

ТРОМБОФИЛИЯ ПРИ ПАЦИЕНТ СЪС СИНДРОМ НА БЪД-КИАРИ

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THROMBOPHILIA IN BUDD-CHIARI SYNDROME PATIENT

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Abstract.

A 27-years old female patient presented with a severe general condition of generalized edema and hypotension. Two months earlier computed tomography imaged thrombosis of the inferior vena cava and the three hepatic veins, or Budd-Chiari syndrome (BCS). Additional findings were thrombosis of the right common iliac vein and thrombosis of the renal veins bilaterally. Genetic testing proved congenital thrombophilia. Anticoagulation therapy did not affect thrombotic occlusions. In another cardiovascular center, an unsuccessful attempt for interventional treatment of the inferior vena cava with a jugular approach was made. The patient was admitted to our hospital for further evaluation and decision on treatment strategy. Laboratory and non-invasive imaging at admission rejected hepatic cirrhosis. An abdominal ultrasound scan demonstrated complete occlusion of the three hepatic veins and post hepatic portal hypertension. When thrombosis of all hepatic veins was detected transjugular intrahepatic portosystemic shunt (TIPS) was an option. An endovascular strategy for inferior vena cava was undertaken and complete revascularization was achieved with the right femoral approach as a bridge to TIPS shunt procedure, since the patient didn't meet the criteria for liver transplantation. In diagnosing disease, the main contributors were the gastroenterologist, diagnostic imaging specialist, and hematologist, while the multidisciplinary team included also cardiologist, interventional cardiologist, and angiologist. In this case the multidisciplinary decisions played a major role in diagnosing and building an appropriate therapeutic strategy for systemic illnesses and conditions for which medical guidance does not yet have clear guidelines.

Key words:

thrombophilia, Budd-Chiari syndrome, vein thrombosis, revascularization, multidisciplinary strategy

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Резюме.

Жена на 27 г. се презентира при кардиологичен преглед в тежко общо състояние с генерализирани отоци и артериална хипотония. При проведена преди 2 месеца компютърна томография с контраст се установява тромбоза на долна празна вена и на трите чернодробни вени, или синдром на Бъд-Киари. Допълнителни находки от образното изследване са тромбоза на дясна обща хълбочна вена и тромбоза на бъбречни вени двустранно. Генетични изследвания доказват вродена тромбофилия. Започнатата антикоагулантна терапия не повлиява тромботичните оклузии. При предходна хоспитализация в друг сърдечно-съдов център е проведен неуспешен опит за ендоваскуларна реканализация на долна празна вена чрез югуларен достъп. Пациентката бе хоспитализирана в нашето лечебно заведение за последваща оценка и изграждане на терапевтична стратегия. Лабораторните и неинвазивните изследвания отхвърлиха чернодробна цирроза. Ултразвук на кореман отдел установи пълна оклузия на трите чернодробни вени и постхепатална портална хипертония. При установяване на тромбоза на всички чернодробни вени възможен терапевтичен метод беше трансюгуларен интрахепатален портосистемен шънт (ТИПС). Предприе се ендоваскуларна ревакуларизация на долна празна вена с пълно възстановяване на кръвотока дистално чрез десен феморален достъп, като мост към последваща ТИПС процедура, тъй като при пациента отсъстват индикации за чернодробна трансплантация. Основен принос за поставяне на диагнозата имаха: гастроентерологът, специалистът по образна диагностика и хематологът, докато към мултидисциплинарния екип, участващ в изграждане на терапевтичния алгоритъм, бяха включени още кардиолог, инвазивен кардиолог и ангиолог. В представения случай решенията на мултидисциплинарния екип бяха в основата както на диагностицирането, така и на изграждането на подходяща терапевтична стратегия при усложнение на системно заболяване, за което не съществуват общоприети ръководства за поведение.

Ключови думи:

тромбофилия, синдром на Бъд-Киари, венозна тромбоза, ревакуларизация, мултидисциплинарна стратегия

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INTRODUCTION

The BCS is characterized by an obstruction (thrombotic or non-thrombotic) of the hepatic venous outflow tract at a different level – the hepatic venules, veins, inferior vena cava (IVC) or a combination of hepatic veins (HV) and IVC block, as isolated IVC obstruction, is relatively low [1].

Different conditions (congenital conditions, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, pregnancy, oral contraceptive intake, anti-phospholipid antibody, malignancy, etc.) could lead to BCS-ranging from hypercoagulable states to malignancies [2- 5]. In primary BCS patients most recently have an underlying thrombophilic disorder – inherited (protein C, protein S, antithrombin III deficiencies or factor V Leiden mutation), or acquired (myeloproliferative disorders). In a study including 45 patients, it was established that the most common reason for thrombosis in primary BCS was a protein C deficiency, followed by a deficit of Protein S and antithrombin III [6]. It concluded that congenital thrombophilia was a major causal factor of BCS. Positive family history also confirms their hereditary etiology [7]. No underlying condition is found in up to 25% of patients [2, 5].

The hepatic vein thrombosis finally leads to end-organ dysfunction of the liver. Due to hepatic venous outflow obstruction, there is an increase in hepatic sinusoidal pressure resulting in portal hypertension and liver congestion. Hypoxia and hepatocyte dysfunction if not corrected in timely leads to hepatic fibrosis and cirrhosis [2, 8, 9]. The venous system obstruction reflects in increased filtration of vascular fluid and forming of ascites, due to increased portal vein and hepatic sinusoid pressures. The venous flow passes through collateral veins leading to esophageal, gastric, and rectal varicosis.

Clinical presentation of BCS varies from asymptomatic to symptomatic including acute, subacute, chronic, or fulminant forms. Classical signs include an abdominal pain, hepatomegaly and ascites, pedal edema, jaundice, splenomegaly, gastrointestinal bleeding, and hepatic encephalopathy.

BCS could be classified based on the etiology, the site of obstruction, and the duration of the disease. According to etiology, it divides into primary (obstruction due to endoluminal venous lesion – thrombosis, webs, endophlebitis), and secondary (lesion outside venous system-tumor, abscess, cyst). Differentiation of acute, subacute, and chronic is mainly based on clinical features [2, 10, 11].

A diversity of endovascular interventions is available (angioplasty, stenting, catheter-directed thrombolysis, and creation of TIPS shunt) [2, 12, 13]. If all hepatic veins are occluded, TIPS shunt may be consid-

ered because angioplasty and stenting are not feasible [14]. TIPS has been extensively studied and found to be effective in patients with chronic BCS [15, 16].

One study in a STROBE-compliant article included 60 BCS patients demonstrating that percutaneous transhepatic balloon angioplasty (PTBA) and TIPS shunt are possible strategies for the treatment of BCS with hepatic veins involvement. The success rates in the PTBA Group were 93.9% compared with 100% in the TIPS shunt Group. It reports an excellent long-term patency rate of hepatic vein and TIPS shunt [17].

CASE REPORT

a 27-years old female patient presented with clinical manifestations of easy fatigue and dyspnea, a significant increase in body weight with abdominal pain, and lower limb swelling. She had a normal childhood and has no family history of thrombophilia. Over the past few years, she experienced abrupt diet changes with a weight loss of about 30 kg.

Two months earlier a contrast computed tomography (CT) demonstrated multiple venous thrombi affecting the IVC, the three hepatic veins but with the intact portal vein. Then vitamin K antagonist therapy was started.

A rheumatologist and hematologist consults provided and rejected systemic rheumatic illness and hematological disease. Genetic studies for thrombophilia demonstrated that the patient is a homozygote on the mutant allele of plasminogen activator inhibitor (PAI) and methylenetetrahydrofolate reductase (MTHFR) mutation. Gastroscopy showed a high-grade esophageal varicosis with increased potential bleeding risk. When the other etiologic causes were rejected, the most likely diagnosis of BCS was thrombophilia.

One month later CT scan didn't show positive dynamics in established thrombotic findings. Then an unsuccessful attempt at hepatic veins interventional revascularization occurred when the vascular approach was the right jugular vein.

Physical examination and admission demonstrated poor general condition, no fever, pale skin, normal pulmonary status, regular rhythm, accelerated pulse, and arterial hypotension. The abdomen was distended with spider angiomas of the abdominal wall skin, enlarged liver size, peritoneal "splashing" and cold pale swelling of the lower limbs.

Electrocardiography showed sinus rhythm and normal repolarization. Laboratory tests emphasized anemic syndrome, thrombocytopenia, hypoproteinemia and hypoalbuminemia, and hyperbilirubinemia in favor of the direct fraction. Echocardiography presented a preserved systolic and diastolic LV function, reduced dimensions of the right ventricular

cavity (Figure 1), and non-significant pericardial effusion. Doppler ultrasound demonstrated occlusion of the right common iliac vein and inferior vena cava. An abdominal ultrasound scan concluded: complete occlusion of the hepatic veins, post hepatic portal hypertension, cavo-caval anastomosis, varicosis, and ascites. We rejected a membranous occlusion. Radiography excluded the availability of pleural effusions.

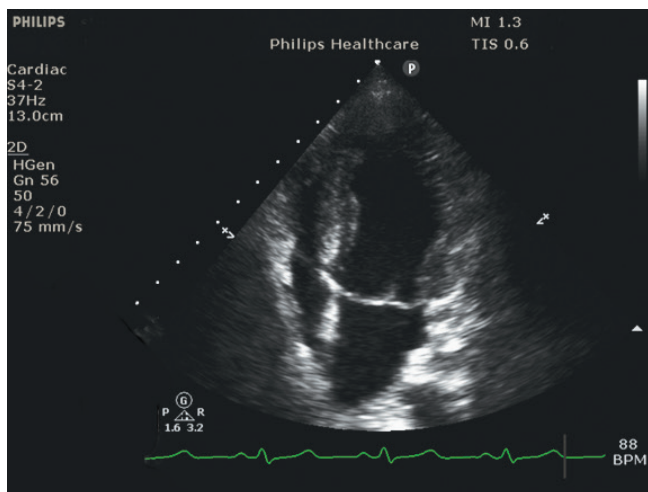


Figure 1. Echocardiography presented a preserved systolic and diastolic LV function, reduced dimensions of the right ventricular cavity.

Therapeutic options

There are many therapeutic approaches to treating IVC thrombosis. A stepwise management strategy includes anticoagulation, angioplasty, TIPS and LT. The initial treatment includes anticoagulation with vitamin K antagonists and thrombolytic agents administered either through a peripheral intravenous or catheter-mediated route. In patients with short-length stenosis, they could be followed by balloon angioplasty/stenting. The next step is TIPS, while liver transplantation (LT) is the ultimate rescue option [18, 19, 20-24].

Surgical shunts and LT are also methods of treatment of BCS with thrombosis, but they could be complicated with bleeding and pulmonary embolism. No guidance is available for the selection of these methods for use in patients with BCS combined with IVC thrombosis [25-26].

LT may be the treatment of choice in patients with unsuccessful TIPS shunt, fulminant liver failure and those with highly advanced liver cirrhosis [27].

In our patient, two months of treatment with vitamin K antagonists didn't show positive CT dynamics in established thrombotic findings. For initial treatment, we used unfractionated heparin in controlling APTT levels. Then we chose an interventional strategy for IVC revascularization.

Interventional procedure

Complete revascularization of the IVC was the interventional strategy. The left femoral approach was the single option, because of obstructions at the level of IVC and the right common iliac vein. The occlusion of IVC was overcome through a microcatheter. Several balloon dilatations were performed. Residual stenosis required stents implantation. The procedure consisted in overlapping the proximal segment of IVC to the femoral vein with stent-grafts. The patient was referred to the creation of TIPS as a bridge to liver transplantation because she didn't meet the criteria for LT.

Resulting complications

Febrile episode, laboratory testing with leukocytosis and elevated markers of inflammation, negative blood culture, which required an antibiotic treatment.

The echo-Doppler with small arterio-venous shunt (Figure 2) at the puncture site between the common femoral vein and the arterial branch of the common femoral artery without hematoma or false aneurysm.

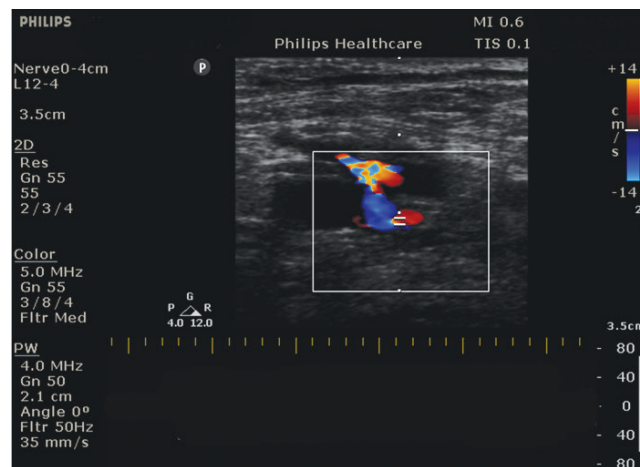


Figure 2. The echo-Doppler with small arterio-venous shunt at the puncture site between the common femoral vein and the arterial branch of the common femoral artery

The recommendation of a vascular surgeon was strict follow-up rejecting the need for revision of the puncture site at that moment.

Medication therapy included mono-antiplatelet therapy, vitamin K antagonist, mineralocorticoid receptor antagonist, a loop diuretic, proton pump inhibitor, beta-blocker – propranolol, antibiotic and probiotic.

DISCUSSION

This clinical case described the role of a multidisciplinary approach in diagnosing and selecting an appropriate therapeutic strategy for rare systemic illnesses.

In our patient, there was a combination of two diseases that are interrelated. The first one – congenital thrombophilia caused the second one – BCS. The genetic screening demonstrated PAI and MTHFR mutations although they were not among the most common ones in thrombophilia and BCS-associated patients.

Several prognostic indices were evaluated to predict outcomes for patients with BCS such as the Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) score [28-29].

According to CTP classification, the patient referred to Class B (moderately severe liver disease). And also used the MELD score, which for our patient was 25 points. Patients with MELD scores above 24, who are liver transplant candidates were probably best served by foregoing TIPS placement [30]. But a sign of transplantation in patients with BCS includes established cirrhosis and acute decompensation. However, we provided a transplant surgeon consultation, which concluded that the patient does not meet the full criteria for performing liver transplantation.

Recently, an expert panel advocated a treating stepwise approach:

1. Anticoagulation,
2. Angioplasty and stenting,
3. TIPS or surgical shunt, and
4. Liver transplantation [31].

A European report [32] revealed that this stepwise management has improved the 5-year patient survival to 72% and transplant-free survival to 72%.

Low molecular weight heparin for the initiation of anticoagulation therapy and subsequent long-term anticoagulation with vitamin K antagonist to achieve an international normalized ratio for prothrombin time of 2.0 to 2.5 are recommended [31]. Anticoagulation therapy with vitamin K antagonists was performed on our patient but it didn't affect the thrombotic lesions.

Acute BCS may be effectively treated by catheter-directed thrombolytic therapy, angioplasty, and stent placement. Thrombolytic therapy is considered for patients with the acute form of BCS and especially in rare situations where angiography reveals a fresh thrombus [33]. Unfortunately, however, angioplasty in combination with anticoagulation therapy was reported to successfully control BCS in only 20-30% of patients, at least in reports from Western countries where hepatic vein thrombosis predominates [34]. In our patient fibrinolytic therapy was contraindicated due to bleeding diathesis (thrombophilia) and spontaneous INR > 2 owing to hepatic insufficiency.

The next recommended step in management is TIPS [33]. It is a salvage therapeutic option for the acute forms of BCS who failed to respond to thrombolytic therapy [31-32]. Compared to an open surgical shunt, TIPS shunt is associated with lower morbidity and mortality [35-36], but its drawback is frequent shunt occlusions requiring repeated interventions. The development of covered stents, however, has significantly improved the patency of TIPS shunt in BCS [37, 38]. The evidence is showing the impact of the TIPS procedure on patient survival demonstrated that it is preferred as the first choice for safe and optimal decompression [33].

A surgical portosystemic shunt is recommended for the subacute form of BCS, associated with a favorable long-term outcome, preserved liver function, and hepatic necrosis, consisting of a liver biopsy [39].

LEARNING POINTS/TAKE-HOME MESSAGES

When treating a patient, it is necessary to assess the benefit, as well as the risk of the chosen treatment strategy. The final aim is to extend the life while improving its quality. At the same time, we need to consider the implementation of all healing strategies over time. With our hybrid approach, including endovascular treatment with stenting, we created a bridge for TIPS shunt procedure. A multidisciplinary team played a major role in diagnosing and building an appropriate therapeutic strategy for systemic illnesses and conditions for which medical guidance does not yet have clear guidelines.

No conflict of interest was declared

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