Case Report

Budd–Chiari syndrome and heparin-induced thrombocytopenia in polycythemia vera: Successful treatment with repeated TIPS and interferon alpha

ABSTRACT

Polycythemia vera (PV) is a common cause of Budd–Chiari syndrome (BCS) and portal vein thrombosis (PVT). The postpartum period is a precipitating cofactor. An additional heparin-induced thrombocytopenia/thrombosis (HIT/T) leads to a life-threatening condition in which transjugular intrahepatic portosystemic shunting (TIPS) seems to be the only life-saving procedure. We describe the case of a subacute BCS and PVT in the late postpartum period. The diagnosis was established using CT scan, MRI, and Doppler ultrasonography of abdominal vessels and the laboratory findings were compatible with PV. After a successful creation of TIPS, a HIT/T worsened the hemorrhagic and thrombotic picture. TIPS procedure was successfully repeated and heparin was replaced with Fondaparinux and then vitamin K antagonist. The treatment with interferon alpha-2A, started after the normalization of liver functions, resulted in a complete remission within 6 months. The JAK2 V617F mutation clone remained undetectable after 2 years’ follow-up.

KEY WORDS: Budd–Chiari syndrome, heparin-induced thrombocytopenia, polycythemia vera

INTRODUCTION

Budd–Chiari syndrome (BCS) is a life-threatening clinical entity characterized by hepatic venous outflow obstruction. An additional portal vein thrombosis leads to a devastating condition with limited therapeutic options.[1,2] In acute and subacute cases alternative venous outflows should be created as early as possible and prompt recognition and control of the underlying thrombophilic disease should be considered when planning subsequent therapeutic approaches.[3] Although, oral contraceptive pills, pregnancy, and postpartum state are precipitating cofactors, polycythemia vera (PV) is the most common cause of BCS.[1,4] The identification of the JAK2 V617F mutation added a useful diagnostic tool in occult forms of PV.[4,5]

Heparin-induced thrombocytopenia and thrombosis (HIT/T) is a rare, paradoxical, autoimmune complication of heparin treatment.[6] Its occurrence deteriorates the course of the disease and precipitates the thrombotic and hemorrhagic events. Here we report the case of a young Middle Eastern woman with Budd–Chiari syndrome, portal vein thrombosis, and polycythemia vera, initially treated with a transjugular intrahepatic portosystemic shunt (TIPS) and low-molecular-weight heparin (LMWH) who then developed HIT/T that causes obstruction of the stents, intra-abdominal hemorrhage, and pulmonary embolism that were successfully managed by repeated TIPS procedure, discontinuing LMWH, and treatment with interferon alpha-2A.

CASE REPORT

A 32-year-old Saudi female was admitted to our clinic, 5 weeks postpartum, for icterus, abdominal pain, and distension. The history includes a full-term first pregnancy 10 years ago (birth weight: 2 kg), a second 30-week pregnancy 4 years later with early pre-eclampsia and stillborn infant, and third and fourth normal pregnancies under aspirin (birth weights: 2.5 and 2.9 kg).

Laboratory studies showed hemoglobin 17.4 g/dl, hematocrit 52.4%, normal white blood cell and platelet count, aspartate transaminase 1020 µ/l [normal (N), <32], alanine transaminase 1466 µ/l (N, <32), direct bilirubin 13 mg/dl (N, <0.2), indirect bilirubin 14 mg/dl (N, <1), alkaline phosphatase: 448 µ/l (N, 35–123), vitamin B12 1967 pg/ml (N, <250), and a low erythropoietin level.
Doppler ultrasonography showed a patent inferior vena cava, a right branch portal vein thrombosis and no flow in the hepatic veins. A CT scan and MRI showed a hepatic segment I hypertrophy, huge ascites but no splenomegaly, no lymph node enlargement or tumor, old right and medium but recently developed left hepatic vein thrombosis. The liver biopsy showed ischemic necrosis of sinusoidal structures [Figures 1 and 2].

The measurement of the red blood cell volume using 51Cr-tagged RBCs was unremarkable and the measurement of the plasma volume using 125I-labeled albumin showed a 53% expansion. Peripheral blood cell culture showed no spontaneous growth of erythroid (CFU-E/BFU-E), myeloid (CFU-GEMM, CFU-GM, CFU-G, CFU-M), or megakaryocytic precursors (CFU-MK). Peripheral blood DNA testing showed a point mutation (V617F) in the JAK2 gene.

The initial management began with 400 ml phlebotomy and LMWH, and then a TIPS. The portal pressure gradient was reduced from 25–28 mmHg to 8 mmHg [Figures 3 and 4].

The progressive drop in the platelet count (platelets: 87 G/l) suggested a HIT/T that was confirmed by the presence of the anti associated-platelet factor 4 antibody (AF4 Ab).

The reocclusion of the TIPS and pulmonary embolism subsequently occurred, documented by arterial blood gage changes, Doppler ultrasonography and D-dimer plasma level. Restenting using the same procedure was performed. Fondaparinux was used in replacement of LMWH and after the improvement of the liver function, interferon alpha-2A was started.

Repeated DNA analyses using the PCR technique showed a steady decrease in the JAK2 mutation clone expression. A complete and persistent molecular remission is seen after 2 years of follow-up.

Figure 1: MRI T2-weighted images showing hypotrophic right sectors of the liver (A, B) with very thin hepatic veins; image (C) shows a hypertrophy of segment I displacing the portal vein

Figure 2: Liver biopsy showing the sinusoidal distension (A) and the hepatocyte necrosis (B)
DISCUSSION

PV is a clonal, chronic myeloproliferative disorder involving multipotent hematopoietic stem cells that give rise to phenotypically normal mature progeny. It is the most common cause of BCS accounting for 10–40% of the cases. Only 4–7% of patients with PV are younger than 40 years and 2–10% of them develop BCS.[1,4] Young women with an occult form of PV, in whom the BCS develops, often have one or more precipitating cofactors such as pregnancy or postpartum state. PVT occurs in 20% of patients with BCS. Its occurrence tumbles the mean survival from 6 years down to 1 month. The outcome depends on early and sustained restoration of the hepatic and portal venous outflow.[2,7]

The initial management of our case began with phlebotomy, LMWH and the creation of a TIPS to alleviate the sinusoidal hepatocyte congestion. Unfortunately, despite the adequate anticoagulation treatment and the normalization of the liver function, an unforeseen HIT/T worsened the clinical picture. It precipitated more extensive thrombotic and hemorrhagic events and caused a reocclusion of the stents. TIPS procedure could successfully be repeated in this patient despite the precarious clinical condition. It was anyway, the only choice at our disposal that resulted in a progressive improvement of the liver function and allowed us to start the interferon therapy. It remains a minimally invasive procedure that should be considered whenever the hepatic venous outflow is obstructed and however great the hemorrhagic risk may be.[7] Furthermore, although uncommon and unpredictable, HIT/T should be recognized in patients who have remote history of exposure to unfractionated or low-molecular-weight heparin.

The occurrence of BCS with or without PVT in a young woman should alert the physician to consider PV. The recent identification of the JAK2 V617F mutation brought a reliable tool to establish the diagnosis. The mutation is present in 97% of cases; however, it is not exclusive to this disorder.[4,5]
JAK2 mutated clone was present in our patient’s peripheral blood. The measurements of blood volumes, serum vitamin B12 level, and leukocyte-alkaline phosphatase expression were helpful in establishing the final diagnosis.4,8,9

Finally, pegylated interferon alpha-2A may induce complete hematological and molecular responses avoiding the long-term toxicity of the alkylating agents. It could eliminate the JAK2 mutated clone in selected cases awaiting more targeted therapy.

REFERENCES


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