peripheral lymphadenopathy. In addition, urine was dark in color. On peripheral blood smear; macrocytosis, anisocytosis-poikilocytosis, polychromasia and Heinz bodies were observed (**Figure 2**). Corrected reticulocyte was determined as 5.2% (0.5-2%); ANA, anti-dsDNA, direct Coombs (IgG) and indirect Coombs' tests were negative. The haptoglobulin level was determined as 8 mg/dl (30-200) and was below the reference range. As

the present hemolytic anemia picture was reasoned to be associated with dapsone, the medication was stopped and 16 mg methylprednisolone was started. No pathological findings were determined on abdominal ultrasonography and lung radiography. Based on the perception that anemia was associated with dapsone, G6PD enzyme levels were examined. The patients' G6PD level was found as 3.52 IU/gHb (7.48-10.20 IU/gHb), and was below the reference. During follow-up, fatigue, subicterus and pallor improved. Hgb levels increased, LDH and indirect bilirubin levels showed a gradual decrease. Blood parameters after 10 days were as follows: Hgb 11,8, gr/dl; leukocyte, 7.6×10^9/L; thrombocyte, 234×10^9/L; MCV, 98 fl; creatinine, 0,6 gr/dl; LDH, 260 U/L; direct bilirubin, 0.42 mg/dl; indirect bilirubin, 0.44 mg/dl.

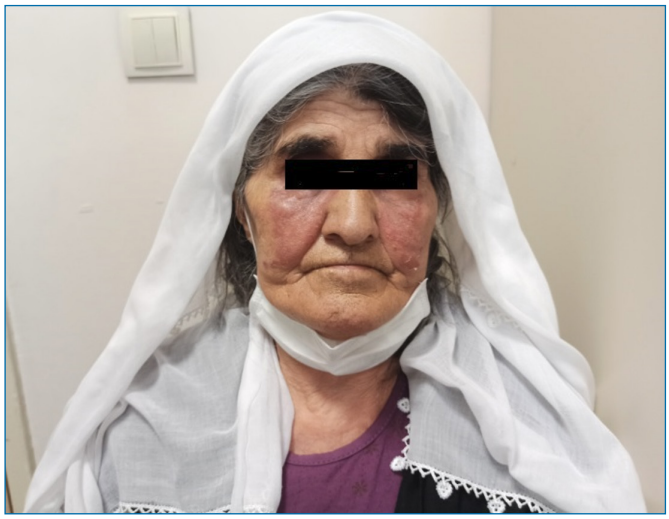

Figure 1. Raised erythematous and bullous lesions on the face, in a butterfly-wing pattern involving the eyelids

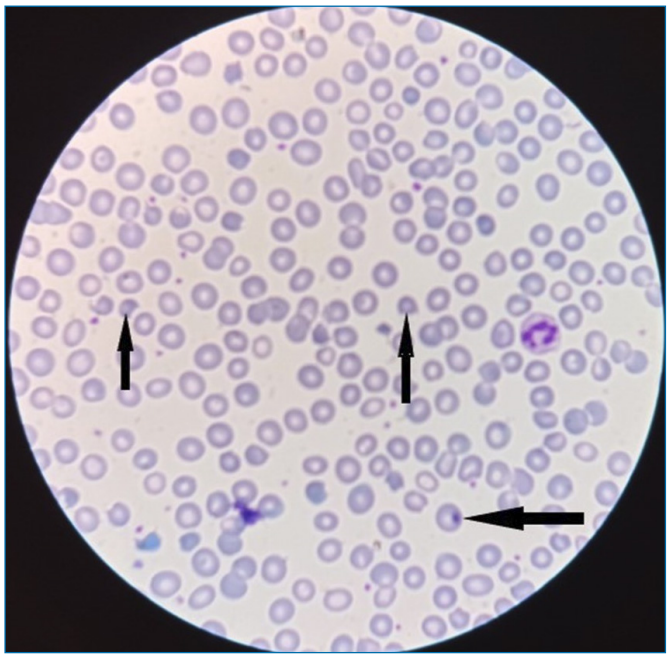

Figure 2. Peripheral smear: macrocytosis, anisocytosis-poikilocytosis, polychromasia and heinz body

DISCUSSION

G6PD enzyme deficiency is hereditary and constitutes one of the causes of metabolic disorder-related hemolytic anemia. It is the most common erythrocyte enzyme deficiency and is more prevalent among males due to its X-linked recessive inheritance (2). It is estimated that this disease affects 400 million individuals worldwide (3). The prevalence of G6PD enzyme deficiency is 0.5% in the general Turkish population, and 8.2% in the Cukurova region (4). The G6PD enzyme is the most important enzyme that protects RBCs against oxidant stress. RBCs are protected against oxidative stress by the production of NADPH, a co-factor of glutathione reductase that reduces glutathione, in the pentose phosphate pathway. In G6PD deficiency, NADPH decreases, and therefore, glutathione reductase levels fall, making the erythrocytes more sensitive to oxidative stress and causing them to be hemolyzed (5). G6PD becomes manifest as neonatal jaundice in 30% of the cases (5). The remaining subsection of the cases become clinically manifest later in life when exposed to oxidative stress due to dapsone, antimalarial medication, infections, operations, as well as consumption of fava, soybeans and fava beans (6). Dapsone is an aniline derivative that belongs to the synthetic dapsone group, and is a sulfone-group antibiotic with both antibacterial and anti-inflammatory effects that inhibits folate synthesis. Dapsone sometimes decreases the oxidation of hemoglobin by inhibiting the hemoglobin reductase enzyme found in the RBC. This effect is more marked in the presence of G6PD enzyme deficiency, and the most common side effects associated with this condition are methemoglobinemia and hemolysis (7). These side effects become more marked in correlation with the G6PD enzyme deficiency (7).

Dapsone is preferred by dermatologists in the treatment of diseases such as lepra, pemphigus vulgaris, pyoderma gangrenosum, bullous lupus erythematosus, bullous pemphigoid, linear IgA dermatosis, aphthous ulcers, lupus panniculitis and dermatitis herpetiformis (7). In our patient, whose G6PD deficiency was unknown, hemolytic anemia occurred after the onset of dapsone therapy for pemphigus vulgaris. Autoimmune hemolytic anemia is an immunologic condition characterized by RBC breakdown induced by antibodies that bind to erythrocyte surface antigens (8). Drug-related autoimmune hemolytic anemia is a condition that occurs due to the interaction between the erythrocyte membrane and the immune system (9). Anti-drug antibodies bind to the medication that is adsorbed and weakly bound to the erythrocyte membrane. Further, antibodies produced in response to medication in the circulation result in an antigen-antibody complex. This complex causes hemolysis by either adsorbing on to the erythrocyte membrane or inducing the complement cascade (10). Based on the occurrence of hemolytic anemia following dapsone use, the presence of negative Coombs' test results and the subsequent detection of G6PD enzyme deficiency in our patient, we were able to exclude drug-related autoimmune hemolytic anemia.

The treatment of G6PD enzyme deficiency-related hemolytic anemia, is avoidance of medications, and conditions such as infections and favism that result in oxidant stress. A blood transfusion may be performed if the Hgb level is below 7 gr/dl, or if it is between 7-9 gr/dl with symptoms or hemoglobinuria (10). In the case of our patient, we stopped dapsone and transfused the patient with 2 units of erythrocyte suspension as her Hgb level was 3.8 gr/dl. Blood parameters spontaneously recovered during follow-up.

CONCLUSION

Dapsone is used widely in the treatment of various disorders, most notably, dermatological disorders. In G6PD deficiency, using dapsone is risky and is associated with a high probability of hemolytic anemia occurrence. In this case presentation, we aimed to stress that hemolytic anemia encountered in a patient on dapsone would be linked to G6PD enzyme deficiency.

ETHICAL DECLARATIONS

Informed Consent: Permission was obtained from the patient for the use of the image, and signed informed consent was obtained.

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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