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Case Report

Small hepatic veins Budd-Chiari syndrome and paroxysmal nocturnal hemoglobinuria - The association of two rare entities: a case report

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Summary
Small hepatic veins Budd-Chiari syndrome is a rare disorder characterized by hepatic venous outflow obstruction limited to the small intrahepatic veins, with normal appearance of the large hepatic veins at imaging. In this case only a liver biopsy can demonstrate the presence of a small vessels outflow block. Paroxysmal nocturnal haemoglobinuria (PNH) is one of the most severe acquired thrombophilic state and represents one of the main aetiological factors of Budd-Chiari syndrome. In patient affected by PNH with liver impairment and/or ascites, Budd-Chiari syndrome must be always taken into consideration and, if necessary, a liver biopsy performed to exclude the small hepatic veins involvement. We report a case of small hepatic veins Budd–Chiari syndrome secondary to paroxysmal nocturnal haemoglobinuria.

Abbreviations:
BCS: Budd-Chiari syndrome, PNH: paroxysmal nocturnal haemoglobinuria, PIG: phosphatidylinositol glycan, INR: international normalized ratio, MRCP: magnetic resonance cholangiopancreatography, NASH: non-alcoholic steatohepatitis, NAFLD: non-alcoholic fatty liver disease, CT: computed tomography.

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Conflict of interest statement
The Authors declare no conflict of interest.

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Introduction

Budd-Chiari syndrome (BCS) is a rare disease characterized by hepatic venous outflow obstruction at each level from the small hepatic veins to the atrio-caval junction. In small hepatic veins Budd-Chiari syndrome the obstruction is limited to the small intrahepatic veins, with normal appearance of large hepatic veins. In this case, liver biopsy is necessary for diagnosis. The major risk factors of BCS are thrombophilic conditions [1]. Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal blood disorder affecting hematopoietic stem cells that is caused by a somatic mutation in the phosphatidylinositol glycan (PIG)-A gene. Principal manifestations are intravascular hemolysis and thromboembolism. Current treatment for PNH includes eculizumab, a monoclonal antibody direct to complement factor C5 blocking intravascular haemolysis and reducing thrombotic events in PNH, and it is also the best prophylaxis [2,3]. We describe the case of a 50-years-old man with the diagnosis of paroxysmal nocturnal haemoglobinuria from 2014 in therapy with eculizumab, administered at the dosage of 900 mg once every two weeks. In October

2017, he was submitted to the replacement of biological aortic valve and ascending aorta prosthesis for the treatment of aortic steno-insufficiency. After the surgical procedure, blood tests documented hyperbilirubinemia: total bilirubin 47 mg/dl (normal 0.3-1.2 mg/dL) and direct bilirubin 29 mg/dl. In December 2017 he was hospitalized for the occurrence of jaundice. Laboratory analyses revealed elevation of total bilirubin of 29 mg/dL and direct bilirubin of 22 mg/dl, of gamma-glutamyl transferase (185 U/L; normal 5-36) and alkaline phosphatase (254 U/L: normal 35-104), INR was 2.2. An abdominal ultrasonography and a magnetic resonance cholangiopancreatography (MRCP) showed cholecystolithiasis and choledocholithiasis, portal vein diameter of 18 mm and spleen diameter of 18 cm. Common bile duct stones were removed using endoscopic sphincterotomy. Despite the treatment of biliary obstruction, blood levels of bilirubin decreased but persisted over upper normal values. All causes of liver disease (alcohol, drugs, viral, autoimmune, hemochromatosis, Wilson disease, NASH/NAFLD) were ruled out. Moreover, also the hypothesis of a liver disease secondary to congestive heart failure was ruled out by echocardiography. To better define the etiology of the hyperbilirubinemia the patient was transferred to our Unit (Hepatology) where a new abdominal ultrasonography was performed showing hepatomegaly, regular liver surface, inhomogeneous liver parenchyma, ascites and patency of the portal vein. The hepatic veins were thinned but patent and the flow was detectable at Doppler ultrasound; liver stiffness measurement showed different values in the different hepatic segments, ranging from 13 to 17 KPa. Blood test documented also low values of albumin (2.4 g/dl), pseudo-cholinesterase 2200 U/L and prolonged prothrombin time (INR 2.3). A contrast enhanced CT-scan confirmed the patency of the hepatic veins and, therefore, a percutaneous liver biopsy was performed. On histology the liver parenchyma showed sinusoidal dilation with marked perisinusoidal fibrosis (Fig. 1A). There was evidence of organizing occlusive thrombosis of centrolobular veins (Fig. 1B). Focal hemorrhages were observed, associated with small foci of hepatocellular necrosis.

To exclude a further cause of thrombophilia in addition to PNH already in pharmacological treatment, an extensive screening for hereditary and acquired thrombophilia was performed and it was negative. Thus, low molecular weight heparin was added to eculizumab therapy but immediately stopped because of the development of melena. An upper endoscopy excluded the presence of gastroesophageal varices and therefore the gastrointestinal bleeding was attributed to the previous sphincterotomy. During hospitalization, the patient developed fever and blood culture isolated methicillin and daptomycin-resistant *Staphylococcus aureus*. A diagnosis of endocarditis with multiple spleen infarctions and periprosthetic aortic abscess was reached and targeted antibiotic therapy (i.v. vancomycin and ceftarolin) was started. Consequently, ascites became less responsive to diuretic therapy, renal function worsened, and the patient was treated with repeated paracentesis and intravenous human albumin. Despite the adequate antibiotic therapy, the patient died for the diffusion of the infection.

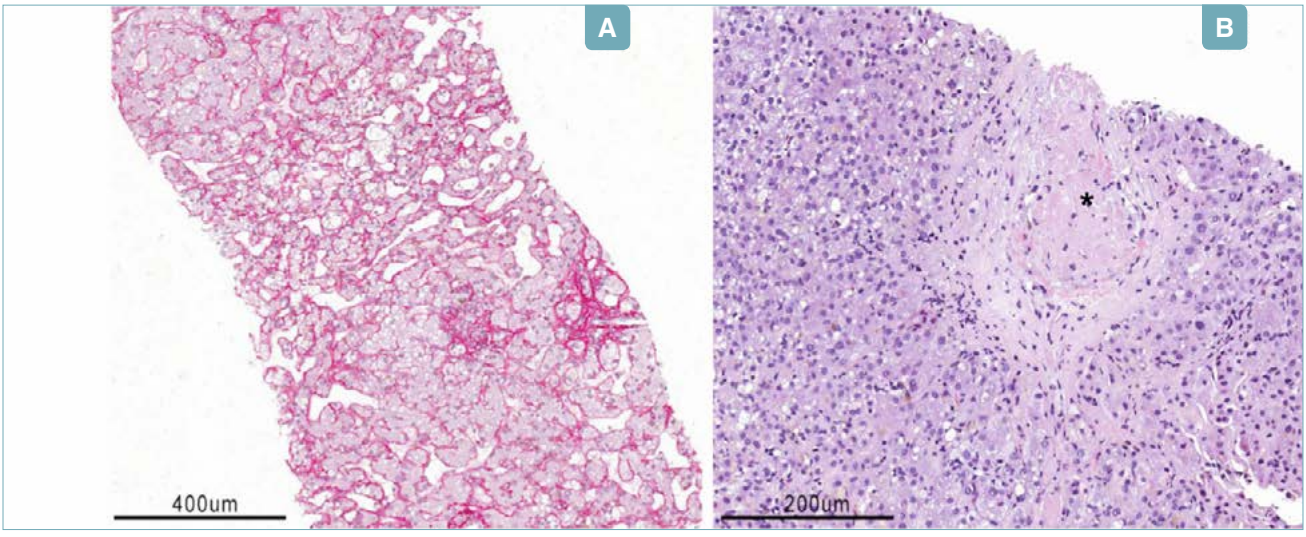

Figure 1. (A) Liver biopsy shows sinusoidal dilation with marked perisinusoidal fibrosis (picrosirius red staining); (B) Organizing occlusive thrombosis (asterisk) of centrolobular vein (hematoxylin and eosin staining).

Discussion

Paroxysmal nocturnal haemoglobinuria is a rare and life-threatening acquired haematological disorder. Budd-Chiari syndrome is a rare vascular liver disease, and, of it, the small vessels Budd-Chiari syndrome represents an even more rare form. However, PNH is considered the most severe acquired thrombophilic state and represents one of the main aetiological factors of vascular liver diseases. In particular it is responsible of the 19% of cases of Budd-Chiari syndrome [4] justifying why the diagnostic work-up suggested by the current guidelines includes the active search for PNH in patients with BCS.

On the other side, in patients affected by PNH the presence of signs of liver disease and in particular the occurrence of jaundice, ascites and alteration of liver function tests should raise suspicion of BCS. Nonetheless, PNH is characterized by chronic intravascular haemolysis that predisposes to the development of bilirubin gallstones often complicated by biliary obstruction [5] which could further confuse the clinical picture. In fact, in our patient, the hyperbilirubinemia could have been correctly attributed only to the presence of cholecystolithiasis and choledocholithiasis and to the increased hemolytic attacks consequently to the surgical procedure. However, the persistence of so high levels of bilirubin despite the endoscopic treatment and the presence of ultrasonographic features suggestive for Budd-Chiari syndrome (ascites, hepatomegaly, inhomogeneous aspect of liver parenchyma) lead us perform liver biopsy. Again, as in our case, in presence of a high suspicion, the patency of hepatic veins should not lead to exclude the diagnosis of BCS but to search for small hepatic veins BCS. Eculizumab is a humanized monoclonal antibody that targets the terminal complement protein C5 and inhibits terminal complement-mediated haemolysis associated with PNH and it reduces the risk of clinical thromboembolism these patients [6]. These facts strongly suggest that the main cause of thrombosis in PNH is complement activation and/or haemolysis [7]. Therefore, current guidelines do not suggest any anticoagulant treatment for prophylaxis of deep vein thrombosis in PNH patients treated with eculizumab. Once a venous thrombotic event occurred, anticoagulant therapy is necessary to solve the thrombosis and to prevent new events [8]. The demonstration of a concomitant BCS and so of the thrombosis of hepatic or small intrahepatic veins requires the start of anticoagulants once the complications of hypertension have been treated. Maybe, in our case, Budd-Chiari syndrome was already present before the start of therapy with eculizumab.

Finally, the more relevant clinical problems of our patient and, after, the cause of his death were the endocarditis and the periprotesic aortic abscess that were not related to the liver disease. Inhibiting the complement protein C5, eculizumab make the patients more susceptible to infections. Thus, the prophylaxis, the prompt diagnosis and the timely treatment of the infection is a crucial point of the management of the patients affected by PNH and in therapy with eculizumab [9].

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