Open Access Original Research Article

MedPeer Publisher
Abbreviated Key Title: MedPeer
ISSN : 3066-2737
homepage: https://www.medpeerpublishers.com

A Triple Hit Mechanism in Budd–Chiari Syndrome: Hormonal, Metabolic, and Vascular Synergy

DOI: 10.70780/medpeer.000QGSP

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ABSTRACT

Budd–Chiari syndrome is a rare hepatic vascular disorder caused by obstruction of hepatic venous outflow, most often related to an underlying prothrombotic condition.
We report the case of a 31-year-old woman with no significant past medical history who presented with 20 days of epigastric pain and asthenia. Clinical examination revealed hepatomegaly associated with ascites. Laboratory tests showed mild hepatic cytolysis, cholestasis, and early hepatic insufficiency. Abdominal CT angiography confirmed Budd–Chiari syndrome with hepatic venous outflow obstruction, hepatic dysmorphy, moderate ascites, and stenosis of the retrohepatic inferior vena cava. Etiological work-up revealed recent reintroduction of estrogen-containing oral contraceptives, elevated homocysteine levels associated with heterozygous MTHFR mutation, and no other major thrombophilic disorder. The patient was treated with oral anticoagulation with favorable clinical evolution. This case highlights the multifactorial nature of Budd–Chiari syndrome and the synergistic interaction between hormonal exposure, metabolic abnormalities, and anatomical venous obstruction.

KEYWORDS :

Budd–Chiari syndrome; oral contraceptives; hyperhomocysteinemia; MTHFR; inferior vena cava stenosis; thrombosis.

MAIN ARTICLE

INTRODUCTION

Budd–Chiari syndrome (BCS) is an uncommon but serious vascular liver disease defined by obstruction of hepatic venous outflow, involving the hepatic veins and/or the inferior vena cava. It represents a heterogeneous clinical entity rather than a single disease, and its presentation reflects diverse underlying etiologies.

Over the past decades, BCS has been increasingly recognized as the hepatic manifestation of systemic prothrombotic disorders. Its pathophysiology is therefore closely linked to conditions that promote venous thrombosis, including acquired, genetic, and combined risk factors. [1]

Current evidence supports a multifactorial pathogenesis in which the interaction of several predisposing conditions is usually required for disease expression. This "multi-hit" model explains why isolated risk factors are often insufficient to trigger clinically evident hepatic venous outflow obstruction. [2]

Accordingly, a comprehensive diagnostic approach is essential, as identifying the underlying prothrombotic milieu has direct implications for management and long-term prognosis. [3]

CASE PRESENTATION

We report the case of a 31-year-old woman, married and mother of two children, with no significant past medical history. She had been taking combined oral contraceptives (Microdiol) for several years, which had been interrupted for two years and reintroduced three months prior to admission.

She presented to the hospital for evaluation of a 20-day history of progressive epigastric pain, initially intermittent and then becoming persistent, associated with asthenia. There was no reported fever, no jaundice, no gastrointestinal bleeding, and no alteration of general condition.

On physical examination, the patient was hemodynamically stable. Abdominal examination revealed a tender hepatomegaly with clinical signs of moderate ascites, evidenced by shifting dullness. No splenomegaly or signs of chronic liver disease stigmata were noted.

Laboratory investigations revealed a mild hepatic cytolysis with alanine aminotransferase (ALT) at 1.7 times the upper limit of normal and aspartate aminotransferase (AST) at 1.2 times the upper limit. A cholestatic pattern was also present with gamma-glutamyl transferase (GGT) elevated to 2.6 times normal. Hepatocellular insufficiency was suggested by a prothrombin time of 64% and a reduced factor V level of 56%. Inflammatory markers

showed a mildly elevated C-reactive protein at 19 mg/L. Renal function and the remainder of the biochemical profile were within normal limits.

Abdominal contrast-enhanced CT scan demonstrated findings consistent with Budd–Chiari syndrome, including hepatic venous outflow obstruction, heterogeneous hepatic parenchymal enhancement with early dysmorphic changes, and moderate ascites. A significant stenosis of the retrohepatic segment of the inferior vena cava was also identified. This stenosis was also suspected on abdominal ultrasound with Doppler examination, which provided early evidence of impaired venous flow at the caval-hepatic junction (Figure 1).

A comprehensive etiological work-up was performed. Viral hepatitis serologies (HBV, HCV) were negative. Autoimmune liver disease markers and iron/copper overload investigations were unremarkable. Thrombophilia screening did not reveal antiphospholipid syndrome, JAK2 mutation, protein C deficiency, or mutations of factor V Leiden or prothrombin gene (factor II).

However, biological assessment showed elevated plasma homocysteine levels associated with heterozygous MTHFR gene mutation.

Based on clinical, radiological, and biological findings, the diagnosis of Budd–Chiari syndrome secondary to a multifactorial prothrombotic state was established. The patient was started on oral anticoagulation therapy, with favorable clinical evolution marked by symptomatic improvement and stabilization.

DISCUSSION

Budd–Chiari syndrome (BCS) is a rare but potentially life-threatening vascular disorder resulting from obstruction of hepatic venous outflow at the level of the hepatic veins, inferior vena cava, or both. It is now well established that BCS is not a single-etiology disease but rather a clinical manifestation of multiple underlying conditions, most commonly prothrombotic disorders that predispose to venous thrombosis in the hepatic circulation. [1]

The pathogenesis of BCS is best understood within a multifactorial framework in which several acquired, genetic, and anatomical risk factors interact to produce hepatic venous obstruction. In most patients, a single isolated factor is insufficient to induce disease, and clinical expression generally occurs when multiple predisposing conditions coexist. This supports the concept of a “multi-hit” mechanism in which the cumulative burden of risk factors determines disease onset. [2]

Among acquired risk factors, estrogen-containing oral contraceptives are among the most frequently implicated triggers of venous thromboembolism in young women. These agents induce a prothrombotic state by increasing the synthesis of coagulation factors while simultaneously reducing natural anticoagulant activity and fibrinolysis. Although oral contraceptives alone rarely lead to Budd–Chiari syndrome, they may act as a critical triggering factor when combined with other underlying predispositions. [3]

Metabolic and genetic thrombophilic abnormalities also play an important role in the development of hepatic venous thrombosis. Hyperhomocysteinemia has been associated with endothelial dysfunction through mechanisms involving oxidative stress, impaired nitric oxide bioavailability, and direct vascular toxicity. These effects promote a prothrombotic environment that may facilitate venous occlusion in susceptible individuals. [4]

The methylenetetrahydrofolate reductase (MTHFR) gene is involved in homocysteine metabolism, and certain variants have been associated with elevated homocysteine levels. However, isolated heterozygous MTHFR mutations are generally not considered strong independent risk factors for thrombosis. Their clinical relevance becomes more significant when associated with documented hyperhomocysteinemia, suggesting that metabolic expression rather than genotype alone determines thrombotic risk. [1]

Inferior vena cava (IVC) stenosis represents another important anatomical contributor to Budd–Chiari syndrome. By causing chronic venous outflow obstruction, IVC narrowing promotes blood stasis, one of the key elements of Virchow's triad. This local hemodynamic disturbance facilitates thrombus formation and may also worsen the severity and extent of hepatic venous obstruction when superimposed on systemic prothrombotic conditions. [2]

In the present case, the coexistence of recent exposure to oral contraceptives, confirmed hyperhomocysteinemia, and IVC stenosis suggests a synergistic interaction between hormonal, metabolic, and anatomical risk factors. Rather than a single causative mechanism, the clinical presentation is best explained by the accumulation of multiple low-to-moderate risk factors acting together to surpass a thrombotic threshold. This pattern is consistent with the currently accepted multifactorial model of Budd–Chiari syndrome. [3]

This case further emphasizes the importance of a comprehensive etiological work-up in all patients diagnosed with Budd–Chiari syndrome. In addition to standard screening for myeloproliferative disorders and inherited thrombophilias, evaluation of metabolic factors such as homocysteine levels and detailed imaging of the inferior vena cava should be

systematically performed. Identifying potentially reversible or modifiable risk factors remains essential for both acute management and long-term prevention of recurrence. [4]

Anticoagulation remains the cornerstone of treatment in Budd–Chiari syndrome, aiming to prevent thrombus extension and promote partial or complete recanalization of the hepatic venous outflow tract. Early initiation of anticoagulant therapy is associated with improved outcomes and may reduce the need for invasive interventions in selected patients. [2]

CONCLUSION

Budd–Chiari syndrome should be considered a multifactorial disease resulting from the interaction of several prothrombotic risk factors. This case highlights the combined role of oral contraceptive exposure, hyperhomocysteinemia associated with MTHFR mutation, and inferior vena cava stenosis in the development of hepatic venous outflow obstruction. Early identification of these factors is essential for optimal management and prevention of recurrence.

FIGURES

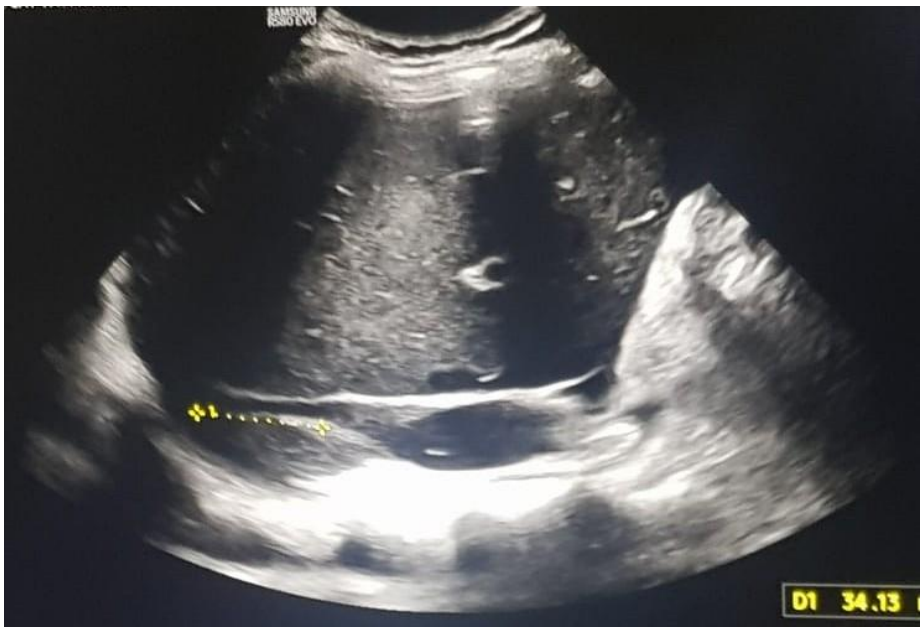

Figure 1 : Doppler ultrasound image showing stenosis of the retrohepatic inferior vena cava with impaired venous flow at the caval-hepatic junction.

ACKNOWLEDGEMENTS

The authors declare no conflict of interest

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