CASE REPORT

Occult myeloproliferative neoplasms: not so occult any more

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Accepted 20 April 2017

SUMMARY

Non-cirrhotic, non-malignant portal vein thrombosis (PVT) is commonly secondary to inherited or acquired prothrombotic states. However, even after extensive workup, 25% of patients with PVT have no apparent prothrombotic aetiology identified (idiopathic PVT). Inherited conditions include factor V Leiden, PT mutation and protein C/SAT deficiency. Acquired conditions include APS, PNH and BCR-ABL 1-negative myeloproliferative neoplasms (MPN). BCR-ABL-1 negative MPNs are the most frequent underlying prothrombotic risk factor for PVT (15%–30%). However, peripheral blood counts often remain within normal ranges in these patients with MPN because of portal hypertension sequel. Despite suggestive features of MPN in bone marrow, these patients lack adequate diagnostic criteria and are classified as occult MPN. The discovery of recurrent molecular abnormalities such as CALR gene exon 9 mutation presented a crucial advance in the diagnosis of occult MPNs. In our patient, the diagnosis of MPN was made on this basis, despite lack of peripheral evidence of MPN.

PMF) has aided in appropriate diagnosis of many patients with occult MPN. Here we describe a case of splenic, mesenteric and PVT in a patient with occult or latent MPN who remained undiagnosed for 6 years, until the discovery of the gene, calreticulin (CALR) exon 9 mutation and its commercial availability in 2014.

CASE PRESENTATION

A 26-year-old Caucasian male with past medical history of recurrent variceal bleeding presented with complaints of abdominal pain and intermittent black stools for the past 2 days. Patient had multiple episodes of variceal bleeding in the past, controlled with nadolol, variceal banding and splenic artery embolisation in March 2009. Patient also underwent splenectomy in June 2013 to prevent recurrent gastrointestinal bleeding. Physical examination was significant for a vitally stable patient with right upper quadrant and epigastric tenderness with moderate ascites. Lung examination revealed diminished breath sounds in right base.

INVESTIGATIONS

Laboratory testing in 2008 revealed haemoglobin of 11 g/dL (baseline 9–11 g/dL), white cell count of $7 \times 10^9/L$ (figure 1) and platelet count of $210 \times 10^9/L$. Liver enzymes were mildly elevated. PT and PTT were within normal limits. Chest X-ray revealed R side pleural effusion. Ultrasound Doppler (figure 2) and CT scan of abdomen/pelvis were performed, which revealed abdominal ascites, portal, splenic and mesenteric vein thrombosis with splenomegaly, complicated by oesophageal and gastric varices. An EGD was performed, which revealed extensive portal hypertensive gastropathy with moderate-sized gastric varices, grade 4 distal and mid-oesophageal varices. All the varices were banded without complications.

Extensive prothrombotic workup was initiated. Fibrinogen levels and thrombin time testing were within normal limits. Testing for protein C, protein S and antithrombin functional activity were normal. Other following tests were normal or negative: lupus anticoagulant, anti β_2 glycoprotein antibodies, anticardiolipin antibodies, JAK2 V617F mutation and MPL mutation. PNH flow cytometry analysis for CD 56 and CD 59 were negative. Further testing with homocysteine and serum ferritin levels, DRVV screen, hepatitis B and C screen were negative. The patient was diagnosed with idiopathic PVT and placed on

BACKGROUND

The incidence of portal vein thrombosis (PVT) among patients without cirrhosis is unclear. Among patients with cirrhosis, PVT is common and is associated with the severity of patient's liver disease. In a study of almost 24 000 autopsies in Sweden, the most common predisposing conditions for PVT were cirrhosis, hepatobiliary malignancies, intra-abdominal infection or inflammation and myeloproliferative neoplasms (MPN). However, in this series, no precipitating factors were identified in 14% of patients. PVT in a previously healthy liver is thought to be due to inherited or acquired prothrombotic states. However, no apparent cause for PVT is identified in more than 25% of patients.¹

As many as 50% of all cases of Budd-Chiari syndrome maybe due to an underlying chronic MPD and an accompanying hypercoagulable state. Peripheral blood evidence of myeloproliferation may not be present in the presence of portal hypertension and splenomegaly.² JAK2 V617F mutations have been described in 26%–59% patients with Budd-Chiari syndrome, many of whom had negative results from standard testing for MPD.³

The availability of JAK2 V617F mutation (present in approximately 90% of PV and 50% of those with ET/PMF) and MPL W515L/K mutation (present in 5%–10% of patients with ET/

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To cite: Karam D, Iyer V, Agrawal B. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-219388

Figure 1 Peripheral smear.

enoxaparin for anticoagulation. CALR exon 9 mutation testing became available and testing revealed the patient to be positive for the same (mutational site p.L367fs*46). Patient was diagnosed with underlying occult MPN with ET phenotype. This was established to be the aetiology of extensive PVT.

Bone marrow aspiration and biopsy performed for evaluation of thrombocytosis after splenic artery embolisation in April 2009 revealed 70%–80% cellularity (figures 3 and 4). All cell lines were present. Granulocytic hyperplasia with M:E ratio of 6:1 with increased megakaryocytes was seen. Few megakaryocytes were hyperlobated whereas few were hypolobated with occasional loose clustering. Immunostaining for CD 34 revealed no increase in positive staining myeloblasts. Bone trabeculae were unremarkable. Reticulin stain revealed no significant increase in reticulin fibrosis. Chromosome staining by banding method revealed 46XY (20). Fish for ABL1 BCR was negative. Fish results for other cytogenetic abnormalities were also negative. The examined cells in metaphases did not reveal abnormalities in the probed regions of chromosome 5, 7, 8 and 20.

TREATMENT

After the diagnosis of MPN with ET phenotype, the patient was started on hydroxyurea and the platelet count decreased from over 2000 to $1000 \times 10^9/L$ in 6 weeks and subsequently

Figure 2 Doppler ultrasound of abdomen revealing portal vein thrombosis in our patient.

Figure 3 Bone marrow histology.

normalised to $250 \times 10^9/L$. The patient continued taking enoxaparin as anticoagulation for hypercoagulable state.

OUTCOME AND FOLLOW-UP

Patient remained symptom free thereafter with resolution of ascites, pleural effusion, hypoalbuminaemia, cachexia and GI bleeding. He is on regular follow-up. Prognosis has been excellent; he is doing well for 8 years since PVT and after MPN diagnosis. ECOG performance status improved from 3 to 1. There has not been any disease-related complications.

DISCUSSION

Primary MPNs are a well-known cause of acquired PVT.⁴ MPNs are clonal haematological malignancies that include polycythaemia vera, essential thrombocythaemia and idiopathic myelofibrosis.^{5,6} The pathophysiology of MPN is thought to be activation of tyrosine kinase secondary to mutations.⁷ Although MPNs are associated with different mutations, they fall broadly into two categories: mutations that activate thrombopoietin receptor such as MPL and mutations that inactivate negative regulators. The most frequent mutation in BCR-ABL-1 negative MPN, ET and PMF is the JAK2 V617F mutation. This is detected in approximately 50%–60% of patients. MPL gene mutations are detected in another 5%–10% of patients with ET and PMF. The

Figure 4 Hypercellular bone marrow.

identification of JAK2 MPL mutation has facilitated identification of inherent thrombophilias in many patients with chronic PVT.^{7,8}

It was recently discovered that CALR somatic mutation (insertion and/or deletion) provides a diagnostic marker in JAK2/MPL wild-type ET and PMF, with a mutation frequency of 56% and 88%, respectively. CALR is a highly conserved calcium-binding chaperone protein. It contains nine exons and is located on chromosome 19p13.2. The protein has three domains: globular amino acid N domain, central proline-rich domain and an acidic carboxy terminal C domain. The exact mechanism of action is unknown. Studies have shown that CALR mutation disrupts the C terminal endoplasmic reticulum-retention sequence (KDEL) and generates a novel C terminus, activating STAT 5 pathway. This may explain clinical response to hydroxyurea.⁹ CALR mutation is not seen in post-PV myelofibrosis and JAK2/MPL-mutated patients with ET or PMF. With use of all three mutations testing, the incidence of occult MPN decreases to <10%.¹⁰ CALR mutations also provide prognostic information. In ET, CALR mutations are associated with higher platelet counts, lesser risk of thrombosis and lower haemoglobin level. In PMF, CALR mutations are associated with better survival compared with JAK2 mutation.¹¹

In patients with PVT, hypersplenism and its sequestration¹² can mask usual phenotypic features of MPN and hence, testing for JAK2, MPL and CALR mutations may be considered to unmask the diagnosis of MPN, especially in young patients.

In our patient, the thrombocytosis after splenectomy was attributed to a postsplenectomy state. While following patient's rising platelet count exceeding $2000 \times 10^9/L$ with extensive PVT,

CALR exon 9 mutation testing became available and patient tested positive for it. An underlying MPN with ET phenotype was determined to be the likely aetiology of the thrombotic event and appropriate cytoreductive therapy was initiated with excellent clinical improvement.

Contributors All authors have contributed to the manuscript individually and agree with the conclusion. DK, PMK and BA were involved in conception and design of the work. DK and VI worked together to draft the article and complete writing the manuscript. PMK and BA critically revised the article and approved the final version to be published.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- In patients with portal vein thrombosis, splenomegaly and its sequel can mask peripheral evidence of myeloproliferative neoplasms.
- We recommend testing for JAK2, MPL and CALR mutations to rule out occult myeloproliferative neoplasms in patients with idiopathic PVT.

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