CASE REPORT

Bumpy road to the diagnosis of polycythaemia vera

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SUMMARY

Polycythaemia vera (PV) is the most common myeloproliferative neoplasm, characterised by increased red cell mass that can present as an unspecified symptom or a thrombohaemorrhagic event. Its diagnosis is based on the presence of erythrocytosis, the identification of the Janus kinase 2 mutation and bone marrow aspirate or biopsy alterations. The challenge of this disease lies on the treatment approach. Its cornerstone is phlebotomy, but depending on the vascular risk, it can include cytoreductive agents, low-dose aspirin or even anticoagulation. We present the case of a 75-year-old woman, whose inaugural presentation of PV was an arterial peripheral occlusion followed by three recurrent events in the same arterial region and a pulmonary embolism. A phlebotomy was initially performed and, after the diagnosis was made, the patient was initiated on low-dose aspirin and anticoagulation with favourable outcome.

BACKGROUND

Myeloproliferative neoplasms are infrequent disorders, with annual incidence rates of 1–2/100 000 people. Polycythaemia vera (PV) is the most common myeloproliferative neoplasm, characterised by the presence of the Janus kinase 2 (JAK2) mutation, erythrocytosis and a hypercellular bone marrow biopsy with panmyelosis. It carries a risk of thrombosis, stratified accordingly to age, previous thrombosis and leucocytosis. The therapeutic approach is individualised, depending on vascular risk and consisting of phlebotomy, cytoreductive agents and low-dose aspirin.^{1 2} This case represents an unusual inaugural presentation of PV, followed by four recurrent thrombotic events, that complicated the path to diagnosis and increased the difficulty of medical management.

CASE PRESENTATION

A 75-year-old woman with arterial hypertension, hypercholesterolaemia and aortic stenosis was admitted with ischaemic signs of her left lower limb and submitted to popliteal embolectomy with adequate reperfusion. Given the acute presentation and unknown occlusive vascular disease, our first hypothesis was arterial occlusion due to embolisation. However, despite being asymptomatic, the patient could also have peripheral arterial disease due to longstanding atherosclerosis or non-atherosclerotic vascular disease. In this particular case, the patient had a sustenance of absolute erythrocytosis with haemoglobin levels >18 g/dL and haematocrit >56.2%, which also gave rise to

suspicion of PV. During hospitalisation, a thoracic, abdominal and pelvic CT scan with angiography, as well as an echocardiogram, were obtained in order to exclude embolic sources, showing no evidence of thromboembolism, excluding embolisation as the mechanism of arterial occlusion and reinforcing the probable diagnosis of PV. In order to exclude it, the patient was tested for the JAK2 V617F mutation, serum erythropoietin (EPO) level was obtained (9.7 mUI/L (N 4.3–29.0)) and a bone marrow aspiration was performed, which showed normocellularity for age and absence of stainable iron. As the patient maintained absolute erythrocytosis, she was submitted to phlebotomy and afterwards discharged on anticoagulation. Two weeks later, there was recurrence of ischaemia in the same arterial territory and the patient was again submitted to popliteal embolectomy. At admission, the patient was hypoxaemic with a PaO₂ of 59 mm Hg and tachycardic with a heart rate of 114 bpm, giving rise to suspicion of acute pulmonary embolism, excluded after thoracic CT angiography was performed. During hospitalisation, there were two new arterial thrombotic recurrences, despite anticoagulation, culminating in above-knee amputation. At this point, one could wonder if she had suffered a complication from her previous surgery that had caused the recurrent occlusions, but one should remember that PV could also explain all the events. Despite lacking the mutation result, given our high suspicion, she was discharged on low-dose aspirin. A month later, she presented with lipothymia, hypotension, hypoxaemia, D-dimer elevation (12.59 mg/L (N<0.50 mg/L)) and N-terminal pro b-type natriuretic peptide (NT-proBNP) elevation (1856 pg/mL), secondary to extensive bilateral pulmonary embolism with right ventricle dilation and probable left lower pulmonary lobe infarction (figure 1). The JAK2 mutation was then available and showed to be positive for V617F. Overall, given the recurrent thrombosis in arterial and venous territories, the sustenance of absolute erythrocytosis and the presence of the JAK2 V617F mutation, we assumed the diagnosis of PV, as she fulfilled all criteria established by the British Committee for Standards in Haematology (BCSH) guidelines. Low-dose aspirin as well as anticoagulation were given simultaneously and a strategy to maintain a haematocrit <42% was developed.

OUTCOME AND FOLLOW-UP

During the remaining period of hospitalisation, there was overall improvement with normalisation

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Figure 1 Coronal section of thoracic angiography showing extensive bilateral pulmonary embolism with permeable pulmonary trunk.

of arterial blood pressure and eupnoea without oxygen supplementation. She was discharged 8 days after admission, and referred to a haematology centre for follow-up.

DISCUSSION

PV is a chronic myeloproliferative disease characterised by the presence of an elevated red blood cell mass. Its diagnosis is established according to WHO guidelines or BCSH guidelines. Concerning the first, regarding women, the presence of all three major criteria (haemoglobin >16.0 g/dL or haematocrit >48% or increased red cell mass; bone marrow biopsy showing panmyelosis and presence of JAK2 V617F or JAK2 exon 12 mutation) or the first two major criteria and the minor criterion (subnormal serum EPO) is necessary for the diagnosis to be made.³ However, in 17% of cases, like the one presented, there is initially normal serum EPO level, not fulfilling all criteria.^{4 5} Nevertheless, in some cases, after retesting, the level drops, making the diagnosis possible.¹ In the literature, we can even find cases of PV copresenting with Budd-Chiari syndrome with elevated EPO level. There is also a study in which the incorporation of EPO level did not improve the diagnostic accuracy.^{6 7} On the other hand, the BCSH standards only require the presence of the JAK2 mutation and a haematocrit above 52% for the diagnosis to be made.^{8 9} Which of the two classifications has the best sensitivity index to diagnose PV is unclear.¹⁰ In the case presented, considering the WHO guidelines, the diagnosis could not be considered; conversely, if one follows the British standards, the patient would have PV. Overall, it is important to remember that guidelines should not be followed blindly. Despite being an uncommon inaugural presentation, being only surpassed by major haemorrhage (4%), in a recent study, which followed 1151 patients, in 16% of cases, PV presented with arterial thrombosis, less commonly affecting the peripheral arterial system, and in up to 7.4% of cases it also presented with venous thrombosis. In the same study, the overall incidence of recurrent events was 12% for arterial thrombosis and 8% for venous thrombosis.^{1 4} The classical risk factors associated with an higher rate of recurrent thrombosis are older age, presence of cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolaemia, atrial fibrillation and smoking) and previous thrombotic event. However, a recent study analysed the rate of recurrence in a cohort of 494 patients, concluding that only age over 60 years and previous thrombosis was associated

with higher probability of recurrence.^{11 12} There is also growing evidence supporting the relationship between recurrent events and leucocytosis, which our patient never presented.^{13 14} Although the physiopathological mechanisms involved in this hypercoagulable state are unclear, abnormalities in blood viscosity, platelets, leucocytes and the burden of the JAK2 mutation have been implied. First, the increased blood viscosity decreases blood flow, leading to modification of platelet-binding sites, platelet activation and platelet-platelet interactions, which promote thrombosis. Some studies have also observed changes in platelet aggregation. There is also abnormal and sustained thromboxane A2 generation, a potent vasoconstrictor and inducer of platelet aggregation, blocked by low-dose aspirin. Another explanation lies in the platelet membrane receptor abnormalities encountered. Overexpression of adhesion molecules such as selectins promotes red blood cell adhesion to endothelium, also contributing to thrombosis. A platelet count above 400 000/ μ L in itself can also increase the risk of thrombosis, being one of the indications to initiate cytoreductive therapy.¹⁵ Recently, leucocytosis has been linked to increased risk of thrombosis, mostly via interactions of adhesion molecules with other blood cell components. Activated neutrophils release prothrombotic substances that can induce endothelial alterations and promote thrombin generation, therefore promoting thrombosis. Finally, some studies have linked the JAK2 mutation to the thrombotic complications, implying a connection between a higher allele burden and a higher thrombotic risk, but there is controversy regarding these results.^{16 17} Given all data available, regarding our case, we could not have guessed or even prevented the elevated rate of recurrent thrombotic events that followed in such a short period of time. Here lies the problem: PV is still incurable, so medical management is complex. The treatment is focused on preventing and treating complications, such as thrombohaemorrhagic events and detecting haematologic transformation. In patients with high vascular risk, the treatment algorithm recommends usage of phlebotomy in order to maintain a haematocrit below 42% in association with cytoreductive agents and low-dose aspirin. If there is a venous thrombosis, anticoagulation is the standard treatment, preferably long term, as it lowers the recurrence rate of thrombotic events.^{2 18} Treatment increases survival in 13 years or more with an overall mortality rate of 3.7 deaths over 100 persons/year.^{12 19} Higher leucocyte count, venous thrombosis, leucoerythroblastic blood smear and abnormal karyotype have adverse prognostic value, while thrombocytosis and pruritus are associated with better prognosis. In a study of 1545 patients, a risk score of survival was developed based on age, leucocytosis and history of venous thrombosis. Patients were stratified according to age into three groups: ≥ 67 years scored five points, whereas 57–66 years scored two points; leucocyte count superior to 15 000/ μ L scored one point and venous thrombosis also scored one point. Low-risk (0 points), intermediate-risk (1–2 points) and high-risk (≥ 3 points) had a median survival of 26, 15 and 8.3 years, respectively.⁴ In the case presented, our patient scores six points, which puts her in the high-risk group and worsens her prognosis. In a nutshell, her follow-up will be crucial, considering her medical history and the high risk of complications at long term. The relevance of this case lies on the unusual inaugural presentation of PV with an unprecedented high rate of recurrent thrombotic events, in arterial and venous systems, which increased the complexity of its approach, treatment and follow-up.

Learning points

- ▶ Thrombotic complications are unusual inaugural presentations of polycythaemia vera that can recur depending on vascular risk.
- ▶ JAK2 mutation is fundamental for the diagnosis.
- ▶ Pathogenesis remains unclear with new evidence supporting the interaction of high blood viscosity, platelet, leucocytosis and the JAK2 allele burden in thrombosis.
- ▶ The therapeutic approach is based on phlebotomy, but considering the vascular risk, the addition of cytoreductive agents or low-dose aspirin may be necessary.
- ▶ There should be close follow-up in order to maintain the haematocrit within target level and detecting haematologic transformation.

Contributors RdSG was involved in conception and design, drafting, editing and final approval of submitted version. She also collected all data regarding the clinical case and interpreted it. AR was involved in conception and design, editing, revising and final approval of submitted version. FMG was involved in editing and revising the article. JPDG was involved in editing and revising the article.

Competing interests None declared.

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