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Case Reports

Portal Vein Thrombosis: A Saga of two Nebulous Etiologies

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Abstract: Portal Vein Thrombosis (PVT) is the most prevalent cause of extrahepatic portal vein obstruction. Cirrhosis, inherited procoagulant conditions (such as Factor V Leiden, Antithrombin III deficiency, etc.), myeloproliferative neoplasms, hepatocellular carcinoma and operative manipulation of the portal vein are all common causes of portal vein thrombosis. Even though a diagnosis is usually made, more than 25% of patients have no clear explanation for their PVT. The authors describe two cases of portal vein thrombosis in an atypical setting-one in a middle-aged female with type 2 diabetes mellitus with pyoperitoneum and the other is in a young male coinfected with human immunodeficiency virus and hepatitis E virus. Both cases had very different outcomes and thus emphasized the notion that PVT is a potentially fatal condition demanding a thorough diagnostic workup and evaluation.

Keywords: Human Immunodeficiency Virus, Hepatitis E, Peritonitis, Venous Thromboembolism

Introduction

PVT is a disorder in which thrombosis occurs in the extrahepatic portal venous system and can spread to intrahepatic portal vein branches as well as the superior mesenteric and splenic veins. The etiology of PVT is heterogeneous. The pathophysiology of PVT is influenced by a few risk factors including cirrhosis, hepatobiliary cancers and pancreatitis. Thrombophilic conditions, are among the systemic etiological causes (Trebicka and Strassburg, 2014). These include congenital disorders such as factor Leiden mutation, protein C deficiency, protein S deficiency and anti-thrombin III deficiency, as well as acquired conditions such as lupus anticoagulant syndrome, disseminated intravascular coagulation, sepsis and myeloproliferative disorders. A substantial number of cases that were previously categorized as "idiopathic" have now been redefined with the addition of specific diagnoses. One such group is myeloproliferative diseases, which include thrombocythemia, polycythemia vera and myelofibrosis with myeloid metaplasia.

Infections that cause a thrombus in the portal vein have only been described seldom in the literature. These infections can be caused by bacteria, viruses, or parasites (Choudhry *et al*., 2016). Pylephlebitis can develop because of any intraabdominal or pelvic infection that develops in an area drained by the portal venous system, such as diverticulitis or appendicitis. Pylephlebitis is an uncommon consequence in such circumstances and because of its ambiguous clinical presentation, the diagnosis is frequently overlooked. When a patient appears with indications of abdominal sepsis, it is critical to examine this differential since it has a high mortality risk. According to case reports, viruses have also been implicated as possible causes of portal vein thrombosis. HIV, CMV, EBV, Hepatitis A, B and C are some of the viruses that have been linked to the development of PVT (Ramanampamonjy *et al*., 2005; Justo *et al*., 2011; Luca *et al*., 2014). A variety of reasons can cause hemostatic abnormalities, but inflammation, especially viral infections, is well established to have a role. These changes might vary from slight abnormalities in the labs to severe disseminated intravascular coagulation. Coagulation can be triggered on a systemic or local level. Viruses can impede fibrinolysis and Tissue Factor (TF)-mediated thrombin production by downregulating natural anticoagulant processes. Thromboembolism during acute CMV infection is a well-known consequence in immunocompromised individuals, most often HIV-positive or post-transplant recipients. PVT has also been reported in HIV-positive individuals, with some cases including HIV and HCV coinfection (Ramanampamonjy *et al*., 2005).

We describe a duo of cases of PVT caused by unusual etiologies: Pylephlebitis consequent to primary peritonitis with Pneumonia sepsis and HIV/Hepatitis E coinfection. The reporting of such incidents is of significant importance since it may aid in determining the elements that contribute to their occurrence.

Case

CASE 1: A 32-year-old man with no significant past medical history presented to our hospital with a fever of 103ºF for 4 weeks along with constitutional symptoms. He was treated by many doctors before coming to our centre with his symptoms. The fever was associated with colicky upper abdomen pain, nausea, non-bilious non-projectile vomiting, generalized weakness and yellowish discoloration of skin and sclera. A history of high-risk sexual behavior was elicited. No history of substance abuse, over-the-counter medications, or blood transfusions was present. He had never undergone any biliary surgeries. On presentation, he had tachycardia (pulse rate 110 beats per minute), respiratory rate of 22 cycles per minute, blood pressure of 100/60 mmHg. On general physical examination, pallor and icterus were noted. On Abdominal examination, he had right upper quadrant tenderness without any organomegaly or abdominal distension. Murphy's sign was negative. The rest of the systemic examination was unremarkable.

His lab parameters revealed anemia, leukocytosis, acute kidney injury along with cholestatic pattern of liver injury, evidence by direct hyperbilirubinemia, elevated levels of alkaline phosphatase and gamma-glutamyl transferase (Table 1). Multiple blood and urine cultures yielded no pathogen. His chest x-ray was normal. Serology was positive for HIV-1&2 and hepatitis E virus. The immunovirological workup revealed a CD4 count of 299/mm^3. The hepatitis B and C serologies were negative. Ultrasound of the abdomen was suggestive of hepatomegaly while color doppler revealed the presence of echogenic, organized thrombotic material in the portal vein. Magnetic resonance imaging of abdomen with contrast supported the ultrasonography findings revealing eccentric T2 hyperintense contents in the main portal vein along with extension into both lobar branches and extending into a superior mesenteric vein and splenic vein confluence along with hepato-splenomegaly (Fig. 1). Magnetic resonance cholangiopancreatography revealed a normal hepatic biliary duct system. It did not show any mass compressing the hepatobiliary tract. Arterial and venous color doppler of the lower limbs, aorta and inferior vena cava was normal. To determine the nature of the PVT, we extended our studies to the patient's coagulation.

Profile and performed extensive screening for thrombophilia, however, didn't reveal any other abnormalities. His direct and indirect Coombs tests were negative. A fundus examination was done to exclude CMV infection, which was normal. Workup for malignancy with cancer markers (CEA, AFP and CA 19-9) was also negative.

He was started on antiretroviral therapy as per NACO guidelines, therapeutic anticoagulation with low molecular weight heparin and later bridged with oral warfarin therapy. Once his PT/INR was in therapeutic range, he was discharged after 10 days of hospital stay with oral warfarin therapy along with a warfarin diet. Once we started him on therapeutic anticoagulation, 3 weeks into treatment, his USG abdomen with color doppler was done and suggested the resolving nature of the thrombus.

CASE 2: A 65-year-old woman, homemaker, a known case of type 2 diabetes mellitus since 20 years, presented with episodic abdominal pain and loose stools for the past 4 months. Abdominal pain was diffuse, severe in intensity, non-radiating and without any relation with food intake. Diarrhea was watery in consistency and voluminous in quantity. These episodes occurred fortnightly and warranted hospital admission, where the patient recovered with non-steroidal anti-inflammatory drugs and fluids. She developed severe abdominal pain, diarrhea, nausea, vomiting and generalized weakness a week before the presentation. The patient also reported one episode of fever – 102ºF, associated with chills. There was no history of recurrent fever, Malena, constipation, radiation of pain, headache, altered mental status, hematemesis, hematochezia, mucus in stools, tenesmus, visual disturbances, menstrual disturbances, or altered bladder habits. The patient was on anti-hyperglycemic agents for her diabetes and was rather non-compliant with medication. The patient was a chronic smoker - one pack of cigarettes per day for the past twenty-five years. No history of any other substance abuse or alcohol consumption was elicited. Family history was unremarkable. The patient was initially taken to a local hospital where she eventually developed abdominal distension and tachypnoea and hence was referred to our tertiary care facility. On presentation, her pulse rate was 120 beats per minute, blood pressure 84/40 mmHg with a respiratory rate of 40 breaths per minute. On general physical examination, pallor was noted. The abdomen was distended with positive shifting dullness without any guarding or rigidity. Lung auscultation revealed reduced breath sounds with dullness on percussion in the right infra-axillary region. Other systemic examinations were unremarkable.

Blood investigations were sent (Table 1). A point of care ultrasound revealed ascites and mild pleural effusion bilaterally. Screening 2D echo was normal. An arterial blood gas analysis revealed type 2 respiratory failure with respiratory acidosis, warranting initiation of non-invasive ventilation support. Abdominal ultrasound revealed extensive portosystemic anastomoses and gross ascites. An ascitic tap was performed, draining a thick purulent fluid from the peritoneum. The fluid report revealed glucose (mg/dl) of 96 (with a random blood glucose of 598), total protein (mg/dl) of 1.52 with albumin 0.6, LDH (mg/dl) of 9140, red-cell count (per µl) of 25, white-cell count (per µl) of 12000 with neutrophils 95% and culture growth of Klebsiella pneumonia. This report suggested primary bacterial peritonitis. With antibiotic coverage, a pigtail catheter was inserted under radiological guidance to drain the collection percutaneously. Once the renal function improved, a contrast-enhanced CT abdomen was done. The main portal

vein was not visualized and non-enhancing partial filling defects were seen in the right and left branches of the portal vein along with the superior mesenteric vein. Portosystemic collaterals were also seen in peri-portal, peri-gastric and peri-pancreatic regions. The splenic vein and left gastric vein were noted to be dilated and tortuous. The spleen was moderately enlarged in size. A perihepatic collection was seen with the enhancement of the overlying peritoneum. A fluid attenuation collection measuring 9*3*15 cm was present at the left lateral abdominal wall. Diffuse subcutaneous edema was also noted. The findings in the contrast-enhanced computerized tomography were suggestive of extra-hepatic portal vein obstruction with peritonitis and fluid collections (Fig. 2). Serum biomarkers of malignancy were tested and reported to be negative.

The patient was primarily planned to undergo laparoscopic exploration of the abdomen, but the procedure was deferred considering the poor performance status. Given her worsening renal function and hyperkalemia, a decision for hemodialysis was made. The patient started developing fever spikes and cultures were sent. Blood and ascitic fluid cultures were positive for pan-resistant Klebsiella pneumonia. Over the next two weeks, 4-5 liters of purulent ascitic fluid was drained. Thick secretions were observed during regular endotracheal tube suctioning and a repeat chest X-ray done was suggestive of ventilator-associated pneumonia with the culture of secretions growing Acinetobacter baumanii. Antibiotics (Colistin and Meropenam) were upgraded accordingly but the patient responded poorly with worsening hemodynamic function requiring inotropic and vasopressor support. Intra-arterial blood pressure monitoring was done. Over the course of her stay, she developed extensive multi-organ dysfunction and Disseminated Intravascular Coagulation (DIC). Fresh frozen plasma and packed red blood cells were transfused in view of DIC and anemia, respectively. Despite all interventions, no improvement was observed and the patient eventually succumbed to the illness.

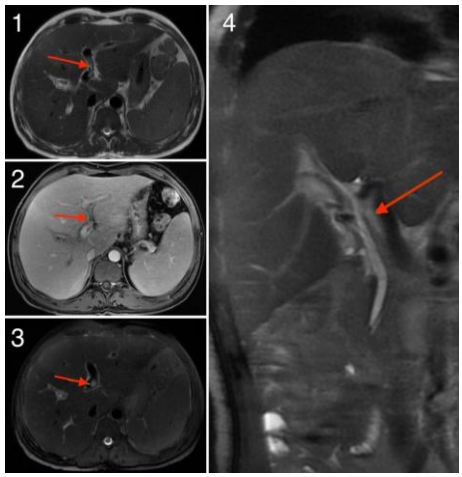

Fig. 1: Contrast-enhanced MRI Abdomen and Pelvis – 1,3,4: Eccentric T2 hyperintense contents are seen in the portal vein extending into portal bifurcation and into both main lobar branches of portal vein with entire segments of right lobe of liver showing hypointense signal compared to the left; 2: T1 filling defect noted in the portal vein suggestive of presence of a thrombus (Red arrows mark the site of thrombus)

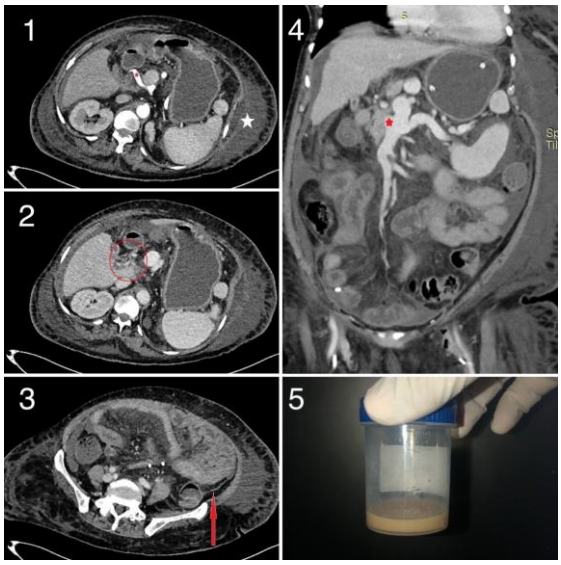

Fig. 2: Contrast-enhanced computerized tomography of whole abdomen – 1, 4: The main portal vein was not visualized (red star) with a fluid attenuation collection measuring 9*3*15 cm along left lateral abdominal wall (white star). Diffuse subcutaneous edema was also noted; 2: Portosystemic collaterals were also seen in peri-portal, peri-gastric and peri-pancreatic regions. Splenic vein and left gastric vein were noted to be dilated and tortuous. Spleen was enlarged in size. 3: Collection seen with enhancement of overlying peritoneum (red arrow); 5: Purulent ascitic fluid drained at admission

Table 1: Laboratory investigations of both cases

	CASE 1		CASE 2		
Investigations	At admission	After 1 week of admission	At admission	After 1 week of admission	Reference range
Hemoglobin (g/dl)	8.96	7.4	8.94	6.2	13.5-17.5
White cell count (per µl)	12,212	12440	17910	15900	4500–11,000
Differential count (per µl)					
Neutrophils	10341	9081	16100	13800	1800–7700
Lymphocytes	805	2488	950	1870	1000–4800
Monocytes	671	572	360	180	200–1200
Eosinophils	205	186	290	20	0–900
Basophils	190	113	210	10	0–300
Platelets (per µl)	314,200	250000	65,000	45000	150,000–400,000
Aspartate aminotransferase (U/L)	20	41.5	42	46	5-40
Alanine aminotransferase (U/L)	42	25.2	34	45	5-45
Total bilirubin (mg/dl)	6.71	1.99	1.27	0.67	0.2-1.1
Direct bilirubin (mg/dl)	2.81	1.59	0.85	0.40	<0.20
Alkaline phosphatase (U/L)	423	1359	207	301	<240
Gamma glutamyl transferase (U/L)	22	234	34	40	5-36
Serum total protein (g/dl)	6.2	7.3	4.5	6.6	6.4-8.1
Serum Albumin (g/dl)	2.56	3.01	2.59	3.17	3.2-4.6
Sodium (mmol/L)	141	139	150	138	135–145
Potassium (mmol/l)	5.3	3.5	5.7	4.6	3.4–5.0
Chloride (mmol/l)	96	98	111	104	100–108
Urea nitrogen (mg/dl)	96.8	35	116	140	8–25
Creatinine (mg/dl)	5.33	1.09	1.8	0.84	0.60–1.50
Glucose (mg/dl)	106	102	598	198	70–110
C-reactive protein (mg/l)	22	16	46	42	<8
Erythrocyte sedimentation rate (mm/hr)	32	28	72	58	0–13
Fibrinogen (mg/dl)	180	124	140	349	200-400
D-dimer (ng/ml)	2140	280	250	>550	<50 ng/ml
Lipase (U/L)	82	74	90	98	7-65 U/L
Amylase(U/L)	106	60	140	106	19-85 U/L
PT (sec)	15.6	33.8	19.8	27	11-13.5 sec
INR	1.16	2.6	1.9	2.04	0.8-1.1

Discussion

Although portal vein thrombosis is a rarely documented phenomenon, pulmonary and deep vein thrombosis has been reported often in HIV patients. Recent literature describes an incidence ranging from 0.26 to 7.6% (Sullivan *et al*., 2000; Saif *et al*., 2001). Individuals with ongoing opportunistic infections or malignancies, as well as patients with HIV, have a greater incidence of thrombosis. Some theories have been advanced to explain the observed hypercoagulability in HIV-positive individuals. These include the presence of antiphospholipid-anticardiolipin antibodies, hyperhomocysteinemia, decreased activities of natural anticoagulants (protein C and protein S) and increased platelet activation. Recent studies have implicated protease inhibitors in the disease causation process (Shen and Frenkel, 2004; Soentjens *et al*., 2006). Anticardiolipin antibodies are linked with arterial and venous thrombosis, whereas proteins C and S deficiencies are associated with venous thrombosis. These pathogenic processes may have orchestrated the development of PVT in our patients, but all possible investigations ruled out this. Therefore, another possible factor considered was pylephlebitis due to coinfection of HIV and hepatitis E. However, since hepatitis E virus has never been linked to thrombus development previously, more investigations and validation are needed to confirm this association.

In the second case, a final diagnosis of primary pyoperitoneum complicated by acute pylephlebitis was made. It is the first reported case of primary peritonitis without an identifiable cause which progressed to pyoperitoneum and stimulated the formation of a septic portal vein thrombus. The sole risk factor in the development of the condition was uncontrolled type 2 diabetes mellitus. Pylephlebitis begins with thrombophlebitis of small veins draining an area of infection (Choudhry *et al*., 2016). When thrombophlebitis spreads to larger veins, it causes septic thrombophlebitis of the portal vein, which can further extend to the mesenteric veins. In 39% of instances, the portal vein is implicated (Soentjens *et al*., 2006). Bacteroides fragilis and Escherichia coli are the most frequent bloodstream isolates. *K. pneumonia* has also been linked in rare cases. The diagnosis of

pylephlebitis requires the demonstration of PVT (pylethrombosis) usually accompanied by bacteremia in a febrile patient (Plemmons *et al*., 1995). The diagnosis is usually delayed because pylephlebitis is not recognized since it is a rare disorder, or because the symptoms are obscure, clinical indicators are often absent from the primary site of infection and the portal vein may be difficult to visualise. Antibiotic therapy, drainage of septic foci, thrombolysis and operative exploration have all been tried to manage this condition but the challenge stems from the fact that its nonspecific presentation often eludes the diagnosis, making it difficult to identify the disease at an early stage, portending a poor outcome in a majority of patients (Choudhry *et al*., 2016; Dean *et al*., 1995). Primary peritonitis is rare and a very high index of suspicion is required to make a prompt diagnosis to perform a laparoscopic surgical procedure in such patients. Losing on that lag phase of the illness proved detrimental in our patient leading to the development of septic portal vein thrombosis thereby increasing its mortality.

Conclusion

PVT can be caused by a wide range of factors, including infections of diverse origins. An exhaustive diagnostic exercise must be undertaken in such instances to arrive at an accurate diagnosis that can further inform treatment.

Author's Contributions

Ashwin Parchani: Manuscript writing, literature search, manuscript editing

Manjunath Totaganti: Manuscript writing, manuscript editing, literature search

Prasan Kumar Panda: Manuscript review, manuscript editing, supervision of the project

Sunil Kumar KS: Manuscript editing, image analysis and post-processing.

Ethics

This article is original and contains unpublished material. The authors declare no ethical issue. Informed consent was obtained from the patient.

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