CASE REPORT

Elevated serum erythropoietin in a patient with polycythaemia vera presenting with Budd-Chiari syndrome

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SUMMARY

Polycythaemia vera (PV) is a clonal disorder of bone marrow stem cells characterised by erythrocytosis. Diagnosis of PV requires exclusion of secondary causes of polycythaemia. It has been held that an elevated erythropoietin (Epo) level strongly indicates secondary erythrocytosis and excludes PV diagnosis, to the extent that the reduced serum Epo level is currently listed as a minor criterion in the WHO classification scheme for PV. However, patients with PV who co-present with Budd-Chiari syndrome have been documented with elevated serum Epo levels. For these patients, identification of the Janus kinase 2 (JAK2) V617F point mutation along with the transient nature of the Epo elevation provides certainty of PV diagnosis, as illustrated by the proband. In this case report, the patient's positive response to cytoreductive therapy (hydroxyurea 500 mg daily) and phlebotomy (750 mL over three phlebotomies) further supports validity of PV diagnosis with elevated Epo. The patient remains on rivaroxaban (Xarelto) for treatment of her portal vein thrombosis.

normal or even elevated Epo level requires additional, supporting genetic and/or pathological findings per current WHO classification.² This is illustrated by the proband of this case report who copresented with Budd-Chiari syndrome (BCS).³

CASE PRESENTATION

A previously healthy, non-smoking 58-year-old woman presented for evaluation of a new onset ascites of 2 months duration. At presentation she was noted to have elevated serum transaminases, leucocytosis (white cell count (WCC) 27.9 K/ μ L), erythrocytosis (Hb 19.8 g/dL) and a normal platelet count (152 k/ μ L). An abdominal ultrasound with Doppler confirmed a suspected diagnosis of BCS with no flow seen within the right or middle hepatic veins. The patient did not have a palpable spleen by physical examination. Abdominal ultrasound demonstrated a normal sized spleen of 8.8 cm. Given the patient's clinical presentation and laboratory findings, a diagnosis of PV was suspected. However, the patient's initial serum Epo level was elevated at 157 mIU/mL (normal 3.7–31.5 mIU/mL).

BACKGROUND

Polycythaemia vera (PV) is a clonal disorder of bone marrow (BM) stem cells characterised by erythrocytosis, and often associated with variable increases in leucocyte and platelet counts. PV is so far the only primary acquired marrow disorder leading to erythrocytosis, versus secondary erythrocytosis from various extramedullary pathological events. Reported PV incidence varies by region but overall it is more common among patients of advanced age. The median age at diagnosis is 60 years. Clinically, PV is associated with splenomegaly, arterial or venous thrombotic events particularly of the mesenteric or portal systems, erythromelalgia and pruritus. Patients may also be identified incidentally after being noted to have elevated haemoglobin (Hb) and haematocrit.^{1 2} The diagnosis of PV also requires exclusion of secondary causes of polycythaemia according to clinical and pathological findings consistent with those defined by the 2008 WHO classification (table 1).²

Even prior to incorporation of serum erythropoietin (Epo) level as a WHO diagnostic criterion, an elevated Epo level has been widely held to be suggestive of secondary erythrocytosis and exclusion of PV. Hence a reduced Epo level is considered a minor criterion and not required for PV diagnosis. Accordingly, the diagnosis of PV for patients with a

INVESTIGATIONS

A repeat test was ordered for serum Epo. The patient's Epo value was 56 mIU/mL 18 h after initial assessment. Evaluation for secondary causes of polycythaemia included radiological evaluation by CT for hepatocellular carcinoma, renal cell carcinoma, hemangioblastoma and uterine fibroids. All CT findings were normal. In addition, there was no history suggestive of hypoxaemia. The patient had normal resting and ambulatory room air oxygen saturations.

The patient had no identifiable cause for leucocytosis; therefore further evaluation for possible PV was pursued. Peripheral blood sent for JAK2 mutation by PCR revealed a positive V617F point mutation. BM examination showed hypercellularity (80% cellularity) for the patient's age, decreased iron stores, focally increased platelets and grade 1 fibrosis consistent with a diagnosis of PV.

TREATMENT

The patient's PV remains under control after total phlebotomy (750 mL) and hydra therapy (500 mg daily). Recent laboratory tests show a Hb of 13.7 and HCT of 41.3. The patient's WCC count has also responded to treatment (reduction of initial count from 27.9 K/ μ L to 6.5 K/ μ L). She is being treated to a target Hb of <42% as has been

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Table 1 WHO classification for PV*

Major criteria	Minor criteria
1. Increased red cell volume, or haemoglobin >18.5 g/dL in men, 16.5 g/dL in women	1. Bone marrow biopsy demonstrating hypercellularity for age with tri-lineage maturation and proliferation
2. Presence of <i>JAK2</i> ^{V617F} or similar <i>JAK2</i> exon 12 mutation	2. Serum erythropoietin level below the reference range for normal
	3. Endogenous erythroid colony formation in vitro

*Diagnosis requires both major and one minor criterion or the first major with two minor criteria.

JAK2, Janus kinase 2.

suggested as the goal in women for reduction of cardiovascular events.⁴ She remains on rivaroxaban (Xarelto) 20 mg daily for treatment of her portal vein thrombosis and her transaminases have normalised. At the time of initial presentation, a transjugular intrahepatic portosystemic shunt (TIPS) procedure was performed for treatment of BCS, and recent imaging demonstrates this is patent. She is currently being followed by hepatology to monitor TIPS patency and potential need for liver transplantation in the future. *JAK2* mutation analysis was not repeated on follow-up in view of the high sensitivity (97%) and specificity (nearly 100%) of this finding for the diagnosis of PV.

OUTCOME AND FOLLOW-UP

Response of the patient's PV to therapy was noted within 2 weeks of initiating treatment with phlebotomy and hydra. She has been on treatment now for 12 months with continued clinical benefit. The patient's Epo level was within normal range (3.9 mIU/mL) as of April 2014.

DISCUSSION

BCS occurs in one in a million individuals.⁵ This syndrome continues to challenge the clinician in terms of arriving at the underlying cause and optimal treatment.⁶ PV is considered to be the most frequent condition causing BCS (10–40% of cases). The patient's serum Epo level can clarify but may also confuse the diagnosis of PV. Reduced Epo is a minor WHO criterion for the diagnosis of PV and commonly used clinically to differentiate primary from secondary thrombocytosis. However, elevated Epo does not exclude the diagnosis of PV. Still, a majority of studies have suggested the contrary. In one study of 125 patients with erythrocytosis, none of the patients with PV with raised Hb (>14.0 g/dL) was observed to have elevated Epo levels, whereas Epo was commonly elevated among patients with apparent and idiopathic erythrocytosis.⁷ In the recent Italian and Austrian study by Rumi *et al*,⁸ the median serum Epo level of 468 patients diagnosed with PV was 2.7 mIU/mL and significantly lower than that of 642 patients with essential thrombocythaemia. These findings have been confirmed with other studies where reduced serum Epo levels are considered to be highly specific (~97%) but lacking in sensitivity (28–64%) for the diagnosis of PV. Raised Epo values similarly lacked sensitivity (47%) towards diagnosis of secondary erythrocytosis.^{7 9 10}

The cytoplasmic tyrosine kinase *JAK2* mediates growth factor receptor signalling. The V617F point mutation in exon 14 results in gain of function proliferative activation for haematopoietic precursors.¹¹ *JAK2*^{V617F} was most prevalent in PV (65–97%) among Western patient populations.^{8 11 12} Prior to the incorporation of *JAK2* mutation analysis as part of the diagnostic criteria, an elevated serum Epo level casts significant

doubt on the diagnosis of PV even in the absence of identifiable causes of secondary erythrocytosis. With a sensitivity of 97% and specificity nearing 100% for the diagnosis of PV in patients with elevated haematocrit,¹³ peripheral blood screening for the *JAK2*^{V617F} mutation allows greater certainty in establishing the diagnosis of PV among patients with elevated Epo levels. This is particularly relevant in patients co-presenting with BCS, as this subpopulation has been described to have high serum Epo.^{3 14} For these patients, arriving at the correct diagnosis of PV is otherwise challenging, as peripheral blood counts can be within the normal range because of portal hypertension and sequelae that include haemodilution or hypercythaemia.

The proband's *JAK2* mutation status also argues against the secondary congenital erythrocytosis (CE). The secondary CE rises from conditions that lead to tissue hypoxia, resulting in increased Epo. These include Hb variants with increased affinity for oxygen (HBB, HBA mutations), decreased 2,3-bisphosphoglycerate due to BBPGM mutations, or mutations in the genes involved in the hypoxia sensing pathway (VHL, EPAS1 and EGLN1).¹⁵ It is the consensus of multiple investigators that every documented secondary CE does not exhibit the *JAK2*^{V617F} mutation.^{16 17}

Screening for the *JAK2*^{V617F} has modified the diagnostic approach to Philadelphia-negative (Ph⁻) myeloproliferative neoplasms (MPNs).¹⁸ Splanchnic vein thrombosis (SVT), including thrombosis of the portal veins (PVT) causing BCS are frequently the first manifestation of PV and essential thrombocytopaenia.¹⁹ Ph⁻ MPNs in turn are among the commonest causes of BCS and PVT, being found in up to 50% and 25% of these patients, respectively.¹⁸ In a meta-analysis, Dentali *et al*¹⁸ first demonstrated the remarkably high prevalence of *JAK2*^{V617F} mutation (32.7%) in SVT. On the basis of meta-analyses and random effects modelling with 1062 BCS and 855 PVT patients, Smalberg *et al*²⁰ confirmed the high frequency of MPNs (40.9%) among patients with SVT, of whom the mean incidence of *JAK2*^{V617F} mutation was 41.1%. Significantly, MPN was diagnosed in 17.1% of patients with BCS without typical haematological features, substantiating the value for routine *JAK2*^{V617F} diagnostic work up for patients with SVT regardless of hallmark MPN haematological presentations.

In Kiladjian *et al*'s²¹ study of 241 SVT patients (104 BCS, 137 PVT), *JAK2*^{V617F} was present in 45% of BCS and 96.5% of patients with BM changes specific for MPD and endogenous erythroid colonies. *JAK2*^{V617F} was also present in 58% of patients with only one of these two BM features, with 7% of patients having neither. The authors posited that BM investigations may be avoidable in up to 40% of patients by stratifying MPD diagnosis with *JAK2*^{V617F} detection as the first test. Primignani *et al*²² similarly advocated prioritising this non-invasive biomarker for initial assessment of patients with chronic myeloproliferative disorder prior to marrow biopsy, based on findings that *JAK2*^{V617F} mutation prevalence was >70% among SVT patients with a BM biopsy diagnostic of chronic myeloproliferative disorders. However, BM is still an important minor WHO criterion, particularly in patients with normal or elevated Epo levels who would otherwise not meet diagnostic criteria for PV. While highly sensitive and specific for a PV diagnosis, the *JAK2* mutation is also found in essential thrombocythaemia and myelofibrosis.²³ It is the current standard practice in this institution to perform a BM biopsy in patients with a new diagnosis of PV.

According to the 2007 WHO consensus criteria, diagnosis of PV for a patient requires meeting two major and one minor criterion or the first major and two minor criteria. The major criteria are: (1) Hb >18.5 g/dL in men or 16/5 g/dL in

women, or other evidence of increased red cell volume (RCV); and (2) presence of *JAK2*^{V617F} mutation. Minor criteria include (1) hypercellular BM for age with panmyelosis with prominent erythroid, granulocytic and megakaryocytic proliferation; (2) a serum Epo level below the reference range; and (3) endogenous erythroid colony formation in vitro.²⁴ Of these criteria, the *JAK2*^{V617F} mutational status is the most important as it is present in nearly all cases of PV.^{8 11 12 24} The demonstration of increased RCV is also highly important as the second major criterion, and can be accurately evaluated by red cell mass determination using ⁵¹Cr. This test, however, is infrequently performed as the patient's Hb and haematocrit values are used routinely as a clinical surrogate despite their inaccuracy in diagnosing PV.^{25 26}

Mechanisms for the elevated serum Epo level in BCS have been proposed for patients whose Epo levels should be otherwise suppressed. Epo production normally occurs in the kidneys of adults and in hepatocytes of fetuses, but in adults, small amounts of extrarenal Epo are produced by liver hepatocytes.^{27 28} Epo production is regulated in an oxygen-dependent manner and driven via hypoxia-inducible transcription factors (HIF)-1 and HIF-2,^{27 28} believed to be upregulated in patients with BCS having hypoxic liver injury and hepatocyte necrosis.^{3 29}

The role of HIFs in hypoxic extrarenal Epo production is supported in mouse models^{30 31} that compared the hepatocyte specific genetic inactivation of HIF-1 α and HIF-2 α . Hepatic Epo production was found to be suppressed in anaemic, HIF-2 α deficient infant mice.³¹ In gene knockdown animal models, an elevated hepatic Epo may constitute an antioxidant and protective cellular mechanism in response to injury and environmental stress.^{30 31} The induction of an acute phase reaction resulted in increased Epo mRNA within the liver in conjunction with increased activity of HIF-1 α and HIF-2 α . The proinflammatory cytokine interleukin 6 was also noted to trigger hepatic HIF-1 α production, in turn upregulating hepatic Epo in vivo.³⁰

PVT would lead specifically to hypoxia within the liver though not generalised hypoxia. Hence, the theorised pathogenesis of the elevated Epo is that BCS causes liver specific hypoxia even though the patient did not have hypoxia on clinical assessment of oxygen saturation. Previously, Thurmes and Steensma³ demonstrated a reduction of Epo following cytoreductive treatment in two patients with BCS. The proband in this case similarly responded positively to cytoreductive therapy with hydrea and total phlebotomy.

Finally, this case report adds to the limited number of studies that report on the use of rivaroxaban for treatment of PVT.^{32 33} This orally active direct factor Xa inhibitor, approved for the

long-term treatment of venous thromboembolism, offers an attractive therapeutic option in view of its predictable pharmacokinetics/pharmacodynamics and high bioavailability with a half life of up to 12 h.³² Van der Hulle's recent systematic review and meta-analysis showed that individual novel oral anticoagulants including rivaroxaban have comparable efficacy as vitamin K antagonists (warfarin), and are associated with a significantly lower risk of bleeding complications.³⁴ In addition to the clinical and pharmacological benefits, rivaroxaban offers greater patient convenience as it is given in fixed, once daily doses without the need for frequent coagulation monitoring.

Contributors CJ and YL provided care of the patient in the case study. YL is the attending physician. He managed the patient's care from point of initial diagnosis, and determined and implemented treatment strategy. CJ and AWT prepared the initial manuscript draft. AWT reviewed the relevant findings in the patient's clinical history, assembled the Discussion section and Learning points based on the literature review, and finalised and revised the case report. All the authors participated in the review of the final manuscript.

Competing interests None.

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Learning points

- In patients presenting with Budd-Chiari syndrome and suspected polycythemia vera (PV), the diagnosis of PV should not be excluded based on elevated serum Epo levels.
- With exclusion of secondary causes of polycythemia as per WHO recommendations and in the otherwise appropriate clinical setting, patients should undergo complete diagnostic evaluation for PV including mutation analysis for *JAK2*^{V617F} to assure accurate diagnosis and treatment.
- The patient's performance supported the chronic use of rivaroxaban, a novel oral anticoagulant, as a viable treatment option for portal veins control.

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