Sub-Acute Budd-Chiari Syndrome
Síndrome de Budd-Chiari Subaguda

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Abstract:

Budd–Chiari syndrome (BCS) is a rare vascular liver disorder characterized by obstruction of the hepatic venous outflow tract that is frequently associated with underlying prothrombotic conditions. Myeloproliferative neoplasms (MPNs), particularly those harboring *JAK2* mutations, represent a major etiological factor.

This case report describes a 53-year-old woman who presented with abdominal pain and ascites. Imaging revealed typical features of BCS, including hepatosplenomegaly, caudate lobe hypertrophy, heterogeneous liver parenchyma and prominent portosystemic collaterals. Hematological workup identified a JAK2 V617F-positive prefibrotic primary myelofibrosis as the underlying cause. Under medical therapy ascites resolved completely. Three years after diagnosis, the patient developed blue toe syndrome as a thromboembolic complication, prompting initiation of cytoreductive therapy with hydroxycarbamide and antiaggregant treatment with aspirin.

This case highlights the importance of early diagnosis and comprehensive evaluation for underlying prothrombotic conditions in patients with BCS. Routine screening for MPNs, including *JAK2* mutations, is essential. Prompt anticoagulation and an individualized, multidisciplinary management approach are crucial for improving patient outcomes.

Keywords: Budd-Chiari Syndrome; Janus Kinase 2/genetics; Myeloproliferative Disorders.

Resumo:

A síndrome de Budd–Chiari (SBC) é uma doença vascular hepática rara, caracterizada por obstrução na drenagem venosa hepática, frequentemente associada a condições protrombóticas subjacentes. As neoplasias mieloproliferativas (NMP), particularmente as associadas a mutações do *JAK2*, representam um importante fator etiológico.

Este caso clínico descreve uma mulher de 53 anos que se apresentou com dor abdominal e ascite. Os exames de imagem revelaram achados típicos de SBC, incluindo hepatoesplenomegalia, hipertrofia do lobo caudado, heterogeneidade do parênquima hepático e circulação colateral portossistémica exuberante. O estudo etiológico identificou uma mielofibrose primária pré-fibrótica JAK2 V617F-positiva como causa subjacente. Sob terapêutica médica, a ascite resolveu completamente. Três anos após o diagnóstico, a doente desenvolveu síndrome do dedo azul como complicação tromboembólica, condicionando o início de terapêutica citorredutora com hidroxicarbamida e terapêutica antiagregante com aspirina.

Este caso salienta a importância do diagnóstico precoce e da avaliação abrangente de condições protrombóticas associadas em doentes com SBC. O rastreio sistemático de NMP, incluindo a pesquisa de mutações do *JAK2*, é essencial. A anticoagulação precoce e uma abordagem terapêutica individualizada e multidisciplinar são cruciais para melhorar o prognóstico dos doentes.

Palavras-chave: Síndrome de Budd-Chiari; Perturbações Mieloproliferativas.

Learning Points

1. Diagnosis of Budd-Chiari syndrome is challenging and needs an interdisciplinary approach.
2. While anticoagulation represents the mainstay of treatment, interventional radiology procedures and liver transplantation may be considered according to the severity and the evolution of the disease.
3. Causes of thrombophilia should always be investigated in patients with BCS.

Introduction

Budd-Chiari syndrome (BCS) is a rare vascular liver disorder with a pooled annual incidence of 1 per million people, usually manifesting at a younger age (20-45 years).[1] It is defined as an obstruction of the hepatic venous outflow tract, located at any level from the small hepatic venules to the junction of the inferior vena cava (IVC) with the right atrium. Outflow obstruction secondary to right heart failure, pericardial disease or sinusoidal obstruction syndrome are excluded from this definition.

BCS can be classified according to etiology, site of obstruction and onset of disease (fulminant, subacute, acute, chronic). However, there is currently no clear consensus on the classification of disease duration.[2] The acute form is defined as presenting with rapid onset of typical symptoms (ascites, hepatosplenomegaly), while the presence of venous collaterals indicates the transition to the subacute form.[3]

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Regarding etiology, BCS is classified in primary and secondary. In primary BCS, the obstruction is originating from endoluminal, caused by thrombosis or a primary disease of the venous wall. Secondary BCS is due to external compression or invasion of the hepatic veins, most notably by malignancies. According to site obstruction, BCS can be classified in obstruction of the small hepatic veins, large hepatic veins, inferior vena cava and combined obstruction of large hepatic veins and inferior vena cava.[2]

In approximately 75% of patients with primary BSC, an underlying condition can be identified, such as a hereditary or acquired hypercoagulable state. These include myeloproliferative disorders, antiphospholipid syndrome, Factor V Leiden or the use of oral contraceptives. In approximately 20% of patients, no underlying cause can be identified and the disease is classified as idiopathic BCS.[4]

The clinical presentation of patients with BCS is very heterogeneous and can vary widely from asymptomatic to acute liver failure (ALF), depending on the extent, as well as the site and rapidity of obstruction. While ALF is very rare and associated with a high mortality rate, most patients present with ascites, hepatomegaly and abdominal pain. Up to 20% of patients are asymptomatic at the time of diagnosis.[5]

In all patients presenting with signs of acute or chronic liver disease, BCS should be excluded using computed tomography (CT) scan or magnetic resonance imaging (MRI) with a complete assessment of all hepatic vessels and the hepatic parenchyma. Imaging characteristics include obstruction of the hepatic veins, caudate lobe hypertrophy and intrahepatic veno-venous collaterals, as well as nonspecific signs of portal hypertension (ascites, splenomegaly, portosystemic collaterals).[5]

Management of BCS also depends on symptoms and severity at diagnosis and include restoration of the hepatic vein flow and treatment of the underlying prothrombotic condition and BCS-associated complications (portal hypertension, malignancies). A stepwise strategy is recommended in all patients, except those who present with ALF, in whom liver transplantation should be considered. The first step in all patients has been initiation of anticoagulation, based on findings reported at the end of the last century with low-molecular-weight heparin (LWMH), followed by vitamin K antagonists.[6] The use of direct oral anticoagulants (DOACs) in BCS was first reported in 20177 and data about the effectiveness and safety of these drugs have been recently published.[8]

In those patients who have stenosis of a short segment, percutaneous transluminal balloon angioplasty or stenting should be considered. In cases with insufficient response to medical treatment and/or angioplasty portosystemic shunting (TIPS) is the next step. In addition to the treatment options mentioned above, complications such as ascites, varices or hepatic encephalopathy should be managed according to clinical guidelines.

Case Report

On August 29, 2019, a 53-year-old woman was admitted to the hospital with suspected intestinal obstruction. The patient had a known history of diabetes mellitus, schizophrenia and multinodular goiter and suffered from chronic constipation. At admission, she reported severe abdominal pain for four days, an increase in abdominal girth and absence of bowel movements. Clinically notable were widespread tenderness to palpation and a markedly distended abdomen. Initial laboratory tests showed leucocytes 11.7 G/L, platelet 200 G/L. aspartate aminotransferase (ASAT) 50 U/L, alanine aminotransferase (ALAT) 58 U/L, bilirubin 20 umol/L, alkaline phosphatase (ALP) 155 U/l and INR 1.4.

CT-scan on the day of admission revealed marked hepatosplenomegaly, prominent portosystemic collateral circulation, a hypertrophic caudate lobe, in homogeneous liver parenchyma and rarefied hepatic veins. Additionally, there was extensive ascites. The Child-Pugh score at the time of initial presentation was B, 8 points.

With a high suspicion of BCS, an ascitic fluid puncture was performed on the same day, revealing a SAAG of 16.8 g/L (albumin concentration of serum 32 g/L, albumin concentration of ascitic fluid 16.2 g/L). Transjugular liver biopsy on September 5 showed findings consistent with Budd-Chiari syndrome, i.e., liver tissue with ventral vein ectasia, congestion of the adjacent sinusoids and minimal fibrosis.

Anticoagulation with LMWH was initiated on August 30, which was switched to apixaban based on patient's preference to avoid INR monitoring on September 12. Diuretic therapy with spironolactone and torasemide was initiated to treat ascites and carvedilol was introduced after endoscopy showing esophageal varices.

For the investigation of the underlying cause, extended hematological diagnostics were performed. After exclusion of thrombophilia and paroxysmal nocturnal hemoglobinuria, further investigations were carried out. Bone marrow puncture on September 12 showed megakaryocytic proliferation and atypia, accompanied by fibrosis, together with age-adjusted increased cellularity. The presence of a *JAK2 V617F* mutation confirmed the presence of a myeloproliferative disease.

Regular hepatological and hematological follow-up evaluations were performed under the established therapy. During the follow-up ascites completely regressed with diuretic treatment.

Three years after the initial diagnosis, the patient developed blue toe syndrome in the right foot, which is the acute onset of purple painful digits due to peripheral microembolism and led to the initiation of cytoreductive therapy with hydroxycarbamide, as well as antiaggregation with aspirin.

The patient initially presented with abdominal pain, hepatomegaly, and ascites, findings typical of BCS. CT imaging revealed hepatosplenomegaly, prominent portosystemic collaterals, hypertrophy of the caudate lobe, heterogeneous liver parenchyma, and attenuated hepatic veins, all characteristic of BCS.

Although liver biopsy is usually not necessary when such typical features are present, it was performed in this case and demonstrated hematopoietic cells within the sinusoids, pointing to an underlying hematologic disorder.

This disorder was identified as primary myelofibrosis, a myeloproliferative neoplasm (MPN) that is frequently associated with BCS. MPNs are clonal diseases of hematopoietic stem cells and are prone to thrombotic complications, with *JAK2* gene mutations among the factors that increase thrombotic risk. MPNs are found in about 35% - 50% of BCS cases, and the *JAK2 V617F* mutation, which was present in this patient, occurs in roughly 35% - 45% of BCS patients. Given the high prevalence of MPN in BCS, screening for *JAK2 V617F* is recommended. For BCS secondary to MPNs, current guidelines recommend anticoagulation with vitamin K antagonists as first-line therapy,[9] although direct oral anticoagulants have been used with increasing frequency, as in this patient.

Long-term, usually lifelong, anticoagulation is generally advised in BCS, especially because the *JAK2* mutation markedly increases the risk of recurrent thrombosis.[10] If anticoagulation alone is insufficient, interventional procedures such as angioplasty or transjugular intrahepatic portosystemic shunt (TIPS) placement are important additional options.

This patient had prefibrotic primary myelofibrosis, an early phase of overt myelofibrosis in which patients are often asymptomatic but typically progress over time to full-blown disease.[11] Depending on risk stratification, an initial watch-and-wait strategy can be appropriate. In patients with a history of thrombosis, cytoreductive therapy is recommended, along with antiplatelet treatment such as aspirin.[12] In this case, these therapies were started after the patient developed blue toe syndrome, following several years of a compensated clinical state.

Poor prognostic indicators in BCS include a higher Child-Pugh score, advanced age, ascites refractory to diuretics, and elevated serum creatinine. Nevertheless, 5 year survival has improved substantially with better management of hypercoagulable states and wider use of endovascular procedures. In patients treated with anticoagulation, transplant-free survival is approximately 92% at 5 years and 82% at 10 years. About 10%-20% of patients who do not respond adequately to these measures become candidates for orthotopic liver transplantation, with 5 year post-transplant survival rates of up to 84%.

In summary, BCS is an uncommon and heterogeneous disorder that can occur in the context of myelofibrosis. Prefibrotic myelofibrosis may present clinically with Budd-Chiari syndrome as its first manifestation. In any patient with signs of acute or chronic liver disease, BCS should be considered and a thorough workup, including appropriate imaging, should be undertaken. Once the diagnosis is confirmed, prompt initiation of anticoagulation is essential, with interventional procedures added as needed, and evaluation for underlying etiologies should always be pursued. For these patients, an individualized, multidisciplinary management strategy is key to achieving the best possible outcomes. ■

Contributorship Statement

SK - clinical management, data interpretation, manuscript drafting, and critical revision.

ADG – Critical review of the manuscript and intellectual content revision.

All authors approved the final version to be published.

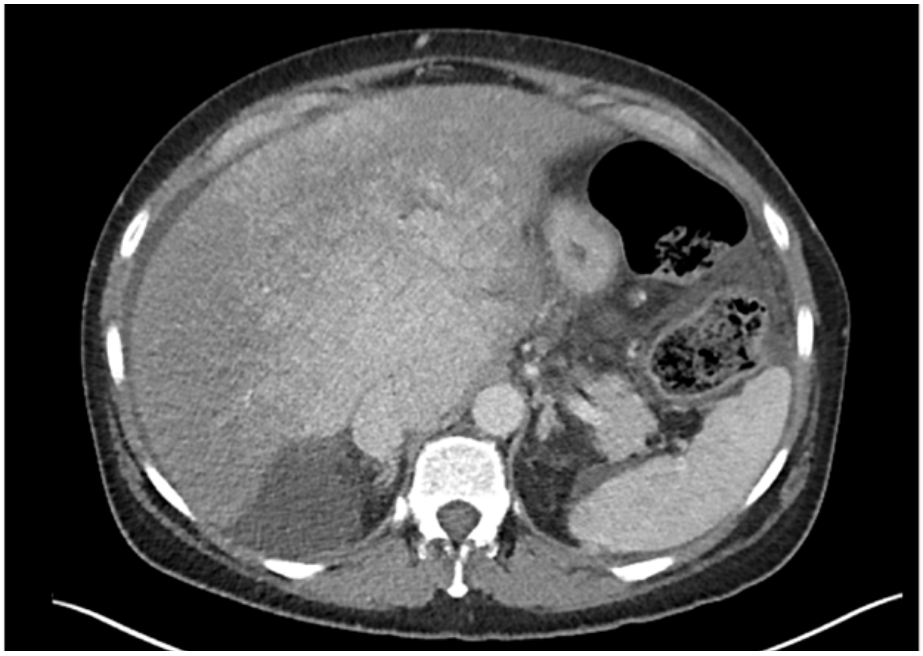

Figure 1: CT scan (portal venous phase) showing hepatomegaly, hypertrophy of the caudate lobe, heterogeneous liver parenchyma, and attenuated hepatic veins.

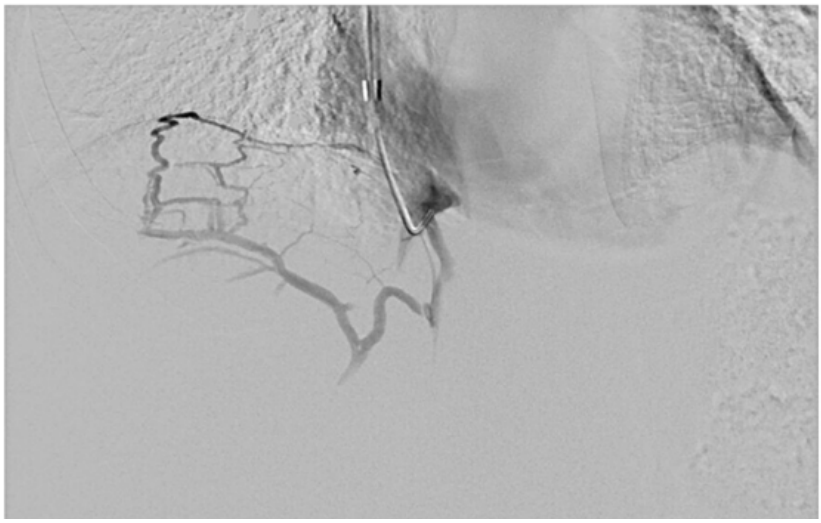

Figure 2: Abdominal phlebography: Repeated attempts to catheterize a hepatic vein were unsuccessful. It was only possible to place the catheter at the confluence of the hepatic veins; in the DSA performed, the main veins did not opacify, but numerous collateral vessels were demonstrated.

Declaração de Contribuição
SK - Gestão clínica, interpretação dos dados, redação e revisão do manuscrito.
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