Portal and mesenteric thrombosis associated with protein S deficiency

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ABSTRACT

Introduction: liver cirrhosis is the main cause of portal thrombosis (PT), while hypercoagulability syndromes are rarely found as the etiology of PT. We report a case of portal and mesenteric thrombosis secondary to protein S deficiency.

Case report: a 74-year-old woman was admitted with melena secondary to upper gastrointestinal bleeding. She reported mild, diffuse abdominal pain in the last 2 weeks. Endoscopy revealed ruptured esophageal varices. Doppler ultrasonography and CT demonstrated a heterogeneous liver, splenomegaly and ascites, and complete non-occlusive PT involving the hilum and portal branches, as well as the superior mesenteric vein, with portosystemic collaterals. At this point a complete study for cirrhosis etiologies was negative, including a liver biopsy that showed nonspecific architectural changes secondary to diminished blood flow, which suggested non-cirrhotic portal hypertension. The search for hypercoagulability states determined a deficiency of S protein, with total pS = 107% and free pS = 56%. The patient was started on anticoagulant treatment and no other thrombotic events occurred.

Discussion: PT usually manifests without specific symptoms. The most common presentation is upper gastrointestinal bleeding, as occurred in our patient. Liver cirrhosis is one of the most frequent cause of PT. Up to 65% of these patients present an associated prothrombotic state, including protein S deficiency. Our case reminds us of the importance of a systematic search for hypercoagulability syndromes in patients with TP, even when the etiology can be conferred to liver cirrhosis.

Key words: Protein S deficiency. Liver cirrhosis. Venous thrombosis. Portal vein.

INTRODUCTION

Portal and mesenteric thrombosis (PMT) is a rare event that is frequently associated with a local precipitating factor that becomes evident and leads to prompt diag-
nosis. However, there are asymptomatic cases where no cause can be clearly established and who often are misdiagnosed. In these cases hypercoagulability syndromes such as protein S deficiency should be ruled out. There are few cases published in the literature as the one we describe here, probably because of its low incidence and the lack of a systematic approach to this entity, which leads to underdiagnosis.

We report a case of protein S deficiency with PMT, and upper gastrointestinal bleeding secondary to portal hypertension as its first manifestation.

CASE REPORT

A 74-year-old female patient was admitted in our center with hematemesis and melena the previous two days. She also reported two weeks of diffuse abdominal pain, hyporexia, and asthenia. She used amiloride/hydrochlorothiazide and lovastatine for hypertension and dyslipemia. There was no history of smoking, NSAID use, contraceptive pills, or alcohol or drug use. Her family history revealed that her mother had died from gastric cancer, her brother had cirrhosis of unknown etiology, and her sister had hepatocellular carcinoma.

On physical exam she was hemodynamically stable and had mild, diffuse abdominal tenderness without rebound tenderness.

On admission: hemoglobin: 13.5 mg/dl; hematocrit: 37.6%; platelets: 120,000 platelets/µl; bilirubin: 247 mg/dl; alkaline phosphatase: 220 IU/L; aspartate-amino-transferase: 59 IU/L; alanine-aminotransferase: 28 IU/L; and gamma-glutamyltransferase: 129 IU/L. An urgent endoscopy revealed large esophageal varices without red color signs (F2 RC(-), according to the Japanese Research Society for Portal Hypertension) as well as multiple gastric and duodenal erosions covered by fibrin and without signs of recent bleeding. Computer tomography and abdominal ultrasonography showed a normal liver with discrete nodular surface and parenchymal heterogeneity. No focal liver lesions were detected. Splenomegaly, ascites, and minimal pleural effusion were also diagnosed. Non-occlusive complete portal thrombosis at the hilum and its branches was diagnosed, as well as a thrombus located in the superior mesenteric vein. Portal-systemic collateral channels were found in the gastro-hepatic and gastro-splenic ligaments (Fig. 1).

Blood tests were ordered to rule out different causes of chronic liver disease, including viral hepatitis (HBV, HCV) and HIV, autoimmunity, ceruloplasmin, ferritin, and urine porphyrins; all were normal.

A transjugular liver biopsy and hemodynamic tests were done, which showed a hepatic venous pressure gradient of 12 mmHg with normal phlebography. Biopsy histopathology showed an altered liver architecture with some acini having zone-1 hepatocyte hyperplasia and some nodulation, but without perinodular fibrous septa.

Portal tracts had the standard duct-artery-vein triad, but some portal vein branches were narrowed and paraportal veins were detected. Portal tracts had discrete periportal fibrosis and mild lymphoplasmocytic inflammatory infiltrates with focal spillover into periportal areas. There was some inflammatory activity at the lobules, without acidophilic bodies or other relevant findings (Figs. 2 and 3). These minimal fibroinflammatory changes, irregular nodular hyperplasia, and absence of perinodular fibrous septa ruled out liver cirrhosis and were consistent with non-cirrhotic portal hypertension. A complete study for hypercoagulability syndromes was performed, since all hepatic changes could possibly be secondary to primary portal thrombosis.

This study discovered a decreased free protein S (pS) antigen, total pS, and free pS activity of 56, 107, and 44%, respectively, consistent with type-I pS deficiency. All other coagulation parameters were normal (including fibrinogen, antithrombin, protein C, anticardiolipin anti-
bodies, activated protein C resistance, factor V Leiden, factor II G 20210A, and homocystein). This result was confirmed in a subsequent test. The patient was started on anticoagulation treatment with acenocumarol and diuretics indefinitely. No other events were reported during follow-up.

DISCUSSION

Splenoportal thrombosis (PT) is a rare event that frequently manifests with symptoms related to portal hypertension in a subacute or chronic way. When symptoms develop they are usually nonspecific – vomiting, abdominal pain, enlarged abdominal girth, and fever, as well as upper gastrointestinal bleeding secondary to variceal rupture, the latter being the most frequent form of presentation (1,2).

TP etiology may be grouped in three categories. First, it may be related to acquired systemic thrombophilic alterations (primary myeloproliferative syndromes, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, and hypercistinemia) or hereditary alterations (Leiden’s factor V mutation, prothrombin G20210A mutation, protein C and S deficiency, or antithrombin deficiency) (3-5). The second group includes risk factors such as oral contraceptive use and pregnancy. The third group is related to local precipitating factors: Inflammatory (omphalitis, diverticulitis, cholecystitis among others) and splenoportal aggressions (splenectomy, colectomy, etc.). Sixty percent of TP cases are caused by systemic thrombogenic factors and 40% by local factors. A coexistence of both, local and systemic factors, is present in 15% of patients, which leads to search for systemic thrombogenic factors even when local factors have already been identified and vice versa (3,6). At present cirrhosis is the most frequent cause of PT. Nonetheless it is important to remark that up to 69.5% of patients with cirrhosis and PT also have hereditary hypercoagulability syndrome when searched (7).

The study by Egesel et al. (8), including 23 patients with PT secondary to hypercoagulability, found that up to 43% had DPS, as in our case.

Protein S is synthesized by hepatocytes and megakaryocytes, and is vitamin-K dependent. It acts as a cofactor for protein C; 50% circulates free and 50% binds C4b protein. Protein S quantitative or qualitative deficiency is transmitted in an autosomal dominant manner; 74% of patients develop deep vein thrombosis at different levels. Annual incidence is 1%, and 56% of episodes are spontaneous. The relative risk of thrombosis is 8.5. One half of patients who develop thrombosis do so by the age of 25 years (9).

There are 2 forms of DPS. Type I is characterized by normal total and low free pS levels. In type II both levels are low. Thrombotic precipitating factors include bed rest, surgery, and oral contraceptive use. In most cases none of these factors is identified (10-12).

In our patient the primary causes of acquired protein S deficiency were reasonably ruled out (liver disease, nephrotic syndrome, disseminated intravascular coagulation, oral estrogen administration, inflammatory syndrome, or HIV). Thus, pS deficiency was probably inherited.

Liver biopsy rarely finds characteristic features inobliterative portal vasculopathy. Due to patchy alterations it is difficult to detect the characteristic fibrous-obliterrative changes, portal vein disappearance, or thrombosis in small veins. More frequently hyperplasia and parenchymal atrophy are the sole findings that suggest an irregular blood flow and guide the diagnosis. Histological changes can be very subtle, and mild fibroinflammatory activity may be confusing and misleading (13,14). This is why clinicians and pathologists must be aware of the possibility of primary portal vasculopathy for a correct diagnosis. TP first manifestation is not always secondary to portal hypertension as in our case. Initially, it may be just a maintained and discrete alteration of liver chemistries, usually a dissociated cholestasis that later develops portal hypertension. Thus in cholestatic cases with no other etiology, with no relevant necroinflammatory changes in liver biopsy, and with no cholangiopathy, steatohepatitis or advanced fibrosis, one should consider portal vasculopathy. Thrombogenic factors must be studied as one of the most probable causes of PT. It must be kept in mind that not all portal hypertensions are secondary to cirrhosis. Liver architectural transformation in portal vasculopathy varies greatly in severity and extent. It can show micronodules and/or focal or diffuse macronodules that can lead to a false clinical diagnosis of cirrhosis and/or space-occupying liver lesion. Biopsy is therefore essential not to confuse these diagnoses.

In our patient histological hepatic findings were probably secondary to thrombosis and not the opposite way. On the other hand, many patients with diffuse regenera-
tive hyperplasia might need several biopsies before a definite histological diagnosis is reached, so this entity cannot be completely ruled out (15). Against the possibility that our patient’s PT was secondary to cirrhosis is that PT is associated with advanced fibrosis (not present in our patient), which slows portal vein flow and favors thrombosis.

Our case corroborates that PS deficiency is a risk factor for PTM, and that systemic thrombogenic factors should be studied in spite of the presence of local factors.

REFERENCES