CASE REPORT

A novel subtype of myeloproliferative disorder? JAK2V617F-associated hypereosinophilia with hepatic venous thrombosis

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To cite: Dasari S, Naha K, Hande M, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2013-200087

SUMMARY

We report the case of a 27-year-old man, presenting with one episode of massive haematemesis and a history of persistent eosinophilia for the past 8 months. An evaluation revealed hepatic cirrhosis with portal hypertension, secondary to chronic Budd-Chiari syndrome. Further investigations confirmed a diagnosis of hypereosinophilic syndrome. Molecular genetic analysis was negative for FIP1L1-PDGFRA gene rearrangement, but positive for JAK2V617F mutation.

BACKGROUND

Hypereosinophilia syndrome (HES) comprises a heterogeneous group of haematological disorders characterised by chronic, unexplained blood and tissue eosinophilia, with evidence of organ dysfunction attributable to eosinophilia.[1] HES has been broadly classified into myeloproliferative and lymphocytic variants based on an improved understanding of underlying pathophysiological mechanisms.[2] Lymphocytic HES results from overproduction of interleukin 5 (IL-5) by dysregulated T-lymphocytes and secondary expansion of eosinophils. Conversely, myeloproliferative HES is characterised by the presence of a gene rearrangement producing a fusion product termed FIP1L1-PDGFRA with constitutive tyrosine kinase activity resulting in clonal proliferation of eosinophils. Although the role of FIP1L1-PDGFRA is analogous to that of the JAK2V617F mutation seen in myeloproliferative disorders like polycythaemia vera and essential thrombocytosis, the JAK2V617F mutation itself is rarely encountered in HES and limited to a few case reports.[3–6] This report describes another patient with HES associated with the JAK2V617F mutation presenting with chronic Budd-Chiari syndrome, and lends further support to the contention that JAK2V617F associated HES represents a distinct and novel subtype of myeloproliferative HES.

CASE PRESENTATION

A 27-year-old man presented with one episode of massive haematemesis. There were no associated symptoms of abdominal pain or distension. He had been detected to have eosinophilia 8 months ago and had received several empirical courses of antihelminthics. There were no symptoms suggestive of allergic rhinitis, asthma or eczema in the past. He denied any history of substance abuse or unprotected sexual exposure. There was no history of liver disease among his family members. He was born of a non-consanguineous marriage.

At admission, the patient was haemodynamically stable except for mild tachycardia. He was conscious and oriented. General physical examination did not reveal any signs of liver cell failure. Per-abdominal examination showed no tenderness. Mild hepatomegaly with moderate splenomegaly was noted. There was no evidence of free fluid within the abdominal cavity and no dilated veins over the abdominal wall. Examination of other systems was normal.

INVESTIGATIONS

Routine laboratory investigations showed gross eosinophilia with mild thrombocytopaenia, but otherwise normal blood counts (haemoglobin 14.4 g/dL, total leucocyte count 9300 cells/μL, absolute eosinophil count 5200 cells/μL and platelet count 80 000 cells/μL). A peripheral smear showed 28% eosinophils; no blasts or abnormal cells were seen. Liver function tests were suggestive of chronic liver disease. Emergent gastroduodenoscopy showed large oesophageal varices. Abdominal ultrasonography confirmed hepatic cirrhosis with portal hypertension. In addition, thrombosis of the hepatic veins was noted, along with extensive collaterals, suggestive of chronic Budd-Chiari syndrome. Other causes of hepatic cirrhosis including chronic infection with hepatitis B and/or C virus, Wilson's disease and haemochromatosis were ruled out by appropriate biochemical tests.

Evaluation for suspected HES was then performed. Stool examination was negative for helminths. Bone marrow aspiration showed increased eosinophils with normal maturation and no abnormal cells. HIV serology by ELISA technique was negative. Transthoracic echocardiography revealed mild ventricular diastolic dysfunction. Molecular genetic analysis for FIP1L1-PDGFRA gene rearrangement was negative. Concurrently, the patient tested positive for JAK2V617F mutation. Karyotyping for t(9;22)(q34;q11) was negative.

DIFFERENTIAL DIAGNOSIS

- HES complicated by chronic Budd-Chiari syndrome and hepatic cirrhosis, in association with JAK2V617F mutation

TREATMENT

The patient was initially managed with intravenous fluid boluses. Endoscopic variceal ligation was performed for oesophageal varices. Subsequently, he was started on oral glucocorticoid therapy for HES (prednisolone 60 mg orally once daily) which was subsequently tapered to a maintenance dose of 10 mg orally once daily.

OUTCOME AND FOLLOW-UP

The patient responded to glucocorticoid therapy with a rapid and sustained fall in eosinophil counts. He continues to be on regular follow-up and is currently asymptomatic. Eosinophil counts have stabilised at around 250 cells/μL.

DISCUSSION

Diagnostic criteria for HES includes mandatory evidence of eosinophil-mediated target organ damage, most frequently involving the skin, heart, lungs and the gastrointestinal tract. Venous thrombosis is a recognised haematological complication of HES; the mechanism is presumably a hypercoagulable state secondary to eosinophilia.[2] Although Budd-Chiari syndrome is the commonest form of venous thrombosis in patients with HES, HES is nevertheless an unusual cause for hepatic vein thrombosis, perhaps due to its relative rarity vis-à-vis other hypercoagulable disorders. The presence of blood eosinophilia is an obvious clue to underlying HES in patients with Budd-Chiari syndrome; however, other prothrombotic diseases associated with eosinophilia such as visceral malignancy should be ruled out. Once a diagnosis of underlying HES has been confirmed, this is an indication for specific therapeutic intervention in the form of corticosteroid or imatinib based on the variant of HES.[2]

There are only a handful of reports describing HES in association with JAK2V617F mutation.[3–6] Of these, the case reported by Mishchenko *et al*[3] is the most similar to our own, where a young woman presenting with Budd-Chiari syndrome was subsequently diagnosed with HES and tested positive for the JAK2V617F mutation. Unlike our patient, however, in that instance Budd-Chiari syndrome developed acutely leading to fulminant hepatic failure and ultimate death.

Interestingly, the JAK2V617F mutation has been linked with Budd-Chiari syndrome in patients without overt myeloproliferative disease.[7 8] This entity has been termed as occult Philadelphia-negative myeloproliferative neoplasm; as the name suggests, these patients are presumed to have an occult myeloproliferative disorder manifesting with venous thrombosis.[7]

Presence of a JAK2V617F mutation also raises important therapeutic questions centreing principally on the role of tyrosine kinase inhibitors. Imatinib is now considered as a first-line drug for FIP1L1-PDGFRA-positive HES, with good clinical and haematological response to therapy. Conversely, FIP1L1-PDGFRA-negative HES as expected responds poorly to imatinib, improving instead with corticosteroids and direct inhibitors of IL-5 such as mepolizumab.[9] Although the presence of JAK2V617F would suggest clonal proliferation rather than IL-5 driven eosinophilia, unavailability of a JAK2-specific tyrosine kinase inhibitor led to corticosteroid therapy; this decision was subsequently justified by achieving haematological remission. The therapeutic aspect of JAK2V617F-associated HES was also raised in the report by Helbig *et al*[4] describing successful management with interferon-α. The patient in question was treated unsuccessfully at first with hydroxyurea and then imatinib. Acceleration of disease with development of blasts then forced a trial of interferon-α which eventually produced disease remission. Somewhat surprisingly corticosteroid therapy was never attempted; this contrasted sharply with our report where corticosteroid produced an acceptable response.

In summary, this case report describes a rare variant of HES with JAK2V617F mutation, presenting with chronic hepatic vein thrombosis and satisfactorily managed with oral corticosteroid therapy. Recognition of JAK2V617F-positive HES as a distinct subtype of myeloproliferative HES is a prerequisite to determine the role, if any, of putative JAK2 inhibitors in this form of HES.

Learning points

- Hypereosinophilic syndrome can present with venous thrombosis.
- Being a form of myeloproliferative disorder, hypereosinophilic syndrome can be associated with JAK2V617F mutation.
- All patients with Budd-Chiari syndrome of unknown cause should be screened for JAK2V617F positivity.
- The roles of tyrosine kinase inhibitors and corticosteroids need to be clarified in the subset of patients with hypereosinophilic syndrome and JAK2V617F positivity.

Contributors SD, KN, GV and MH were involved in the concept, design, definition of intellectual content, literature search, and in the preparation, editing and review of the manuscript. In addition, SD and KN were involved in data acquisition. SD and MH were involved in clinical care of the patient.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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