Radiology Case Reports 20 (2025) 1257–1262

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Behçet's disease and factor V Leiden: A thrombogenic synergy causing budd-chiari syndrome ☆,☆☆

Ameer Awashra[a,*], *Zaid Sawaftah*[a], *Salsabeel Bishawi*[a], *Aseel Eid*[a], *Aya Milhem*[a], *Dawoud Hamdan*[a], *Ali Bani Odah*[a], *Ahmad Sawafta*[a], *Jehad Khamaysa*[b], *Yazan Ghannam*[c], *Hadi Rabee*[d]

[a] *Department of Medicine, An Najah National University, Nablus, Palestine*
[b] *Department of Radiology, Tubas Turkish Governmental Hospital, Tubas, Palestine*
[c] *Department of Internal Medicine, Tubas Turkish Governmental Hospital, Tubas, Palestine*
[d] *Department of Internal Medicine, An Najah National University Hospital, Nablus, Palestine*

ARTICLE INFO

Article history:
Received 11 October 2024
Revised 7 November 2024
Accepted 13 November 2024

Keywords:
Budd chiari syndrome
Thrombosis
Behçet's disease

ABSTRACT

Behçet's Disease (BD) is a multisystem inflammatory disorder that can lead to severe vascular complications, including Budd-Chiari Syndrome (BCS), a rare but life-threatening condition characterized by hepatic vein obstruction. The co-occurrence of BD and inherited thrombophilia, such as Factor V Leiden mutation, significantly increases the risk of thrombosis, complicating the clinical management of affected individuals. In this case, a 16-year-old female initially presented with nonspecific symptoms of generalized fatigue and bone pain, which later progressed to abdominal distension and significant hepatosplenomegaly. Imaging and further diagnostic evaluation confirmed BCS as the initial manifestation of BD, a rare but severe complication. Genetic testing revealed a heterozygous mutation for Factor V Leiden and the presence of the HLA-B51 allele, highlighting a thrombogenic synergy between BD and inherited thrombophilia. Aggressive anticoagulation therapy was initiated, resulting in partial recanalization of the hepatic veins and stabilization of the patient's condition. This case emphasizes the need for early consideration of BCS in BD patients, especially in those with concurrent prothrombotic disorders, as timely intervention is crucial for improving clinical outcomes. The interplay of autoimmune and genetic factors in this case provides valuable insights into the complex pathophysiology and management of BCS associated with BD.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☆☆ Acknowledgments: We express our deep gratitude to the medical ward staff for their invaluable support in completing this report. No specific grant from funding agencies was received for this work.

* Corresponding author.
E-mail address: Ameer.Awashra7@gmail.com (A. Awashra).

https://doi.org/10.1016/j.radcr.2024.11.041

Introduction

Behçet's Disease (BD) is a chronic, relapsing condition of unknown cause that leads to inflammation of blood vessels [1]. It manifests through various symptoms, including eye inflammation (uveitis), mouth ulcers, skin lesions, and genital sores. While it can also affect the nervous, gastrointestinal, and vascular systems, these are less commonly involved [2]. BD impacts multiple organ systems because it affects arteries and veins of all sizes, leading to complications like an increased risk of thrombosis due to vascular inflammation [3]. A rare but serious complication of BD is Budd Chiari syndrome (BCS), which occurs in less than 5% of patients with vascular involvement and is more common in men (89.5%) [4].

BCS is characterized by the blockage of blood flow from the hepatic veins to the inferior vena cava [5]. It can be classified as primary BCS, caused by internal factors like vein stenosis due to thrombosis or phlebitis, or secondary BCS, caused by external compression from a lesion such as a malignancy [6]. BCS typically presents with symptoms like abdominal pain, ascites, and hepatomegaly [7]. The primary cause of hepatic vein obstruction in BCS is thrombosis, and most patients have an underlying condition that increases their tendency to form thrombosis. In 75% of cases, at least 1 hereditary or acquired hypercoagulable state, such as factor V Leiden, can be identified. Multiple factors may contribute to the condition in 25% of patients [8].

In our case, we describe a 16-year-old female presented with generalized fatigue and bone pain, which progressed to significant abdominal distension and hepatosplenomegaly, leading to a diagnosis of BCS. Genetic testing confirmed BCS as the initial manifestation of BD, with additional findings of a heterozygous Factor V Leiden mutation contributing to her thrombosis risk. She was treated with aggressive anticoagulation therapy, resulting in partial recanalization of hepatic veins and stable management of her condition, allowing her to maintain a good quality of life with ongoing monitoring.

Case presentation

A 16-year-old female with no significant past medical history began experiencing generalized fatigue and bone pain localized to her upper limbs, shoulders, and back. These symptoms persisted for approximately 2 months before she sought medical attention. Initially, her presentation was nonspecific, prompting consideration of a broad differential diagnosis that included viral infections, autoimmune conditions, and hematologic disorders. Despite visiting a private clinic where she was prescribed iron supplements and multivitamins, her symptoms did not improve, raising suspicion of an underlying chronic condition. Additionally, she reported a history of recurrent aphthous ulcers and genital ulcers, which had been intermittently present but were initially overlooked as minor issues.

Ten days after her initial consultation, the patient noticed increased abdominal girth and a sensation of fluid accumulation. However, she delayed seeking further medical advice. At the same time, her menstrual cycle was slightly delayed with reduced flow, which was initially overlooked but later understood to be part of the systemic manifestations of her condition. As her abdominal distension worsened, her family sought additional medical attention, leading to her referral for further evaluation.

A comprehensive assessment, including a PAN CT scan, revealed significant hepatosplenomegaly, a large volume of peritoneal ascites, and a nutmeg liver appearance. These findings suggested a serious underlying pathology, with the differential diagnosis including portal hypertension, congestive hepatopathy, and hepatic vascular obstruction. The scan also indicated diminished right hepatic vein opacification, raising significant concerns of hepatic vascular pathology and leading to a strong suspicion of BCS (see Fig. 1).

To further investigate the extent of her condition, 1700 cc of straw-colored ascitic fluid was drained. Analysis of the fluid revealed a low white blood cell count and negative culture re-

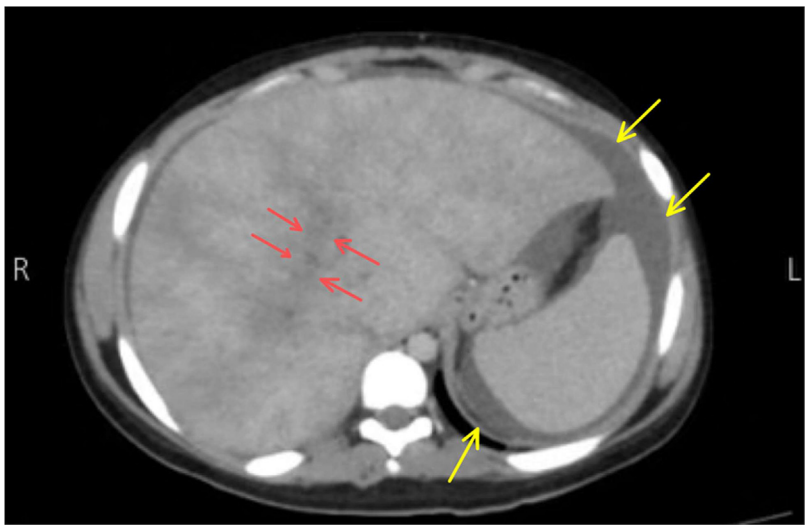

Fig. 1 – CT scan with contrast reveals an Occluded intrahepatic segment of the IVC and hepatic veins, which are relatively small in caliber (Red arrow), Large ascites (yellow arrow).

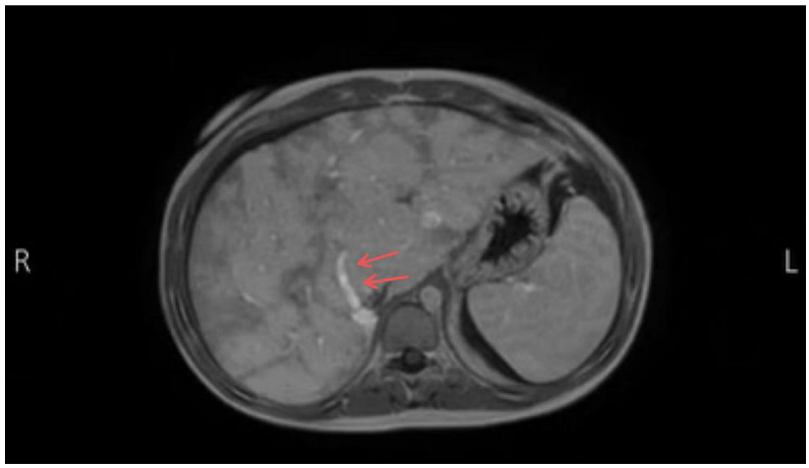

Fig. 2 – Liver MRI with contrast presents partial recanalization after long treatment by anticoagulant.

sults, consistent with noninfectious ascites. The absence of infection, coupled with imaging studies, confirmed the diagnosis of BCS. A subsequent MRI of the liver with IV contrast revealed no visible hepatic veins, confirming the chronic nature of BCS. The MRI also noted a significantly enlarged liver (21.5 cm) with heterogeneous parenchymal enhancement and an enlarged spleen (15.5 cm).

Further diagnostic evaluation, including genetic testing, confirmed that BCS was the initial manifestation of BD. The diagnosis was substantiated by the identification of the HLA-B51 allele, along with corresponding clinical findings, which collectively accounted for the hepatic complications observed in the patient. Additionally, a thrombophilia workup identified a heterozygous mutation for Factor V Leiden, further explaining the patient's predisposition to thrombosis. A positive pathergy test was later documented, further supporting the diagnosis of Behçet's disease (BD). This genetic mutation, combined with the vascular manifestations of BD (see Table 1), necessitated aggressive anticoagulation therapy.

The patient was initiated on enoxaparin 60 mg subcutaneously twice daily to address the thrombosis. In addition, propranolol was prescribed to manage portal hypertension, thereby reducing the risk of variceal bleeding. To further control fluid retention, spironolactone and furosemide were added to her regimen. Omeprazole was included as a prophylactic measure against gastrointestinal bleeding, a known risk associated with both portal hypertension and anticoagulation therapy.

Following this treatment plan, the patient required ongoing monitoring to ensure therapeutic efficacy and to manage any potential complications. This included regular INR monitoring, imaging studies, and gastrointestinal management, such as endoscopic evaluation to assess for varices. Notably, after prolonged anticoagulation therapy, follow-up imaging revealed partial recanalization of the hepatic veins and the intrahepatic segment of the IVC, indicating a positive response to treatment (see Fig. 2).

Throughout her follow-up, the patient's condition remained stable. She continued on anticoagulation therapy with regular INR monitoring to ensure therapeutic levels were maintained, preventing both clotting and bleeding complications. Despite the chronic nature of her condition, the patient maintained a good quality of life. The long-term management plan included continued anticoagulation therapy, regular imaging to monitor liver size and function, and close follow-up with hepatology and hematology specialists. Additionally, the patient was educated on the signs and symptoms of potential complications, such as gastrointestinal bleeding, which could necessitate urgent medical attention.

Table 1 – Results of thrombophilic genetic testing.

Genetic factor	Results
MTHFR (Ala1298Cys)	Heterozygous
Factor V Leiden (FV Arg506Gln)	Heterozygous
MTHFR (C677T)	Heterozygous
PAI-I 5G/4G	Heterozygous
MTRR (Ala66Gly)	Heterozygous

Discussion

BD, an auto-inflammatory systemic vasculitis of unknown cause, was first described by Hulusi Behçet who reported 3 cases with the triad of symptoms: aphthae, genital ulcers, and uveitis. Over time, other features were identified and added to the disease spectrum. BD is also referred to as "Silk Route disease" due to its geographic distribution in Mediterranean countries along the ancient trade routes that passed through these regions [9,10], as it is most prevalent in Turkey, with rates ranging from 80 to 370 cases per 100,000 people, while in countries such as Japan, Korea, China, Iran, Iraq, and Saudi Arabia, the prevalence ranges between 13.5 and 35 per 100,000. Outside the Silk Road region, immigrants and refugees from the Mediterranean countries are at an increased risk of developing the disease. In the U.S. and Europe, prevalence estimates range from 0.12 to 7.5 per 100,000. BD tends to affect males more in the eastern Mediterranean and females more in northern Eu-

Table 2 – Demonstrates the most common etiologies of BCS.

Etiology	Notes
Myeloproliferative Disorders (MPD)	The leading cause of BCS. This occurs due to the associated hypercoagulability. Polycythemia vera constitutes 10%-40% of MPD-related cases, while essential thrombocythemia and myelofibrosis are fewer common contributors [6,8].
Malignancy	Responsible for 10% of cases. The mechanism can be direct, through vessel compression or invasion, or indirect by inducing hypercoagulability. The most common cancer associated with BCS is hepatocellular carcinoma [6].
Pregnancy and oral contraceptives' use	By inducing hypercoagulability, they account for 20% of BCS cases [6].
Liver lesions	These space-occupying conditions compress the vasculature directly resulting in obstructive BCS. Such lesions include hepatic cysts, adenomas, amoebic and pyogenic liver abscesses [6,8].
Inherited thrombophilia	These include deficiencies in protein C, protein S, and antithrombin III, as well as the Factor V Leiden (FVL) mutation. The FVL mutation is the most prevalent among them [8].
Idiopathic	20% of cases are idiopathic [6].

rope [11–13]. The patient in our case is from Tamoun, Palestine, which lies in the Mediterranean area, making her more susceptible to the disease.

BCS is the obstruction of hepatic venous outflow anywhere along the venous system connecting the hepatic venules to the inferior cavoatrial junction. This condition is uncommon, with a prevalence of one in a million. BCS may be caused by thrombotic or nonthrombotic events, with the latter being more common. Most cases of BCS have underlying hypercoagulable conditions with at least 1 inherited or acquired blood clotting disorder identified [8]. The following table shows the most common etiologies of BCS (See Table 2):

Over 8 years, a study was conducted on 493 patients with BD to investigate the incidence of BCS and its impact on the disease progression. The findings revealed that BCS is a common complication in people with BD, contributing to a poorer clinical prognosis [14]. Furthermore, a multicenter European survey identified BD as the primary cause of BCS in less than 5% of cases. However, in regions where BD is more common, such as Turkey, studies report a higher frequency, with BD accounting for 9-13% of BCS cases [15]. In general, BCS is a relatively frequent complication of BD with an incidence of 0.3% to 26% [16] it increases the mortality rate up to 61% in BD patients [17].

Several potential mechanisms have been proposed for the development of BCS in patients with BD, including endothelial dysfunction, Factor V Leiden (FVL) mutation, protein C and S deficiencies, and impaired fibrinolysis [18]. FVL mutation, where factor V in the coagulation pathway becomes resistant to inhibition by natural anticoagulants, has been found responsible for nearly 38% of the genetic defects linked to venous thrombosis in BD, increasing its risk sixfold [19]. Regarding the BD patient presented in our case, a heterozygous change in the FVL gene was detected. This combination of prothrombotic conditions is believed to be the cause of the patient's development of BSC.

BCS is often underdiagnosed due to its varied clinical presentations, which can range from asymptomatic to acute, chronic, or fulminant forms [20]. Most patients with BCS, however, present with symptoms such as fever, hypertension, abdominal pain, ascites, abdominal distention, liver failure, gastrointestinal bleeding, lower extremity edema, and encephalopathy. These symptoms are generally linked to the rate of the underlying obstructive process. In managing cases with abdominal pain, it is critical to exclude common and rare causes, including conditions such as focal necrosis of the falciform ligament, and spontaneous angiomyolipoma rupture, which can present with similar clinical features. This comprehensive approach ensures a more accurate diagnosis and targeted treatment [21–26].

A crucial step in diagnosing BCS is to consider it in patients who present with fulminant liver failure accompanied by sudden onset of ascites and hepatomegaly, severe ascites with relatively preserved liver function or a known thrombogenic disorder presenting with liver disease [25]. The diagnosis is confirmed by identifying obstruction in the hepatic venous outflow tract using imaging methods such as conventional and Doppler ultrasound, MRI, CT, and catheter venography [20,22]. Furthermore, BCS is classified into 3 types based on the location of the obstruction: Type I involves the inferior vena cava (IVC), Type II affects the hepatic veins, and Type III is a mixed type [21].

In terms of management, the initial approach typically involves medical treatment, including anticoagulation therapy, to control clinical outcomes. However, its effectiveness can be limited; thus, many patients will require interventional procedures during follow-up [25,27]. The choice of intervention depends on the length of the obstructed segment and the degree of occlusion. For short-segment stenosis (less than 4 cm) of the IVC or hepatic veins, angioplasty with or without stent placement is preferred to restore blood flow. Conversely, in cases of long-segment thrombotic occlusion of the hepatic veins, which is more severe, a transjugular intrahepatic portosystemic shunt (TIPS) may be necessary to alleviate congestion. If these treatments fail, liver transplantation might be required [27].

In a specific study, treatment options for BD-associated BCS included immunosuppressive agents and corticosteroids as central components of the therapeutic strategy. For BCS caused by other factors, the study emphasized that treatment generally involves a combination of anticoagulants and surgical interventions [15]. Another study proposed an algorithm for managing BD-associated BCS. For uncomplicated cases, corticosteroids and immunosuppressants are recommended as first-line treatments. In cases complicated by refractory thrombosis, anticoagulants may be added. If refractory portal hypertension persists despite medical therapy, a transjugular intrahepatic portosystemic shunt (TIPS) can be employed. If

TIPS fails or in cases of hepatic failure, liver transplantation is considered the final option [28].

The prognosis for BCS is influenced by factors such as the extent of liver damage and the effectiveness of treatment. Recent data reveal a 5-year survival rate exceeding 80% [29]. Early and accurate diagnosis, coupled with prompt intervention, can result in favorable outcomes, especially in acute cases [22]. In contrast, chronic BCS often presents with more variable prognoses; however, patients who respond effectively to medical management or interventions such as TIPS tend to fare better. Liver transplantation remains a viable option for patients with end-stage liver disease, though its success is contingent upon the pretransplant liver condition and the presence of comorbidities [21,22]. Consequently, diligent monitoring and adherence to lifestyle modifications are essential for optimizing long-term management and improving overall outcomes [22].

Conclusion

This case exemplifies the complex interplay between genetic factors and autoimmune conditions, specifically how the combination of Factor V Leiden mutation and BD led to the development of BCS in an adolescent patient. The early onset of BCS underscores the importance of vigilant monitoring and prompt diagnosis, especially in regions with high BD prevalence. The successful management through targeted anticoagulation therapy and comprehensive long-term follow-up highlights the need for personalized treatment strategies. This case also emphasizes the importance of considering genetic predispositions in the diagnostic process and demonstrates the value of an integrated, multidisciplinary approach to patient care, ultimately leading to a favorable outcome and improved long-term prognosis.

Patient consent

Written informed consent was obtained from the patient's Herself for her anonymized information to be published in this article

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

REFERENCES

[1] Nair JR, Moots RJ. Behcet's disease. Clin Med 2017;17(1):71–77.

[2] Takeno M. Positioning of apremilast in treatment of Behçet's disease. Mod Rheumatol 2020;30(2):219–24.

[3] Oblitas CMA, Galeano-Valle F, Toledo-Samaniego N, Pinilla-Llorente B, Del Toro-Cervera J, Álvarez-Luque A, et al. Budd-Chiari Syndrome in Behçet's Disease successfully managed with immunosuppressive and anticoagulant therapy: a case report and literature review. Intractable Rare Dis Res 2019;8(1):60–6.

[4] Carvalho D, Oikawa F, Matsuda NM, Yamada AT. Budd-Chiari syndrome in association with Behçet's disease: review of the literature. Sao Paulo Med J 2011;129(2):107–9.

[5] Elhence A, Gamanagatti S, Das P, Shalimar. Budd Chiari Syndrome and intrahepatic cholangiocarcinoma, an unusual combination: case report and review of the literature. Perm J 2020;24:1–3.

[6] Hitawala AA, Gupta V. Budd-Chiari Syndrome. StatPearls, Treasure Island (FL): StatPearls Publishing; 2024. [Accessed September 12, 2024]. Available from http://www.ncbi.nlm.nih.gov/books/NBK558941/ .

[7] Goel RM, Johnston EL, Patel KV, Wong T. Budd-Chiari syndrome: investigation, treatment and outcomes. Postgrad Med J 2015;91(1082):692–7.

[8] Aydinli M, Bayraktar Y. Budd-Chiari syndrome: etiology, pathogenesis and diagnosis. World J Gastroenterol 2007;13(19):2693–6.

[9] Bani Odah A, Awashra A, Sawaftah Z, et al. Diagnosing Behçet's disease in the presence of pulmonary artery aneurysm and systemic symptoms: a case report. SAGE Open Med Case Rep 2024;12:2050313X241282383. doi:10.1177/2050313X241282383.

[10] Adil A, Goyal A, Quint JM. Behcet disease. StatPearls, Treasure Island (FL): StatPearls Publishing; 2024. [Accessed September 12, 2024]. Available from http://www.ncbi.nlm.nih.gov/books/NBK470257/ .

[11] Feigenbaum A. Description of Behçet's syndrome in the hippocratic third book of endemic diseases. Br J Ophthalmol 1956;40(6):355–7.

[12] Mahr A, Maldini C. Epidemiology of Behçet's disease. Rev Med Inter 2014;35(2):81–9.

[13] Yurdakul S, Hamuryudan V, Yazici H. Behçet syndrome. Curr Opin Rheumatol 2004;16(1):38–42.

[14] Bayraktar Y, Balkanci F, Bayraktar M, Calguneri M. Budd-Chiari syndrome: a common complication of Behçet's disease. Am J Gastroenterol 1997;92(5):858–62.

[15] Seyahi E, Caglar E, Ugurlu S, Kantarci F, Hamuryudan V, Sonsuz A, et al. An outcome survey of 43 patients with Budd-Chiari syndrome due to Behçet's syndrome followed up at a single, dedicated center. Semin Arthritis Rheum 2015;44(5):602–9.

[16] Allaoui A, Echchilali K, Fares M, Belabbes FZ, Jabbouri R, Naitlho A, et al. Budd–Chiari syndrome associated to Behcet disease: an observational retrospective multicenter study in Morocco. Medicine (Baltimore) 2022;101(44):e31308.

[17] Orloff LA, Orloff MJ. Budd-Chiari syndrome caused by Behçet's disease: treatment by side-to-side portacaval shunt. J Am Coll Surg 1999;188(4):396–407.

[18] Korkmaz C, Kasifoglu T, Kebapçı M. Budd–Chiari syndrome in the course of Behcet's disease: clinical and laboratory analysis of four cases. Joint Bone Spine 2007;74(3):245–8.

[19] Gül A, Ozbek U, Oztürk C, Inanç M, Koniçe M, Ozçelik T. Coagulation factor V gene mutation increases the risk of venous thrombosis in behçet's disease. Br J Rheumatol 1996;35(11):1178–80.

[20] Sharma A, Keshava SN, Eapen A, Elias E, Eapen CE. An update on the management of Budd-Chiari Syndrome. Dig Dis Sci 2021;66(6):1780–90.

[21] Ferral H, Behrens G, Lopera J. Budd-Chiari syndrome. AJR Am J Roentgenol 2012;199(4):737–45.

[22] Martens P, Nevens F. Budd-Chiari syndrome. United European Gastroenterol J 2015;3(6):489–500.

[23] Awashra A, Sawaftah Z, Odah AB, et al. Spontaneous splenic rupture as a primary manifestation of angiosarcoma: a case report. J Surg Case Rep 2024;2024(10):rjae633. doi:10.1093/jscr/rjae633.
[24] Awashra A, Sawaftah Z, Milhem F, et al. Spontaneous angiomyolipoma rupture: a case of hemorrhagic shock and urgent embolization. Radiol Case Rep 2024;19(12):6286–91. doi:10.1016/j.radcr.2024.09.034.
[25] Awashra A, Nouri A, Hamdan D, Rabee H. Focal necrosis of the falciform ligament as a rare cause of abdominal pain: a case report. SAGE Open Med Case Rep 2024;12:2050313X241252738. doi:10.1177/2050313X241252738.
[26] Shakhshir A, Dweekat MZ, Awashra A, et al. Dramatic devastative complications in a patient with catastrophic antiphospholipid syndrome: a case report and literature review. SAGE Open Med Case Rep 2024;12:2050313X241272678. doi:10.1177/2050313X241272678.
[27] Rössle M. Interventional treatment of Budd-Chiari Syndrome. Diagnostics (Basel) 2023;13(8):1458.
[28] Oblitas CM, Toledo-Samaniego N, Fernández-Yunquera A, Díaz-Fontenla F, Galeano-Valle F, Del-Toro-Cervera J, et al. Chronic Budd-Chiari syndrome in Behçet's disease successfully managed with transjugular intrahepatic portosystemic shunt: a case report and literature review. Clin J Gastroenterol 2020;13(4):572–8.
[29] Plessier A. Budd-Chiari syndrome. Rev Med Interne 2013;34(12):741–5.