Case Report

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Common Symptom, Rare Etiology: A Case Metastatic Cancers of Unknown Primary Origin Presenting with Epistaxis and Gingival Bleeding

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Abstract

Introduction: Epistaxis and gingival bleeding are among the most common presentation to the emergency department for patients with thrombocytopenia. Here, we present a case who was admitted to the emergency department with thrombocytopenia and was diagnosed with metastatic cancer of unknown primary origin.

Case Report: A 26-year-old male patient was admitted to the emergency department with gingival bleeding and epistaxis. The body temperature was 38.3 °C. Petechial rash, ecchymosis or organomegaly was not detected on physical examination. Laboratory results revealed thrombocytopenia as 31x 10^3 (159-388 x 10^3/µL). Although hemoglobin and leukocyte counts were normal, no band or precursor cell was observed in the patient's peripheral blood smear. There was no history of weight loss, night sweats, arthritis, malar rash, photosensitivity, contact with ticks, animals, or a COVID-19 patient. Serological tests performed for infections such as HIV, EBV, HCV, Crimean-Congo hemorrhagic fever were negative. Bone marrow biopsy was performed due to the unexplained cytopenia, reported as "signet ring cell metastatic adenocarcinoma". Gastrointestinal system endoscopy was performed to detect primary cancer. A biopsy was taken from the antrum and corpus revealed gastritis. An FDG PET-CT was revealed heterogeneously pathologically increased FDG attitude in all axial and appendicular bones. Despite all the modalities of diagnosis, the origin was not found and the patient was transferred to the oncology department for treatment with a diagnosis of cancer of unknown origin with bone marrow infiltration.

Conclusion: Bone marrow metastases should be kept in mind in patients presenting with thrombocytopenia.

Key words: epistaxis,gingival bleeding,thrombocytopenia,Bone Marrow metastases of Unknown Primary Origin

Introduction

Metastatic cancer of unknown primary origin (MCUP) that is 1-2% of all cancer types, is defined by metastatic tumors that primary origin not able to be detected despite all patient's history, laboratory findings and radiological imagine methods[1,2]. %60 of these tumors are adenocarcinoma and more common in male patients around 60 years old[3,4]. Survival of 25 % of the patients is less than one year[5]. Clinical presentation of the heterogeneous tumor group is depends on the site of metastases. While liver and thoracic metastases are mostly detected at older age, brain and bone metastases are seen more in younger population[3].

Bone marrow metastases are seen less than 10% of solid tumors that mainly originated from lung, breast and prostate cancers[6]. According to the article published by Kılıçkap et al, the most common cancers that metastasize to bone marrow are the breast (28%) and lung cancer (23%) while tumors of unknown primary origin are 8 %[7].

Signs and symptoms of the patients with bone marrow metastases are mostly related to cytopenia. Most frequent findings are anemia and thrombocytopenia, respectively[8,9]. Patients can be complicated with bleeding and infections.

In this report, we present a case who was admitted to emergency department (ER) with fever, epistaxis and gingival bleeding, which are frequent complaints of admissions to ER. The patient had thrombocytopenia in the first-line of laboratory tests and diagnosed with MCUP with further examinations. In this perspective, the literature regarding the clinical approach and the etiology is discussed.

Case Presentation

26 year-old male with no significant medical history was admitted to ER with epistaxis and gingival bleeding. Concomitantly he had backache and loss of appetite. There was no history of fever, weight loss, night sweats, arthritis, ma-

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lar rash, photosensitivity, contact with ticks / animals and with a COVID-19 patient. On admission, he was febrile with a temperature of 38°C, with otherwise unremarkable vital signs. In physical examinations, minimal leaky epistaxis and gingival bleeding were detected. There were no petechia or ecchymosis all over the skin. The liver and the spleen were not palpable. In the first step laboratory examination; hemoglobin was 13.1 mg/dl (11.7-15.5), white blood cell count was 8700/ µL (4100-11200), platelet count was 31x10^3/µL (159-388x10^3), aPTT was 29.1 sec (22.5-32) and Prothrombin Time (INR) was 1.47 (0.8-1.2). Dipstick protein (+) and 64 erythrocytes were seen in the complete urinalysis. In the peripheral smear examination, 1-3 % fragmented erythrocytes and 2-3 thrombocytes per high power field are seen thus pseudothrombocytopenia was ruled out. In leukocyte subtype analysis; neutrophil, lymphocyte and monocyte percentages were 70, 20 and 8 respectively. The other remarkable laboratory test results are seen in Table-1.

Since thrombotic thrombocytopenic purpura (TTP) was in the differential diagnosis, ADAMTS-13 enzyme activity test specimen was sent to a private laboratory. Because the patient were from endemic area of the Crimean Congo Hemorrhagic Fever (CCHF), the blood sample was sent to The Public Health Laboratory for PCR. The patient was transferred to the internal medicine ward with high suspicion of CCHF and ribavirin treatment started. On the third day of the treatment, CCHF PCR was reported as negative and ribavirin stopped. Bone marrow biopsy was performed due to unexplained cytopenia. The pathology was metastatic signet ring cell adenocarcinoma. Gastrointestinal system endoscopy performed that revealed hyperemic and edematous antrum and corpus in line with gastritis. Tumor FDG PET-BT was taken to the patient to investigate the primary origin of the tumor. Heterogeneously pathologically increased FDG attitude was detected in all axial and appendicular bones.

Despite all the modalities of diagnosis, the primary origin of the tumor was not able to be detected and the patient was transferred to the oncology department for treatment of CUP with bone marrow infiltration.

Table-1.

	Patient's Value on admission	Reference
ALT (U/L)	86	<50
AST (U/L)	53	<50
ALP (U/L)	663	30-120
GGT (U/L)	28	<55
Bilirubin,total (mg/dl)	4,35	0,3-1,2
Bilirubin,indirect (mg/dl)	3,74	0-1,2
INR	1,47	0,8-1,47
aPTT (sec)	29,1	22,5-32
Fibrinogen (mg/dl)	139,2	180-350
D-dimer (mg/L)	25, 4	0-0,55
LDH (U/L)	519	<248
B2 microglobulin (ng/ml)	1108	609-2366
Na (mEq/l)	139	136-146
K (mEq/l)	3,9	3,5-5,1
Total Ca (mg/dl)	9,7	8,8-10,6
P (mg/dl)	3	2,5-4,5
Albumin (g/dl)	5	3,5-5,2
Globulin (g/dl)	3	1,5-4,6
BUN (mg/dl)	22	6-20
Creatinine (mg/dl)	0,65	0,67-1,17

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: gama glutamil transferase, INR: international normalized ratio, aPTT: activated partial thromboplastin time, LDH: lactate dehydrogenase, Na: sodium, K: potassium, P: phosphorus, BUN: blood urea nitrogen

Discussion

Admissions to ER with epistaxis or gingival bleeding are not uncommon[10,11]. The complete blood count is the first laboratory examination for the patients with bleeding diathesis, thus thrombocytopenia can be detected. Thrombocytopenia is defined by thrombocyte count is less than 150x10^3/µL. Reasons of thrombocytopenia are divided into 3 main groups: decreased production, increased destruction and splenic sequestration. Two main situations can explain decreased production in the bone marrow; bone marrow failures, like aplastic anemia and myelodysplastic syndrome, and bone marrow infiltrations such as leukemia, lymphoma, multiple myeloma, and metastatic tumors. Disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and portal hypertension are examples for increased destruction and splenic sequestration, respectively[12].

Thrombotic microangiopathies should be considered if thrombocytopenia and hemolytic markers (increased lactate dehydrogenase, decreased haptoglobulin, schistocytes in peripheral blood smear etc.) are present. Since TTP causes major organ damage rapidly and threatens life, it should be noticed in the early period and treatment should be initiated as soon as possible. It is valuable for the ER physicians to suspect TTP and take blood sample for ADAMTS-13 enzyme activity as soon as possible. DIC can be excluded by normal prothrombin time and activated partial thromboplastin time. In our case, thrombotic microangiopathies were excluded with absence of hemolytic markers and normal level of ADAMTS-13 enzyme activity.

Although CCHF was thought in the differential diagnosis as the patient came from an endemic region with fever and bleeding, it was excluded due to the PCR negativity.

Bone marrow biopsy is not recommended routinely for isolated thrombocytopenia[12]. If thrombocytopenia cannot be

explained despite all detailed patient history, physical examination, peripheral blood smear, hemolytic markers, liver and kidney function tests and viral serology; bone marrow biopsy should be performed.

Though bone marrow involvement is more frequent in hematologic malignancies, bone marrow metastasis is seen in 0.17- 1.19 % of solid tumors[13]. The most common solid tumors infiltrating bone marrow are lung, prostate, and breast cancers[14]. Although it is known that bone marrow metastases of solid tumors are seen in advanced stages, it were seen as the initial presentation in the case series of 25 patients reported in 1993 by Wong et al.[8]

Median life expectancy of the patients is five months after cancer diagnosis. Survival of 28% of the patients is only one year and thrombocytopenia is a predictor for poor prognosis[7]. Low mean thrombocyte volume may be a sign of bone marrow metastases of solid tumors[15]. When anemia, thrombocytopenia, increased alkaline phosphatase, hypercalcemia or leukoerythroblastic syndrome at peripheral blood smear are detected in chemo-radiotherapy naive solid tumor patients, bone marrow should be analyzed in terms of metastasis[16].

Conclusion

Epistaxis and gingival bleeding are common complaints for admission to ER. Complete blood count and peripheral blood smear are the first step laboratory examinations. In patients with thrombocytopenia, a wide differential diagnosis should be made by a clinical workup. Although MCUP with bone marrow metastases is rare (1-2% of all cancers) it should be kept in mind in patients with thrombocytopenia.

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Conflict of Interest

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