CASE REPORT

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Conservative short-term treatment of non-cirrhotic and non-malignant portal vein thrombosis

Kratkotrajno konzervativno lečenje bolesnika sa trombozom vene porte bez maligniteta i ciroze

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Abstract

Introduction. Portal vein (PV) thrombosis (PVT) is a partial or complete obstruction of blood flow as a result of a thrombus mass in the lumen of PV. In the acute phase, the symptoms such as right upper quadrant pain, nausea, and fever are unspecific. A diversity of subacute and chronic symptoms is associated with complications related to PVT and portal hypertension. **Case report.** A 50-year-old female was admitted to the hospital due to acute abdominal cramping pain. The pain lasted for 15 to 20 min and was followed by defecation of normal stool and hematochezia on three occasions. The abdominal pain recurred after several hours, again followed by hematochezia and tenesmus every 10 min. After admission, a colonoscopy was performed, and it revealed vulnerable, erythematous mucosa of the colon with contact bleeding from the lienal flexure to the rectosigmoid junction. During the colonoscopy, a biopsy was performed. A computed tomography (CT) scan revealed partial PVT of intrahepatic branches of PV, and thrombosis of the inferior mesenteric vein. After conservative treatment with low molecular weight heparin (LMWH) and other supportive measures, the digestive bleeding ceased, and defecation became normal. During the one-month follow-up, the patient had no complications, and the control CT scan revealed normal PV flow without thrombosis. **Conclusion.** Although rare, a non-malignant and non-cirrhotic PVT should not be neglected in the differential diagnosis because timely and vigilant therapy with LMWH can lead to complete resolution without serious complications.

Key words:
diagnosis, differential; diagnostic techniques and procedures; heparin, low-molecular-weight; liver; treatment outcome; venous thrombosis.

Apstrakt

Uvod. Tromboza vene porte (TVP) je delimična ili potpuna opstrukcija protoka krvi, nastala kao rezultat prisustva trombne mase u lumenu portalne vene (PV). U akutnoj fazi, simptomi kao što su bol u desnom gornjem kvadrantu, mučnina i groznica, nespecifični su. Raznolikost subakutnih i hroničnih simptoma povezana je sa komplikacijama vezanim za TVP i portalnu hipertenziju. **Prikaz bolesnika.** Žena starosti 50 godina, primljena je u bolnicu zbog akutnih bolova u stomaku u vidu grčeva. Bol je trajao od 15 do 20 min, nakon čega je usledila defekacija normalne stolice i hematohezija u tri navrata. Bol u stomaku se ponovio kroz nekoliko sati, nakon čega su ponovo usledili hematohezija i tenezmi, svakih 10 min. Nakon prijema, urađena je kolonoskopija pomoću koje je otkrivena vulnerabilna, eritematozna sluznica debelog creva, sa kontaktnim krvarenjem u dužini od lijenalne fleksure do rektosigmoidnog prelaza. Tokom kolonoskopije urađena je i biopsija. Primenom kompjuterizovane tomografije (KT) otkrivena je parcijalna TVP, tromboza intrahepatičnih grana PV i tromboza donje mezenterične vene. Nakon konzervativnog lečenja niskomolekularnim heparinom (NMH) i drugom suportivnom terapijom, krvarenje u digestivnom traktu je prestalo, a defekacija je postala normalna. Tokom mesec dana praćenja, bolesnica nije imala komplikacija, a kontrolni pregled KT pokazao je normalan protok kroz PV, bez tromboze. **Zaključak.** Iako je retka, TVP kod bolesnika bez maligniteta i ciroze ne treba da se zanemari u diferencijalnoj dijagnozi, jer pravovremena i adekvatna terapija NMH može dovesti do potpunog izlečenja, bez teških komplikacija.

Ključne reči:
dijagnoza, diferencijalna; dijagnostičke tehnike i procedure; heparin, niskomolekulski; jetra; lečenje, ishod; tromboza, venska.

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Introduction

Portal vein (PV) thrombosis (PVT) is a partial or complete obstruction of blood flow as a result of a thrombus mass in the lumen of the portal vein (PV) [1]. In the morphological definition of PVT, it is more concise to define it as thrombosis of all or parts of the portal venous system, which includes the lienal vein, superior mesenteric vein, and inferior mesenteric vein (IMV), or extrahepatic and intrahepatic parts of PV and its branches.

The frequency of thrombosis of separate segments varies, but the most common one is the thrombosis of the PV itself (40%), followed by multiple vein thrombosis (38.5%), mesenteric vein thrombosis (9%), splenic vein thrombosis (7.5%), and hepatic vein thrombosis (5%) [2, 3].

Clinical presentation of PVT is diverse, depending on whether it is acute or chronic, complete or partial, and which part of the portal venous system is afflicted. Clinical features may range from asymptomatic to major complications with high morbidity and mortality rates. Complications of PVT are the results of consecutive portal hypertension [2, 4, 5] or are related to intestinal infarction [2, 6].

The symptoms of an acute PVT include persistent severe abdominal or lumbar pain associated with systemic inflammatory response syndrome, fever, general malaise, organ failure, metabolic acidosis, abundant ascites, rectal bleeding, abdominal contracture, nausea, postprandial fullness, intestinal infarction [7, 8]. The most common laboratory findings in PVT diagnosis are the slightly lowered prothrombin time and coagulation factors, while the D-dimer is elevated [9, 10]. PVT has a global incidence of 0.05–0.5% [11], and the most common causes are malignancies, progressive chronic liver diseases, processes localized to the epigastrium and hepatobiliary system, and acquired as well as inherited thrombophilia [12]. According to the etiological characteristics of PVT causes, there are three main categories: malignant PVT, cirrhotic PVT, and non-malignant and non-cirrhotic PVT [12]. PVT in non-cirrhotic and non-malignant individuals is rare. It can occur in the setting of abdominal inflammatory processes such as pancreatitis, infections, inflammatory bowel diseases, and after abdominal surgeries. In the absence of mentioned states, PVT may also occur; however, underlying causes may be found, such as clotting factor deficiencies, malignancy, or AIDS. In the absence of known factors possible for PVT occurrence, the prognosis and treatment are mainly empirically orientated. Literature is very sparse regarding this group of PVT, especially in those with "idiopathic" PVT, and there are no randomized controlled trials.

Case report

A 50-year-old female was admitted to the hospital with acute abdominal cramping pain that spread diffusely after an initial physical examination. The pain itself lasted for 15 to 20 min and was followed by defecation of a harder consistency stool with hematochezia afterward on three occasions. The abdominal pain returned in several hours, again followed by hematochezia and tenesmus every 10 min.

The patient reported similar abdominal pain followed by defecation on several occasions 20 years ago when a colonoscopy was performed without any pathological findings. She was not on hormone replacement therapy. She stated that she had never had abdominal surgery.

On physical examination, the abdomen was painless and soft, with normal peristalsis on auscultation. Laboratory findings on admission showed elevated D-dimer of 23 μg/mL [reference range (RR): 0.22–0.46 μg/mL], leucocyte count of 12.2×10^9/L (RR: $4.5–11.0 \times 10^9$/L) and sedimentation rate of 18/45 mm/hr (RR: 20/25 mm/hr). Other biochemical parameters in serum, including protein C (125%), antithrombin III (74%), and coagulation factors, were in RR. The patient was tested for influenza virus, human immunodeficiency virus, hepatitis B and C virus, herpes simplex virus, and cytomegalovirus, and the results of acute viral infection were negative. Immunological analysis: antimitochondrial antibodies, anti-nuclear antibodies, anti-smooth muscle antibodies, anti-liver kidney microsome type 1 antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, as well as anti-tissue transglutaminase antibodies, were also negative. The patient was not tested for JAK2 mutation because it had no clinical and laboratory indicators for myeloproliferative disease. After admission, a colonoscopy was performed, which determined vulnerable, erythematous mucosa of the colon, and contact bleeding, in part between the lienal flexure of the colon to the rectosigmoid junction. During the colonoscopy, a biopsy was performed, and pathohistological findings demonstrated ischemic colitis (Figure 1) and suspected bacterial infection. A computed tomography (CT) scan revealed partial main PVT, thrombosis of intrahepatic branches of PV, and thrombosis of the IMV (Figure 2). During the hospitalization, X-ray diagnostics were performed on the patient [Chest X-rays, CT aortography and

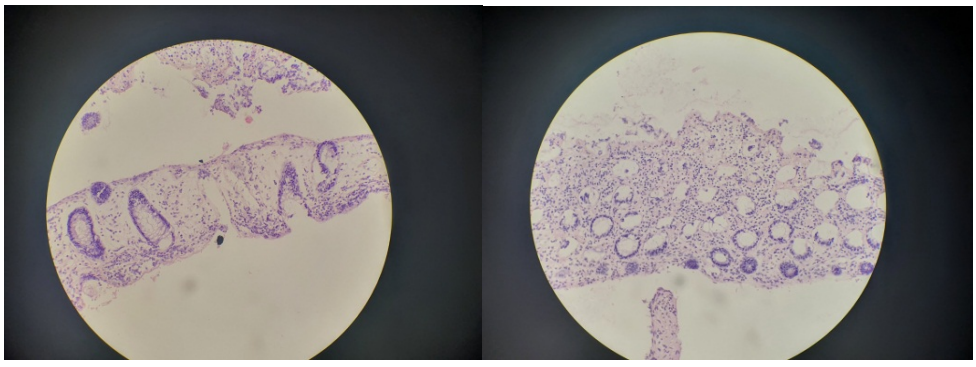

Fig. 1 – Pathohistological finding: ischemic colitis (hematoxylin and eosin staining, ×20).

splenoportography (SP), and ultrasound (US) of the upper abdomen], where there were no findings that would indicate a malignant disease. Thrombophilia was suspected only when it was discovered that the patient did not have any malignancies, that no infection was present, she was younger, and that there were also no findings that would indicate autoimmune or inflammatory diseases of the digestive tract. After that, heterozygous plasminogen activator inhibitor-1 (PAI-1) (carriers) was detected. Lupus anticoagulant and anticardiolipin antibodies were negative.

The patient was treated with low molecular weight heparin (LMWH) (enoxaparin sodium, Clexane®, 150 IU/kg) during hospitalization (seven days), anti-Xa (0.4 mL solution for injection, subcutaneous injection), antibiotics (ciprofloxacin, Ciprocinal® tablet 500 mg, twice a day and metronidazole, Orvagil® tablet 400 mg, three times a day), and proton pump inhibitors (pantoprazole, Nolpaza® tablet 20 mg, twice daily, half an hour before meals). After the applied measures, the digestive bleeding ceased, and defecation became normal.

A week after treatment initiation, the patient did not report any discomfort and was discharged from the hospital with a recommended therapy of novel oral anticoagulants (apixaban, Eliquis® tablet 5 mg, twice daily for six months), ciprofloxacin, and metronidazole.

One month after hospital discharge, the control CT scan showed a total resolution of the PVT (Figure 3). During the follow-up of three months, the patient was without any pathognomonic signs and symptoms.

Discussion

Consistent with every thrombosis, the basic pathophysiological mechanism that causes PVT is Virchow's triad (venous stasis, hypercoagulability, and endothelial injury) [2, 13]. The pathological entities that contribute to the development of this triad can be classified as local, in 70% of the PVT cases, and systemic, which cause PVT in 30% of the cases [9, 14–17]. The most common local risk factors of PVT are neoplasms, focal inflammatory lesions, neonatal omphalitis, umbilical vein catheterization, diverticulitis, appendicitis, pancreatitis, duodenal ulcer, cholecystitis, tuberculous lymphadenitis, Crohn's disease, ulcerative colitis, cytomegalovirus hepatitis, portal venous system injuries, splenectomy, colectomy, gastrectomy, liver transplantation, abdominal trauma, and cholecystectomy [9, 14]. On the other hand, the most common systemic risk factors of PVT are hereditary thrombophilia, factor V Leiden mutation, factor II mutation, protein C deficiency, protein S deficiency, antithrombin deficiency, acquired thrombophilia, myeloproliferative disorder, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, oral contraceptives, pregnancy, puerperium, and hyperhomocysteinemia [9, 14]. According to the guidelines of the American Association for the Study of Liver Diseases (AASLD) from 2009, the diagnostic approach to suspected PVT considers the methods of choice, such as B-mode US with a Doppler examination and CT scan with SP (Table 1) [18].

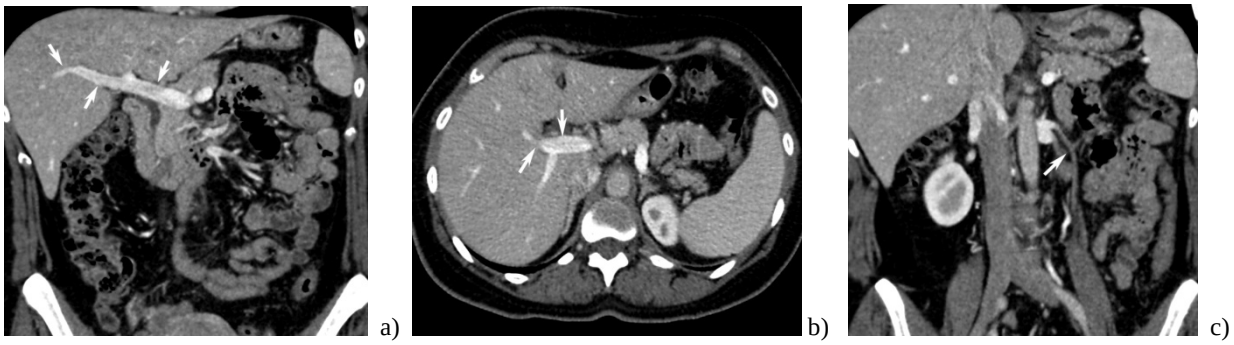

Fig. 2 – Multislice computed tomography angiography of the abdomen on admission to the hospital: a) PVT-coronal plane (white arrows); b) PVT-axial plane (white arrows); c) IMVT-coronal plane (white arrows). PVT – portal vein thrombosis; IMVT – inferior mesenteric vein thrombosis.

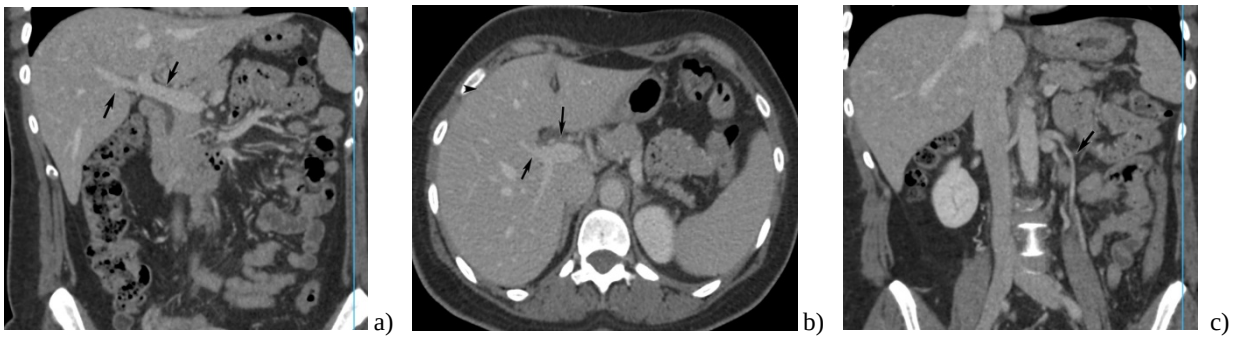

Fig. 3 – Multislice computed tomography angiography of the abdomen, control scan, month after discharge from the hospital: a) Resolved PVT-coronal plane (black arrows); b) Resolved PVT-axial plane (black arrows); c) Resolved IMVT-coronal plane (black arrows).
For abbreviations, see Figure 2.

Table 1

Recommendations for the diagnosis of acute portal vein thrombosis (PVT) [18]

Consider the diagnosis of acute PVT in any patient with abdominal pain longer than 24 hours, whether or not there is also fever or ileus.
If acute PVT is suspected, a CT scan, before and after injection of vascular contrast agent, should be obtained for early confirmation of diagnosis. If a CT scan is not rapidly available, obtain Doppler-sonography.
In patients with acute PVT and high fever and chills, septic pylephlebitis should be considered, whether or not an abdominal source of infection has been identified, and blood cultures should be routinely obtained.
In acute PVT, the possibility of intestinal infarction should be considered from presentation until the resolution of pain. The presence of ascites, thinning of the intestinal wall, lack of mucosal enhancement of the thickened intestinal wall, or the development of multiorgan failure indicates that intestinal infarction is likely and surgical exploration should be considered.

CT– computed tomography.

The US is a harmless, fast, and easily available technique with sensitivity and specificity ranging from 80 to 100% depending on the objective circumstance and the experience of the radiologist [15, 19]. An eventual finding that supports the diagnosis of PVT is the presence of a homogeneous (in acute thrombosis) or a heterogeneous (in chronic thrombosis) formation in the anechogenic blood vessel lumen without a Doppler signal in the thrombosed vessel. The US is not suitable for peripheral vein examination, mostly pertaining to mesenteric vessels [17].

The multislice computed tomography (MSCT) SP, besides being more sensitive compared to the US, also offers information on possible bowel ischemia or perforation [10]. A finding that indicates PVT is the presence of hyperdense thrombus masses in the vein lumen, which, after intravenous application of the contrast agent, gives a filling effect disrupting the normal opacification in the vessel lumen. Bland thrombus will not enhance in radiodensity, while tumor thrombus will have a certain post-contrast enhancement. The thrombus masses will have different densities [expressed in Hounsfield Units (HU)] depending on the thrombus maturation, meaning that MSCT can help evaluate the thrombus age. Newly formed thrombus masses have a density of around 55 HU, while older ones have around 30 HU [10]. Generally, the sensitivity and specificity of detecting a PVT vary for the US from 66–100%, but in the combination of US with color Doppler, sensitivity is 100%, and specificity is 93% [20]. The sensitivity and specificity of CT scan with SP in diagnosing PVT amounts to at least 90% [21].

On the other hand, the treatment of PVT ranges from observation without active therapy, thrombectomy, and other interventional procedures such as transjugular intrahepatic portosystemic shunt (TIPS). The aim of the treatment consists of the resolution of symptoms, prevention and treatment of mesenteric ischemia, and prevention of thrombus extensions. Treatments and outcomes of an acute PVT depend on the involvement of the remaining splanchnic circulation, as well as associated factors such as liver cirrhosis or malignancy.

The American College of Chest Physicians (ACCP) and AASLD have separated clinical guideline recommendations for the treatment of non-cirrhotic and non-malignant acute PVT.

The first aforementioned society recommends anticoagulation for symptomatic PVT with a grade 1B level of evidence; however, they do not suggest anticoagulation for asymptomatic, incidentally diagnosed PVT, which has a grade 2C level of evidence. The second society suggests anticoagulation for all acute PVT regardless of symptomatology.

Plessier et al. [22] showed that the use of anticoagulants for treating non-cirrhotic and non-malignant PVT led to complete recanalization in 38.3% and partially recanalization in 14% of patients. Most patients were treated with LMWN or unfractionated heparin. Thrombosis of a proximal portal venous system portion showed a better response to thrombolysis, and nine patients had digestive bleeding. The length of therapy is not clearly defined; however, recanalization is recommended after 4–6 months of therapy initiation. Long-term therapy is recommended in case of a confirmed prothrombotic disorder (thrombophilia), recurrent thrombotic episodes, or positive family history of venous thrombosis [23].

The PVT thrombolysis is controversial without relevant data or guidelines. Various studies have shown different treatment modalities for thrombolysis with inconclusive, inconsistent, and controversial data. Those include the usage of tissue plasminogen activator, streptokinase, or urokinase, indirectly by catheterization of the superior mesenteric artery or directly, percutaneously, by trans-hepatic approach into the PV or a TIPS; all of this is available as a therapeutic course [24–27]. Since the incidence of bleeding as a complication of thrombolytic therapy remains high (up to 60%), this approach may be offered only in selected cases. Therefore, the principal therapy for non-malignant and non-cirrhotic PVT should be conservative [27]. Surgical thrombectomy is not recommended nowadays due to PVT recurrence, surgical morbidity, and high mortality rate [28].

A recently published study by Klinger et al. [29] showed that in 17 patients who underwent thrombolytic therapy with a transjugular approach, recanalization was achieved in 94%, without recurrence of PVT in 88% of patients during the two-year follow-up. This kind of treatment may be offered in cases when anticoagulation fails or in the setting of the occurrence of PVT complications.

Further studies are necessary to confirm the effectiveness of combined conservative and minimally invasive

treatment of this serious clinical condition. Furthermore, follow-up studies may evaluate the adequate length of conservative therapy in preventing PVT recurrence.

PVT, once considered a contraindication for TIPS, has indeed become an "indication" in cirrhotic and non-cirrhotic cases [18, 30, 31]. The potential concerns in performing TIPS in a patient with acute PVT would be the following: increased technical difficulty in performing the procedure as their blood cannot be freely aspirated from the portal vein after the puncture, a gradient across the stent cannot always be established, and the risk for pulmonary embolism when portal venous thrombolysis is done through TIPS tract. As experience has grown and technology has evolved, the US guidance of transvenous access to the portal vein from the hepatic vein contributes to the overall higher success rate of performing the TIPS procedure and reducing the procedure-related complications.

Conclusion

Non-malignant and non-cirrhotic PVT is a rare and potentially serious clinical condition. The differential diagnosis for PVT should not be neglected because timely and vigilant therapy with LMWH can lead to complete resolution without serious complications.

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