CASE REPORT

Tamoxifen-associated portal vein thrombosis causing severe oesophageal variceal bleeding

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SUMMARY

A 46-year-old woman with medical history of breast cancer on tamoxifen presented with syncope. On arrival to the hospital, the patient developed massive haematemesis and a subsequent esophagogastroduodenoscopy revealed oesophageal varices without any known history of liver disease. Further evaluation identified portal vein thrombosis probably caused by tamoxifen use.

BACKGROUND

Tamoxifen-associated venous thromboembolic disease is a well-documented phenomenon that can lead to an increased risk of developing deep venous thrombosis and pulmonary embolism.^{1 2} In rare instances, this can result in thromboembolic disease including tibial artery thrombosis, Budd-Chiari syndrome, or cerebral sinus thrombosis.^{1 3 4} Despite the known risk of thromboembolic disease, tamoxifen has not been reported as a cause of portal vein thrombosis.

CASE PRESENTATION

We present a case of a 46-year-old woman, a non-smoker, with a medical history significant for cutaneous mastocytosis and invasive ductal carcinoma of the left breast, status post lumpectomy with radiation in 2012, on tamoxifen 20 mg daily, who presented to the emergency department after experiencing two syncopal episodes. On arrival at the emergency department, laboratory work revealed haemoglobin of 6.2 g/dL and haematocrit of 19.5%. It was presumed that the patient's syncopal episodes were likely secondary to anaemia due to acute blood loss, and the patient received 2 units of packed red blood cells for resuscitation. While in the emergency department, the patient developed massive haematemesis. Owing to her haemodynamic instability, she was transferred to the intensive care unit (ICU), where she underwent an esophagogastroduodenoscopy (EGD), which revealed large oesophageal varices in the lower third of the oesophagus in the setting of no previously known liver disease (figure 1). These were banded with complete eradication of the varices.

INVESTIGATIONS

A four-phase CT of the abdomen and pelvis revealed left portal vein thrombosis and splenomegaly (spleen measured 14.8 cm along the maximal longitudinal distance) (figure 2); however, the CT scan did not reveal any obvious liver disease or liver lesions suggestive of malignancy. The initial differential diagnosis for the portal vein thrombosis

included: recurrent metastatic breast carcinoma, tamoxifen use, systemic mastocytosis and thrombosis due to an occult malignancy.

As part of further investigation, the patient underwent a transjugular liver biopsy that was negative for fibrosis, inflammation, sinusoid or vascular injury, or evidence suggesting systemic mastocytosis. In addition, her trypsin level was normal. Her liver function tests, serum ammonia, albumin and international normalised ratio (INR) were all within normal limits. Of note was that the patient's activated partial thromboplastin time (aPTT) was <19 s on admission, which improved but remained shortened at 21.8 s at time of discharge. A viral hepatitis panel, ceruloplasmin, antimitochondrial antibody, antismooth muscle antibody, antiphospholipid and antinuclear antibody were all negative. She underwent mammography, which did not reveal any recurrent disease. The patient also underwent a CT of the chest, which did not reveal any evidence of malignancy in the chest.

An outpatient Rapid Heme Panel, which tested for 96 mutations associated with haematological and myeloid disorders, was notably negative for any JAK-2 mutations, mutations associated with myeloproliferative neoplasms and inherited or acquired thrombophilia. Of note, the patient was not screened for hereditary thrombophilia during her hospitalisation given the acuity of her portal vein thrombosis, lack of personal or family history suggestive of inherited thrombophilia and the unlikelihood of a positive test altering her management.^{5 6}

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the patient's portal vein thrombosis included: recurrent, metastatic breast carcinoma versus tamoxifen use versus systemic mastocytosis versus thrombosis due to an underlying malignancy. Although thrombosis due to an underlying malignancy could not be completely ruled out, there have been no reported cases of thrombosis

Figure 1 Esophagogastroduodenoscopy images, on presentation, demonstrating large oesophageal varices in the lower third of the oesophagus.

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Figure 2 (Left) Coronal view of four-phase CT scan demonstrating left portal vein thrombosis. (Right) Transverse view of four-phase CT scan demonstrating splenomegaly measuring 14.8 cm in diameter, and small ascites and moderate fluid in the retroperitoneal space.

caused by an underlying malignancy in patients with a history of a cancer that was in remission. Second, the patient did not display any evidence of a second primary malignancy during her hospitalisation or during her subsequent follow-up visits.

TREATMENT

During the patient's initial EGD, five bands were successfully placed, resulting in the eradication of the varices. Following her EGD, the patient was haemodynamically stable and transferred from the ICU to the medical floor. The patient's tamoxifen was discontinued and she was not placed on an anticoagulant given her recent gastrointestinal bleed and her risk of rebleeding.

OUTCOME AND FOLLOW-UP

The patient had no further episodes of oesophageal variceal bleeding after discharge. She was started on nadolol to prevent variceal rebleeding. Six weeks after her initial presentation, the patient had a repeat EGD that showed recurrence of her varices, but these were smaller in size when compared to her initial presentation (figure 3). Two additional bands were placed with complete eradication of her varices during her 6-week follow-up. The patient returned for two additional follow-up visits, with the most recent EGD showing small varices that were not bleeding (figure 4). The patient was scheduled for 6-month follow-up EGD for further surveillance. A CT of the abdomen 4 months after her presentation revealed cavernous transformation (cavernoma) of the portal vein and persistent left portal vein occlusion without any focal hepatic lesions (figure 5). The patient followed up with her oncologist who changed her adjuvant therapy to leuprolide and anastrozole. She was scheduled for a four-phase CT of the abdomen 10 months following her hospitalisation for further evaluation.

DISCUSSION

Portal vein thrombosis is frequently associated with advanced liver disease; however, in developed countries, it is relatively

rare in patients with no liver disease.⁷ The classic causes of thrombosis are hypercoagulable states, endothelial dysfunction/injury and stasis in blood flow. Hypercoagulable states leading to portal vein thrombosis in those without known liver disease can be categorised into inherited and acquired causes. Inherited causes include prothrombin G20210A mutations, factor V Leiden deficiency, protein C and protein S deficiency and antithrombin deficiency. Acquired causes include antiphospholipid syndrome, paroxysmal nocturnal haemoglobinuria and myeloproliferative disorders such as polycythaemia vera, essential thrombocythaemia or idiopathic myelofibrosis.^{7 8} Of note, the work-up for these inherited and acquired causes were negative in our patient. Other causes of a hypercoagulable state leading to portal vein thrombosis include physiological conditions such as pregnancy, and medications such as oral contraceptives and hormone replacement therapy. All of which were not associated with our patient.

Factors leading to endothelial dysfunction/injury can be divided into three categories. The first category includes local inflammation. This is exemplified by septic portal vein thrombosis or pylephlebitis, which is commonly caused by appendicitis, diverticulitis or an intra-abdominal abscess.^{7 9} The second category includes intentional and unintentional injury to the portal vein during a procedure.⁹⁻¹¹ The third category leading to endothelial dysfunction/injury involves direct invasion of the portal vein by a malignancy (most commonly hepatocellular carcinoma), though a cancer-related hypercoagulable state also plays a role in the formation of thrombosis in this instance.⁹ In our patient, there was no evidence of an inflammatory, intra-abdominal infection or malignancy. Furthermore, the patient had no recent procedural history and the four-phase CT scan was negative for any lesions in the liver or portal system.

Stasis in blood flow can result from thrombosis itself, invasion of a malignancy leading to turbulent blood flow, or vessel compression from an adjacent malignancy such as an adenocarcinoma of the pancreas or biliary tract.⁹ However, given the

Figure 3 Esophagogastroduodenoscopy images demonstrating non-bleeding, medium oesophageal varices at 6-week follow-up.

Figure 4 Esophagogastro-duodenoscopy images demonstrating non-bleeding, small oesophageal varices at 4-month follow-up.

negative findings on the four-phase CT scan, this was unlikely in our patient.

Once there is development of portal vein thrombosis, several compensatory mechanisms occur, which can lead to the development of oesophageal varices as early as within 1 month.⁷ Collateral veins quickly develop within a few days, forming cavernous changes known as cavernomas.^{7–12} The development of these collateral veins maintains hepatic blood flow; however, portal pressure is increased to allow for adequate perfusion through the collateral veins. The result of this compensatory mechanism is portal hypertension and the development of oesophageal varices, as was the case in our patient.

The development of portal hypertension can be broadly divided into two categories: cirrhotic portal hypertension and non-cirrhotic portal hypertension. Cirrhosis is the most common cause of portal hypertension; however, our patient had no evidence of cirrhosis, leading us to consider non-cirrhotic causes for her portal hypertension. Causes of non-cirrhotic portal hypertension can be divided into several categories: chronic infections (recurrent infections of the gut leading to septic emboli); medication-induced and toxin exposure (most commonly associated with azathioprine, 6-thioguanine, arsenic); thrombophilic disorders (inherited thrombophilia, myeloproliferative neoplasms, antiphospholipid syndrome), immunological disorders (Crohn's disease, connective tissue disease, common variable immunodeficiency) and genetic disorders (Adams-Oliver syndrome, Turner disease).^{13–14} Our patient's work-up was negative for an infectious aetiology or underlying thrombophilic or immunological disorders. Furthermore, our

patient had no known history of genetics disorders that would predispose her to developing non-cirrhotic portal hypertension. The liver biopsy was negative for fibrosis, steatosis, hepatocellular necrosis, or cellular degeneration that is typically seen in medication or toxin-induced liver injury. Her liver function tests, serum ammonia, albumin and INR were all within normal limits. Lastly, the diagnostic criteria for non-cirrhotic portal hypertension include: evidence of portal hypertension; absence of cirrhosis, advanced fibrosis, or other causes of chronic liver disease; and the absence of thrombosis of the hepatic vein or portal vein on imaging.¹⁴ Since our patient was discovered to have a thrombus in the left portal vein, our investigation focused on the possible cause of her portal vein thrombosis.

Given that our patient had no known liver disease or cirrhosis, we looked for non-cirrhotic causes for her portal vein thrombosis. These included thrombophilic disorders, genetic disorders and immunological disorders, which were negative after extensive work-up. Furthermore, chronic infections leading to septic emboli have also been known to cause portal vein thrombosis; however, an infectious work up, including imaging studies, was negative. Another possibility included medications or toxin exposure. The patient's liver biopsy was negative for any of evidence of toxic-induced liver injury. Therefore, our investigation focused on medications leading to her portal vein thrombosis. Classically, medications associated with the development of portal vein thrombosis include azathioprine and 6-thioguanine, which the patient was not taking. Her home medication list included tamoxifen, levothyroxine and a multi-vitamin tablet. Given that tamoxifen is associated with thromboembolic disease, this was the most likely cause of her portal vein thrombosis after excluding other possibilities.

Tamoxifen is a selective oestrogen-receptor modulator with both oestrogen agonist and antagonist potential. The exact mechanism of how tamoxifen leads to increased risk of thromboembolic events remains unclear. Studies have shown that tamoxifen leads to changes in the coagulation cascade and the fibrinolytic system (antithrombin III, protein C, protein S). However, these same studies have demonstrated that these changes are neither clinically nor statistically significant and unlikely to account for the increased risk of thromboembolic events.^{15–18} In terms of changes in the coagulation profile, studies have demonstrated a shortened aPTT when compared to control groups; however, changes in the fibrinolytic factors and fibrinogen were not significantly different when compared to the control group.¹⁸ It is interesting to note that our patient had a persistently shortened aPTT with normal prothrombin time and INR during her hospitalisation.

This case illustrates the need to consider tamoxifen as the underlying aetiology of any thromboembolic disease in patients

Figure 5 Four-month follow-up CT of the abdomen demonstrating cavernous transformation (cavernoma) of the portal vein.

taking tamoxifen. This is especially important as tamoxifen is widely used in the treatment of breast cancer, the most common cancer among women worldwide.

Learning points

- ▶ Portal vein thrombosis is frequently associated with advanced liver disease; however, in developed countries, it is relatively rare in patients with no liver disease.
- ▶ Consider tamoxifen as the cause of thromboembolic disease in patient's taking tamoxifen.
- ▶ Tamoxifen leads to changes in the coagulation cascade and fibrinolytic system; however, these changes are not clinically significant and unlikely to account for the increased risk of thromboembolic disease.

Contributors All the authors were involved in the patient's care. AH wrote the case report. SH assisted in revising the case report and obtained and edited the images used. SH, EB and RP helped edit the manuscript and approved the final version.

Competing interests None declared.

Patient consent Obtained.

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