Idiopathic portal hypertension during a catastrophic attack in a patient with primary antiphospholipid syndrome

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Abstract

A 43-year old male patient with hyponatremic hypertensive syndrome was diagnosed as catastrophic primary antiphospholipid syndrome (PAPS). He subsequently developed hepatosplenomegaly. The patient also carried thrombophilia- and haemochromatosis-associated gene mutations. Further investigations upon persistence of splenomegaly indicated development of idiopathic portal hypertension. (Acta gastroenterol. belg., **2010**, 73, **521-526**).

Key words : antiphospholipid syndrome, idiopathic portal hypertension, catastrophic, thrombophilic mutations, low INR.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder with the presence of antiphospholipid antibodies in serum along with morbidities associated with pregnancy and/or thrombosis. It may be primary or secondary to autoimmune diseases such as systemic lupus erythematodes (SLE), rheumatoid arthritis, or to malignancies and infections (1-4). The accelerated form characterized with multi-organ failure due to small vessel occlusions is named catastrophic APS (5).

Idiopathic portal hypertension (IPH) is a condition of elevated portal pressure without cirrhosis or portal venous obstruction (6). The etiopathogenesis is yet to be elucidated. Infections, exposure to trace metals and chemicals, medications, autoimmune and genetic factors and thrombophilia are among the proposed causes (7). The prominent characteristic of IPH is presinusoidal portal hypertension due to intrahepatic presinusoidal portal vein blockage (6). Histopathological characteristics include phlebosclerosis, portal fibrosis, obliteration of small vein branches along with aberrant neovascular formation (sometimes referred as portal vein herniation), sinusoidal dilatation and hepatocellular nodular formation (6-10). Microthrombi causing obstruction are thought to occur in the small intrahepatic portal vein branches during the very early phases of IPH (6,7). In genetically predisposed individuals, recurrent abdominal or intestinal infections can lead to thrombus formation as a result of inflammation in the portal tract. Repetitive microthrombi in the small intrahepatic portal vein branches are thought to occur also in thrombophilia (6,7).

Idiopathic portal hypertension occurring during catastrophic course in a patient with primary antiphospholipid syndrome is presented below.

Case report

A 43-year old male presented to the outpatient clinic with headache, weakness, restlessness, intermittent agitation periods, and uncontrolled hypertension 2 years before.

The patient never consumed alcohol and quitted smoking 7 years ago. He experienced repeated deep venous thrombosis (DVT) attacks for the last two years. He had used warfarine, however in an irregular manner.

At physical examination, the patient was cooperative but restless and slightly confused. The distal part of the left lower extremity showed brown discoloration and swelling (chronic venous insufficiency). His blood pressure (BP) was 220/110 mmHg. Cardiac and respiratory examination were normal and he had no hepatosplenomegaly. Traube's space was not obliterated. Babinsky was bilaterally positive.

Blood cell count was normal, erythrocyte sedimentation rate (ESR) was16 mm/h, C-reactive protein (CRP) negative, urinanalysis normal, fasting glucose 143 mg/dL, aspartat aminotransferase (AST) 18 U/L, alanine aminotransferase (ALT) 24 U/L, alkaline phosphatase (ALP) 100 U/L (40-129), gamma glutamyl transpeptidase (GGT) 55 U/L (8-61), albumin 3.98 mg/dL, globulin 2.42 g/dL, and protein electrophoresis were normal. Iron 55 μg/dL (59-158), total iron binding capacity (TIBC) 230 μg/dL (110-370), ferritin 285 ng/mL, Na 116 mEq/L, K 2.5 mEq/L, Cl 80 mEq/L, HbA1C 5.8%. Other routine biochemical tests were normal.

Five days after hospitalization, delirium developed and he was admitted to the intensive care unit and intubated. His BP was controlled by nitroprussiate infusion.

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After discharge from intensive care, the BP was partially regulated by a combination of ramipril 10 mg, amlodipine 10 mg, metoprolol 100 mg, doxazosine 4 mg and furosemide 40 mg (170/100-150/90 mmHg). The patient remained confused. Cranial CT was normal.

Renal color Doppler ultrasound revealed no findings indicative of renovascular hypertension (HT). The long axis of the right and left kidney wer 85 mm and 115 mm respectively. Ten days after admission, the patient's liver and spleen were found to be palpable, being 4 cm and 3 cm below the costal margin, respectively. Cranio-caudal dimension of the liver was 21 cm and long axis of the spleen was 17 cm on contrast enhanced abdominal CT. Liver and spleen parenchyma appeared normal. Hypodense masses of 4 × 2.5 cm and 2.5 × 1.6 cm were detected in the right and left adrenal glands, respectively. The patient had no fever nor sweating ; repeated urinanalysis, blood cell count, CRP, ESR, AST, ALT, ALP, GGT, bilirubin, albumin and globuline were normal. Adrenal gland functions were normal, except an elevated cortisol level (30 μg/dL). Plasma renin activity (PRA) was elevated (23 ng/mL), whereas aldosteron level was normal (46 mg/mL, after IV hypertonic NaCl). Plasma antidiuretic hormone level was elevated (5.7 ng/mL, inconsistent with plasma osmolarity), plasma osmolarity (242 mOsm/kg) and urine osmolarity (150 mOsm/kg) were low, urine K 10mEq/L, urine Na 35 mEq/L, daily urine volume was 5000 mL. Resistant hypertension (HT) and elevated PRA were findings in favor of renovascular HT. Renal MRI angiography revealed presence of stenosis at the proximal portion of right renal artery, small right kidney and focal linear hypodense signals that might be suggestive of infarcts at the upper pole of right kidney parenchyma.

The clinical and laboratory findings so far suggested the diagnosis of hyponatremic hypertensive syndrome (HHS).

Small improvements were achieved in Na (125 mEq/L) and K (4.1 mEq/L) levels through hypertonic NaCl and KCl infusions. During that period, urea increased to 126 mg/dL and creatinine to 3.78 mg/dL. Contrast nephropathy was considered. Fluid infusions were given continuously. Given the patient's condition, renal arteriography and percutaneous angioplasty could be hazardous due to the risk of contrast nephropathy. Right kidney constituted 18% and left kidney constituted 82% of the total renal function through DTPA renal scintigraphy. DMSA scintigraphy revealed signs of atrophy in the right kidney (Fig. 1). On renal MRI angiography right kidney was shrunken (Fig. 2).

While the need for a nephrectomy was being discussed upon no improvement in the clinical condition of the patient with medical treatment, pain appeared in the right foot, and pulses in the dorsalis pedis and posterior tibialis arteries were absent. Color Doppler ultrasound revealed an ischemic flow pattern in right crural arteries. The patient developed thrombocytopenia in the meantime.

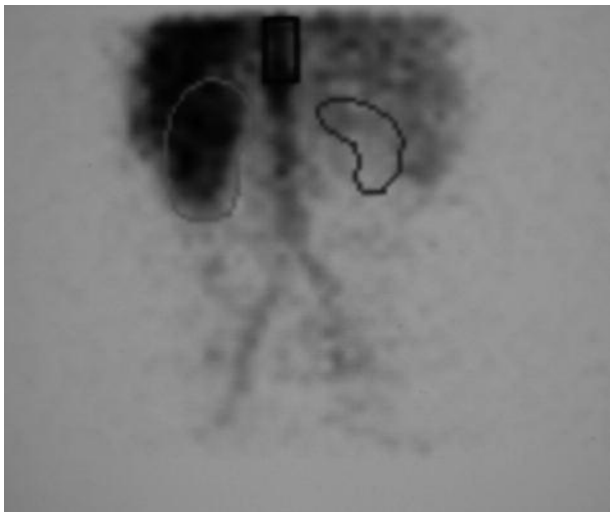

Fig. 1. — DMSA Renal scintigraphy ; signs of atrophy in the right kidney.

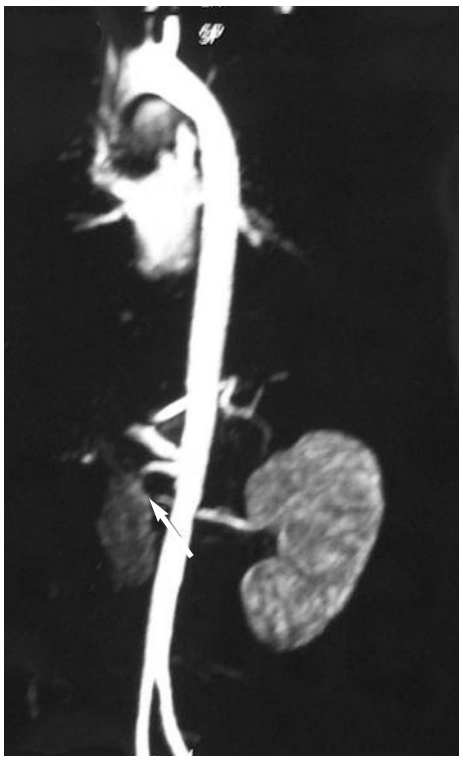

Fig. 2. — MRI angiography of the renal artery ; stenosis in right renal artery (arrow) and shrunken right kidney.

Thrombocytopenia, repetitive DVT attacks, ischemic flow pattern in right crural arteries, and presence of stenosis in the renal artery suggested the possibility of antiphospholipid syndrome (APS). Activated partial tromboplastine time (aPTT) was prolonged. Lupus anticoagulant (by kaolin coagulation time) and anticardiolipin antibody (ACA) were found to be positive. ACA IgM 17.3 type IgM anti phospholipid units (MPLU)/mL, ACA IgG > 100 type IgG antiphospholipid units

(GPLU)/ mL. (Three months later repeat lupus anticoagulant was positive, ACA IgM was 20.3 MPLU/mL, ACA IgG > 100 GPLU/mL). 1000 mL 10% dextran and 2 × 600 mg pentoxyphylline perfusion were given to increase the arterial blood flow in the right leg (11,12). The patient was taking warfarin irregularly and received no anticoagulants during the last two months. Starting the standard treatment for antiphospholipid syndrome was considered appropriate. Subcutaneous enoxaparin (2 × 8000 IU), 300 mg/day acetylsalicylic acid and 200 mg/day hydroxychloroquin tablets were started (13). Kidney functions began to improve upon this therapy. ANA and anti double stranded-DNA were negative. Since there was no additional condition that could lead to secondary APS, the clinical picture was judged to be primary antiphospholipid syndrome (PAPS).

The patient's confusional state persisted with intermittent delirium episodes. Serum Na and K values immediately dropped when no replacement was given. BP was still high (170/100 mmHg). The long axis of the right kidney was 50 mm by ultrasound. Therefore he underwent right nephrectomy as well as right adrenalectomy due to the adrenal mass. The patient's general condition and consciousness rapidly improved during the post-operative phase. His blood pressure was more easily controlled ; urea, creatinine and serum electrolytes approached to normal and polyuria disappeared.

Twelve days after the operation, the patient's skin darkened. Vomiting, loss of appetite, adynamia, hyperkaliema**,** hyponatremia appeared and azotemia occurred again. Cortisol level was low (8 μg/dL), and ACTH was increased (948 pg/mL). He was started on hydrocortisone, and treatment was continued with prednisolon and fludrocortison tablets.

Histopathological examination of the removed right kidney showed intimal thickening, organized and fresh thrombi in renal arteries, multiple fresh focal infarction areas and sparse pyelonephritic scars and of the right adrenalectomy material showed extensive coagulation necrosis (infarction), intimal thickening in a few vessels within the area surrounding the necrosis. No adrenal tumour was observed.

At the assessment performed 2.5 months after the patient's admission, the liver was 1 cm and the spleen was 3 cm below the costal margin. Physical examination revealed no other pathological finding. At the color Doppler USG examination of the portal system, craniocaudal dimension of the liver was 17 cm, spleen long-axis was 16 cm, and liver and spleen parenchymal echoes were normal. Portal vein, splenic vein and hepatic vein displayed normal diameters and flow patterns. No intraabdominal collateral circulation and free fluid were detected. Abdominal MRI and thoracal CT were found to be normal, except for hepato-splenomegaly.

AST, ALT, ALP, GGT, bilirubin, and protein electrophoresis were normal. Transferrin saturation was 30% and ferritin was increased (571 ng/mL). Acute phase reactants were negative and the patient's general condition was good. Platelet count returned to normal. Leucocyte count was also normal but he had a mild polycytemia (Hct 46%). Arterial blood gases were normal and JAK2 gene mutation was negative. Anti-mitochondrial antibody, anti-smooth muscle antibody, liver kidney microsomal antibody 1, anti-soluble liver antigen, anti-HCV, HBsAg, and anti-HIV1-2 were negative.

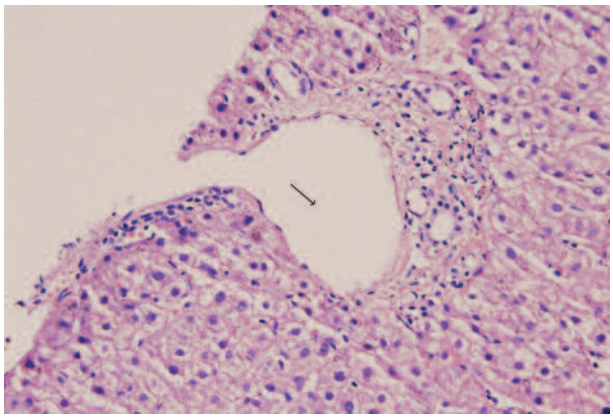

Fig. 3. — Liver biopsy ; portal venular dilatation (arrow). Hematoxylin and eosin ×200.

The assessments performed 3, 6 and 9 months after the last check revealed a further increase in ferritin (600 ng/mL), whereas all other clinical and laboratory findings were more or less similar to the previous ones. We investigated the haemochromatosis-associated gene mutations and found compound heterozygote positivity for the H63D and E168Q gene mutations. Abdominal MRI showed no iron accumulation in the liver. Gastroscopy showed grade 1 lower esophageal varices.

Percutaneous liver biopsy showed no inflammation in the portal regions and lobular areas ; portal venules were significantly dilated with herniation to the parenchymal area (Fig. 3). There was no increase in fibrotic connective tissue with Masson's trichrome staining. With periodic acid Schiff (PAS) and PAS-diastase stains, no specific feature or microangiopathic finding was observed. There was no iron staining with Prussian blue.

Clinical, laboratory and histologic findings so far led us to consider our patient as a case of idiopatic portal hypertension.

Sixteen months after admission, the patient presented with normal blood pressure, but he had headache and lightheadedness. These complaints improved evidently through phlebotomy. Desferrioxamine was administered subcutaneously via pump. Hematocrit was kept around 42%. Ferritin decreased to 270 ng/mL and transferrin saturation to 21%.

Two years after admission, the patient's general condition was good ; portal system color Doppler USG and MRI angiography (Fig. 2-3) revealed an increase in the diameters of portal vein (18 mm) and splenic vein (14 mm) at the hilum level. No collateral circulation or ascites were detected. Long axis of the spleen was 16 cm.

Liver size and parenchyma were observed to be normal. A repeat endoscopy showed the presence of grade 1 lower esophageal varices. Anti-beta 2- glycoprotein-1 (IgA-IgG-IgM) was 5,42 border index (BI) (normal < 1). Haematological and biochemical values were all normal.

Discussion

One of the most serious complications of renovascular disease is the hyponatremic hypertensive syndrome (HHS). Refractory hypertension and intense natriuresis are the main features, resulting in sodium and water depletion (14). HHS can manifest with a variety of signs and symptoms such as weakness, weight loss, polydipsia, polyuria, salt craving, headache, blurred consciousness, neurological symptoms and signs of hypertensive encephalopathy (14,15). Diagnosis of HHS due to renal ischemia is made employing the following criteria : (i) hyponatremia, (ii) hypertension (systolic BP > 165 mmHg and diastolic BP > 95 mmHg in the sitting or supine position with or without antihypertensive medications), (iii) evidence of renal ischemia (> 80% stenosis or total occlusion of a major renal artery on selective angiography) or strongly suggestive evidence of severe ischemia on captopril DTPA scintigraphy, doppler ultrasound or MRI angiography. However, the following should be absent : renal parenchymal disease beyond the presence of proteinuria, recent thiazide or potassium-sparing diuretic therapy, or a plasma creatinine > 0.15 mmol/L.

Our case was a HHS related to renal artery stenosis in the setting of APS. Being the first case in the literature, the prominent feature is the presence of primary APS in its etiology.

It is well known that APS can affect all renal vessels, from large and small arteries to venes and venules (16). Our patient had a proximal truncal stenosis in the renal artery.

The pathophysiology of the syndrome is not fully clear, however the following mechanism has been proposed by Peco-Antic ; “Renal ischemia irrespective of its etiology induces increased renin secretion resulting in high circulating angiotensin II (A2). A2 leads to arterial hypertension and induces pressure diuresis through the normal kidney, which gives rise to polyuria and hyponatremia. Morover, A2 exerts a direct natriuretic action on the kidney, induces internal shift of Na and K, and stimulates ADH secretion. Finally A2 is a potent dipsogen, which probably, by acting on thirst centre in the brain, stimulates the need to drink and increases polyuria” (15). As a consequence, volume depletion and hyponatremia leads to further increases in renin and A2 secretion and a vicious circle ensues (14).

The first step in treatment is administration of angiotensin receptor blockers and ACE inhibitors. The following step is abolishing renal ischemia by balloon angioplasty, surgical revascularization or nephrectomy (14,15).

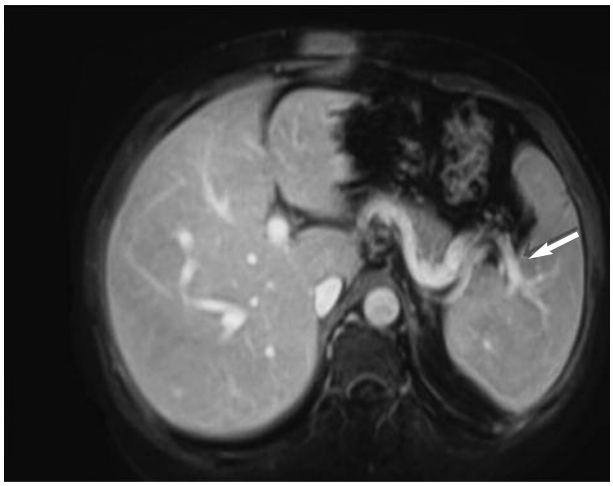

Fig. 4. — MRI angiography of the portal system ; mildly dilated splenic vein (arrow).

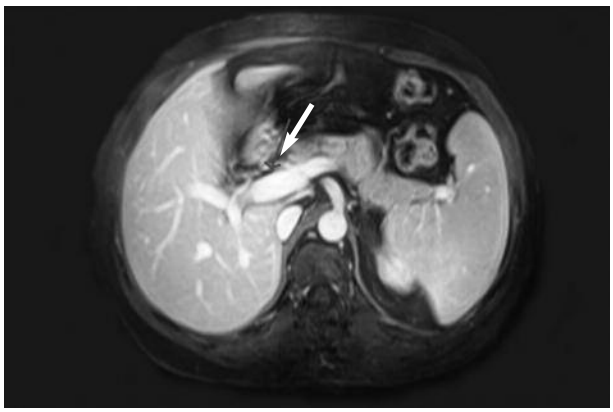

Fig. 5. — MRI angiography of the portal system ; mildly dilated portal vein (arrow).

Our patient’s hyponatremia was only partly responsive to intensive sodium replacement. At the beginning, hypertension did not respond even to a five-drug combination ; however it was reduced to more acceptable levels later on, which we consider that adrenal insufficiency played a role. After nephrectomy, blood pressure and natremia returned to normal.

MRI revealed masses in both adrenals. The excised adrenal tissue showed necrosis and arterial thrombosis. Development of adrenal insufficiency after unilateral adrenalectomy suggests the presence of ischemic necrosis in the other adrenal. In our patient, adrenal insufficiency was not the first picture ; the basal cortisol level was high. We consider that adrenal insufficiency occurred later, because hypertension and hypokalemia were present in the beginning, but hypokalemia was controlled partially with potassium replacement later in the course of the disease prior to adrenelectomy. Adrenal insufficiency became manifest as ischemic necrosis widened in the adrenals and especially after unilateral adrenalectomy. In the literature, adrenal masses were

reported to be detected by CT or MRI in 7% of 69 patients with antiphospholipid syndrome and adrenal involvement (17).

Our case fulfills the classification criteria for catastrophic antiphospholipid syndrome ; however the condition has developed over a prolonged period (1). Kidney, adrenal gland and brain involvement occurred probably within the same period, followed by hepatic involvement and crural arterial involvement within weeks. Although the patient's initial confusional state, agitation and headaches might be argued to be associated with hypertensive encephalopathy and hyponatremia, their relation to PAPS is highly probable, because blurred consciousness persisted despite the correction of hyponatremia and hypertension. Cranial MRI on the 5th post-operative day revealed cortico-subcortical ischemic signals at the late subacute-chronic period. Hyperintensive signals were observed at T1 sections which were consistent with protein denaturation products. This was thought to arise from disorders in the microcirculation (cranial MR angiography was normal).

The case was published previously with referral to hyponatremic hypertensive syndrome and adrenal failure (18). Because the diagnosis of idiopathic portal hypertension was established later on, the case was reviewed again within this perspective.

Thrombophilia theory is the most argued theory in the etiology of IPH. In patients with IPH, a variety of causative reasons of thrombophilia have been found at an increased incidence, which was beyond a mere coincidence (6,7). It is the most frequently encountered etiologic factor in IPH cases in Western populations (7). In a study of 28 Western patients with IPH, evidence for various prothrombotic disorders was 50% positive (19). IPH is frequently seen in India and repetitive intestinal and abdominal infections were held responsible for the high frequency (7). Our patient did not have other etiologic factors leading to IPH, except for thrombophilia.

Typical findings of polycytemia vera were absent and JAK 2 gene mutation was negative in our patient. Paroxysmal nocturnal hemoglobinuria was excluded through evaluation of CD55, CD59 clusters.

We also investigated inherited thrombophilic mutations and natural anticoagulant deficiency in our patient : Prothrombin G20210A mutation, beta fibrinogen-455 G > A mutation, APO B R3500Q mutation, Factor V H1299R and MTHFR C677T gene mutations were negative ; in addition PAI 4G/5G polimorphism, APO E genotyping, ACE I/D genotyping, and HPA-1 a/b genotyping were normal. Antithrombin 3 level was found to be normal, protein C activity was 136% (normal values 70-130) and protein S activity was > 150% (normal values 80-120).

The following mutations were also detected : Factor XIII V34L gene mutation was heterozygous positive, Factor V Leiden gene mutation 1691 GA heterozygous, and MTHFR gene mutation 1298 CC was homozygous positive (homocystein 14.5 μmol/mL).

Low INR can lead to a catastrophic course in PAPS (20). Other than this, causes of inherited thrombophilia were proposed to cause catastrophic condition in PAPS (21). Both were present in our case. The association of thrombophilic mutations with PAPS might have also contributed to the development of IPH.

To our knowledge, there are 5 case reports on the coexistence of IPH with APS (22-26). The first four cases reported (22-25) are together with SLE. The only PAPS associated case is a condition of porto-pulmonary hypertension (26). Our case is the first case in terms of being associated with PAPS in the absence of pulmonary hypertension (echocardiography of our patient was normal). This case report and other papers indicate the co-existence of antiphospholipid antibodies with IPH (7,19,26). As to our case, the patient both fulfills the diagnostic criteria of the antiphospholipid syndrome (a typical case), and has the characteristics of being prospectively evaluated. In addition, IPH development during a catastrophic attack has not been reported up to now.

Our case is the first to develop IPH during the catastrophic course, and the only case being associated with PAPS without accompanying pulmonary hypertension.

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