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Budd-Chiari Syndrome: a Clinical Approach

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Abstract Budd-Chiari syndrome is characterized by supra-hepatic veins obstruction, leading to post-sinusoidal portal hypertension that often evolves to hepatic failure. It is usually related to prothrombotic conditions, such as trombophilia, myeloproliferative diseases or nocturnal paroxysmal hemoglobinuria. Spontaneous remissions are rare and less than a third of the patients survive one year without treatment. We recommend that anticoagulation should be started as soon as possible with full-dose subcutaneous heparin, postponing warfarin therapy until substantial improvement of ascites and liver congestion. This approach optimizes anticoagulation, decreasing the chances of bleeding. Since January 2000, among 350 patients followed at the Anticoagulation Clinic, three fulfilled the criteria for primary Budd-Chiari syndrome and were started on scheduled anticoagulation protocol. During three to ten years follow-up, supra-hepatic thrombosis completely resolved in all patients and hepatic function normalized without resorting to invasive procedures or liver transplantation. Neither recurrence of thrombotic events, nor serious bleeding events were documented. Scheduled anticoagulation is safe and improves patient's outcomes.

Keywords Budd-Chiari Syndrome, Thrombophilia, Anticoagulation, Heparin, Warfarin

1. Introduction

Budd-Chiari syndrome is an uncommon disease, defined as hepatic venous outflow obstruction, when right cardiac failure, constrictive pericarditis or sinusoidal venooclusive disease are excluded. Primary form usually results from prothrombotic disorders, such as myeloproliferative disorders[1], nocturnal paroxysmal hemoglobinuria[2] or thrombophilia[3,4], combined with a trigger that includes infection, hormonal therapy and pregnancy[5-7]. Particularly, up to 45% of patients with primary Budd-Chiari syndrome have a myeloproliferative disorder, about 10% have antiphospholipid antibody syndrome and no aetiology can be found in 5%[5]. Secondary form results from extrinsic hepatic venous compression[8]. Inadequate hepatic venous outflow increases sinusoidal pressure, resulting in peri-sinusoidal hepatocyte necrosis that ultimately progresses to hepatic failure[5].

Most Budd-Chiari patients have a dull abdominal pain on presentation, but about 15% can be asymptomatic[5]. Ascites, hepatomegaly, splenomegaly, and serum to ascites albumin ratio > 1.1, indicating portal hypertension, are a rule[5,10]. Diagnostic accuracy of hepatogram is low for Budd-Chiari syndrome: ALT, AST, γ-GT and alkaline phosphatase levels can be increased or within normal range[5]. Early diagnosis is fundamental, so when Doppler-scan does not show the suspected venous obstruction, angio-CT or angio-MRI must be performed as soon as possible[5,10]. Liver biopsy is indicated in assessing hepatocellular injury.

Although obstruction site, thrombus extent and clinical presentation may vary significantly among patients, full-dose anticoagulation should be promptly started, thus preventing evolution to cirrhosis[5,9].

We report three patients in whom full-dose subcutaneous heparin was given for an extended period and warfarin was postponed until significant resolution of ascites and liver congestion. During three to ten years of follow-up, they all remain asymptomatic with normal hepatic function without resorting to angioplasty, transjugular intrahepatic portosystemic shunt (TIPS) or liver transplantation.

2. Case Reports

● Patient 1. EAM, a 37-year-old woman, smoker since 21, with a past history of alcohol abuse, sought for medical help four months after having noticed abdominal and lower limbs swelling. On admission, she had severe ascites and collateral abdominal circulation (Figure 1). Laboratory tests revealed sideropenic anemia, high γ-GT and alkaline phosphatase levels, hypoalbuminemia, homozygosis for methylene tetrahydrofolate reductase C677T with normal homocysteinemia, and serum-ascites albumin gradient = 1.8. Two samples taken more than 12 weeks apart were strongly positive for

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lupus anticoagulant and antiphospholipid antibody syndrome was diagnosed. A Doppler-scan disclosed inferior vena cava thrombosis and MRI showed supra hepatic venous thrombosis. EAM was discharged with full-dose subcutaneous UFH twice a day and warfarin was introduced three months later, after ascites absorption (Figure 2). She remains in remission on oral anticoagulation five years after diagnosis.

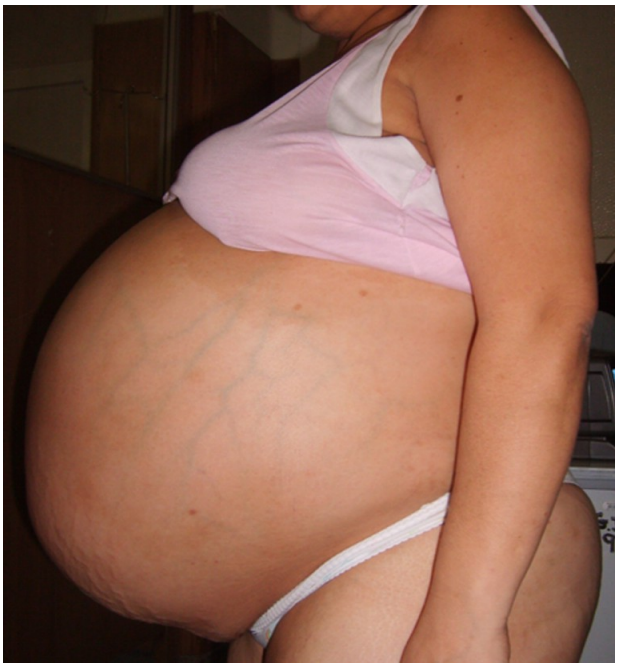

Figure 1. Patient 1 before full-dose subcutaneous heparin

● Patient 2. GPS, heavy drinker and former smoker, sought for medical advice at the age of 40 due to left lower limb deep venous thrombosis and pulmonary embolism. He was placed on warfarin for six months. During the next three years a safenectomy was performed to treat a lower limb deep venous thrombosis and an ileoectomy, to treat a mesenteric venous thrombosis. At the age of 47, he was admitted complaining of excruciating abdominal pain. Mesenteric venous thrombosis was diagnosed and an extended ileocolectomy was performed. Post surgically, a Doppler-scan performed to elucidate persistent bloody diarrhoea showed inferior vena cava, portal vein and supra-hepatic thrombosis. Anticardiolipin antibody was 78 GPL (85 GPL 12 weeks later) and antiphospholipid antibody syndrome was diagnosed. Seven months after full-dose subcutaneous UFH was started, ascites subsided and warfarin replaced heparin. The patient remains in remission ten years later.

● Patient 3. JPHO, a 2 year-old boy whose parents are first cousins was admitted to investigate massive splenomegaly, hepatomegaly and severe ascites that had begun four months earlier. Screening for thrombophilia, paroxysmal nocturnal hemoglobinuria and myeloproliferative diseases were all negative; due to parental consanguinity, we postulate that an uncommon mutation would be responsible for the thrombotic tendency. Alkaline phosphatase and γ-GT levels were high and a Doppler-scan showed supra-hepatic venous thrombosis. Full-dose subcutaneous UFH was started and two months later he had lost 4 kg, returning to his previous weight, 12 kg. An ultrasound showed complete ascites resolution and heparin was replaced by warfarin. Three years later, he remains in partial remission, with minimal ascites.

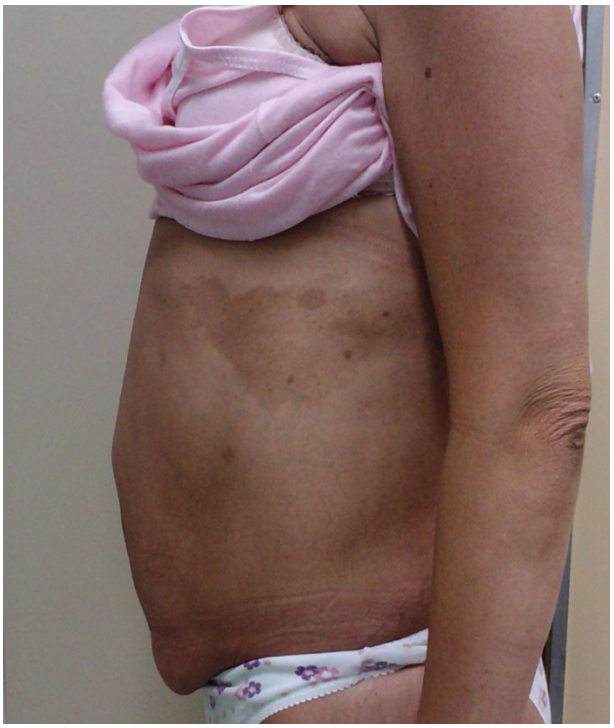

Figure 2. Patient 1 after full-dose subcutaneous heparin

3. Thrombophilia Screening

We strongly recommend that the decision to start anticoagulation do not depend on a thrombophilia diagnosis.

Thrombophilia tests include a complete blood cell count, a lipidogram, fibrinogen, antithrombin III, functional protein C, protein S, polymorphisms for factor V Leiden, prothrombin (factor II) G20210A, methylene tetrahydrofolate reductase (MTHFR) C677T and A1298C, anticardiolipin antibodies IgG and IgM, lupus anticoagulant and β2 glycoprotein 1 IgG and IgM.

Factor V Leiden and factor II G20210A increase the thrombotic risk in hetero or homozygosis, whereas MTHFR increases the thrombotic risk in homozygosis or double heterozygosis.

Antiphospholipid antibody syndrome diagnosis requires the presence of any positive antiphospholipid antibody on two or more occasions, at least 12 weeks apart. Antiphospholipid antibodies comprise:

● Lupus anticoagulant (screening, mixing and confirmation tests must be performed according to ISTH guidelines), IgG and IgM anticardiolipin antibodies and IgG and IgM anti-β2 glycoprotein antibodies (Elisa).

● IgG and IgM anticardiolipin antibodies are considered positive when the value is higher than 40 GPL or MPL or > 99th percentile and high positive when the value is higher than 80 GPL or MPL.

● IgG and IgM anti-β2 glycoprotein 1 antibodies are considered positive when the value is > 99th percentile[11].

A bone marrow aspiration and biopsy must be performed on all patients suspected of having a myeloproliferative disease on complete blood cell count and blood film examination. Enhanced platelet and leukocyte activation and plasma hypercoagulability associated with Janus kinase 2 (JAK2) V617F positivity have been postulated as pathogenic mechanisms of thrombosis in myeloproliferative disorders. Interestingly, this mutation can be also detected in up to 44% of all Budd-Chiari patients without overt myeloproliferative neoplasms[1,12]. The presence of the (JAK2) mutation is determined by polymerase chain reaction.

Factor V Leiden, factor II G20210A or MTHFR polymorphisms and JAK2 mutation, coded in DNA, are searched with polymerase chain reaction for once in a lifetime and are not influenced by the thrombotic event or anticoagulation. In contrast, screening for hereditary anticoagulant deficiencies or antiphospholipid antibodies presents some challenges:

● Thrombosis itself can consume antithrombin III, functional protein C, protein S and antiphospholipid antibodies. For this reason, testing should be done at least six weeks after the thrombotic event.

● Anticoagulation may interfere with thrombophilia testing: antithrombin III levels are usually reduced during heparin treatment and low levels of protein S and functional protein C levels can be seen during warfarin treatment. Testing for antithrombin III, functional protein C and protein S are usually delayed until at least one month after completion of anticoagulation, but Budd-Chiari patients are often placed on long-term anticoagulant therapy.

● Antithrombin III and functional protein C are synthesized only by hepatocytes, while protein S synthesis occurs mainly in the liver. Chronic and acute hepatopathy may decrease antithrombin III, protein S and functional protein C levels.

● Protein S levels are reduced during infections, hormonal therapy, pregnancy and puerperium, and inflammation, such as inflammatory bowel disease.

Paroxysmal nocturnal hemoglobinuria is a rare acquired disease characterized by a clone of blood cells lacking GPI-anchored complement inhibitors CD55 and CD59 on erythrocytes, which leads to intravascular hemolysis upon complement activation and a highly increased risk of thrombosis[13]. CD55- and CD59-deficient populations can be demonstrated with flow cytometry.

4. Budd-Chiari Treatment

Prompt anticoagulation with full-dose subcutaneous heparin may prevent progression to cirrhosis. Both unfractionated (UFH) and low-molecular-weight heparin (LMWH) can be given as outpatient basis with the same efficacy, without being monitored[14]. LMWH do not have antidote and should be avoided whenever variceal bleeding risk is high. Heparin doses are:

● UFH: 333 IU/kg of "dry weight" (excluding ascites and edema), followed by 250 IU/kg every 12 hours.

● LMWH, such as enoxaparin: 1 mg/kg of "dry weight" every 12 hours.

Protamine sulfate can be used for the reversal of heparin; together they form a stable salt complex. Protamine is a weak anticoagulant and it is important to avoid overdosing. UFH short half-life must be taken into account when calculating the dose of protamine sulfate[15]. To minimize side effects, such as anaphylaxis and hypotension, protamin must be dissolved in saline and infused slowly. Protamin doses are based on the length of time elapsed since heparin was discontinued and the size of the dose:

● If the last heparin SC injection occurred less than 3 hours before, 1 mg for each 100 IU UFH.

● If the last heparin SC injection occurred 3 to less than 6 hours before, 0.75 mg for each 100 IU UFH.

● If the last heparin SC injection occurred 6 to less than 9 hours before, 0.5 mg for each 100 IU UFH.

● If the last heparin SC injection occurred less than 3 hours before, 0.25 mg for each 100 IU UFH.

Although protamine sulfate can fully reverse the effect of UFH, it only partly neutralizes the effect of LMWH. Recombinant activated factor VII (rFVIIa) is a good alternative for reversal of LMWH anticoagulation; unfortunately, rFVIIa may increase the risk of thromboembolic events[16].

Because many patients present with prolonged PT-INR and thrombocytopenia, physicians are cautious to prescribe drugs that could increase the risk of variceal bleeding[5]. However, it must be considered that:

● Patients with primary Budd-Chiari have a thrombotic tendency. Synthesis of most coagulation factors occur in the hepatocyte. Also, synthesis of natural anticoagulants and components of the fibrinolytic pathway occurs mainly in the liver.

● Neither low-platelet count nor prolonged PT-INR prevents thrombotic events.

Also, when prolonged PT-INR is due to liver injury, vitamin K seldom corrects the problem.

Warfarin therapy should be postponed until significant resolution of ascites and liver congestion, which normally occurs many weeks after hospital discharge. This approach avoids frequent warfarin adjustments related to progressive liver congestion remission and diuretics tapping. In addition, when invasive procedures such as biopsies or paracentesis are required, heparins but not warfarin can be discontinued for few hours.

Treatment with warfarin must be monitored by someone with extensive experience in handling of this medication, because food, caffeine-containing beverages and many other medications, particularly β-blockers, spironolactone, and omeprazole, may impair or potentiate the anticoagulant effect of warfarin[17-23].

It must be remembered that long-term anticoagulation is associated with an increased risk of osteoporosis and fractures[24, 25]. To prevent bone loss, patients on oral anticoagulants or heparins must be advised to engage in low- impact exercise on a daily basis.

Estrogens, tamoxifen, third-generation progestins and antiangiogenic drugs, such as thalidomide or lenalidomide, increase the risk of venous thromboembolic events and must be avoided[6,12,26]. Variceal bleeding prophylaxis is indicated for portal hypertension and diuretics or paracentesis for ascites relief[5]. It is important to consider that dehydration increases the risk of thrombosis.

Polimorphisms as homozygous methylene tetrahydrofolate reductase C677T or A1298C, or double heterozygous C677T/A1298C increase the risk for hyperhomocysteinemia in patients deficient in folic acid, pyridoxine (vitamin B6) or cobalamin (vitamin B12). Hyperhomocysteinemia is a modifiable risk factor for thrombotic diseases. Daily supplementation with folic acid 5-10 mg usually prevents hyperhomocysteinemia or normalizes homocysteine plasmatic levels. Some patients may require additional vitamin B6 and vitamin B12 supplementation.

Some issues must be addressed regarding paroxysmal nocturnal hemoglobinuria patients. It has been shown that anticoagulation reduces the risk but does not completely prevent thrombosis.Eculizumab, a monoclonal antibody against complement factor C5, has clearly improved the prognosis of the disease, effectively reducing intravascular hemolysis and thrombotic risk[13].

Angioplasty is frequently recommended for symptomatic patients with short stenosis[5,10]. However, invasive procedures and mechanical devices could trigger additional thrombotic events or enhance extension of preexisting ones and should be performed with caution. Furthermore, recurrence after liver transplantation is about 27% and, as might be expected, antithrombotic prophylaxis with aspirin and hydroxiurea for myeloproliferative syndromes or anticoagulation for patients with thrombophilia after the procedure has dramatically improved the results[27,28].

5. Conclusions

Major goal in Budd-Chiari syndrome is to restore vessel patency, preventing evolution to hepatic failure. Because hepatic congestion and frequent adjustments of other drugs can interfere with warfarin, patients with portal hypertension are difficult to manage with oral anticoagulants. We suggest that Budd-Chiari patients be treated initially with full-dose subcutaneous heparin, postponing warfarin therapy until substantial resolution of ascites and liver congestion. Scheduled anticoagulation reduces the risk of bleeding and increases the chances for long-term remission without resorting to angioplasty, TIPS or liver transplantation.

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