



Causes of Budd-Chiari Syndrome: A Review based on a Case Report

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Abstract

Budd-Chiari syndrome (BCS) is an obstruction of hepatic venous flow at any level, from small hepatic veins to the junction of the inferior cava vein and the right atrium. Studies report that BCS is associated with prothrombosis. The authors present a review of the topic based on a case report of BCS where several risk factors are involved. These factors were genetic, such as mutation of the plasminogen activator inhibitor with 4G polymorphism and acquired, such as ulcerative colitis and oral contraceptives.

Keywords: Budd-Chiari Syndrome; Colitis, Ulcerative; Thrombophilia; Contraceptives, Oral

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Introduction

A 35-year-old woman with a history of untreated ulcerative colitis (UC) who had been taking oral contraceptives was treated in the emergency room for the third time in the same week for pain in the suprapubic area, vomiting and diarrhea. The physical examination revealed blood pressure of 98/53 mmHg, tachycardia at 115 beats per minute, 98% saturation, tympanic temperature of 37°C, dry mucous membranes, abdominal distension and pain with superficial and deep palpation across the abdomen, especially in the suprapubic region, without masses or hepatosplenomegaly. Laboratory findings showed: 10.600/L leukocytes, 71% neutrophils, hyponatremia at 128 mmol/L, CRP of 25, 63 mg/dL and negative beta-HCG. The electrocardiogram showed a sinus tachycardia pattern. The abdominal-pelvic ultrasound showed “segment V changes apparently suggestive of thrombosis”. An abdominal-pelvic CT-scan was performed which showed “hepatomegaly and, in segment V, changes in attenuation dependent on the hypodensity of the middle hepatic vein”, which confirmed thrombosis. It also showed the “colon with loss of the haustras with aspects of internal parietal uptake related to inflammatory changes (probably a flare of UC) and multiple mesenteric, lombo aortic and iliopelvic lymphadenopathies” (Figure 1). The patient started anticoagulation treatment with enoxaparin 60

mg/twice daily, mesalazine 500 mg/three times daily and prednisolone 50 mg/daily. During hospitalization, other exams were requested and it was determined that factor V, antithrombin III, protein S and protein C were within normal values. She made a good recovery, remained symptom free and was discharged. After the acute episode, a genetic study for thrombophilia revealed a plasminogen activator inhibitor (PAI) 4G mutation.

Definition and Concept

Budd-Chiari Syndrome (BCS) is a rare clinical entity first described by Budd in 1845 ¹ and then in 1899 by Chiari.²⁻³ In 2003, at the 36th meeting of the European Association for the Study of the Liver in Prague, a panel of experts defined BCS as an obstruction of hepatic venous flow at any level, from the small hepatic veins to the union of the inferior cava vein (IVC) and the right atrium, regardless of the cause of the obstruction⁴. Obstruction caused by hepatic veno-occlusive disease, cardiac disorders or sinusoidal obstruction syndrome are excluded from the definition⁴. According to the etiology, BCS can be classified as primary if the obstruction is endoluminal or secondary venous injury if the obstruction is caused by compression or extrinsic invasion.^{3,4}

Physiopathology

The venous obstruction produces an increase in

hydrostatic pressure in the portal capillaries which causes sinusoidal dilation and leakage of fluid into the interstitial spaces. The fluid passes through the Glisson capsule when the capacity of the lymphatic drainage is

exceeded.⁵ The resulting increase in portal pressure and decrease in hepatic perfusion causes cellular damage secondary to hypoxia.^{3,6}

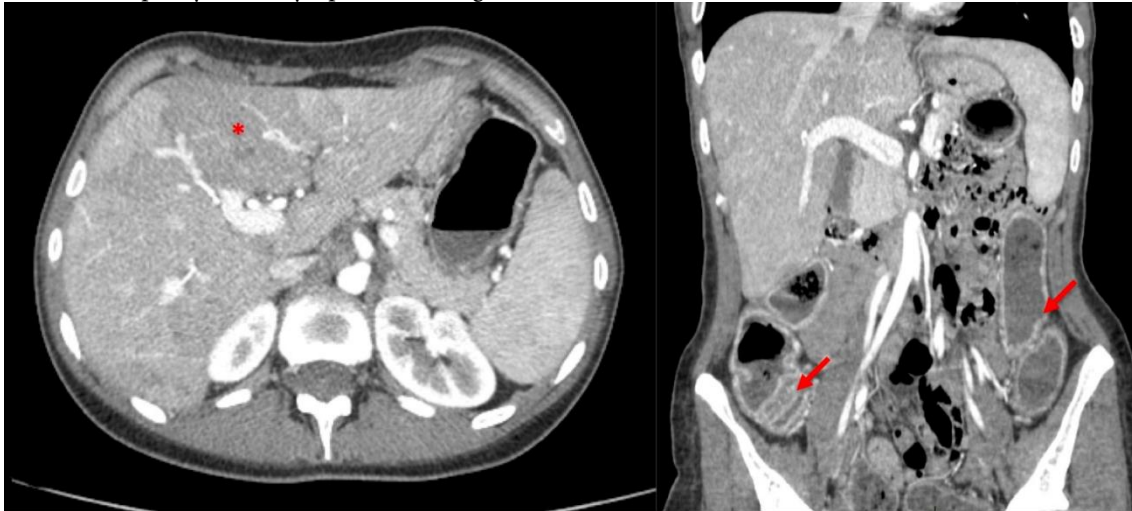


Figure 1. Changes in Attenuation in Segment V dependent on the Middle Hepatic Vein (Asterisk) and loss of the Haustras with Inflammatory Changes (Arrows)

Etiology

Studies have associated BCS with prothrombotic states.^{3,7} Darwish et al. found that 84% of patients with BCS had at least one thrombophilic disorder and 74% of these patients had more than one prothrombotic disorder.⁸ An underlying cause can be identified in over 80% of patients with BCS.⁹ In this paper, we will focus on the main causes found in the reported clinical case. Patients with UC have an increased risk of venous thromboembolism because of the incidence hypercoagulability.⁹⁻¹¹ This risk is eight times higher during an outbreak than at baseline.¹¹ BCS is a rare complication of UC,⁹⁻¹¹ although the incidence in necropsies of venous thrombosis in UC was found to be 39%.⁹ A diagnosis of UC usually precedes or is simultaneous to a diagnosis of BCS.¹⁰ Despite this relationship, thrombotic disorders in patients with UC are considered to be the result of multiple interactions between other acquired (oral contraceptives) or inherited (thrombophilic genetic alterations)¹⁰ risk factors. The use of combined oral contraceptives has also been associated with BCS and has been documented in 33% of BCS patients who take them.¹² Valla et al. showed that patients who had recently used combined oral contraceptives had a 2.37 times greater risk of liver vein thrombosis than patients who had not used these drugs.^{3,13} Combined oral contraceptives appear to play a role, at least as coadjuvant agents, in the development of suprahepatic vein thrombosis.¹⁴ PAI-1 is an inhibitor of fibrinolysis and studies show that in IBD there is an imbalance that promotes a hypofibrinolytic state which contributes to venous thromboembolism.¹⁵ This is higher in the mutant 4G allele variety of the PAI polymorphism.¹⁵⁻¹⁷

Clinical Manifestations

The clinical manifestations of BCS depend on the degree of obstruction.³ A single blocked hepatic vein may not be sufficient for manifestation of the syndrome.³ Clinical presentation is heterogeneous and ranges from the absence of symptoms to fulminant hepatic failure. In a multicenter prospective study of a large cohort of patients with BCS at the time of diagnosis, the following symptoms predominated: ascites (83%), hepatomegaly (67%), abdominal pain (61%), esophageal varices (58%) and gastrointestinal hemorrhage (5%).^{8,18} Cheng et al. studied the clinical manifestations of patients with BCS and reported ascites (53%), distended abdomen (31%), hepatomegaly (28%) and abdominal pain (21%).^{3,19} The clinical course is variable depending on the extension of the venous obstruction and the installation. This can be classified as fulminating form (less than 5% of all cases), subacute form (most cases) or chronic form (cirrhosis).^{9,14} The clinical manifestations of the subacute form have been previously described. Signs of objective portal hypertension, such as splenomegaly and esophageal varices, may also be observed. BCS can also go unnoticed because it is paucisymptomatic and can be detected when a diagnostic study is performed in the presence of hepatosplenomegaly or alterations in hepatic biochemistry.^{9,14} Novacek et al. found that the majority of patients with recurrence of VTE (54.3%), had concomitantly active disease.^{17,20}

Diagnosis

Laboratory testing found no pathognomonic changes. An increase in transaminases to 50 and 200 U/l, hyperbilirubinemia and a decrease in prothrombin time

could be observed. The ascitic fluid in BCS is normally rich in protein (more than 20-30 g/L) and scarce cellularity has been observed.¹⁴ An abdominal ultrasound performed by an experienced professional may detect partial or complete thrombosis in the suprahepatic veins, but abdominal Doppler ultrasound is the exam of choice for BCS screening.¹⁴ Doppler ultrasound has a diagnostic sensitivity of more than 75% and is the exam for first-line investigation.¹⁸ Radiological techniques such as CT-scan or MRI could detect thrombosis of the suprahepatic veins, although there is

no advantage to their use compared to Doppler ultrasound.¹⁴ The diagnosis will be established when obstruction of the hepatic venous flow is confirmed. Venography is recommended if there are doubts in the diagnosis or to characterize the anatomy before treatment. If the images do not demonstrate an obstruction of the large venous trunks, a liver biopsy can be performed to evaluate intrahepatic venous thrombosis.¹⁸ We propose the following diagnostic algorithm (Figure 2).

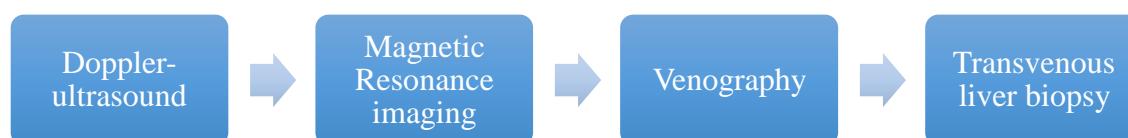


Figure 2. Diagnostic Algorithm ⁴

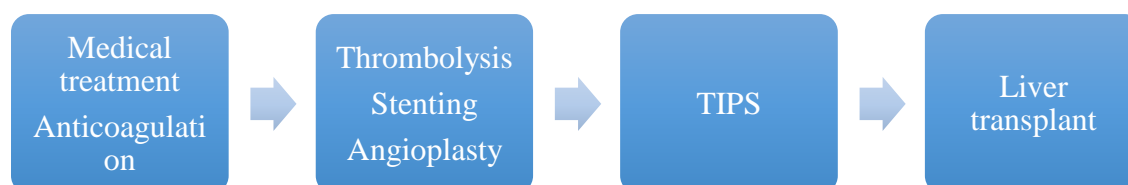


Figure 3. Therapeutic Algorithm ^{4, 8, 18}

Treatment

Patients with BCS should initiate anticoagulation as soon as possible for an indefinite period of time to reduce the risk of clot expansion and new thrombotic events. Treatment of the underlying prothrombotic causes should be initiated concomitantly.¹⁸ In accordance with recommendations for deep vein thrombosis, the patient should be treated with low molecular weight heparin (LMWH) for 5 to 7 days and oral anticoagulant treatment with vitamin K antagonist to obtain an international standardized rate (INR) between 2 and 3.²¹ LMWH can be stopped when the INR is within the target range for two consecutive measurements.¹⁸ Rauton et al. reported in a cohort study of BCS patients receiving anticoagulation therapy that more than 50% had bleeding complications due to invasive procedures and portal hypertension.²¹ Seijo et al., in another prospective cohort of BCS anticoagulated patients, reported that bleeding complications were observed in 17% of patients due to portal hypertension.^{18, 22} The experience with thrombolysis in the correction of hepatic venous flow obstruction is limited. Good results have been observed in patients with recent and incomplete thrombosis treated with local and early infusion of a thrombolytic agent combined with angioplasty or stenting.^{18, 23} Thrombolysis should be reserved to cases where venous flow cannot be restored using conventional anticoagulant therapy or stents. It should be remembered that thrombolysis complications can be fatal.^{18, 24} Derivative techniques, either surgical shunts or

a transjugular intrahepatic portosystemic shunt (TIPS), aim to transform the portal system into an outflow tract.²⁵ There are several forms of shunting described in the treatment of BCS. The choice will depend on the state of permeability of the IVC and the pressure gradient between the portal vein and the IVC.²⁵ Liver transplantation could be considered in three cases: BCS that presents as fulminant hepatic insufficiency, end-stage chronic liver disease and those that deteriorate rapidly after a bypass procedure. Other cases should be analyzed case-by-case by a multidisciplinary team.²⁵ TIPS was introduced for the treatment of cirrhosis and portal hypertension. The use of TIPS in BCS patients is an alternative to shunt surgery or liver transplantation when the disease cannot be controlled by medical treatment alone.^{18, 26} Neumann et al. determined that TIPS can improve survival, reduce the need for diuretics and lower the need for liver transplantation.^{26, 27} All therapeutic options are included in the algorithm in Figure 3.

Conclusions

BCS is an obstruction of hepatic venous flow. Its association with prothrombotic states can be identified in over 80% of cases. It should be suspected where the patient presents with ascites, distended abdomen, hepatomegaly and abdominal pain. The importance of an early diagnosis is related to the different forms of clinical BCS presentation as fulminate, subacute or

chronic (cirrhosis). The obstruction should be identified to confirm the diagnosis using Doppler ultrasound, CT-scan, MRI or liver biopsy to identify intrahepatic venous thrombosis. Anticoagulation must be started as soon as possible concomitantly with the treatment of the underlying prothrombotic causes identified.

Ethical Approval

Not applicable.

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Author's Contributions

All authors contributed equally to this study.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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