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EDITORIAL

Dear Colleagues, Our Valuable Readers,

Welcome to the second issue of the "**Intercontinental Journal of Emergency Medicine (ICJEM)**".

This issue includes research on various aspects of clinical medicine, from the analysis of health system costs to intriguing case reports.

The inaugural research article, "*Cost analysis of poisoning cases admitted to the emergency department*" delves into the economic impact of poisoning cases in emergency departments. The study underscores the importance of preventive health measures to manage this significant burden.

The review article, "*Inflammation and blood cells in cardiovascular diseases*" underscores the crucial role hematological parameters play in diagnosing and understanding coronary artery disease.

This issue further contains three case reports that provide unique insights into varying clinical scenarios in emergency medicine. "*Infective Endocarditis Diagnosed by Embolic Complication: Reports of Two Cases*" sheds on light the diagnostic challenges posed by infective endocarditis and its diverse clinical manifestations.

"*Electrocardiographic acute inferior myocardial infarction with right ventricle involvement due to acute thrombotic left anterior descending occlusion in a patient with atrial septal defect*" illustrates the complexities involved in diagnosing acute myocardial infarction in patients with underlying structural heart diseases like atrial septal defect.

Lastly, "*Can mRNA vaccine against COVID-19 cause pancytopenia? A case report*" presents an uncommon adverse event following mRNA COVID-19 vaccination, emphasizing the importance of continued vigilance and research into the potential side effects of vaccines in a broader population.

We believe that these articles provide a spectrum of clinical insights, potentially illuminating various facets of emergency medicine and also enriching our scientific understanding and practice, and we eagerly await your feedback.

Sincerely,

Umut OCAK, MD
Editor-in-Chief
ICJEM

The Intercontinental Journal of
Emergency Medicine

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The Intercontinental Journal of Emergency Medicine

Original Article

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Cost analysis of poisoning cases admitted to the emergency department

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ABSTRACT

Aims: Poisoning incidents are frequently encountered and can often result in fatal outcomes in emergency departments. This study aimed to examine the demographic characteristics of patients diagnosed with drug poisoning in the emergency department and to analyze the associated healthcare costs.

Methods: The study retrospectively analyzed patients admitted to the Nevşehir State Hospital emergency service between January 1, 2017, and December 31, 2018, due to both accidental and intentional drug poisoning. The number of patients diagnosed with drug poisoning in the emergency department was assessed by month and year. Aspects such as the demographic characteristics of the patients, the times of their admission to the emergency department, the outcomes in the emergency department, and the associated costs were compared.

Results: The emergency department received a total of 520,672 patients. Among these, 659 patients who were diagnosed with drug poisoning and had complete data were included in the study. Women constituted 65% of the study population. The patients were categorized into two groups: children under the age of 18 and adults aged 18 and over. The average age of the pediatric patients was 7.7, while the mean age of the adult patients was 30.2. When the emergency service costs were compared with the age and gender variables of the admissions, no statistically significant difference was observed ($p>0.05$). However, a statistically significant difference was noted in terms of cost when the times of admission for patients in the emergency department were compared ($p<0.05$).

Conclusion: Given the morbidity and mortality rates associated with poisoning, the financial burden it imposes is substantial. It is necessary to develop targeted preventive health services to reduce the incidence of poisoning cases.

Keywords: Emergency department, poisoning, cost

INTRODUCTION

Poisoning refers to the emergence of undesirable signs and symptoms in the organism due to exposure to potentially harmful chemical, physical, or organic substances.[1] Poisoning, which is one of the most common causes of emergency service admissions; it is an important public health problem all over the world with its high relationship with mortality.[2,3] There are many causes of poisoning, such as alcohol, drugs, illegal substance use, some foods, carbon monoxide and various chemicals.[4]

Although the tendencies and causes of poisoning differ between geographical regions, early diagnosis helps to reduce morbidity and mortality.[3] Causes of poisoning can be grouped as accidental, suicidal and substance abuse.[2] Regardless of the cause, poisonings are accepted as forensic; again, when the health care cost amounts are evaluated, the burden it brings to the country's economy cannot be ignored.[5]

In this study, cases diagnosed with poisoning due to both accidental events and suicidal drug intake in the emergency department were examined. It was aimed to investigate the relationship between data such as demographic characteristics, admission times, outcome status of the patients, and associated costs.

METHODS

Our study was conducted in accordance with research and publication ethics, and approval was obtained from the Nevşehir Hacı Bektaş Veli University Ethics Committee (Date: 21.02.2022, Decision No: 2022.01.06). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient visits to the Nevşehir State Hospital emergency department between 01.01.2017-31.12-2018 due to both accidental events and poisoning due to suicidal drug intake were analyzed retrospectively. Patients with ICD-10 diagnosis code X44 were recruited after preliminary evaluation. Through the hospital registration system; A data set including the demographic characteristics of the patients, the time of admission to the emergency department (year, month and hour basis), the emergency service costs

and the outcome was created. Cases involving alcohol and substance use, as well as food or smoke-related poisoning, were not included in the study. Again, patients with missing data entries through the registration system were excluded from the study.

The number of patients diagnosed with drug poisoning in the emergency department was evaluated according to months and years. The demographic characteristics of the patients, the hours of admission to the emergency department, the outcome in the emergency department, and the cost of the emergency department were compared.

The conformity of the data to the normal distribution was evaluated by histogram, Q-Q plots, and the Shapiro-wilk test. Mann-Whitney U test was used for quantitative variables in comparisons between groups. The Kruskal Wallis test was used for comparisons between groups of more than two. Dunn-Bonferroni test was used for multiple comparisons. Analysis of the data was carried out in the software R 4.0.3 (www.r-project.org). Significance level was accepted as $p<0.05$.

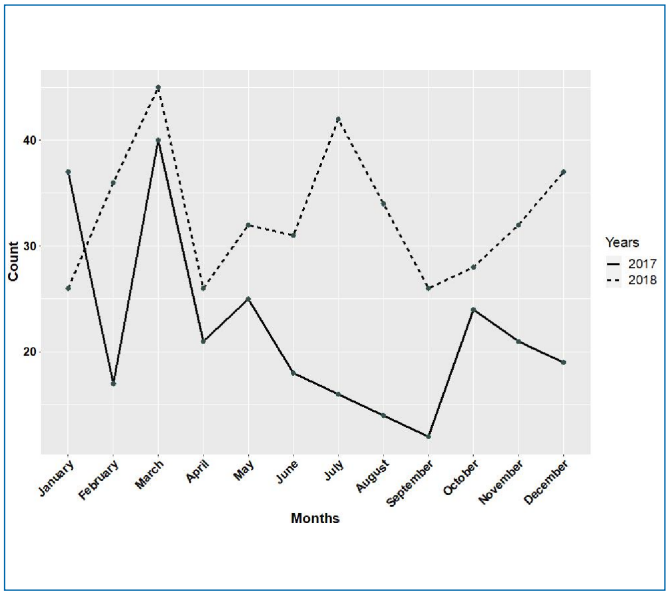

Figure 1. Distribution of poisoning cases by months and years

RESULTS

During the two-year study period, a total of 520,672 patients visited the emergency department. A total of 659 patients who were diagnosed with poisoning due to drug intake in the emergency department and whose data were not deficient were included in the study. When compared to all applications to the emergency department, poisoning due to drug intake constitutes 0.12% of the applications. 65% of the patients included in the study were women. The patients were divided into two groups as children under 18 years of age and adults aged 18 years and over. The mean age of pediatric patients was 7.7; The mean age of adult patients was calculated as 30.2. While 293 (68.4%) of the female patients applied for suicide; 133 (57.5%) of male patients applied. While 78 (32.2%) of the patients under the age of 18 took drugs for suicide, 348 (83.4%) of the adult patients took drugs. Infants and young children are much more likely to take drugs accidentally. The cost analyzes of the patients were determined by calculating the procedures performed in the emergency department for each patient and calculating the costs per patient. Age and gender variables of the admissions were compared with the costs of the emergency department, and no statistically significant difference was found ($p>0.05$) (**Table 1**).

Table 1. Comparison of demographic data with cost amounts

	n (%)	Cost (TL)	p
Gender			0.055
Female	428 (65%)	192.0 (143.0-256.8)	
Male	231 (35%)	176.0 (120.0-267.0)	
Age			0.149
<18	242 (36.7%)	186.0 (120.8-263.3)	
≥18	417 (63.3%)	192.0 (137.0-257.5)	

During the study period, the distribution of the number of patients diagnosed with poisoning due to drug intake in the emergency department by months and years was examined (**Figure 1**). The number of patients admitted due to poisoning was higher in 2018 (59.9%). It was observed that the number of applications in March was higher than the other months in both years.

The time of admission of the patients to the emergency department; they were divided into three groups as 08:00-15:59, 16:00-23:59 and 00:00-07:59. The highest number of applications was made between 16:00-23:59 hours (50.2%). The cost of emergency department for patients diagnosed with drug poisoning was calculated as 72,648 Turkish Lira (₺) (approximately $20,000) for 2017 and 130.811 ₺ (approximately $27,000) for 2018. While calculating the cost of 2017, only emergency service costs are taken into account, hospitalization or referral costs are not included. The hours of admission and the cost of the patients in the emergency department were compared. There was a statistically significant difference in cost between the patient group admitted between 16:00-23:59 hours and the patient group admitted between 00:00-07:59 hours ($p<0.05$) (**Table 2**).

According to the patients' outcome; were divided into 4 groups as referral to another institution, discharge from the emergency department, hospitalization in the department and hospitalization in the intensive care unit. Most of the patients were discharged from the emergency department (66.8%). The outcome status of the patients and their costs in the emergency department were compared, and no statistically significant difference was found ($p>0.05$) (**Table 2**).

Table 2. Comparison of patients' admission hours and outcomes with cost amounts

	n (%)	Cost (TL)	p
Application Time			0.027
08:00-15:59	204 (31%)	188.0 (132.0-263.0)[ab]	
16:00-23:59	331 (50.2%)	195.0 (137.0-282.0)[a]	
00:00-07:59	124 (18.8%)	176.5 (119.3-231.5)[b]	
Ending			0.455
Transport	56 (8.5%)	191.0 (121.0-261.5)	
Discharged	440 (66.8%)	185.5 (131.0-256.0)	
Hospitalization (Service)	137 (20.7%)	201.0 (144.5-278.5)	
Hospitalization (ICU)	26 (4%)	194.5 (148.5-278.5)	

*The same letters in the same column indicate the similarity between the groups, and different letters indicate the difference. * ICU: Intensive Care Unit

DISCUSSION

Poisoning; it is one of the most common causes of emergency department admissions and hospitalizations worldwide in relation to its high mortality and morbidity rates.[2,6] There are many factors affecting poisonings such as geographical conditions, socio-cultural level, education and seasons.[7] Cases of poisoning; in addition to causing an increase in patient density, it is considered as a burden in the health system worldwide due to its social and economic effects.[4]

In the study of Doğan et al.[1] in which they evaluated the poisoning cases who applied to the emergency department over a one-year period; 0.77% of all patients admitted to the emergency department were diagnosed with poisoning. In our study, similar to this study, although the total number of patients who applied to the emergency department was close to each other; the rate of patients diagnosed with poisoning was found to be 0.12%. Since only the patients diagnosed with drug poisoning were included in our study, the rate was thought to be lower compared to the study of Doğan et al.[1]

Similar to the literature, the majority of the patients included in the study were women.[8-10] There are studies emphasizing that this is due to the presence of societal pressure on women in some cultures and the delayed use of medical care.[6] In the study, the mean age was calculated separately for patients younger than 18 years of age; when compared with studies conducted with similar groups, the mean age was found to be similar to the literature.[3,11,12] Independently of factors such as age and gender in emergency services, the basis of the procedures applied in cases diagnosed with drug poisoning is similar. For this reason, the cost of health care services does not make a significant difference when compared with these factors.

It has been reported that suicidal cases are more common in March and April; carbon monoxide poisoning associated with the use of heating equipment and mushroom poisoning are more common in the winter months.[1] In this study, the higher number of patients in the spring and summer months was attributed to the fact that cases other than drug-induced poisoning were not included in the study. However, it is thought that the cases are high in March and April due to the fact that suicidal cases apply in the form of poisoning due to drug intake.

Similar to the studies conducted by both Dal et al.[8] and Deniz et al.[13] in which cases admitted to the emergency department due to poisoning were evaluated, it was found that the most frequent admission was between 16:00 and 23:59 hours in this study. It was thought that most applications to the emergency service were made during this time period, since there was no alternative unit that could provide health services other than the emergency service after working hours and the hours when all family members were at home, especially in suicidal applications. In the previous studies; it has been emphasized that the health care costs of patients admitted with poisoning are a major burden on the health system economy.[4,5,7] It was determined that the cost of emergency service care increased in the years during the study period compared to the previous year; the increase in the number of patients, inflation and changes in care services are thought to be the factors that cause this. However, there is a statistical difference between the application hours in terms of cost amounts; This may be due to the fact that the number of patients admitted between these hours is higher compared to other time intervals and that the cost of the treatments applied is high due to the fact that the majority of drug intake are for suicidal purposes.

Similar to the literature, most of the patients were discharged from the emergency department.[3,9] It was thought that most of the patients were discharged from the emergency department because of the completion of the treatment and follow-up of poisoning cases due to non-toxic drug intake in the emergency departments, and the discharge of the patients and their companions who declined hospitalization. In this study, only the emergency service care costs were calculated, since the ongoing care costs of the patients outside the group discharged from the emergency room were not added; It was thought that there was no statistical difference between the cost amounts and the outcome status of the patients.

The biggest limitation of our study is that it was single-centered and retrospective. More detailed data can be evaluated through multicenter and prospective studies with larger patient groups.

CONCLUSION

Poisoning has an important place among all patient groups admitted to the emergency department due to high mortality, morbidity rates and health care costs. Especially in the prevention of poisoning due to drug intake; It may be helpful to control over-the-counter drug sales, to make drugs in forms that will not attract the attention of children or to open them, and to keep them out of reach of children, and not to keep unnecessary and excess drugs at home. Again, as a result of a raising awareness of people about unnecessary drug use and suicidal cases at the stage of preventive health services, health care costs due to poisoning will be reduced.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Nevşehir Hacı Bektaş Veli University Ethics Committee (Date: 21.02.2022, Decision No: 2022.01.06).

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

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Review

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Inflammation and blood cells in cardiovascular diseases

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ABSTRACT

Coronary artery disease (CAD) is still the most important cause of death in developed societies. Atherosclerosis is recognized as a systemic immune inflammatory disease. Inflammation in CAD can be both local and systemic. The main advantage of hematological parameters and indices is that they are relatively inexpensive and therefore common and easy to find in daily clinical practice. In this review, we will try to explain the main hematological parameters and their effects on pathophysiology in patients with atherosclerotic cardiovascular disease.

Keywords; Cardiovascular disease, inflammation, white blood cells, red blood cells

INTRODUCTION

Despite all the advances in diagnosis and treatment at a dizzying pace, coronary artery disease (CAD) is still seen as the most important cause of death in developed societies. Atherosclerosis is the most common cause and is accepted as a systemic immune inflammatory disease.[1] Chronic low-grade inflammation plays a key role in every stage of the atherosclerotic plaque (from the initial stage of the plaque to the complicated stages such as the rupture-thrombus stage). In addition, inflammation is accepted as one cause of diseases such as diabetes, hyperlipidemia and endothelial dysfunction in the etiology of atherosclerosis.[2]

Inflammation in CAD can be both local and systemic. Increased myeloid activity and sympathetic activity lead to the proliferation of stem cells in the bone marrow and induce systemic inflammation.[3] The main advantage of hematological parameters and indices is that they are relatively inexpensive and therefore common and easy to find in daily clinical practice. Almost all the inflammation parameters have been primarily used in malignancy studies and have been found to be a prognostic indicator of negative outcomes.[4,5] Since it has similar pathophysiological factors, it is thought that it can be used in atherosclerotic vascular diseases. They have also proven their diagnostic and prognostic value in many cardiovascular diseases, including heart failure (HF), cardiac arrhythmias, and pulmonary hypertension.

In this review, we will try to explain the main hematological parameters and their effects on pathophysiology in patients with atherosclerotic cardiovascular disease. In recent years, these cells have become increasingly important as they can provide independent information on pathophysiology, risk stratification and optimal management.

RED BLOOD CELLS (RBC)

While evaluating the outcome of studies, the effect of the diseases on RBCs is searched since it is considered a result of the disease process rather than a cause of the disease. The Red Blood Cell Distribution Width (RDW) index is utilized extensively. RDW is a measure that signifies the variability in the size of red blood cells, thereby indicating their heterogeneity.[6]

Studies show that increased RDW values are associated with adverse outcomes and mortality after coronary intervention in patients with HF, stroke, acute myocardial infarction (AMI), peripheral artery disease (PAD), and also acute coronary syndrome (ACS).[7,8] Lower RDWs are associated with a lower risk of major cardiovascular events in patients with ACS.[9]

Inflammation, increased adrenergic and neuroendocrine system activity, and activation of the renin-angiotensin system seem to cause altered maturation of RBCs, anisocytosis, and an increase in RDW. Oxidative stress is also effective in increasing RDW in acute inflammatory conditions by damaging RBC membranes and causing the bone marrow to release immature RBCs into the peripheral blood.[10]

WHITE BLOOD CELLS (WBC)

Many studies have demonstrated that leukocytosis seen at presentation in both chronic coronary syndromes and ACS is associated with increased cardiovascular mortality and morbidity (microvascular damage, congestive heart failure, and shock development).

As a result of the studies, it has been shown that using the ratios of each other rather than evaluating WBC individually in the evaluation of CAD and inflammation. (neutrophil-

lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, etc.)

Neutrophils

Neutrophils belong to the polymorphonuclear leukocytes family, as they have a segmented nucleus. Neutrophils are the most common among leukocytes. These cells have a relatively short lifespan and contain granules containing highly toxic compounds. The primary task of neutrophils in physiological conditions is to kill harmful microorganisms that enter the body. Neutrophils also have the capacity to phagocytize bacteria killed by released proteases and antimicrobial factors.

The neutrophil-to-lymphocyte ratio (NLR) is easily calculated by dividing the neutrophil count by the lymphocyte count. It is one of the most studied hematological biomarkers that provides prognostic and diagnostic information in CAD. Its role in cardiovascular disease has been extensively studied over the past few years.

A high NLR can be used as an indicator of both the onset and progression of atherosclerosis.[11] It has been investigated as an indicator of mortality and morbidity in both ACS patients and patients undergoing coronary angiography.[4,12] However, it was concluded that it is associated with intra-coronary events (coronary flow velocity, no-reflow, etc.) after percutaneous coronary intervention (PCI).[13] It was concluded that an elevated NLR in patients undergoing coronary artery bypass graft (CABG) was more associated with mortality after CABG.[14] The study conducted also revealed a relationship between NLR and coronary collateral development.[15]

In addition, there are studies claiming that NLR can also be used as a predictor for the development of arrhythmia. It has been shown in studies on the development of atrial fibrillation (AF) both after various operations and after CABG and PCI. In addition, it is also predictive for ventricular arrhythmias.[16] As a matter of fact, in our studies, we have shown that it is a predictor of AF development in patients with COVID-19 disease and after CABG.[17,18] An NLR of patients with acute decompensated HF was associated with frequent decompensation and long-term mortality.19 It has been shown that patients with severe mitral stenosis have a higher NLR compared to patients with moderate and mild aortic stenosis.[20] It was also confirmed that high NLR is an independent indicator of severe rheumatic mitral stenosis.[16]

There is an increasing number of studies showing that NLR can be used to determine the degree and prognosis of the disease in carotid artery disease (CAD). They showed NLR can be used to determine the prognosis after endarterectomy.[21] Studies have shown the relationship between NLR and the incidence, severity, response to treatment and prognosis of PAD.[22-26]

Neutrophils play an important role in the pathophysiology of CAD, given their effect on the instability of atherosclerotic plaques. In the first stage, they penetrate the endothelial cells and become activated when they reach the tunica intima.[27]

It has been hypothesized that the interaction between neutrophils and endothelial tissue causes increased endothelial damage. Severe inflammation is present in cases of ischemic tissue damage in which leukocytes play a key role.[28] Various processes have been suggested, including plaque disruption caused by neutrophil infiltration and increased neutrophil adhesion. It has been shown that neutrophil invasion in atherosclerotic plaque.[29] The plaques can also be more vulnerable by the release of neutrophils, proteolytic enzymes, arachidonic acid derivatives and superoxide radicals. Neutrophils also secrete inflammatory mediators and are associated with an acute inflammatory response to tissue damage.[29] In addition, necrotic core area was positively correlated with lesion size and plaque sensitivity, while neutrophil count was inversely related to smooth muscle cell count and fibrous cap thickness in atherosclerotic lesions.30 Cytokines released from neutrophils regulate vascular tone by blocking nitric oxide synthesis and enhancing endothelin-1 release, and contribute to the development of proliferative vascular lesions by stimulating smooth muscle and interstitial cell proliferation.[31,32]

It may be related to dysfunction of the autonomic nervous system and neutrophil count and thus inflammation. In fact, it has been reported that the distribution of leukocyte subtypes is regulated by the autonomic nervous system. Neutrophils have adrenergic receptors, and the number and function of neutrophils are stimulated by sympathetic nerve endings.[33] Therefore, an imbalance in the autonomic nervous system may play a role in the development and progression of atherosclerosis.[34]

Lymphocyte

Lymphocytes are cells with a diameter of 8-12 microns, large nuclei, and narrow cytoplasm. There are approximately 2 billion lymphocytes, and millions of them are released into the bloodstream daily. In humans, lymphocytes make up 20-40% of the WBCs in the blood. T cells and B cells provide protective immune responses against various pathogens and form long-lasting immunological memory. To maintain a competent and strong immune system, the peripheral pool of mature lymphocytes is tightly regulated by a careful balance of cell production, survival, death and proliferation.

When evaluating the relationship between CAD-inflammation and lymphocyte, the ratios obtained by dividing 3 different cell numbers by each other were used in the overlaps. NLR, the monocyte-lymphocyte ratio (MLR), and the platelet-lymphocyte ratio (PLR). The work of NLR was mentioned a little above.

The no-reflow phenomenon and its association with negative in-hospital outcomes have been demonstrated in patients undergoing primary PCI for lymphocyte-monocyte ratio (LMR), ST elevation AMI.[35] It has been reported that there may be a relationship between LMR and the severity of CAD and in-stent restenosis after PCI in patients with CAD.[36-38] LMR is an independent risk factor for subclinical CAD.[39] LMR appears to be an independent predictor of mortality in patients with acute pulmonary embolism.[40] LMR is independently associated with a higher risk of mortality in acute HF and aortic dissection.[41,42] In addition, LMR levels can be used to evaluate the severity of CAD.[43]

It has been shown that PLR is correlated with higher overall mortality and morbidity in ACS patients.[44,45] In addition, PLR seems to be helpful in predicting complications after emergency and elective PCI and in selecting risky patient groups.[46,47] The PLR has the ability to predict sub-clinical atherosclerosis, atherosclerosis progression in CAD, and the tendency for carotid stenosis to become symptomatic after carotid interventions with morbidity.48 PLR is associated with PAD and may indicate the degree of atherosclerosis.49 Increased PLR may be a helpful biomarker for severity and survival prognosis in HF patients.[50]

Lymphocytes, which are located in the regulatory pathway of the immune system, are inversely related to inflammation and play a very important role in the atherosclerosis process by regulating the inflammatory response.[51,52] Lymphocytes have an active role in the anti-inflammatory response by increasing the immune response during the systemic stress response and regulating serum levels of catecholamines and cortisol.[53,54] Inflammation contributes to atherosclerosis plaque formation and progression; it is regulated by immune cells, cytokines and other biomedical markers and may increase atherosclerotic plaque progression and CAD development.[13,55] Lymphopenia occurs as a result of physiological stress and the cause of possible mechanisms such as decreased cell production, tissue-level redistribution, or cell apoptosis. With the increase in lymphocyte apoptosis in atherosclerotic plaque, plaque development progresses and destabilization occurs in the plaque.[56,57]

Monocyte

Monocytes are the largest cells in the blood. They have a diameter ranging from 14 to 20 micrometers. It has cytoplasmic granules and, due to the phagocytic and motile nature of monocytes, its surface has an irregular structure. They are formed in the bone marrow and circulate in the blood for about 1-3 days before migrating to tissues where they differentiate into macrophages or dendritic cells. Monocytes have functions of phagocytosis, antigen presentation, cytokine secretion, tissue repair, and modulating the immune response by influencing other inflammatory cells. When evaluating the relationship between CAD-inflammation and monocytes, LMR and the ratio of monocytes to high-density lipoprotein cholesterol (monocyte-HDL-C ratio, MHR) are often used as indicators in cardiovascular disease studies. The significance of LMR in cardiovascular health was mentioned in the previous section.

Several studies reported that MHR is independently and significantly associated with long-term mortality in patients with ST-segment elevation myocardial infarction (STEMI), as well as with high SYNTAX scores.[58,59] High MHR is associated with the slow flow/no-reflow phenomenon.[60] Studies suggest that a higher MHR is associated with an increased prevalence of CAD, a hogher mortality rate, and the potential for complications in ACS.[60] There are also few studies showing that MHR is independently and significantly associated with the SYNTAX score in patients with chronic coronary syndrome.[61]

Monocyte migration to the arterial wall is considered one of the early events in atherogenesis and persists in all stages of the disease. They migrate to plaque areas with chemotactic stimuli. There are 3 main roles played by monocytes in the progression of atherosclerosis. First, they play a role in the long-term process of initiation and formation of atherosclerotic plaque by going to the plaque site where adhesion occurs. In the subendothelial space, they differentiate into macrophages that take up oxidized LDL via scavenger cells to form foam cells. Second, they are involved in the acute inflammatory phase following destabilization and rupture of the atherosclerotic plaque and acute thrombus formation. It causes thinning of the fibrous cap due to the enzymes that occur with monocyte-platelet interactions. Finally, they play a role in promoting a variety of beneficial or harmful inflammatory processes in the myocardial tissue during the healing process, particularly during the hypoxic phase.[62-64] The resulting reactive oxygen species increase inflammation.[65]

PLATELETS

Platelets are anuclear and are not amorphous, they have a characteristic discoid shape in their resting state. They originate from megakaryocytes in the bone marrow. Their average lifespan is 7-10 days. It is responsible for initiating the hemostatic mechanisms for repairing the damaged endothelium. Platelets have four main tasks: binding, activation-secretion, aggregation and interaction with coagulation factors. PLR, platelet distribution width (PDW) and mean platelet volume (MPV) are used in studies to evaluate the relationship between CAD-inflammation and the platelet. The work of PLR was mentioned a little above. PDW indicates the changed platelet size. The large number of immature platelets results from increased bone marrow activity during the process known as thrombocytopoiesis. PDW measured at admission is a biomarker that predicts the development of HF in patients with ACS after PCI. It has also been shown to be associated with the severity of CAD. Positive correlations have been reported between a high PDW and a high Gensini score. There are studies showing that PDW can be used in the differentiation of stable and ACS patients and can serve as a useful prognostic factor for mortality in patients after AMI.[4]

MPV is a useful, indirect and easily labeled biomarker of platelet activity. Numerous studies support the association of MPV with adverse cardiac outcomes in patients with CAD. MPV was a strong and independent predictor of impaired reperfusion and mortality in ACS patients undergoing PCI, and has been shown to be associated with the development of restenosis-thrombosis in patients undergoing PCI.[66-71]

An ever-increasing number of data suggests platelets are a population of cells actively involved in atherosclerosis, and that there is also a crucial cross-link between inflammation and thrombosis.[72] Although platelets do not adhere to the vascular endothelium under normal (physiological) conditions, endothelial cell activation or disruption of the endothelial layer leading to a proinflammatory phenotype facilitates platelet adhesion to the vascular wall.[73]

With adhesion, platelets release copious amounts of proinflammatory chemokine that attract circulating leukocytes and facilitate their uptake to the vascular wall.[74] In addition, inflammatory mediators released from activated platelets promote vascular inflammation at lesion sites. It contributes to the progression of atherosclerosis by promoting the aggregation of other platelets and inflammatory cells.[75] In addition, some chemokine help activate angiogenesis. In addition, activated platelets contribute to extracellular matrix degradation and local activation of factors that promote plaque rupture and thrombus formation.[76,77]

CONCLUSION

It is clear that there is a need for a reliable, accessible, non-invasive and hematological prognostic marker to identify patients with high cardiovascular risk in both primary and secondary prevention in CAD, as well as determining treatment modalities after the disease occurs - predicting complications and mortality. The review presented here has attempted to reflect the complex pathophysiology of CAD. Inflammatory processes play a key role in the development

of atherosclerosis, destabilization of atherosclerotic plaques, and clot formation on the plaque surface. It is reasonable to assume that a better understanding of the multifaceted roles of these hematological cells in the inflammatory processes that occur during atherosclerosis may provide clues for additional targets for diagnostic and/or therapeutic intervention.

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Case Report

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Infective endocarditis diagnosed by embolic complication: reports of two cases

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ABSTRACT

Infective endocarditis (IE) is an acute, subacute, and chronic infectious disease affecting the heart valves and endocardium. Although IE is a rare disease, it is still important because of the morbidity and mortality it causes. Because of non-specific clinical manifestations of IE such as fever, malaise, anemia, and embolic complications, the disease may be confused with many disease manifestations and the diagnosis may be delayed. This article reported two cases with an initial diagnosis of meningitis and cellulitis as a result of embolic complications of IE.

Keywords: Infective endocarditis, embolism, *S. aureus*

INTRODUCTION

Infective endocarditis (IE) is an infectious disease caused mostly by bacteria and characterized by the involvement of heart valve endocardium, congenital cardiovascular lesions, or prosthetic valves.[1] The prevalence of IE in developed countries is approximately 6/100 000 people. Epidemiological studies have shown that the frequency of IE has increased in recent years and this increase has occurred especially in the elderly and the rate of IE in people over 70 years of age has been determined as 11.7-19/100 000. There is no incidence study on IE in our country. However, when compared with developed countries, it is possible that the prevalence of IE is higher in our country due to the high prevalence of conditions that increase the risk of IE such as acute rheumatıc fever (ARF) and rheumatic heart disease (RHD, and nosocomial bacteraemia.[2]

Although IE is rare, it still maintains its importance because of the high morbidity and mortality it causes. Clinical signs and symptoms of IE are highly variable and findings including fever, new cardiac murmur, anemia, and splenomegaly may not always be present in most patients.[3] Embolic events are common and life-threatening complications in patients with IE. Since embolic presentation may be confused with clinical findings of many diseases, it may cause difficulties in diagnosis. In this article, two cases of IE presenting with embolic presentation and different diagnoses are presented.

CASE

Case 1

A 36-year-old female patient with no medical history was admitted to the emergency department with a headache and confusion. On physical examination, the patient was unconscious and wasn't oriented and cooperative, there was 2-3/6 systolic murmur in the mitral focus, and hepatosplenomegaly. The general examination was normal. Her parameters were fever: 39°C, heart rate 110/min, arterial blood pressure 110/80 mmHg, and respiratory rate 26/min. Laboratory investigation showed white blood cells (WBC): 17400/mm³ (75% neutrophils), hemoglobin: 8.3 g/dL, platelets (PLT): 282000/mm³, urea: 38.5 mg/dl, serum creatinine: 0.51 mg/dl, aspartate transaminase (AST): 183 IU/L, alanine transaminase (ALT): 91.4 IU/L, serum albumin 2.3 g/dL, prothrombin time (PT) 16.3 min., international normalised ratio (INR): 1.48, C-reactive protein (CRP): 24.4 mg/dl (N:0-0.5), erythrocyte sedımentation rate (ESR): 68 mm/h. A lumbar puncture and blood cultures were performed. The cerebrospinal fluid (CSF) contained 10 leukocytes/mm³ cell count and Gram staining showed no microorganisms. The patient was hospitalised in the infectious diseases unit. An antibiotic therapy with ceftriaxone 2 gram IV bid and vancomycin 1 gram IV bid was started for presumptive diagnosis of acute meningitis. On cranial magnetic resonance imaging (MRI), there was a 5×6 mm nodular hemorrhage area on the cortical surface at the junction of the frontoparietal lobe on the left (**Figure 1**) (This appearance was interpreted as a septic embolism by the radiologist.). All blood cultures were positive for Methicillin-susceptible *Staphylococcus aureus* (MSSA) growth. On transthoracic echocardiography (TTE), 1x1 cm vegetation was detected on the aortic valve. Ceftriaxone and vancomycin treatments were stopped. Considering infective endocarditis, cefazolin 3 gram IV bid and gentamicin 3 mg/kg/day IV were started. The patient's confusion and fever regressed during the follow-up. There was no need for surgery in terms of IE. The patient was discharged after 6 weeks of treatment.

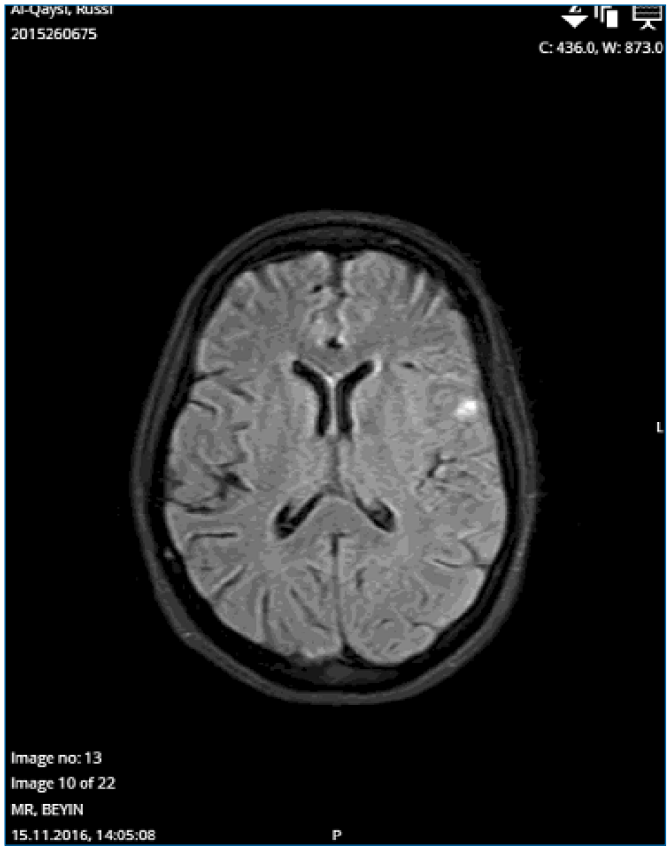

Figure 1. Cranial diffusion MRI: nodular hemorrhage area

Case 2

A 60-year-old male patient was admitted to the emergency department with erythema in both upper extremities (**Figure 2**). On physical examination, his parameters were fever: 38°C, pulse rate: 100/min, blood pressure: 110/80 mmHg, and respiratory rate: 22/min. The patient reported a history of presenting to the emergency department 2 days ago with fever and malaise and was prescribed amok-clav 2 gram bid oral with the diagnosis of cellulitis. The tests performed in the emergency department revealed haemoglobin: 11 mg/dl, WBC: 14000/mm³, PLT: 196000/mm³, CRP: 36.2 mg/dl, ESR: 98 mm/h. Other examination findings were normal and the patient was hospitalised in the infectious diseases ward with a prediagnosis of cellulitis. Blood cultures were performed. Ampicillin-sulbactam 1.5 g 6 hourly treatment was started. During follow-up, the fever persisted and a detailed physical examination revealed painful red skin lesions on the soles of the feet. and fingers. On the third hospital day, the blood cultures drawn on admission returned positive for MSSA. TTE was performed for infective endocarditis and 8 mm vegetation on the aortic valve and pericardial fluid were revelaed. Extensive erythema around a small papule on both arms and lesions on the soles of the feet were evaluated as septic embolism. Ampicillin-sulbactam treatment was stopped and cefazolin 3×2 (6 weeks) and gentamicin 3 mg/kg/day (5 days) were started. Aortic valve insufficiency developed in the fourth week of treatment and the patient was transferred to cardiovascular surgery for valve replacement. Aortic valve replacement was performed and the patient was discharged without complications.

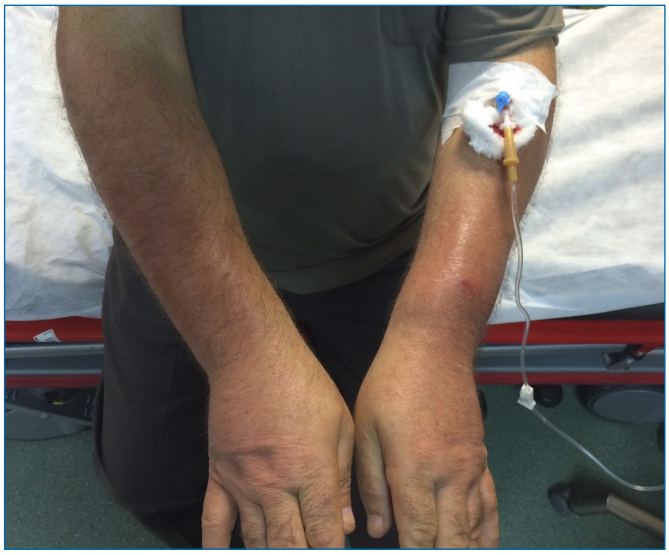

Figure 2. Erythema in both upper extremities

DISCUSSION

In epidemiological studies conducted in developed countries, it has been observed that the incidence of IE, which is approximately 6/100,000, has increased in recent years and IE is the fourth most life-threatening infectious disease after sepsis, pneumonia and intraabdominal infections.[1] The frequency of IE, causative microorganisms, mortality and morbidity rates differ between countries. In developed countries, survival rates in IE are 80% in the hospital, 70% at the end of the 1st year after discharge and only 60% at the end of the 5th year.[2] In Turkey, mortality rates are higher and are 25-30% even during hospitalisation.[3] Acquired valvular diseases or congenital heart diseases and a history of previous IE are the most common predisposing conditions for the development of IE.[3] Endothelial damage is held responsible for the pathogenesis of IE. After mechanical damage or inflammation in the endocardium, small masses called vegetation are formed by bacteria settling in the region. As a result of the arrival of platelets in the region and formation of a fibrin network, the vegetation grows even more.

In recent years, it has been found that the clinical features and common factors of IE have changed.[4] Today, the population at risk is different for several reasons: a decrease in rheumatic heart disease, haemodialysis patients, widespread prosthetic valves, intracardiac devices, intravenous drug use and an increase in healthcare-associated infections, *S. aureus* and coagulase-negative staphylococci (CNS) are more common causes, while the proportion of viridans streptococci has relatively decreased.[5] The most common pathogens in the etiology have shown a microbiological shift from streptococci to *staphylococci*.[6] *S. aureus*, *Streptococcus* spp. and CNS are the most common agents in cases of IE reported in Turkey. These are followed by enterococci and *Brucella* spp. HACEK group bacteria (*Haemophilus* spp., *Aggregatibacter*, *Cardiobacterium* spp., *Eikenella* spp., *Kingella* spp.), *Coxiella burnetii* and *Bartonella* spp., gram-negative rods and fungi (especially *Candida* spp.) are other IE agents.[3] In our cases, the causative microorganism was MSSA as in the literature. There were no underlying risk factors including congenital or acquired valvular disease, intracardiac foreign body or haemodialysis history in our patients. Although the initial clinical pictures of the patients suggested different diagnoses, MSSA grown in blood culture brought infective endocarditis to our mind in the differential diagnosis.

Although the most common clinical finding in IE is fever, it is a multisystem disease with highly variable clinical symptoms. Classical findings such as fever, anorexia, cardiac murmur and anaemia may not always be present. Various organ systems such as skin, mucosa, central nervous system and kidney may be affected due to embolic and immunological complications. The disease may be acute or chronic with subacute or subfebrile fever and silent findings. In a study conducted in Turkey, the most common examination findings in patients were found to be fever (94%) and newly developing murmur (45%).[7] In both cases, infective endocarditis was not initially considered. In the first case, meningitis was considered with a presentation of fever and confusion and in the second case, cellulitis was considered because of fever and erythema in the arms. In both cases, the clinical presentation was actually caused by embolic complications of IE, and the diagnosis of IE was initially missed.

Currently, echocardiography is the most commonly used imaging modality for diagnosis of IE and TTE should be the first investigation to be performed in a patient with suspected IE. Transesophageal echocardiography (TEE) should be performed in the presence of high clinical suspicion even if TTE is negative. On echocardiographic examination, endocardial vegetation, abscess, valve perforation or recent detachment of the prosthetic valve and newly developing valve insufficiency support the diagnosis of IE. Imaging modalities including cardiac CT/MRI and labelled leukocyte scintigraphy are other diagnostic modalities that may be helpful in demonstrating endocardial involvement and detecting cardiac or non-cardiac complications.[8] In both of our cases, the vegetations were quite large and were also seen on TTE and there was no need for TEE.

Embolic events are the most common non-cardiac complications of IE and frequently occur in the initial phase of IE. The diameter, mobility, structure and rapid growth of vegetation are important risk factors for embolism. The risk of embolism varies according to the causative microorganism. Endocarditis caused by staphylococci, *Candida* spp., HACEK and *Abiotrophia* is more risky in terms of septic embolism.[9,10] Septic emboli may affect many tissues and organ systems such as the brain, kidney, spleen, skin, and coronary arteries.[11] Various studies had reported septic embolies are frequently seen in the central nervous system.[12] Neurological involvement includes complications such as stroke, intracerebral haemorrhage, meningitis and abscess.[13] Neurological complications may be associated with poor prognosis. The most common neurological complication is cerebral ischaemia, which is associated with increased morbidity and mortality. Our first case initially presented with neurological findings and was diagnosed with meningitis because of findings compatible with bacterial meningitis on LP performed due to fever. A brain MRI that was performed because the patient's clinical findings did not improve revealed nodular haemorrhage and septic embolism. TTE was performed and the diagnosis of IE was thus made.

Initial treatment of IE is started empirically according to the patient's risk factors. However, once the causative microorganism is identified, treatment directed towards the causative agent constitutes the basis of IE treatment. However, surgery performed in appropriate indications has a very important role in the prognosis of IE.[14] Treatment of septic emboli is best performed with antimicrobial therapy, but anticoagulant therapies are also recommended.

CONCLUSION

Infective endocarditis is a disease with high mortality and morbidity and is being seen more and more frequently today. Especially in cases with subacute courses and without fever, these patients may be misdiagnosed because IE does not come to mind in the initial diagnosis. These patients may present with systemic embolism complications before showing clinical findings specific to infective endocarditis. In case of bacteremia or fungemia of unknown cause or an embolic event, IE should be kept in mind in the differential diagnosis. Also, our cases are important in terms of drawing attention to the different presentations of infective endocarditis and the importance of physical examination in the diagnosis.

ETHICAL DECLARATIONS

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

Referee Evaluation Process: Externally peer-reviewed.

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Case Report

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Electrocardiographic acute inferior myocardial infarction with right ventricle involvement due to acute thrombotic left anterior descending occlusion in a patient with atrial septal defect

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Abstract

Detecting the anatomic location of the lesion with the help of electrocardiography (ECG) is an important and time-saving decision in cases of acute ST-segment elevation myocardial infarction. However, it can be difficult in some patients with different coronary anatomies or underlying structural heart diseases. Here, we reported a 34-year-old male patient with an underlying atrial septal defect (ASD) who presented with acute inferior myocardial infarction with right ventricle (RV) involvement due to acute thrombotic left anterior descending artery occlusion.

Keywords: Electrocardiography, acute coronary syndrome, atrial septal defect

INTRODUCTION

The diagnosis of acute ST elevation myocardial infarction (STEMI) needs a time-sensitive approach based on symptoms and electrocardiography (ECG) findings.[1] Classical expressions of ST elevations in groups over inferior (II, III, aVF), high lateral (I, aVL), precordial (V1-6), posterior (V7-9) or right precordial (V3R-V6R) leads along with new-onset, ongoing angina may easily suggest acute STEMI.[1,2] However, it is not easy to make a diagnosis in case of bundle branch block, pacemaker rhythm, underlying structural heart disease, or anatomically-dislocated heart.[1-3] Additionally, the localization of a culprit artery via looking at the ECG findings can be time-saving in case of unstable patients, but correlation of culprit artery and ECG findings cannot be perfect always, especially in the presence of underlying ECG changes. Thus, reporting this kind of "out-of-standard" example may have potential benefit for the physicians in their clinical judgment. Here, we reported a 34-year-old male patient with an underlying atrial septal defect (ASD) who presented with acute inferior myocardial infarction with right ventricle (RV) involvement due to acute thrombotic left anterior descending occlusion.

CASE

A 34-year-old male patient without chronic illnesses was brought to the emergency department due to approximately 150 minutes of ongoing central chest pain radiating towards the back with a hotline ECG showing acute inferior STEMI with RV involvement (ST elevation over III, aVF, V1-2, V4R-V6R and ST depression over I, aVL, and V4-6). Other findings of the ECG included right ventricle hypertrophy without bundle branch block (**Figure 1A, 1B**).

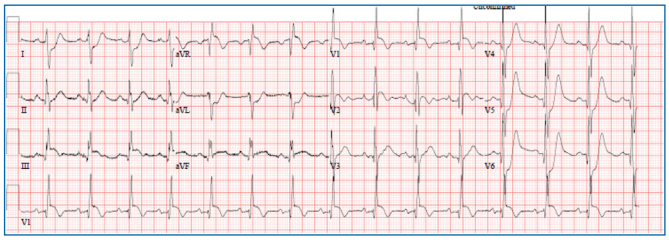

Figure 1A. Standart twelve-lead electrocardiography of the patient at the first medical contact

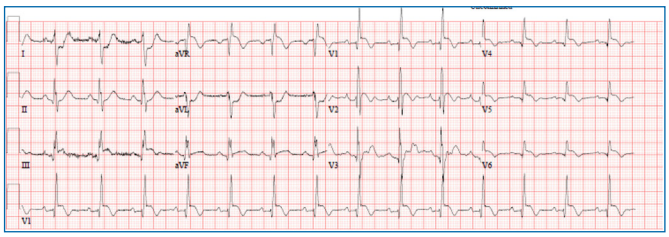

Figure 1B. The right-sided precordial leads (V3R, V4R, V5R, V6R) of the patient at the first medical contact

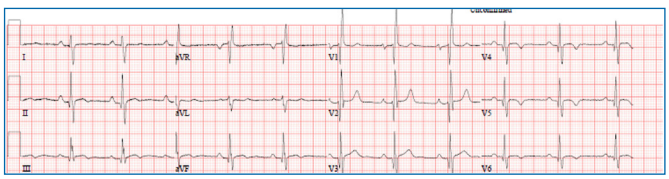

Figure 1C. 12-lead electrocardiography of the patient after the discharge

On arrival, physical examination showed a blood pressure of 102/83 mmHg, a heart rate of 89 bpm with oxygen saturation of 98% at room air, and a soft middiastolic murmur at the upper left sternal border without any crackles or wheezing at chest examination. The bedside echo examination revealed the left ventricular ejection fraction (LVEF) was approximately 40% with a dilated RV chamber without valvular stenosis, or aortic dilation, or pericardial effusion. The patient was transferred to the cath lab promptly. The coronary angiography (CAG) showed normal left circumflex and normal right coronary artery but 100% thrombotic occlusion at the proximal part of the left anterior descending coronary artery (LAD). Primary percutaneous coronary intervention (PCI) was performed to the proximal LAD with a 3.5 mm × 20 mm drug eluting stent following predilation without any complication (**Figure 2A, 2B,** and **2C** respectively) and received guideline-based post-PCI care.

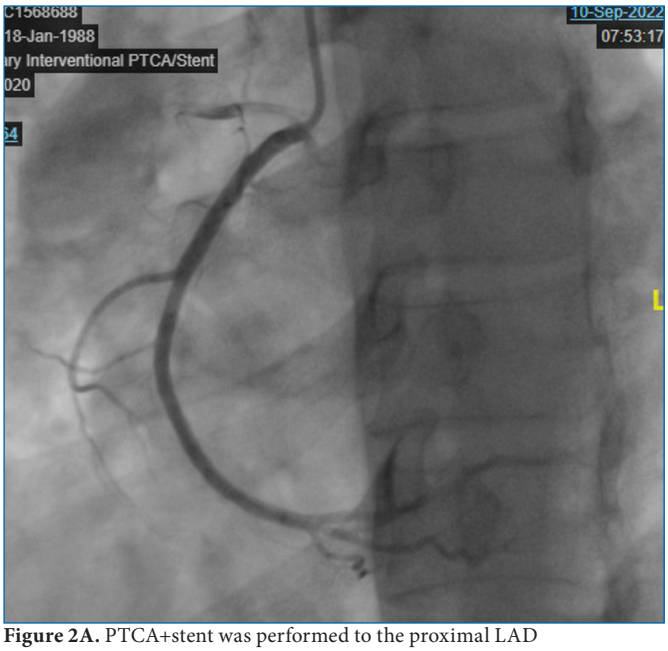

Figure 2A. PTCA+stent was performed to the proximal LAD

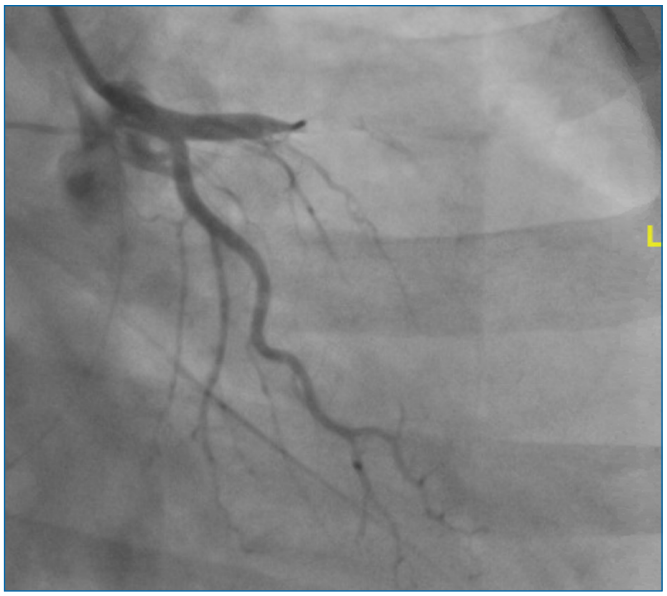

Figure 2B. After PTCA+stent was performed coronary blood flow in LAD

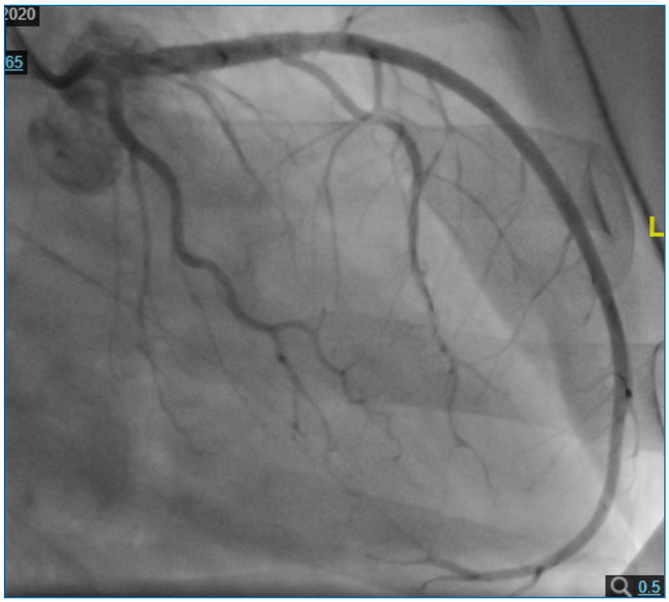

Figure 2C. After PTCA+stent was performed completely coronary blood flow open in LAD

A chest X-ray showed cardiomegaly along with prominent pulmonary vasculature (**Figure 3**). A detailed echocardiographic exam showed LVEF of 42% with regional wall motion abnormalities over the apex and anterior septal segments, a severely dilated RV with normal RV ejection fraction, moderately dilated right atrium, and large secundum ASD with diameter of 3.1 cm (**Figure 4**). RV systolic pressure was 45 mmHg with mild tricuspid regurgitation. In laboratory findings, high-sensitivity troponin T levels were elevated (206 ng/L on admission, 17442 ng/L at peak level six hours after the primary PCI, and 8014 ng/L 24 hours after the primary PCI respectively, with reference values of troponin T of 0-14 ng/L) under normal renal function. The patient had a total cholesterol level of 3.0 mmol/L, LDL of 1.9 mmol/L, triglycerides of 0.8 mmol/L, and HDL of 0.8 mmol/L. His lactate level was 2.6 at arrival (normal range: 0.36 to 1.60 mmol/L). The patient remained clinically stable throughout hospital course and discharged safely. He refused to perform transosephageal echocardiography or ASD closure at the follow-up. ECG changes subsided one month after the discharge, showing T inversions over V4-6, II, III, aVF without any significant ST changes (**Figure 1C**).

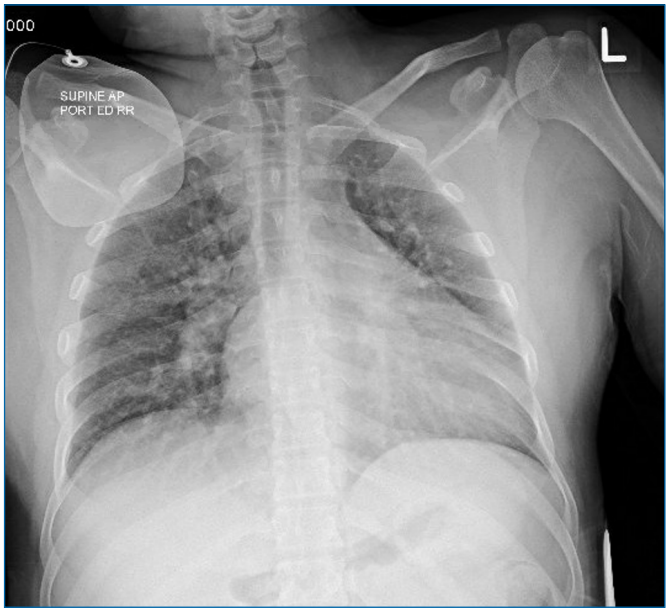

Figure 3. The chest Xray of the patient at admission

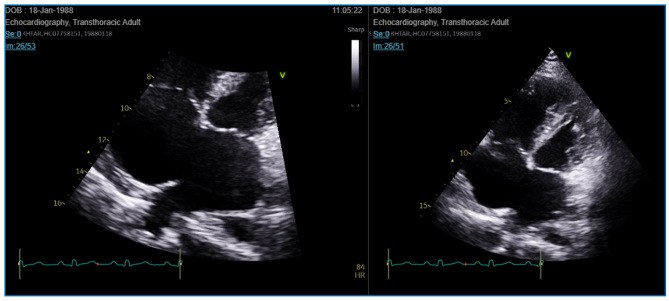

Figure 4. Echocardiographic evidence of secundum type atrial septal defekt at apical four-chamber views with significantly dilated right chambers

DISCUSSION

ST elevation myocardial infarction is a life-threatening condition, and its prompt diagnosis will significantly decrease the related mortality and morbidity. The ECG is the culprit test in the initial evaluation and the keystone in the diagnosis. The ECG will give important information about the culprit lesion and can decrease the-door-to-balloon time. However, some conditions can mask the ECG changes that make diagnosis and locating the culprit artery in the STEMI setting difficult. Here, we report a case of electrocardiographic acute inferior myocardial infarction with right ventricle involvement due to acute thrombotic LAD occlusion in a patient with ASD.

A wrap-around LAD is well-known STEMI that produces ST segment elevation over precordial leads along with ST segment elevation over inferior leads.[4] In our case, the patient had single-vessel disease, and the proximally-occluded LAD turned around the apex but without producing any ST elevation over lead V3-6. The main cause of this situation may be due to anatomic distortion of cardiac chambers by anatomic ASD-related RV changes. The distortion will change RV depolarization forces that overcome the effect of the left ventricular depolarization wave in cases of acute anterior STEMI.[5]

Bodi et al. showed that one-third of the right ventricle may be at risk in cases of extensive anterior STEMI, but the ECG changes of RV involvement will be masked due to dominant LV depolarization vectors in this setting. Following the prompt reperfusion, the infarct size became small enough to be negligible.[6] However, the ECG changes can be more prominent in case of severe right ventricle hypertrophy (RVH). The ECG changes that developed in our case can be explained by this fact.

CONCLUSION

The ECG changes in an acute STEMI setting can be challenging in cases of out-of-normal underlying cardiac states such as RVH. ST elevations in such cases may not be prominent enough to reflect the culprit artery.

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.

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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Can mRNA vaccine against COVID-19 cause pancytopenia?

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ABSTRACT

COVID-19 pandemic changed the world. The fight against acquiring this virus went from social distancing, lockdowns and wearing masks, to mass vaccinations. Several vaccines invaded the market, and nations raced towards vaccinating all the population in order to reach herald immunity. mRNA vaccine is one of the most commonly used vaccine nowadays, and although it has a very high efficacy rate, many side effects were reported. A previously healthy young woman presented to our hospital, 1 week after receiving her first COVID-19 mRNA vaccine due severe aphthous ulcers, fatigue and fever. The patient was found to have pancytopenia. Although several side effects were reported to all the COVID-19 vaccines, pancytopenia is not one of the most commonly reported side effects in the literature. In this case report, we talk about is mentioned in the literature, the clinical picture of this patient, the evolution during her hospitalization, and the outcome.

Keywords: COVID-19, SARS-COV-2, pancytopenia, vaccine, mRNA vaccine, side effects

INTRODUCTION

The novel coronavirus has been identified in 2019 after its massive spread in China. After causing acute medical conditions and high death rates in several countries, the World Health Organization (WHO) considered the Corona Virus Disease 2019 (COVID-19) as a pandemic in March 2020.[1] Moreover, several policies have been imposed in order to hinder the spread of the virus. Each country had its own, such as social distancing, mandatory wear of masks, total or partial lockdowns, and developing medicinal remedies. Rapidly, vaccines were developed and introduced to the market worldwide. Different companies and countries were involved and at least 5 brands are currently available.[2] After roughly one year, The United States Food and Drug Administration (FDA) approved the urgent use of the mRNA vaccine with a minimum 21-day period between the first and the second doses 3. Subsequently, a large and a growing body of literature has recognized the common side effects following the administration of the vaccine.[3-6]

In a study conducted among healthcare workers in the Czech Republic, have identified injection site pain as the most common side effect, followed by fatigue, headache, and muscle pain.[4] Moreover, the majority of these side effects have lasted 1 to 3 days.[4] A more comprehensive description was proposed by El-Shitany et al. who investigated side effects after the first dose and the second dose separately. Adverse events were more prevalent after the second dose, these included injection site pain, flu-like symptoms, and hypersensitivity reactions such as tachycardia and dyspnea.[3] Furthermore, the center of disease control (CDC) has identified 47 cases of anaphylaxis following the administration of mRNA vaccine and in most cases, patients received urgent care.[5]

A lot of less prevalent symptoms and reactions were reported in the literature, some including gastrointestinal, hematologic, musculoskeletal and neurologic.[6] In this article we present the case of a previously healthy female who presented to the emergency department with pancytopenia post the first shot of mRNA COVID-19 vaccine.

CASE

A 31year-old female patient presented to the emergency department of our university medical center with fatigue, low grade fever, aphthous ulcers and subsequently decreased oral intake. Patient reports that symptoms began 6 days prior to presentation, started with generalized fatigue, a fever of Tmax 38 degree Celsius, and a progressive eruption of painful oral ulcers, disabling her from tolerating food intake. Symptoms were not associated with any genitourinary symptoms, gastrointestinal or respiratory symptoms. Patient is previously healthy, with no significant social history, does not smoke nor consumes illicit drugs or alcohol. She denied any food or drug allergies and her family history is negative for rheumatologic disorders, immunodeficiency or autoimmune diseases.

To note that the patient had received her first dose of mRNA COVID-19 vaccine 24 hours prior to the initiation of her symptoms.

On bedside exam, patient was ill-looking, in distress and pale. Cardio-pulmonary exam was normal; abdomen was soft and non-tender. Extremities showed mild skin dryness, but peripheral pulses were palpated, and no edema or rash was detected. However, she had multiple erosive ulcers of the buccal mucosa, not involving the lips nor the perioral area. Vaginal exam was not done but patient denied any itchiness or ulcers. Her blood pressure, heart rate and oxygen saturation were within normal range and her temperature in the emergency department was 37.8 degree Celsius. The patient's blood tests showed decrease in the counts of all the hematopoietic lineage (**Table 1**). Other findings were sodium of 134 mEq/L, potassium 3.4 mEq/L, chlore 101 mEq/L, bicarbonate 17 mEq/L. Liver enzymes were all normal, lactic acid was normal and C-reactive protein was 3.8 mg/dl (elevated). Patient was admitted for further evaluation.

During her stay, blood test to identify causes of pancytopenia were conducted. For instance, HIV 1 and 2 testing came out negative, serology for herpes virus 1&2, and parvovirus B19 were also negative along with, ANA, Tzanc smear, blood cultures and cultures from the oral ulcers and mucosa. Patient was not malnourished; her BMI was above 20 kg/m² with normal albumin blood levels; and there was no family history of similar disorder. No exposure to chemicals or recent medicine was noted in the personal history.

Furthermore, her complete blood count was daily repeated and showed improvement within two days, as described in **Table 1**. Her management consisted of conservative, supportive measures such as daily oral proton pump inhibitor, anti-pyretics, xylocaine topical for oral ulcer, repetitive mouth washes, intravenous hydration, and later was started on itraconazole 200 mg daily to cover for possible oral fungal infection. Nevertheless, 72 hours later, no improvement in the patient's clinical status was observed and especially concerning her oral ulcers and tolerance of oral intake, and little increase was noted on the blood exams. Patient was diagnosed with transient pancytopenia secondary to the vaccine against COVID-19 infection.

On her routine checkup 6 months later the patient had recovered clinically with normal complete blood count.

DISCUSSION

In this case, a previously healthy young female presented with decrease in number of all hematopoietic cell lineage and diffuse oral ulcers. The reference range for hemoglobin, white blood count (WBC) and platelets differ among laboratories, standard values were issued by the WHO: Hemoglobin < 12 gm/dL for non-pregnant women, WBC < 1800 × 10^9/L, and platelets <150,000 10^9/L.[7] For this patient, no biological or metabolic cause was identified, and symptoms were thought to be related to COVID-19 mRNA vaccine. In fact, it is not new to point out pancytopenia as a vaccine side effect. Measles, mumps and rubella vaccine, which is mandatory for children, has been shown to cause bone marrow aplasia in cases as reported by Manoochehr Mahram.[8] It was also seen post hepatitis B vaccine.[9] On the other hand, physicians have identified pancytopenia as one of the adverse events of infection with COVID-19 virus, Yi Zaho et al.[10] presented a case where a 69-year-old male patient suffering from Corona Disease had pancytopenia, where platelet count was the first to normalize with supporting care. A similar case was discussed by Bridwell et al.[11] where the patient required multiple transfusions. Likewise, in our case, the vaccinated patient showed rapid improvement of platelet count first, and slower recovery of hemoglobin and leukocytes. Therefore, it is not out of the norm for patient vaccinated with messenger RNA to have pancytopenia.

Furthermore, this patient presented with severe oral ulcers, which usually are a manifestation of viral infections such as herpes or autoimmune disorders such as Behçet. Nevertheless, our patients ANA and viral panel were negative. In addition, a large retrospective study that targeted the side effects of different COVID-19 vaccine, including mRNA, showed that of the 922 participants, 14% had oral ulcers, and 36% had oral blisters both of which seen in our patient.[3]

Finally, COVID-19 could also be a trigger for autoimmune disorders. Two cases of Goiter were described in the literature post vaccination against COVID-19, and as per the authors, they both met the diagnostic criteria for autoimmune/inflammatory syndrome induced by adjuvants (ASIA), which in their cases and our case is the vaccine.[12] Giving the fact that this patient improved on colchicine, her presentation can be linked to an underlying autoimmune disorder suppressing her bone marrow, triggered by the vaccine. The hypothesis could not be clear whether the vaccine triggered a hidden autoimmune disease, or the pancytopenia and oral ulcers are separate side effects of mRNA vaccine.

CONCLUSION

This female patient received the first dose of COVID-19 mRNA vaccine and few days later, she started complaining of fatigue explained by pancytopenia and eruption of oral

Table 1. CBCD trend during the hospitalization

CBCD	Ref Range	Units	09/08/21	08/08/21	07/08/21 Day 1 post Colchicine	06/08/21	05/08/21	04/08/21
			OK	OK	OK	OK	OK	
WBC	5.2-12.4	x10^3/µL	3.29	4.17	4.32	3.86	3.48	3.52
RBC	4.2-5.4	x10?/µL	4.61	4.56	4.32	4.01	3.66	4.09
HGB	12-16	g/dL	11.9	11.8	11.6	10.6	10.1	10.9
HCT	34-47	%	38.4	38.3	36.0	34.0	31.2	34.7
MCV	81-99	fL	83.2	83.9	83.4	84.7	85.2	84.7
MCH	27-31	pg	25.9	25.9	26.8	26.5	27.7	26.5
MCHC	32-37	g/dL	31.1	30.9	32.1	31.3	32.5	31.3
CHCM	32-37	g/dL	30.6	30.6	30.2	29.7	30.2	30.1
RDW	11.5-14.5	%	14.1	14.6	14.3	14.2	14.9	14.7
HDW	2.2-3.2	g/dL	3.29	3.32	3.27	3.09	3.07	3.13
PLT	150-400	x10^3/µL	211	195	151	113	100	109

lesions. With the negative social and family history and non-significant blood tests, viral serology, nutritional assessment, blood and wound cultures workup, the whole picture was identified as triggered by the vaccine but nevertheless no correlation can be surely identified. The patient however could have benefited from a whole autoimmune workup, as the ANA alone is not 100% sensitive nor specific. The physicians could have also pushed the investigations further, to include a dental checkup, lesion biopsy and bone marrow analysis. A time window after which symptoms can be related to the vaccine is also not specified in the literature; closer observations and broader studies and data collections should be made.

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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