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A case of Budd-Chiari syndrome secondary to multiple thrombogenic conditions: A case report and review of literature*

Multipl trombojenik duruma bağlı olarak gelişen bir Budd-Chiari sendromu vakası: Vaka takdimi ve literatürün gözden geçirilmesi

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This report describes a case of Budd-Chiari syndrome caused by latent polycythemia vera and factor V Leiden mutation. This syndrome usually occurs due to thrombosis of hepatic veins or membranous obstruction of inferior vena cava. The most common reasons for thrombosis are manifest polycythemia vera and the other prothrombotic conditions. Recently, latent polycythemia vera and factor V Leiden mutation have been reported in increasing frequency. In this report, we aimed to emphasize that all prothrombotic conditions must be evaluated while investigating the etiology of Budd-Chiari syndrome, including latent polycythemia vera and factor V Leiden mutation, and appropriate antithrombotic and surgical therapies must be performed without delay.

Key words: Budd-Chiari syndrome, latent polycythemia vera, factor V Leiden mutation, antithrombotic therapy, liver transplantation

Bu makalede latent polisitemia vera ve faktör V Ledien mutasyonuna bağlı olarak gelişen bir Budd-Chiari vakası sunulmaktadır. Bu sendrom genellikle hepatik venlerin trombozu veya inferior vena cava'nın membranöz obstrüksiyonu sonucunda meydana gelir. Trombozun en sık nedeni aşikar polisitemia vera ve diğer protrombotik durumlardır. Son zamanlarda ise latent polisitemia vera ve faktör V Ledien mutasyonu giderek artan sıklıkta rapor edilmeye başlanmıştır. Bu sunumdaki amacımız, Budd-Chiari sendromunun takibinde, latent polisitemia vera ve faktör V Ledien mutasyonu da dahil olmak üzere, tüm protrombotik nedenlerin araştırılması gerektiğini ve zaman geçirmeksizin uygun antitrombotik ve cerrahi tedavilerin uygulanması gerektiğini vurgulamaktır.

Anahtar kelimeler: Budd-Chiari sendromu, latent polisitemia vera, faktör V mutasyonu, antitrombotik tedavi, karaciğer transplantasyonu

INTRODUCTION

Budd-Chiari syndrome (BCS) is characterized by venous outflow obstruction of the liver. In western countries, BCS usually occurs due to thrombosis of hepatic veins, whereas in eastern Asia and Africa it is most frequently seen due to membranous obstruction of the inferior vena cava (IVC) (1).

While manifest or latent polycythemia vera (PV) is the most frequently responsible disease for BCS, hepatic venous thrombosis because of factor V Leiden mutation has been reported in increasing frequency, and in recent literature, it is presented as the second most frequent etiologic factor after PV (2). In this report, we present a patient with BCS caused by latent PV accompanying factor V Leiden mutation.

CASE REPORT

A 42-year-old otherwise healthy male patient admitted to our Gastroenterohepatology Department with complaints of newly onset abdominal swelling, abdominal pain and weight loss **in** the last two months. There was no family or personal history of venous thrombosis. Furthermore, there was no history of alcohol or tobacco consumption or exposure to drugs and hepatotoxic chemicals.

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Physical examination on admisson revealed subicteric sclera, abdominal distention, an enlarged and tender hepatomegaly with tense ascites. The spleen was not palpable. Other physical examination findings were unremarkable.

The laboratory findings were as follows: aspartate transaminase 268 IU/L (normal range, 0-32 IU/L), alanine aminotransferase 370 IU/L (normal range, 0-31 IU/L), alkaline phosphatase 475 IU/L (normal range, 60-240 IU/L), γ-glutamyl transpeptidase 11 IU/L (normal range, 6-28 IU/L), total protein 7.6 g/dl (normal range, 6.6-8.7 g/dl), albumin 3.7 g/dl (normal range, 3.4-4.8 g/dl), total bilirubin 2.03 mg/dl (normal range, 0-1.1 mg/dl), direct bilirubin 0.93 mg/dl (normal range, 0-0.3 mg/dl), erythrocyte count 7.25 X 10^6/μL (normal range, 3.83-5.08 X 10^6μL), hemoglobulin concentration 18.9 g/dl (normal range, 11.7-15.5 g/dl), hematocrit concentation 58.2% (normal range, 38.5-48.2%), leukocyte count 18200/μL (normal range, 4100-11200/μL), platelet count 198 X 10^3μL (normal range, 159-388 X 10^3/μL), prothrombin time 20.49 seconds (normal range, 11.0-15.0 seconds), international normalized ratio (INR) 1.84 (normal range, 0.8-1.2), activated partial thromboplastin time 39.46 seconds (normal range, 22.95-38.0 seconds) and fibrinogen 490 mg/dl (normal range, 170-390 mg/dl). Serological tests were negative for hepatitis A, B, C, and E, cytomegalovirus, Epstein-Barr virus, and antinuclear, antimitochondrial and anticardiolipin antibodies. Serum iron, total iron binding capacity, ferritin, ceruloplasmin and alpha-1-antitrypsin levels and copper level in 24-hour urine were normal. Ascitic fluid analysis revealed a leukocyte count of 52/μL, total protein level of 2.6 g/dl, an albumin level of 1.4 g/dl, and a serum ascites albumin gradient of 2.3 g/dl, indicating portal-hypertensive ascites. Ascites cytology revealed only rare mesothelial cells.

Abdominal ultrasonography showed hepatomegaly and massive ascites while there was no splenomegaly. On abdominal computed tomography (CT), a relative increase in caudate lobe size in addition to hepatomegaly, compression of the IVC at the level of the hepatic portion and nonhomogeneous contrast absorption by the liver in early phase after contrast injection were noted. Color flow Doppler examination of portal system revealed obstruction of right and left hepatic veins by the thrombosis, but the middle hepatic vein, portal vein and IVC were patent.

We performed liver biopsy to make definite diagnosis, which showed intensive congestion in zone I-II and widespread centrilobular ischemic necrosis. These histological findings were found to be compatible with BCS. Thrombophilic reasons were investigated to determine the etiology of the thrombosis. Elevated levels of hemoglobin and hematocrit concentations were noted. Arterial oxygen saturation and erythropoietin levels were measured to exclude the causes of secondary erythrocytosis, and were normal (98% and 27.6 IU/ml, respectively). For this reason, the cause of erythrocytosis was thought to be a primary condition. Bone marrow biopsy showed hypercellularity and evident erythroid hyperplasia but no megakaryocyte hyperplasia. In our patient, there was no splenomegaly, thrombocytosis or leukocytosis. Furthermore, both leukocyte alkaline phosphatase and vitamin B_{12} levels were within normal limits (48 ml IU/ml and 348 pg/ml, respectively). Thus, because all diagnostic criteria for PV were not fulfilled, latent PV was diagnosed (3).

Laboratory investigations concerning thrombophilia revealed that protein S, and anticardiolipin antibody IgG and IgM levels were in normal limits. Ham test for paroxysmal nocturnal hemoglobinuria was negative, but protein C and antithrombin III levels were found to be under normal levels, due to liver dysfunction since two of his brothers had normal factor levels. Further genetic investigations were performed and homozygote Arg506-Gln506 mutation on genes encoding factor V protein was found without prothrombin G20210A mutation.

For these reasons, hepatic vein thrombosis was thought to have developed as a result of homozygote factor V Leiden mutation and latent PV. Standard heparinization for three days followed by warfarin orally were given to the patient to keep the INR between 3 and 3.5 to maintain the patency of the middle hepatic vein and portal system. Hematocrit level was lowered to 38% to improve the existing erythrocytosis by performing phlebotomy twice.

Nevertheless, the patient was referred to the Department of Hepatobiliary Surgery for portasystemic shunt operation because of progressive worsening of the liver functions, intractable ascites and no clinical improvement in the following days. During the preoperative period hepatic decompensation and hepatorenal syndrome developed and shunt surgery could not be performed. Despite

plans for urgent liver transplantation, the patient died due to hepatorenal syndrome and hepatic encephalopathy preoperatively.

DISCUSSION

Clinical reports have revealed that hepatic vein thrombosis usually results from more than one thrombogenetic disease together with a triggering factor (4-6). Most frequent causes are primary myeloproliferative diseases (especially PV), antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, genetic deficiencies of anticoagulation factors that are found naturally in peripheric circulation (such as protein C, protein S and antithrombin III**)** and other prothrombogenic diseases (such as prothrombin gene mutation). Abdominal trauma, pregnancy and oral contraceptive use act as triggering factors initiating thrombogenesis in the presence of the mentioned diseases (7).

Recently, demonstration of Arg506-Gln506 mutation located on genes encoding factor V clarified that many cases of BCS previously reported as having undetermined etiology, actually occurred as a result of factor V deficiency. A mutant factor V (called factor V Leiden) cannot be activated by protein C and this makes the patient prone to coagulation. The prevalence of factor V Leiden mutation is 5% among healthy people and 25 to 31% in patients with BCS (8). In our patient, factor V Leiden mutation had been detected in genetic analysis for etiology of the thrombosis.

Deltrene et al. showed that another prothrombotic condition or thrombotic risk factor had also contributed in 70% of Budd-Chiari patients with factor V Leiden mutation (9). This finding suggests that factor V Leiden mutation alone cannot be sufficient for thrombogenesis in hepatic veins and, more importantly, is effective by increasing thrombogenetic potentials of the other factors. Consequently, the presence of other prothrombotic disorders must be investigated in patients with BCS who have factor V Leiden mutation.

In our patient, the presence of erythrocytosis and leukocytosis were noticed in addition to factor V Leiden mutation. For this reason, we initially thought the patient had manifest PV coursing with complications, but we then determined that he did not have all the criteria described for PV as described by the Polycythemia Vera Study Group (3). Despite an evident erythroid hyperplasia together with hypercellularity on bone marrow biopsy, there was no rise in plasma erythropoietin level to produce this effect. We thus decided the patient had a latent PV. This condition appears clinically as a hepatic vein thrombosis or deep vein thrombosis years before the PV manifests, and it is characterized only by erythroid and myeloid hyperplasia in bone marrow biopsy (10,11). The deficiencies of protein C, protein S and antithrombin III are seen rarely and inherited as an autosomal dominant trait (12). One must be very careful when drawing a conclusion that congenital deficiencies of these factors are responsible for the etiology of patients with BCS having hepatic dysfunction, because liver dysfunction could be the main reason for deficiencies in such patients. It is necessary to show deficiency of these factors in the first-degree relatives to be able to discriminate.

Even though the levels of protein C and antithrombin III were found to be under the normal values in our patient, they were due to liver dysfunction because the factor levels of the two siblings were normal.

The main purpose for the treatment of BCS is the correction of the liver functions rapidly by diminishing centrilobular congestion. Anticoagulant therapy with heparin and warfarin is sufficient in only a small number of patients to correct the obstruction. Most patients require invasive radiological techniques (i.e. transjugular intrahepatic portasystemic shunt, balloon dilatation or stenting of hepatic veins), surgical decompression or liver transplantation (13). Liver cirrhosis can develop in a short time, about six months, in patients having persistent obstruction, and death may occur attributable to fulminant hepatic failure (14). Consequently, many authors advise treating those patients with hepatic vein obstruction and sufficient liver functions using invasive radiological techniques (TIPS) or portasystemic shunt operations (mesoatrial, mesocaval or portacaval) as soon as possible. But in the presence of a prothrombotic condition, initiating antithrombotic treatment in the early period is quite important to maintain the patency of the IVC and portal vein, and to prevent stenosis after shunt surgery. Therefore, it is recommended for all patients without active bleeding (15). If hepatic encephalopathy develops in a rapid course accompanying manifestations of liver failure (fulminant or subfulminant liver failure), orthotopic liver transplantation (OLT) is the only appropriate treatment (16-17).

CONCLUSION

We present a case of BCS caused by latent PV accompanying factor V Leiden mutation. The course of BCS may be fast and lead to death in a couple of months. Because of this, especially in the patients known to have prothrombotic and facilitating factors, BCS must be considered in case of sudden onset of abdominal pain, ascites and hepatomegaly. After diagnosis with appropriate radiological methods, antithrombotic medications must be given immediately and thereafter invasive radiological and surgical treatment options must be evaluated without delay. Prothrombotic factors, particularly latent PV and factor V Leiden mutation, must be scrutinized carefully to determine the etiology of BCS.

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