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A metastatic gastric cancer mimicking a chronic myeloproliferative disorder

Case Report

Esin Beyan[1], Cengiz Beyan[2*]

[1] *Department of Internal Medicine, Ankara Numune Education and Research Hospital, 06100 Ankara, Turkey*

[2] *Department of Hematology, Gulhane Military Medical Academy, 06018 Ankara, Turkey*

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Abstract: It is known that coexistence of extreme thrombocytosis and thrombosis is observed frequently in chronic myeloproliferative disorders. In this paper, we report a patient who was prediagnosed with chronic myeloproliferative disorder; however, later on the diagnosis was confirmed as metastatic gastric cancer. The patient was a 75-year old female who was admitted with pain, swelling and erythema on her right arm. White blood cell count was 20 x109/l, hemoglobin 5.2 g/dl and platelet count 1 088 x10^9/l. Doppler ultrasonography revealed acute thrombotic process in right brachial vein. Since brachial vein thrombosis, thrombocytosis and anemia were seen together, the presumed diagnosis for this patient was chronic myeloproliferative disorder, and therapy with hydroxyurea, allopurinol and enoxaparin was started. One day after the heparin treatment, hematemesis and melena occurred. Eusophagogastroduodenal endoscopy showed an ulcerated and hemorrhagic polipoid lesion extending towards the cavity in the cardia region. Hydroxyurea treatment was stopped since the myeloproliferative disorder was excluded. Abdominal ultrasonography and tomography proved multiple metastatic lesions in the liver. Gastric and liver biopsies revealed "well differentiated adenocarcinoma" and 5-fluorouracil chemotherapy plus folinic acid was planned. As a result, in cases with thrombocytosis and thrombosis, metastatic cancers should be kept in mind besides chronic myeloproliferative disorders.

Keywords: *Myeloproliferative disorders • Stomach neoplasms • Thrombocytosis • Thrombosis • Venous thrombosis*

1. Introduction

It is known that coexistence of extreme thrombocytosis and thrombosis is observed frequently in chronic myeloproliferative disorders. In this paper, we report a patient who was prediagnosed with chronic myeloproliferative disorder; however, later on the diagnosis was confirmed as metastatic gastric cancer following detailed clinical and laboratory evaluation.

2. Case Report

The patient was a 75-year old female who was admitted with pain, swelling and erythema in her right arm. Her complaints began one month ago and antibiotics were given for her treatment. But no amelioration was observed in her complaints. She experienced fatigue, which had increased in recent days. She did not report any nausea, vomiting and melena. Body temperature was 37.5 °C, arterial blood pressure was 140/80 mmHg and pulse was 92/min and rhythmic. Tenderness, erythema and swelling were determined on her right arm. Liver and spleen were not palpable and none of the lymph nodes were enlarged. White blood cell count was 20 x10^9/l, hemoglobin 5.2 g/dl, hematocrit 16.7%, mean corpuscular volume 78.3 fl, mean corpuscular hemoglobin 24.2 pg and platelet count 1 088 x10^9/l in complete blood count. Hypochromia, anisocytosis and poikilocytosis were observed in peripheral smear and platelet clumps were seen. AST was 38 u/l (0-34), ALT 43 u/l (0-55), alkaline phosphatase 507 u/l (40-150) and GGT 189 u/l (5-64) in biochemical analysis. Ferritin

* *E-mail: cbeyan@yahoo.com*

was 37.2 ng/ml (5-148), serum iron 15 µg/dl (25-156), serum iron binding capacity 168 µg/dl (110-370) and serum vitamin B_{12} level 332 pg/ml (145-980). Doppler ultrasonography revealed acute thrombotic lesion in right brachial vein and inflammatory changes in adjacent tissues. Since the coexistence of acute thrombosis in the right brachial vein, thrombocytosis and anemia, chronic myeloproliferative disorder was presumed. Hydroxyurea, allopurinol and enoxaparin treatment was started. The cause of anemia was defined as iron deficiency and therefore etiological screening of gastrointestinal system was planned. One day after the heparin treatment, hematemesis and melena occurred. Eusophagogastroduodenal endoscopic examination showed an ulcerated and hemorrhagic polipoid lesion extending towards to cavity in the cardia region. Sclerotherapy was introduced to bleeding focuses and multiple biopsies were taken. Hydroxyurea treatment was stopped since myeloproliferative disorder was excluded. Because of probable malign gastric lesion, radiological screening for metastasis was performed. Abdominal ultrasonographic and tomographic examination established multiple metastatic lesions in the liver. Gastric and liver biopsies revealed “well differentiated adenocarcinoma”. The patient was consulted with the Medical Oncology department, and therapy with 5-fluorouracil chemotherapy plus folinic acid was planned.

3. Discussion

An elevated platelet count may be caused by reactive mechanism or autonomous overproduction of platelets [1-3]. Autonomous thrombocytosis refers to thrombocytosis in the presence of an established diagnosis of a chronic myeloproliferative or myelodysplastic disorder. Reactive thrombocytosis has rarely been associated with thrombosis [4]. Coexistence of thrombocytosis and thrombosis supports the presence of autonomous thrombocytosis and occlusion of the hepatic and/or inferior vena cava, portal, or splenic vein is suggestive of the presence of autonomous thrombocytosis [5]. In the case of thrombosis, immediate platelet apheresis is recommended if the platelet count is >800 $x10^9$/l. Therapy with a platelet-lowering agent should be started with the goal of keeping the platelet count below 400 $x10^9$/l [6,7].

Chronic myeloproliferative disorders are classified as classic and atypical myeloproliferative disorders. Classic myeloproliferative disorders include polycythemia vera, essential thrombocytosis, chronic myelogenous leukemia, and primary myelofibrosis. Atypical myeloproliferative disorders include those chronic myeloid disorders which are currently not classifiable as either myelodysplastic syndrome or classical myeloproliferative disorders: chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, systemic mastocytosis, hypereosinophilic syndrome, chronic neutrophilic leukemia, chronic eosinophilic leukemia, chronic basophilic leukemia, and unclassified myeloproliferative disease. Among the classic myeloproliferative disorders, only chronic myeloid leukemia is genetically characterized by the reciprocal chromosomal translocation between chromosomes 9 and 22. The discovery that JAK2 mutations are found in virtually all patients with polycythemia vera and approximately 50 percent of those with either essential thrombocytosis or primary myelofibrosis, has refined current diagnostic criteria in classic myeloproliferative disorder. Polycythemia vera is considered to be present when an otherwise unexplained increased hematocrit is accompanied by the presence of a JAK2 mutation along with a decreased erythropoietin level. Primary myelofibrosis is characterized by the presence of bone marrow fibrosis that cannot be attributed to another myeloid disorder such as chronic myeloid leukemia or myelodysplastic syndrome. Essential thrombocythemia is a diagnosis of exclusion, representing clonal or autonomous thrombocytosis not classifiable as polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, or myelodysplastic syndrome. Within the context of the myeloproliferative disorders, an elevated red cell mass is specific for polycythemia vera. However, occasionally both chronic myeloid leukemia and the myelodysplastic syndrome may present with either isolated thrombocytosis suggesting essential thrombocythemia, or associated bone marrow fibrosis suggesting myelofibrosis. As a result, the diagnostic work up of patients with suspected chronic myeloproliferative disorder should always include cytogenetic studies and careful morphologic evaluation to exclude the presence of t(9;22) and myelodysplastic syndrome, respectively. The important biologic complication shared among the myeloproliferative disorders is the significant risk of thrombotic complications, most pronounced in polycythemia vera and essential thrombocythemia. Because of the coexistence of acute thrombosis in the right brachial vein, thrombocytosis and anemia in our case, chronic myeloproliferative disorder was presumed and the treatment with hydroxyurea, allopurinol and enoxaparin was started. Obviously, presenting symptoms were not enough to ascertain the chronic myeloproliferative disorder diagnosis, and tests, such as, bone marrow aspiration and biopsy, Philadelphia chromosome, JAK2 mutation, red cell

mass index, erythropoietin level, should be performed. Hydroxyurea treatment was started because the presenting symptoms of the patient (acute thrombotic event, thrombocytosis and anemia) strongly supported the chronic myeloproliferative disorder. Also, rapid reduction of platelets is suggested in case of thrombosis with thrombocytosis. During the course of the disease, most of the above mentioned tests became unnecessary since the early findings supported gastric cancer.

Patients with cancer are in a hypercoagulable state. The spectrum of haemostatic abnormalities ranges from abnormal coagulation tests in the absence of clinical manifestations to massive thromboembolism [8]. Clinical thromboembolism occurs in as many as 11 percent of patients with cancer and is the second leading cause of death in patients with overt malignant disease [9,10]. Autopsy series have described even higher rates of thrombosis for certain tumor types. Tumor types commonly associated with thromboembolic complications are pancreatic cancer, carcinomas of the gastrointestinal tract, ovary, prostate, and lung. The tumor type of our patient was well differentiated adenocarcinoma of gastric origin.

The relation of thrombocytosis with solid tumors is known for a century. Solid tumors are one of the leading causes of thrombocytosis with 13% frequency [11] and are discovered with 14% frequency among cases with extreme thrombocytosis (platelet count >1 000 $x10^9$/l) [12]. Frequency of thrombocytosis and platelet count varies in different malignant diseases. It is especially seen in lung, colon, gynecological, and renal cell cancer [13]. The specific mechanism by which thrombocytosis develops in malignancies remain speculative and several hypotheses have been proposed on this subject. In recent years, humoral mediators are suggested to play role in the pathogenesis of thrombocytosis occur with the response of host against the malignant tissue [13]. Excess amount of cytokines were found to be associated with thrombocytosis in cancers. Interleukin-6, interleukin-1, vascular endothelial growth factor, macrophage colony stimulating factor, granulocyte-macrophage colony stimulating factor, and granulocyte colony stimulating factor, and tumor necrosis factor-α are some of the cytokines studied in malignancy associated thrombocytosis. Thrombocytosis might be a sign of poor prognosis and cause morbidity and/or mortality in cancers. It can be in relation with different processes occurring during the course of malignant tumors as cell invasion and metastasis. Ikeda et al was reported thrombocytosis is a poor prognostic factor in gastric cancer and showed parallelism with tumor extension [14]. Our patient also had extensive disease with liver metastasis.

As a result, in cases with thrombocytosis and thrombosis, metastatic cancers should be kept in mind besides chronic myeloproliferative disorders.

References

[1] Dame C., Sutor A.H., Primary and secondary thrombocytosis in childhood, Br. J. Haematol., 2005, 129, 165-77

[2] Taksin A.L., Couedic J.P., Dusanter-Fourt I., Masse A., Giraudier S., Katz A., Wendling F., et al., Autonomous megakaryocyte growth in essential thrombocythemia and idiopathic myelofibrosis is not related to a c-mpl mutation or to an autocrine stimulation by Mpl-L, Blood, 1999, 93, 125-39

[3] Schafer A.I., Thrombocytosis, N. Engl. J. Med., 2004, 350, 1211-9

[4] Coon W.W., Penner J., Clagett P., Eos N., Deep venous thrombosis and postsplenectomy thrombocytosis, Arch. Surg., 1978, 113, 429-31

[5] De Stefano V., Teofili L., Leone G., Michiels J.J., Spontaneous erythroid colony formation as the clue to an underlying myeloproliferative disorder in patients with Budd-Chiari syndrome or portal vein thrombosis, Semin. Thromb. Hemost., 1997, 23, 411-8

[6] Lengfelder E., Hochhaus A., Kronawitter U., Höche D., Queisser W., Jahn-Eder M., et al., Should a platelet limit of 600 x 109/L be used as a diagnostic criterion in essential thrombocythaemia? An analysis of the natural course including early stages, Br. J. Haematol., 1998, 100, 15-23

[7] Regev A., Stark P., Blickstein D., Lahav M., Thrombotic complications in essential thrombocythemia with relatively low platelet counts, Am. J. Hematol., 1997, 56, 168-72

[8] Goldenberg N., Kahn S.R., Solymoss S., Markers of coagulation and angiogenesis in cancer-associated venous thromboembolism, J. Clin. Oncol., 2003, 21, 4194-9

[9] Sack G.H. Jr., Levin J., Bell W.R., Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: Clinical, pathophysiologic, and therapeutic features, Medicine (Baltimore), 1977, 56, 1-37

[10] Donati M.B., Cancer and thrombosis: From phlegmasia alba dolens to transgenic mice, Thromb. Haemost., 1995, 74, 278-81
[11] Griesshammer M., Bangerter M., Sauer T., Wennauer R., Bergmann L., Heimpel H., Aetiology and clinical significance of thrombocytosis: analysis of 732 patients with an elevated platelet count, J. Intern. Med., 1999, 245, 295-300
[12] Buss D.H., Cashell A.W., O'Connor M.L., Richards F. 2nd, Case L.D., Occurrence, etiology, and clinical significance of extreme thrombocytosis: a study of 280 cases, Am. J. Med., 1994, 96, 247-53
[13] Arslan C., Coskun H.S., Thrombocytosis in solid tumors: review of the literature. Turk. J. Haematol., 2005, 22, 59-64
[14] Ikeda M., Furukawa H., Imamura H., Shimizu J., Ishida H., Masutani S., et al., Poor prognosis associated with thrombocytosis in patients with gastric cancer, Ann. Surg. Oncol., 2002, 9, 287-91