CASE REPORT

Vertebral artery thrombosis: a rare presentation of primary polycythaemia

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SUMMARY

Primary polycythaemia, also known as polycythaemia vera (PV), is a myeloproliferative neoplasm (MPN) which is associated with arterial and venous thrombosis and which can contribute to significant morbidity and mortality if untreated. Arterial thrombosis accounts for a large proportion of PV-related thrombotic events which may manifest as stroke and myocardial infarction. There is an abundance of literature documenting thrombosis arising in the cerebral vasculature secondary to PV. However, vertebral artery thrombosis associated with PV has not been previously described. We present a case of vertebral artery thrombosis as the presenting manifestation of PV. This case demonstrates the importance of recognising MPNs as a cause of an unusual presentation of thrombosis.

BACKGROUND

Primary polycythaemia (PV) is a myeloproliferative neoplasm (MPN) characterised by erythrocytosis and associated overproduction of granulocytic and megakaryocytic elements, as a result of clonal haematopoiesis due to genetic mutations in affected stem cells.¹

It has been widely documented that morbidity and mortality in PV occur from venous or arterial thrombosis, haemorrhage and transformation to myelofibrosis and acute leukaemia, with thrombotic events being the dominant feature.¹ The reported incidence of thrombosis ranges from 12% to 39% in PV. Arterial thrombosis accounts for 60–70% of PV related thrombotic events; this includes stroke, acute myocardial infarction and digital ischaemia.^{2,3} Venous thrombosis accounts for the remaining 30%, comprising deep vein thrombosis, pulmonary embolism and cerebral vein thrombosis, as well as thrombosis at unusual sites such as intra-abdominal vasculature. In PV, the unusually high prevalence of cerebral vein thrombosis is often the presenting feature of the disease.²

When a patient presents with thrombosis, it is important to recognise the possibility of an MPN as a cause and initiate appropriate investigations and treatment early to prevent further complications. A study by Bonicelli *et al*⁴ showed that leucocytosis and thrombosis at diagnosis are associated with poor survival in patients with PV. Early studies have shown a high incidence of thrombosis without treatment, with a median survival of 18 months.⁵ Aggressive treatment involving phlebotomy and cytoreductive treatments is required to reduce the number of thrombotic complications and improve survival.⁶

CASE PRESENTATION

A 40-year-old Caucasian man who was normally fit and well presented with sudden onset of neck and bilateral arm pain on getting out of the bath. He also reported associated shoulder cramps and paraesthesia in both hands. He does not have a history of diabetes, previous thromboembolism, cardiac or chronic lung disease and is a non-smoker. There is no family history of malignancy, polycythaemia or venous/arterial thrombosis. On general inspection, he was plethoric. He was normotensive, saturating 97% on room air and had a body mass index within normal range. Examination revealed arm weakness and reduced power recorded as Medical Research Council (MRC) grade 2/5 in the deltoid and biceps brachii bilaterally. There were no other neurological signs. The rest of the physical examination was normal. He did not describe features of erythromelalgia.

INVESTIGATIONS

Initial blood tests showed polycythaemia, neutrophilia and thrombocytosis; haemoglobin 21.5 g/dL (11.9–14.9 g/dL), haematocrit 0.67 L/L (0.36 L/L), white cell count $15.4 \times 10^9/L$ ($3.7\text{--}10.0 \times 10^9/L$), neutrophils $14.1 \times 10^9/L$ ($1.7\text{--}6.6 \times 10^9/L$), platelets $548 \times 10^9/L$ ($150\text{--}400 \times 10^9/L$). His erythropoietin (EPO) level was 2.2 mIU/mL (2.6–18.5 mIU/mL).

MRI of the head with contrast demonstrated anterior cervical cord ischaemia and inflammation secondary to right vertebral artery thrombosis (figures 1 and 2); there was no evidence of vertebral artery dissection from the MR angiogram. Abdominal ultrasound revealed mild splenomegaly (spleen length 14.9 cm). No renal abnormalities were detected.

Figure 1 T2 weighted MRI scan; transverse section at level C3 showing right vertebral artery thrombosis (loss of normal flow void).

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Figure 2 Abnormal signal of the anterior cord on T2 weighted MRI extending from the cranio-cervical junction to C4.

He was diagnosed with PV and a positive result for the Janus kinase 2 mutation (JAK2), specifically a V617F mutation, later on confirmed an MPN. A bone marrow biopsy was not performed as JAK2 positivity combined with a raised haematocrit is considered to be diagnostic of PV.

According to the 2008 WHO criteria for PV, a diagnosis requires meeting two major criteria and one minor criterion or the first major criterion and two minor criteria. Major criteria include a haemoglobin greater than 18.5 or 16.5 g/dL for men and women, respectively, (or other evidence of increased cell volume) and the presence of JAK2V617F or another functionally similar mutation. Minor criteria include a bone marrow biopsy showing hypercellularity for age, panmyelosis with prominent erythroid, granulocytic and megakaryocytic proliferation; serum erythropoietin level below the normal reference range or endogenous erythroid colony forming in vitro.⁷

DIFFERENTIAL DIAGNOSIS

Patients with PV usually have a low serum EPO level. In cases of erythrocytosis with a high or normal EPO level, one should be prompted to investigate for secondary causes of polycythaemia. Secondary polycythaemia can be classified into either congenital or acquired.

Congenital polycythaemia is rare and includes high oxygen affinity haemoglobins, familial erythrocytosis and Chuvash polycythaemia.¹

Acquired secondary polycythaemia is driven by EPO response to various factors, and these can be divided into appropriate and inappropriate increases in EPO. EPO level is appropriately increased in response to hypoxaemia in chronic lung disease, right to left cardiac shunt, sleep apnoea, high altitude, obesity and red cell defects such as carbon monoxide poisoning. Inappropriate increase in EPO is usually due to unregulated EPO-producing neoplasms such as renal cell carcinoma, hepatocellular carcinoma and haemangioblastoma.^{1 8–10}

Other causes of arterial thrombosis

The pathophysiology of arterial thrombosis is a complex process that is probably most simply explained by Virchow's triad

abnormalities in the blood content (haemostasis), the vessel wall (endothelium) and blood flow. However, there is considerable overlap among the three mechanisms. Some of the common causes are explained below.

Metabolic syndrome is defined by the presence of at least three of the following diagnostic criteria: elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure and elevated fasting glucose.¹¹ Metabolic syndrome causes endothelial dysfunction and heightened platelet reactivity, as well as being prothrombotic, proinflammatory and proatherogenic, leading to arterial thrombosis.¹²

It has also been observed that as age increases, the arterial walls stiffen due to the degeneration of elastic fibres and an increase in the collagen and calcium content. Endothelium-dependent dilation is also reduced due to the low prostacyclin and nitric oxide levels.¹³ Additionally, there is increased binding of the platelet-derived growth factor to arteries, which enhances the progression of atherosclerosis, increasing the risk of arterial thrombosis.¹⁴

Antiphospholipid syndrome is known to cause arterial thrombosis. Antiphospholipid antibodies interact directly with the vessel wall, causing alterations in the plasma lipoprotein function leading to increased atherothrombotic risk.¹⁵

It is well recognised that other myeloproliferative disorders apart from PV such as essential thrombocythaemia cause arterial thrombosis, more so than haemorrhage. Moreover, leukocytosis, but not thrombocytosis, has been shown to be a risk factor for arterial thrombosis in both essential thrombocythaemia and PV.¹⁶

TREATMENT

The patient was initially treated with isovolumic venesection, to reduce the haematocrit level, and was started on aspirin initially at 300 mg daily. The thrombocytosis was aggravated by venesection, with the platelet count having risen to $1025 \times 10^9/L$, and the decision was made to start treatment with interferon alpha α .

OUTCOME AND FOLLOW-UP

The patient has been followed up in the clinic every 3 months. Subsequently, his symptoms have resolved and his myeloproliferative disease is well controlled with a target haematocrit level of below 0.45 L/L. There has been no recurrence of thrombotic events.

DISCUSSION

Thrombosis arising in the cerebral vasculature and unusual sites of venous thrombosis as a result of underlying PV is well documented.² A case of spinal cord ischaemia as a presenting feature of PV has been published.¹⁷ However, to the best of our knowledge, vertebral thrombosis as the initial presentation of an MPN has not previously been published. It may, however, occur otherwise in a transient/intermittent manner, or may be associated with another disorder like Moya Moya disease.^{18 19}

Vertebral artery occlusion may present in several ways depending on the area of ischaemia and the type of occlusion. Dizziness, nausea, vomiting and head or neck pains are common initial symptoms. Other common signs include weakness, ataxia, diplopia, speech abnormalities and changes in mental status.^{20 21} As was the case with our patient, he presented in a very non-specific manner with symptoms that could be attributable to a wide variety of diagnoses. The non-specific manner and vast spectrum of possible presentations of thrombosis heighten the need for thorough investigations and to be aware of myeloproliferative disease as an underlying cause.

Embolism, atherothrombosis and vertebral artery dissection are the main documented causes of vertebral artery occlusion. Local atherothrombosis is thought to contribute to vertebral artery occlusion in the elderly. Occlusion in younger patients is traditionally thought to arise from embolism from a cardiovascular source.²⁰

The cause of increased thrombotic tendency in PV is not fully understood and several mechanisms have been proposed. The two main mechanisms responsible for the development of a hypercoagulable state include the abnormalities of the blood cells arising from the clonal haemopoietic progenitor cells, which are thought to express a prothrombotic phenotype, and the inflammatory response of vascular cells from the cytokine mediated insult.²

An elevated haematocrit is thought to correspond to an increase in thrombotic risk in PV and may be an important factor in the causation of occlusive vascular diseases, particularly in the cerebral circulation, due to increased blood viscosity. Several retrospective studies have identified leukocytosis as a potential risk factor for arterial and venous thrombosis in patients with essential thrombocythaemia and PV. Leukocytosis was also a risk factor for recurrent arterial thrombosis in young affected patients. Furthermore, because neutrophils represent the most abundant proportion of the circulating leucocytes, a role for neutrophils in the thrombosis of MPN has been hypothesised. They play a central role in the inflammatory response and also in linking the inflammatory response to the activation of coagulation. It has also been demonstrated that endothelial damage causes the release of specific markers into the circulation including thrombomodulin, selectins and the Von Willebrand factor (VWF). This is of particular relevance in the pathogenesis of thrombosis in MPN because once platelets bind to VWF, they become activated and able to aggregate and strengthen the clot.^{2 22}

JAK2 mutation is typical of myeloproliferative disease and is present in over 95% of patients with PV. This suggests that although the platelets are produced in normal numbers, they are functionally activated, causing thrombotic complications. Evidence suggests that the JAK2 mutation represents an independent risk factor for thrombosis and is useful for predicting cardiovascular risk.²³ Second, malignant cells can release cytokines and other mediators, provoking an inflammatory response from the host vascular cells.²

The possible pathophysiology of the extra-cranial steno-occlusive disease is that a prothrombotic state could lead to repeated endothelial injury, resulting in intimal hyperplasia and subsequent progressive steno-occlusion.¹⁹ In our patient, it would appear that thrombotic occlusion of the right vertebral artery occurred as a result of the hypercoagulable nature of PV.

Learning points

- The life expectancy of patients with polycythaemia vera is strongly determined by disease-related haemostatic complications, especially thrombosis.
- It is important to recognise the possibility of a myeloproliferative neoplasm (MPN) as a cause of ischaemic events in cerebral, spinal or vertebral territories.
- It is important to initiate prompt and appropriate treatment for MPNs to prevent associated thrombotic complications.

Contributors HLG was involved in the writing of the case report, literature review and discussion section and approved the final draft of the report. SYML contributed to the writing of the 'Discussion' section and literature review. DC-L supervised the writing of the case report and was involved in patient care. J-PN supervised the writing of the case report.

Competing interests None.

Patient consent Obtained.

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