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Hematology Quiz – Case 64

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2023, 40(4):572–574

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A 40-year-old woman was referred to the hematology clinic by her primary care physician as a case of possible, undiagnosed hereditary thrombophilia. Six years earlier a computing tomography (CT) scan obtained because of abdominal pain which showed portal-vein, splenic-vein, and superior-mesenteric-vein thrombosis; the spleen was enlarged measuring 16.5×13×7 cm. There was no history of fever, night sweats, weight loss, pregnancy, use of alcohol, tobacco or oral contraceptives, hepatitis B or C infection, thrombophlebitis, or trauma but she had performed unusually intense physical work, including carrying heavy objects, the previous day. Her family history was unremarkable. Extensive diagnostic work-up did not reveal a cause (tab. 1). She was discharged from the hospital with a diagnosis of idiopathic splenic-portal-mesenteric thrombosis and scheduled for an appointment in the hepatology/gastroenterology clinic. Esophagogastroduodenoscopy revealed varices in the esophageal and gastric veins. Over the ensuing years, she was managed with acenocoumarol, propranolol, and endoscopic band ligation for large varices.

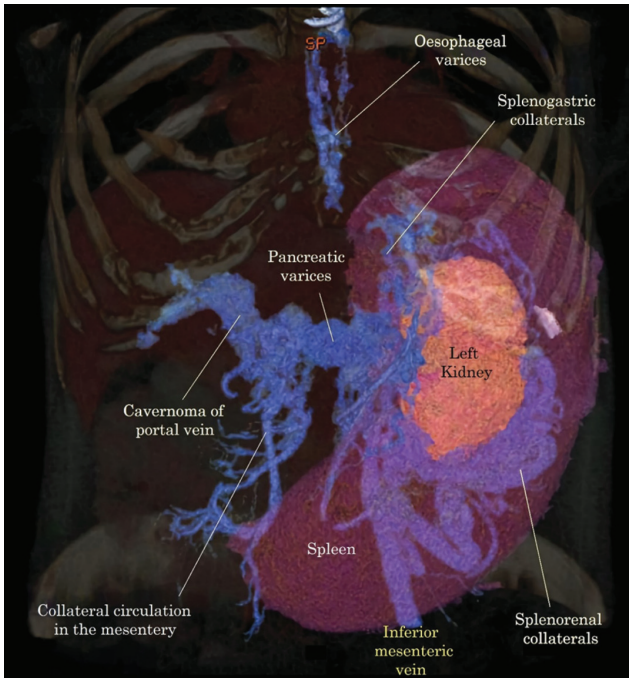

Figure 1. Reconstructed coronal computed tomography (CT) image, during the phase of portal venous enhancement. There is replacement of the thrombosed portal vein by a mass of tortuous vessels ("cavernoma"), extensive porto-systemic collateral paths due to chronic portal hypertension, a normal appearing liver, and a 27×17×13 cm spleen extending into the pelvis. Noteworthy is the gross dilatation of the splenorenal collateral vessels, concordant with a massive flow rate from spleen.

Physical examination revealed massive splenomegaly. Stigmata of cirrhosis, hepatomegaly, and lymphadenopathy were absent. Laboratory test results are shown in table 1. A repeat contrast-enhanced CT scan disclosed cavernous transformation of the portal vein with an extensive portal-systemic circulatory shunt; the spleen had reached enormous proportions (fig. 1).

Comment

The precise reason for hypercoagulability may prove a challenging and, frequently, a frustrating clinical problem. Clinicians may be faced with patients who present with splanchnic vein thrombosis (SVT) and who despite extensive medical evaluation remain without a diagnosis. In this case, hereditary thrombophilia

Table 1. Results of laboratory tests.

Results of laboratory tests	Initial presentation	Current presentation	Reference range
White cell count ($\times 10^9$/L)	5,200	8,400	4.0–10.0
Hemoglobin (g/L)	12.2	12.0	120–160
Platelet count ($\times 10^9$/L)	295	330	140–440
Mean corpuscular volume (fL)	85.0	83.0	80.0–96.0
Total bilirubin (mg/dL)	1.05	0.86	0.3–1.2
Alanine aminotransferase (U/L)	96	30	5–40
Alkaline phosphatase (U/L)	51	82	40–150
Amylase (U/L)	101	74	10–100
Albumin (g/dL)	4.2	4.0	3.5–5.2
Lactate dehydrogenase (U/L)	240	339	125–220
Erythrocyte sedimentation rate (mm/h)	11	18	
Ferritin (µg/L)	55	46	13.0–150.0
Antinuclear antibodies, anti-smooth-muscle antibodies	Negative		
Alpha-fetoprotein (ng/mL)	7		0–15
JAK2 V617F mutation	Absent		
Screening for paroxysmal nocturnal haemoglobinuria	Negative		
Prothrombin time (international normalised ratio)	1.12	2.37*	0.8–1.2
Lupus anticoagulant screen	Negative		
Anticardiolipin IgG, IgM antibody	None detected		
Thrombophilia screen			
Antithrombin III activity (%)	105		80–120
Protein C activity (%)	84		70–130
Protein S activity (%)	77		60–120
Factor V Leiden G1691A mutation	Absent		
Prothrombin gene mutation (G20210A)	Absent		
Homocysteine (µmoL/L)	10.56		4.45–12.42

*On acenocoumarol therapy

was a prime concern as the cause of hypercoagulability. Standard screening, however, ruled out all major genetic defects associated with hereditary thrombophilia (tab. 1). Additional tests that are sometimes performed, such as tests determining the activity of elevated coagulation factors (FVIII, FIX and FXI), decreased plasminogen levels, and the 4G/5G PAI-1 promoter polymorphism are not advisable as they are unlikely to confer particular susceptibility to thrombosis. Accordingly, MTHFR C677T testing is relevant only if there is hyperhomocysteinemia.

The mechanisms underlying thrombosis of the splenoportal venous system fall into four categories. One is abdominal trauma, the second is intraabdominal infection or inflammation, the third comprises intraluminal events (e.g. portal hypertension caused by cirrhosis, hepatoma invading the portal veins) or extraluminal compression (e.g. pancreatic carcinoma) producing stasis of portal venous flow, and the fourth consists of hypercoagulable states (hereditary thrombophilia, antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, myeloproliferative neoplasms, oral contraceptives, pregnancy). Epidemiologic studies suggest that 20–27% of cases are "idiopathic".

Considering this patient's massive splenomegaly, it is surprising that she had a normal platelet count, since patients with long-standing portal hypertension and congestive splenomegaly typically have thrombocytopenia. The elevated serum lactate dehydrogenase level provides another clue regarding increased blood element production. Viewed in this context, an occult myeloproliferative disorder emerges as the most likely diagnosis. A bone marrow biopsy showed histologic features consistent with essential thrombocythemia, and additional molecular testing revealed an exon 9 mutation in the calreticulin (CALR) gene. The patient began cytoreductive treatment with hydroxyurea. One might question whether heavy exertion might have played a role. For this sequence to fit one could speculate that the patient might have performed repeated Valsalva manoeuvres while carrying heavy objects, thereby increasing intrathoracic and

intraabdominal pressure, with a parallel rise in portal pressure.

Over the long term, patients with SVT are at risk for the development of portal hypertension and its sequelae such as variceal hemorrhage, marked splenomegaly, and portal biliopathy. The myeloproliferative neoplasms are clonal stem cell disorders characterized by an increase in one or more blood cell lines. This case illustrates that some patients suspected to have idiopathic SVT may have an occult myeloproliferative neoplasm, without elevated peripheral blood counts. These patients may be a source of confusion in practice, and the diagnosis may be delayed. Where JAK2 results are negative but a high suspicion remains, testing for CALR mutations may be useful to uncover an occult myeloproliferative neoplasm. Management involves long-term anticoagulation to prevent recurrence of SVT or thromboses of other sites, cytoreduction for the underlying myeloproliferative disorder, and endoscopic surveillance of gastroesophageal varices. The goal of cytoreduction is to reduce spleen size since an extremely large spleen may itself act as an arteriovenous shunt with 20–55% of cardiac output flowing through spleen (normally 2–4%) leading to hyperkinetic portal hypertension. Early diagnosis and treatment can prevent the development of life-altering complications, such as the devastating portal hypertension seen in this patient.

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