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# A 79-year-old with acute portal vein thrombosis

**A** 79-YEAR-OLD MAN presented with chills and fever. He had a history of polymyalgia rheumatica and had been tapered off corticosteroids 1 month before admission. One week before he presented, he had developed generalized myalgia, chills, and fatigue. A cortisol stimulation test at that time was normal, prednisone was restarted, and his symptoms had improved. But 1 day before he presented, the chills had returned, this time with fever. Laboratory testing at an outpatient clinic had revealed abnormal liver enzyme levels.

On the day he presented, he felt worse, with persistent chills, fever, and vague lower abdominal pain, but he denied nausea, vomiting, changes in bowel habits, melena, hematochezia, and hematemesis. He was admitted for additional evaluation.

His medical history also included coronary artery disease (for which he had undergone coronary artery bypass grafting), hypertension, stable liver cysts, and gout. He had no known inflammatory bowel disease and no recent abdominal surgery. His medications included prednisone, atorvastatin, atenolol, aspirin, niacin, and cholecalciferol. He had no history of smoking, significant drinking, or use of illicit drugs. He had no respiratory or cardiac symptoms or neurologic symptoms consistent with a transient ischemic attack or stroke. He denied any rashes.

On admission, he was febrile, with temperatures reaching 102°F (38.9°C). His blood pressure was 137/63 mm Hg, pulse 54 beats per minute, respiration rate 18 breaths per min-

ute, and oxygen saturation 97% on room air. A harsh systolic murmur was noted on physical examination. His abdomen was nondistended, nontender, and without bruits.

Laboratory testing (TABLE 1) revealed leukocytosis, anemia, mildly abnormal aminotransferase levels, elevated alkaline phosphatase, and markedly elevated C-reactive protein.

A full workup for fever was performed, including blood and urine cultures; chest radiography; contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis; magnetic resonance imaging (MRI) of the abdomen; and colonoscopy. No source of infection—bacterial, viral, or fungal—was found. However, CT revealed new extensive thrombosis of the right portal vein and its branches (FIGURE 1).

## CLINICAL PRESENTATION

**1** Which of the following is least consistent with the clinical presentation of *acute* portal vein thrombosis?

- Abdominal pain
- Fever and chills
- Hematemesis
- Leukocytosis
- Absence of symptoms

Of these signs and symptoms, hematemesis is the least likely to be associated with acute portal vein thrombosis, although it can be associated with chronic cases.

### Symptoms of portal vein thrombosis

Portal vein thrombosis causes extrahepatic obstruction of the portal venous system, which provides two-thirds of the total hepatic blood flow.

**The patient, who had a history of polymyalgia rheumatica treated with corticosteroids, presented with chills and fever**

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**TABLE 1**  
**The patient's laboratory values on presentation**

Test	Value	Normal range
<b>Complete blood count</b>		
White blood cell count ( $\times 10^9/L$ )	18.69	3.70–11.00
Red blood cell count ( $\times 10^{12}/L$ )	4.07	4.2–6.0
Hemoglobin (g/dL)	12.7	13.0–17.0
Hematocrit (%)	37.0	39.0–51.0
Mean corpuscular volume (fL)	90.0	80.0–100.0
Platelet count ( $\times 10^9/L$ )	342	150–400
Neutrophils (%)	80.7	1–56
Lymphocytes (%)	10.2	1–34
Monocytes (%)	8.9	1–4
Eosinophils (%)	0.1	1–27
<b>Complete metabolic panel</b>		
Sodium (mmol/L)	137	135–146
Potassium (mmol/L)	5.1	3.5–5.0
Chloride (mmol/L)	101	98–110
Carbon dioxide (mmol/L)	25	23–32
Blood urea nitrogen (mg/dL)	36	10–25
Creatinine (mg/dL)	1.10	0.70–1.40
Glucose (mg/dL)	96	65–100
Protein (g/dL)	7.8	6.4–8.0
Albumin (g/dL)	3.3	3.5–5.0
Calcium (mg/dL)	9.9	8.5–10.5
Bilirubin, total (mg/dL)	0.5	0.0–1.5
Alkaline phosphatase (U/L)	267	40–150
Alanine aminotransferase (U/L)	73	5–50
Aspartate aminotransferase (U/L)	52	7–40
<b>Other</b>		
D-dimer (ng/mL)	5,200	< 500
C-reactive protein (mg/dL)	20.8	0.0–1.0
Lactate (mmol/L)	2.0	0.5–2.2

**Acute.** Often, thrombotic occlusion of the portal vein produces no acute symptoms because of immediate, compensatory vasodilation of the hepatic arterial system.<sup>1</sup> Additionally, in the ensuing days, the thrombus becomes an organized collagenous plug, and

collateral veins develop to bypass the blocked vein and maintain portal perfusion in a process called cavernous transformation.<sup>1,2</sup> Thus, many patients have no symptoms.

If symptoms occur, portal vein thrombosis can initially present as transient abdominal pain with fever, as seen in this patient.<sup>3</sup> Many patients with acute portal vein thrombosis experience abdominal pain due to intra-abdominal sepsis, also referred to as pylephlebitis.<sup>2,4</sup> High, spiking fevers and chills also occur, caused by infected thrombi associated with intra-abdominal infections such as appendicitis, diverticulitis, and pancreatitis.<sup>5,6</sup>

**Chronic.** In contrast, symptomatic chronic portal vein thrombosis commonly presents with sequelae of portal hypertension, most notably gastrointestinal bleeding. Hematemesis from ruptured esophageal varices is the most frequent reason for seeking medical attention, though varices also develop in the stomach, duodenum, jejunum, gallbladder, and bile ducts.<sup>2,7</sup> Abdominal pain is less common in chronic portal vein thrombosis unless the thrombus extends into the mesenteric veins and causes bowel ischemia or infarction. Long-standing portal vein thrombosis may also lead to dilated venous collaterals that compress large bile ducts, resulting in portal cholangiopathy.<sup>1,8</sup>

Portal vein thrombosis may present as acute intestinal ischemia and bowel infarction, though this is uncommon. This is generally seen with extensive occlusive portal vein thrombosis and concomitant mesenteric venous thrombosis.<sup>1,2</sup>

Other symptoms that are common but nonspecific are nausea, vomiting, diarrhea, weight loss, and anorexia.<sup>2</sup>

**Signs of portal vein thrombosis**

On examination, patients with acute portal vein thrombosis have minimal physical signs unless they have other contributing conditions. For example, acute portal vein thrombosis can result in abdominal distention secondary to ileus, or guarding and ascites secondary to intestinal infarction.<sup>3,9</sup>

Some patients with chronic portal vein thrombosis also have normal physical findings, but many have signs. Splenomegaly is seen in 75% to 100% of patients.<sup>2,7</sup> Hepato-

megaly, abdominal tenderness, and low-grade fever are common as well.<sup>2,10</sup> Ascites is usually not present without underlying cirrhosis; however, mild and transient ascites can develop immediately after the thrombotic event before the patient develops collateral circulation.<sup>2</sup>

### Laboratory testing for portal vein thrombosis

Laboratory test results are typically unremarkable. Liver function tests show preserved hepatic function but may reveal mild increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin.<sup>2,10</sup>

In acute cases, elevations of acute-phase reactant levels can occur.<sup>9</sup> Leukocytosis and blood cultures growing *Bacteroides* species are seen in septic cases or pylephlebitis.<sup>11,12</sup> There may be mild anemia, particularly after a recent bleeding episode, or mild leukopenia and thrombocytopenia due to hypersplenism. Suspicion of an underlying myeloproliferative disorder is high if thrombocytosis is present.<sup>2</sup>

### ■ DIAGNOSIS

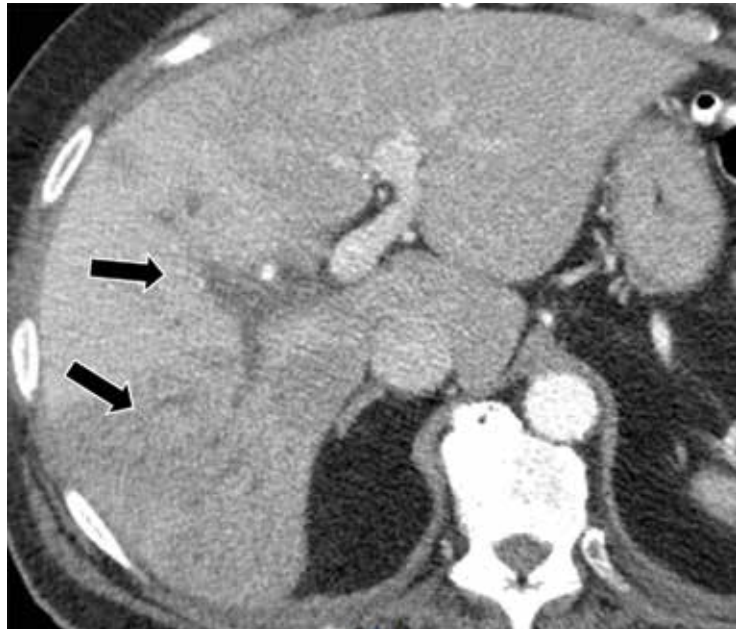
**2** All of the following would be appropriate *initial* diagnostic studies for portal vein thrombosis except which one?

- Doppler ultrasonography
- Contrast-enhanced CT
- Contrast-enhanced MRI
- Angiography

Portal vein thrombosis is most often diagnosed with noninvasive techniques, namely Doppler ultrasonography, CT, and MRI—not angiography.

Ultrasonography can reveal an echogenic thrombus in the vessel lumen with distention of the portal vein proximal to the occlusion and extensive collateral vessels. Plain ultrasonography fails to reveal the thrombus in up to one-third of patients. However, duplex ultrasonography with color flow Doppler imaging can confirm partial or complete absence of flow in the vein with 89% sensitivity and 92% specificity.<sup>13,14</sup>

On contrast-enhanced CT, the thrombus appears as a filling defect within the portal venous segment. Complete occlusion of the vein may produce a “train track” appearance due to



**FIGURE 1.** Axial contrast-enhanced computed tomography demonstrated branching—hypodense areas (black arrows) in the right hepatic lobe compatible with extensive thrombosis of the right portal venous system.

PHOTO COURTESY DR. ANDREI PURYSKO

contrast around the vessel.<sup>10</sup> Without contrast, the clot will appear as hyperattenuating material in the portal vein, but contrast-enhanced imaging may be necessary to differentiate the thrombus from the vessel wall.<sup>15</sup> Gas within the portal venous system is specific for pylephlebitis.<sup>4</sup> Evidence of cavernous transformation is seen in chronic portal vein thrombosis.

Contrast-enhanced magnetic resonance angiography can also be used to evaluate patency and flow direction. In addition, it provides detailed anatomic information about the entire portal venous system, including the intrahepatic portal vessels, which is limited in CT imaging.<sup>2,10</sup> CT and MRI can also help to identify predisposing conditions (eg, intra-abdominal infection, hepatocellular carcinoma) and complications (eg, intestinal infarction) associated with portal vein thrombosis.

Angiography can be considered if noninvasive techniques are inconclusive but is generally not necessary, given the increased use of CT and MRI.

In our patient, abdominal CT revealed occlusive thrombosis of the right portal vein and its branches (**FIGURE 1**). The left and main por-

**Gas within the portal venous system is specific for pylephlebitis**

**TABLE 2**

**Underlying causes of portal venous thrombosis**

**Hypercoagulable states**

**Inherited**

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden
- Prothrombin (factor II) gene mutation
- Hyperhomocysteinemia

**Acquired**

- Myeloproliferative disorders (eg, polycythemia vera)
- Antiphospholipid antibody syndrome
- Paroxysmal nocturnal hemoglobinuria
- Oral contraceptives
- Pregnancy and postpartum
- Malignancy (most common: hepatocellular carcinoma and pancreatic cancer)

**Inflammation and infection**

**Inflammatory bowel disease**

- Pancreatitis
- Cholecystitis
- Cholangitis
- Appendicitis
- Liver abscess
- Schistosomiasis
- Diverticulitis
- Duodenal ulcer
- Behçet syndrome

**Injury to portal venous system**

- Abdominal surgery
  - Splenectomy
  - Cholecystectomy
  - Liver transplantation
  - Hepatic chemoembolization
- Gastrectomy
- Gastric banding
- Colectomy
- Surgical shunting
  - Transjugular intrahepatic portosystemic shunt placement
  - Surgical portosystemic shunt placement
- Blunt trauma

**Impaired portal vein flow**

- Cirrhosis
- Budd-Chiari syndrome
- Malignancy
  - Hepatocellular carcinoma
  - Pancreatic cancer
  - Cholangiocarcinoma

**Inherited deficiencies in antithrombin, protein C, and protein S pose a high risk but have a low prevalence**

tal veins were patent. There was no evidence of intra-abdominal infection or infarction.

**FINDING THE CAUSE**

**3** Which of the following is not a common cause of portal vein thrombosis?

- A hypercoagulable state
- Immune deficiency
- Intra-abdominal infection
- Malignancy
- Portal hypertension

Once portal vein thrombosis has been diagnosed, the cause should be identified (TABLE 2). The differential diagnosis is broad, including both local factors (eg, injury to the portal vein, local inflammation, infection) and general factors (eg, inherited and acquired hypercoagulable conditions). Thrombophilias are identified in 60% of patients with portal vein thrombosis and local factors in 40%.<sup>7</sup> Moreover, the etiology is often multifactorial. However, immune deficiency is not a common cause.

**Hypercoagulability**

Prothrombotic disorders can be either inherited or acquired.

**Inherited** deficiencies in the natural anticoagulants antithrombin, protein C, and protein S are associated with a high risk of thrombosis but have a low prevalence in the general population. In the setting of liver abnormalities, familial testing may be helpful to distinguish inherited causes of portal vein thrombosis from defective liver function as a consequence of portal vein thrombosis. The factor V Leiden mutation (G1691A) and the G20210A mutation in the prothrombin gene are more prevalent (> 2%) but generally confer a lower thrombosis risk.<sup>16</sup> The prothrombin gene mutation G20210A is the most common risk factor for portal vein thrombosis, with prevalence of 2% to 22% in adults with non-malignant, noncirrhotic portal vein thrombosis.<sup>3</sup>

Hyperhomocysteinemia due to a methylene tetrahydrofolate reductase (*MTHFR*) mutation (C677T) is another inherited associated risk factor for portal vein thrombosis, but hyperhomocysteinemia can also arise as a complication of portal vein thrombosis-related liver disease.<sup>3</sup>

**Acquired** prothrombotic disorders, particularly myeloproliferative diseases, are found in 22% to 48% of cases of portal vein thrombosis. Many young patients with myeloproliferative disorders present with portal vein thrombosis as the first symptom, and testing for the G1849T point mutation in *JAK2* can make the diagnosis.<sup>17</sup> Splenectomy with underlying myeloproliferative disorder confers a particularly high risk for portal vein thrombosis.<sup>18</sup>

Other thrombophilic disorders including antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, and malignancy can contribute to portal vein thrombosis.<sup>3</sup> Pregnancy and oral contraceptive use have also been associated with hypercoagulability, and cessation of oral estrogen is recommended in such cases. The risk may be further increased in patients on oral contraceptives who have a previously unrecognized hypercoagulable state.<sup>3</sup>

### Inflammation and infection

Inflammation and infection are local risk factors for portal vein thrombosis. Acute portal vein thrombosis has been associated with intra-abdominal infections (eg, appendicitis, cholecystitis) and with inflammatory conditions such as inflammatory bowel disease and pancreatitis.<sup>16,19</sup> From 3% to 5% of all portal vein thrombosis cases result from pancreatitis, either from a single acute episode or from repeat inflammation of chronic pancreatitis.<sup>10</sup> Portal vein thrombosis in the setting of inflammatory bowel disease can occur even when the disease is in remission, particularly in ulcerative colitis.<sup>20,21</sup>

### Injury to the portal venous system

Abdominal surgery, particularly splenectomy, portosystemic shunting, colectomy, and blunt abdominal trauma can cause injury to the portal venous system, resulting in portal vein thrombosis. This is usually seen only in patients with portal hypertension, an underlying prothrombotic condition such as myeloproliferative disease, or inflammatory bowel disease.<sup>10,19,22</sup>

### Impaired portal vein flow

Cirrhosis and malignancy are major risk factors for portal vein thrombosis. In case series, cirrhosis was found in 24% to 32% of patients

with portal vein thrombosis.<sup>2,23</sup> However, the overall prevalence of portal vein thrombosis in cirrhotic patients varies widely, from 0.6% to 28%, depending on the degree of cirrhosis.<sup>10</sup>

The pathogenesis of portal vein thrombosis in cirrhosis is unclear but may be multifactorial. Decreased portal blood flow (with subsequent stasis) and periportal lymphangitis and fibrosis are thought to stimulate thrombus formation.<sup>3,10</sup> Additionally, patients with advanced cirrhosis are prothrombotic because of reduced hepatic synthesis of antithrombin, protein C, protein S, and coagulation factors.

Malignancy is associated with 21% to 24% of cases of portal vein thrombosis in adults, with pancreatic cancer and hepatocellular carcinoma being the most common.<sup>2,3</sup> Others include cholangiocarcinoma and carcinomas of the stomach, lung, prostate, uterus, and kidney. Cancer causes portal vein thrombosis through a combination of tumor invasion into the portal vein, extrinsic compression by the tumor, periportal fibrosis following surgery or radiation, and hypercoagulability secondary to malignancy.<sup>9,16,24</sup>

### Idiopathic portal vein thrombosis

Portal vein thrombosis is usually caused by one or more of the underlying factors mentioned above but is idiopathic in 8% to 15% of cases.<sup>10</sup>

### Back to our patient

The cause of this patient's portal vein thrombosis is unclear. He did not have a history of cirrhosis, inflammatory bowel disease, trauma, or abdominal surgery. His febrile illness could have precipitated the formation of a thrombus, but no definitive source of infection or inflammation was discovered. His workup was negative for pancreatitis, appendicitis, cholecystitis, diverticulitis, and prostatitis. No occult malignancy was found. It is also possible that his fever was the result of the thrombosis.

A full hypercoagulability panel revealed no striking abnormalities. He did have elevated fibrinogen and factor VIII levels that were consistent with an acute-phase reaction, along with an elevated erythrocyte sedimentation rate (> 90 mm/hr) and C-reactive protein level. Aside from the portal vein thrombosis, no potential source of inflammation could be identified.

**Cirrhosis and malignancy are major risk factors for portal vein thrombosis**

Mildly reduced levels of antithrombin III activity were attributed to enoxaparin therapy and ultimately normalized on repeated testing. The patient had very minimally elevated titers of anticardiolipin immunoglobulin G (1:10 GPL) and anti-beta-2 glycoprotein immunoglobulin M (21 SMU), which were not thought to be significant. Tests for lupus anticoagulant, prothrombin gene mutation, activated protein C resistance, and JAK2 mutation were negative.

### ■ TREATMENT

**4** Treatment of symptomatic portal vein thrombosis generally includes which two of the following?

- Anticoagulation
- Intravenous gamma globulin
- Broad-spectrum antibiotics

#### Anticoagulant therapy

Treatment of acute, symptomatic portal vein thrombosis involves anticoagulant therapy to prevent extension of the thrombus and, ultimately, to allow for recanalization of the obstructed veins. Anticoagulant therapy is initially intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin, eventually bridged to an oral agent such as warfarin.<sup>3,9</sup> Currently, there are inadequate data on the use of oral or parenteral factor Xa inhibitors or direct thrombin inhibitors in the treatment of this disease.

When started immediately, anticoagulation therapy is associated with complete recanalization in 38.3% and partial recanalization in 14% of patients presenting with complete thrombosis. Without anticoagulation, spontaneous recanalization is unusual.<sup>25</sup>

Although the optimal duration of anticoagulant therapy is unclear, a minimum of 3 months is generally recommended.<sup>9,26</sup> If a hypercoagulable state is present or if the portal vein thrombosis is unprovoked (eg, by surgery, trauma, or an intra-abdominal infection), long-term treatment should be considered.<sup>26</sup>

Experience with thrombolytic therapy or mechanical recanalization has been limited, but the use of catheter-based techniques for pharmacomechanical thrombolysis has been reported.<sup>27-29</sup> Transjugular intrahepatic porto-

systemic shunting is also an alternative to anticoagulation, but its role in treating portal vein thrombosis is complicated by technical difficulties of the procedure, postoperative complications, and recurrent occlusion of the shunt.<sup>25</sup>

Currently, there are no data comparing the risk-benefit ratio of early anticoagulation and that of invasive procedures. These more aggressive treatments are generally considered only when there is extensive thrombosis or ascites (which are both predictive factors of poor response to anticoagulation alone) and in patients for whom anticoagulation has failed.<sup>3</sup> Surgical thrombectomy is rarely indicated, typically only in instances in which laparotomy is being performed for suspected bowel infarction.<sup>3</sup>

#### Antibiotics

In addition to anticoagulation, broad-spectrum antibiotics covering gram-negative and anaerobic bacteria are indicated for those cases of portal vein thrombosis associated with underlying infection.<sup>9</sup>

For chronic cases, the goals of management are to prevent and treat gastroesophageal variceal bleeding and to prevent recurrent thrombosis.<sup>9</sup> Nonselective beta-blockers (eg, propranolol) and endoscopic band ligation have shown evidence of reducing the incidence of recurrent bleeding and prolonging survival in retrospective studies.<sup>9,30,31</sup> Long-term anticoagulation is generally indicated to prevent further thrombosis and to increase the likelihood of recanalization only for patients with a permanent prothrombotic condition.<sup>9</sup> In patients with clinically significant portal hypertension, the benefit of continued anticoagulation therapy must be weighed against the risk of esophageal and gastric variceal bleeding.

There is controversy regarding how to manage portal vein thrombosis that is incidentally identified and asymptomatic (eg, if it is discovered on an imaging study for another indication). Current guidelines recommend against anticoagulation in patients with incidentally discovered and asymptomatic splanchnic vein thrombosis, including portal vein thrombosis.<sup>26</sup>

Intravenous gamma globulin is not part of the treatment.

**Without anticoagulation, spontaneous recanalization is unusual**

■ CASE CONTINUED

The patient's presenting symptoms of fever, chills, and abdominal pain completely resolved after a course of antibiotic therapy. The erythrocyte sedimentation rate subsequently normalized and factor VIII activity improved. We believed that an underlying infectious or inflammatory process had contributed to the development of portal vein thrombosis, though the specific cause could not be identified. The patient was treated with enoxaparin

1 mg/kg twice a day and transitioned to warfarin.

Magnetic resonance venography done 3 months after diagnosis showed persistent right portal vein thrombosis that was largely unchanged. Anticoagulation was continued for 1 year with no change in his portal vein thrombosis on sequential imaging and was subsequently discontinued. To date, no malignancy or infectious process has been found, and the patient continues to do well 2 years later. ■

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