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Rapid resolution of portal vein thrombosis and noncirrhotic portal hypertension following cyto-reductive therapy in a patient with chronic myeloid leukemia

Kronik myeloid lösemili bir hastada sitoredüktif tedaviden sonra portal ven trombozu ve nonsirotik portal hipertansiyonun hızla kaybolması

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The case of a 65 year old woman referred for further evaluation of back pain and with abnormalities at ultrasound including increase in portal vein diameter and splenomegaly is presented. Other tests, including bone marrow biopsy and Doppler ultrasound, led to a diagnosis of portal vein thrombosis secondary to chronic myleoid leukemia. After prompt cytoreductive threrapy with leukapheresis and hydroxyurea, resolution of portal vein thrombosis and portal hypertension was achieved within a in one-month period.

An abnormal increase of cells in circulating blood may lead to portal vein thrombosis in patients with myeloproliferative disorders such as chronic myleoid leukemia. Chronic myleoid leukemia is an unusual cause of portal vein thrombosis and portal hypertension. Early administration of cytoreductive therapy may lead to the resolution of portal vein thrombosis. In this report, etiopathogenetic factors of portal vein thrombosis and the role of cytoreductive therapy in the dissolution of thrombosis are discussed.

Key words: Chronic myeloid leukemia, cyto-reductive threapy, hydroxyurea, leukapheresis, myeloproliferative disorders, portal hypertension, portal vein thrombosis.

Bu takdim edilen vaka raporunda, 65-yaşındaki bir bayan yan ağrısının değerlendirilmesi için doktora müracat eder. Ultrason tetkikinde splenomegalî ve portal ven çapında artma gibi anormallikler görülünce daha ileri değerlendirme için gastroenteroloji kliniğine gönderilir. Doppler ultrason ve diğer tetkiklerle hastanın kronik myeloid lösemiye sekonder gelişen portal ven trombozu olduğu anlaşılır. Lökoferez ve hidroksiüre ile yapılan hızlı tedaviyi takiben bir aylık period içinde portal hipertansiyon ve portal ven trombozunun kaybolduğu gözlenmiştir.

Kronik myeloid lösemi gibi myeloproliferatif hastalığı olan hastalarda dolaşan kanda anormal sayıda artmış hücreler portal ven trombozuna neden olabilirler. Kronik myleoid lösemi, portal hipertansiyon ve portal ven trombozunun nadir bir sebebidir. Erkenden sitoredüktif tedavinin uygulanması portal ven trombozunun erimesiyle sonuçlanabilir. Bu vaka sunumu dolayısıyla, portal ven trombozunun etyopatogenetik faktörleri ve trombozun erimesindeki sitoredüktif tedavinin rolüde ayrıca tartışılmıştır.

Anahtar kelimeler: Kronik myeloid lösemi, sitoredüktif tedavi, hidroksiüre, lökofarez, myeloproliferatif hastalıklar, portal hipertansiyon, portal ven trombozu.

INTRODUCTION

The presence of abdominal pain and splenomegaly in any patient should alert the physician to the possibility of a serious problem and differential diagnosis should be cautiously made among infectious, hematologic, collagenous, hereditary, vascular and surgical causes. Portal vein thrombosis is one of the rarest causes and is classified as vascular in origin. Thrombosis in the portal vein has many causes. These may be classified as

a)-hypercoagulation states such as latent myeloproliferative disorders (1,2), the prescription of anticoagulant drugs (3), antiphospholipid syndromes (3), prothrombotic genetic defects such as protein-S, protein-C and antithrombin-III deficiency (4), thrombosis (5), hematologic disorders like paroxysmal nocturnal hemoglobinuria, polycythemia vera and sickle cell diseases, pregnancy and use of oral contraceptives.

b)-Inflammatory disorders such as ulcerative colitis (6), Crohn's disease, Behçet's disease (7) and pancreatitis caused by marathon running.

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c)-iatrogenetic causes such as alcohol injection, ambulatory dialysis, chemoembolization, islet cell injection, liver transplantation (8), partial hepatectomy, sclerotherapy, splenectomy, TIPS and abdominal surgery (8),

d)-infections such as actinomycosis, Candida albicans and abdominal infection including appendicitis and diverticulitis (9) and

e)-miscellaneous disorders including cirrhosis, tumors or blunt abdominal trauma.

The portal system collects blood from the abdominal part of alimantary tract, spleen, pancreas and gallbladder and enters the liver at the porta hepatis in two main branches. Union of the superior mesenteric and splenic veins forms the portal vein. Normal portal blood flow is about 1000-1200 ml/s and portal pressure is about 7 mmHg. After portal vein thrombosis, portal circulation may be obstructed both within and outside the.liver which can cause portal hypertension and consequent splenomegaly, ascites, edema and remarkable collateral circulation if the etiologic cause persists. Generally, diagnosis is made by abdominal and portal vein Doppler ultrasound examination, where an increase in portal vein diameter and thrombotic material are seen on ultrasonographic evaluation.

Leukemia is a hematologic disorder of unknown etiology characterized by an abnormal increase in peripheric white blood cells following bone marrow stimulus, which may be seen in either acute or chronic forms. Thrombosis may occur during the course of chronic myleoid leukemia. Changes in viscosity state, accumulation of leukemic cells in the vascular system and alterations at the surface of blood cells are some of the causes of thrombosis formation.

CASE REPORT

A 65-year-old woman was evaluated by an urologist for complaints of left sided colicky back pain. After physical examination, urinalysis and abdominal ultrasonography (USG) revealed microscopic hematuria, a left lower ureter stone, splenomegaly and an increase in portal vein diameter (18 mm). Following treatment for the colicky pain, she was referred to our clinic for evaluation of splenomegaly. In her past history, the patient had cholecystectomy and appendectomy 20 and 15 years ago respectively and more recently, an upper gastrointestinal hemorrhage four months previously. On physical examination, there was tachycardia (110/min), pale conjunctivae and diffuse, painless and unfixed lymphadenopathy in the cervical, submandibular, axillar and inguinal regions. She also had mild degree hepatomegaly and moderate splenomegaly. Among the abnormal laboratory findings, she had leucocytosis (=319.000/mm3), anemia (2.820.000/mm3, hematocrit value 25%, hemoglobin: 10.1gr/dl), thrombocytosis (494.000/mm3), hyperuricemia (12mg/dl) and a high LDH level (1373 IU/L). Liver studies, protein-S, protein-C, anti-thrombin III levels and viral hepatitis markers were found to be normal expect for anti-Hbs positivity. Thrombophilic gene mutations were not ordered due to the patient's financial situation (she was unable to pay for these). There was hepatomegaly, splenomegaly and increase in portal vein diameter (portal hypertension) at abdominal USG examination. Doppler sonography revealed echogenic material three centimeters in size, which was interpreted as a chronic partial thrombus in the proximal portion of the portal vein and an increase in the diameter of the portal vein (12.8mm). Portal vein flow velocity was 3985ml/min. There was no variceal dilatation and portal hypertensive gastropathy at upper endoscopicexamination.

Bone marrow biopsy was taken due to markedly increased leucocyte levels and a diagnosis of chronic myleoid leukemia (CML) was found to be the cause of portal vein thrombosis (PVT) (myleoblast ratio: 6.6%, promyelocyte ratio: 4.4%, myleocyte ratio: 4.4%, band cells: 12.6%, neutrophils: 43.4%, eosinophils: 2.2%, monocytes: 20.3%, erythroid series: 5.5%, lymphocytes: 4.4%). Therapy was commenced with leukapheresis for CML, without heparin: hydroxyurea 4 gr/day, acethyl salycilic acid 300 mg/day, allopurinol Ixl/day. Four leukapheresis sessions were performed during the admission period and 15 days later, leucocyte count was 10.000/mm3 and thrombocyte count 338.000/mm3, with liver and spleen size also decreasing to half of that on the first day of her admission. Follow-up Doppler ultrasound revealed that thrombosis was absent and portal vein diameter was within normal range (10.5 mm).

DISCUSSION

A provisional of diagnosis CML was made by the elimination of other etiological causes during evaluation of history, physical examination and labo-

ratory and radiologic studies, with definitive diagnosis on the basis of blood smear and bonemarrow biopsy resutls. Liver sinusoids are areas of increased resistance against portal blood flow in myleoproliferative disorders (10). Thrombosis occurs with massive infiltrations of atypical cells (11) and additional accumulation of collagen results in perisinusoidal fibrosis. Pre and posthepatic localizations may be seen. Sinusoidal dilatation, peliosis and nodulary regenerative hyperplasia are the structural differences seen in liver pathology. Thrombosis is a risk factor for the development of PVT and it is a finding of myeloproliferative disorders (10). This patient's thrombocyte count was between 338.000 and 843.000/mm3. The studies of Hillarie et al (11) and Loringetal (12) in myleproliferative disease patients have shown increased risk of PVT of 8.3% and 9.8% respectively. Although one study (13) has shown that this can be successfully cured with anticoagulants, a contrary case report (14) found that despite therapy with heparin, fatal PVT resultad in gut necrosis and liver insufficiency in a 45 year old patient with myleoproliferative disorder. In another interesting case report (15), development of PVT and mesenteric vein thrombosis occurred after splenectomy. In addition to injections of fibrinolytic agents via the percutaneous or transhepatic route, balloon dilatations and stents have also been used in PVT therapy.

Abdominal ultrasound, intraoperative USG, Doppler USG, computerized tomography, portovenography and magnetic resonance angiography are helpful in radiologic diagnosis. In our patient, PVT was confirmed by Doppler USG on the first day of admission, and had resolved on the second Doppler UGS study performed by same radiologist one month later. Eight months later, esophagogastroduodenoscopy and abdominal CT were found to be normal, as was liver and spleen size. It is suggested that the decrease in leucocyte count from 320.000/mm3 to 10.000/mm3 by leukapheresis and hydroxyurea threapy played a primary role on the disappearance of PVT in our patient. Decrease in thrombocyte numbers, thrombopoietin hormone levels (16) and increase in vasodilator effects of nitric oxide levels (17), in addition to the antithrombotic effects of hydroxyurea may play a secondary role in resolution of thrombosis. Leukapheresis without heparin may prevent the aggregation of blast cells and formation of thrombus (18-19), especially in the microcirculation. The use of heparinated leukapheresis may bring additional benefit. One reason for the development of PVT in myeloproliferative disorders such as polycythemia vera essential thrombocytosis is caused by an abnormal increase in cell types and cell numbers and PVT can spontaneously regress by normalization of cell numbers.

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