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Polycythaemia vera

Synonyms: polycythaemia rubra vera, plethora vera, primary polycythaemia, Osler-Vaquez disease

What is polycythaemia vera?

Polycythaemia vera (PV) is a clonal disorder of haematopoietic stem/progenitor cells. It manifests as an expansion of red cell mass. It is the most common chronic myeloproliferative neoplasm. In virtually all cases, it is characterised by a V617F point mutation in JAK2 exon 14 or less common mutations in exon 12.[1]

PV is characterised by pronounced symptoms, including fatigue, pruritus and symptomatic splenomegaly, along with an increased risk of thrombosis and the potential for evolution to myelofibrosis and secondary acute myeloid leukaemia.[2]

How common is polycythaemia vera? (Epidemiology)

- Polycythaemia vera is rare:[3]
  - Registry-based studies from the European Union suggest an incidence of between 0.4 and 2.8 per 100,000 per year.
  - A large study of US-based health plan data estimated a prevalence of 44 to 57 per 100,000.
- The reported median age at diagnosis ranges from 65-74 years.[4]
- Familial cases are very rare and usually present in elderly patients.[5]

Polycythaemia vera symptoms[3]

The disease starts with the plethoric stage and then progresses to the spent stage.

- It may be discovered on routine blood count in a person with no related symptoms or there may be nonspecific complaints of lethargy and tiredness.
- Thrombotic events are the major cause of morbidity and mortality in polycythaemia vera. About a third present with symptoms due to thrombosis. Three quarters of this is arterial thrombosis and a quarter is venous thrombosis. Features include stroke, myocardial infarction, deep vein thrombosis and pulmonary embolism.[6]
- About 30% of patients complain of headaches, dizziness and sweating - in decreasing order of frequency.
- Budd-Chiari syndrome:
    - Occurs in about 2-10% of cases of PV but when it occurs it should always raise suspicion of the condition. It may be in an early stage of the disease before the haemoglobin is markedly raised, and this develops later.
    - Hepatic or splenic vein thrombosis may be unrecognised but cause portal hypertension.
- Peptic ulceration is also more common with PV.
- Bleeding from gums or easy bruising is usually mild but gastrointestinal haemorrhage can be more severe.
- Pruritus is common, occurring in up to 85% of people with PV.[6]
- Fewer than 5% of patients have erythromelalgia:
    - This is erythema, warmth, pain and even sometimes infarction of the distal extremities.
    - The hands and feet have a painful burning sensation. It also occurs in thrombocythaemia, suggesting that high platelets are important.

- A small number may present with myocardial infarction, congestive heart failure, features of compression of the spinal column from extramedullary haematopoiesis or gout from increased cell turnover.

Polycythaemia vera is uncommon in females of reproductive age, occurring in less than 0·3 per 100,000. However, pregnancy is a prothrombotic state with increased risk of thromboembolism in patients with polycythaemia vera. Consequently, there is a significant risk of obstetric complications, such as fetal loss throughout all trimesters, intrauterine growth restriction, prematurity, maternal thromboembolism and haemorrhage.[6]

Examination

- The patient may look plethoric with a ruddy complexion. There is a greater chance of cyanosis with a high haemoglobin.
- Splenomegaly is not uncommon (present in about 75% of patients at the time of diagnosis).
- Tenderness of the sternum may indicate transformation to acute myeloid leukaemia.
- Hypertension is common in patients with PV.

Diagnostic criteria[7]

Major changes to diagnostic criteria were made in the 2016 revision of the World Health Organization (WHO) classification, with both haemoglobin and haematocrit thresholds lowered to 165 g/L and 49% for men, and 160 g/L and 48% for women, respectively. The main reason leading to these changes was the recognition of "masked PV", as this has a worse outcome, possibly due to missed or delayed diagnoses and lower intensity of treatment.

- Major criteria:
    - Hb >16.5 g/dL in men/Hb >16.0 g/dL in women, or Hct >49% in men/Hct >48% in women, or increased red cell mass.
    - Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature, megakaryocytes (differences in size).
    - Presence of JAK2V617F or JAK2 exon 12 mutation.
- Minor criterion:
    - Subnormal serum erythropoietin level.

Criteria required for diagnosis: all three major or the first two major and the minor criterion.

Differential diagnosis[3]

It is important to distinguish three causes of raised haemoglobin level:

- In the first, red cell volume is normal but circulating volume is depleted:
    - Relative polycythaemia is characterised by a decrease in plasma volume which causes an apparent increase in the red blood cell mass. Any condition causing fluid loss, such as any cause of dehydration and severe burns, will result in relative polycythaemia.[8]

- In the second two, circulating volume is normal or raised but red cell mass is elevated:

    - Essential polycythaemia:

        - Usually PV but a genetic condition has been described in which there is excessive responsiveness to erythropoietin.

    - Secondary polycythaemia:

        - Is due to hypoxia causing erythropoietin release as in Eisenmenger's syndrome, chronic obstructive pulmonary disease (COPD) or smoking.
        - It can also result from abnormal production of erythropoietin as with clear cell carcinoma of kidney, Wilms' tumour, hepatocellular carcinoma, cerebellar haemangioma and, occasionally, uterine myomas.
        - Other tumours have been reported to produce erythropoetin or a similar substance.
        - Chronic myelogenous leukaemia may be clinically indistinguishable from polycythaemia vera, although thrombosis is much less common with CML. Diagnosis is confirmed by screening for Philadelphia chromosome 9;22 translocation or its fusion protein product, BCR-ABL.

Investigation[3]

- Initial blood tests:

    - FBC in PV will show not only elevated Hb and packed cell volume but WCC and platelets will be elevated too. In secondary polycythaemia only red blood cells are raised.
    - Ferritin is often low in primary polycythaemia because of increased demand for iron. In secondary causes it is usually normal..

- Radiology:
    - Radioisotopes can be used to measure circulating volumes. Red cells can be labelled with 51Cr and albumin with 131I. This is expensive, needs skill and is not widely available.
    - CT, MRI or ultrasound scanning of the abdomen may show enlargement of the spleen as is often found in PV. It should also check for abnormalities of the renal system.
- Bone marrow and aspirate:
    - Tend to be hypercellular in PV.
    - In the plethoric phase, the blood smear shows normal erythrocytes, variable neutrophilia with myelocytes, metamyelocytes, and varying degrees of immaturity, basophilia, and increased platelet counts.
    - In the spent phase, the blood smear shows abundant teardrop cells, leukocytosis, and thrombocytosis.
    - Generally the findings are not specific to PV. The bone marrow can be normal in PV.
- Serum erythropoietin levels are often low in PV. This can differentiate secondary erythrocytosis and pseudoerythrocytosis from PV but there is overlap in the levels found and it cannot reliably differentiate.
- Cytogenetic studies. An abnormal test is useful but a normal test does not exclude PV.
- Clonal assays (using glucose-6-phosphate dehydrogenase (G6PD) markers) are not generally available for clinical use. Even if they were available they are only of use in female patients.

JAK2 testing [3]

With the development of new techniques for detecting the Janus kinase 2 (JAK2) V617F mutation this may become a clinically useful marker for PV. It has been recommended as a diagnostic marker.

JAK2-positive PV is diagnosed if:

- The JAK2 mutation is identified; and
- The haematocrit is more than 0.48 in women or more than 0.52 in men, or the red cell mass is 25% higher than normal.

JAK2-negative PV is diagnosed if:

- The JAK2 mutation is not identified; and
- The haematocrit is more than 0.56 in women or more than 0.60 in men, or the red cell mass is 25% higher than normal; and
- There is no identifiable secondary cause for polycythaemia; and either

    - There is palpable splenomegaly or the presence of an acquired genetic abnormality in the haematopoietic stem cells or both; or
    - Any two of the following clinical features are identified: an abnormally increased platelet count, an abnormally increased neutrophil count, radiological evidence of splenomegaly, and abnormally low serum erythropoietin.

Polycythaemia vera treatment and management[9] [10] [11]

The cornerstone of therapy of low-risk patients remains strict control of cardiovascular risk factors, the use of phlebotomy and low-dose aspirin. Higher risk patients should also receive cytoreductive treatments. Hydroxycarbamide and interferon alfa represent standard first-line options for newly diagnosed high-risk PV patients.

For patients who fail first-line cytoreductive therapy (hydroxyurea and/or interferon), existing treatment options include alkylating agents, (eg, busulfan, chlorambucil or pipobroman) and P-32. However, there is evidence that these agents are associated with an increased incidence of leukaemic transformation in patients with PV.

The discovery of mutations in JAK2 as the underlying molecular basis of PV has led to the development of several targeted therapies, including JAK inhibitors - eg, ruxolitinib, which is a selective inhibitor of the Janus-associated tyrosine kinases JAK1 and JAK2 and is licensed in the UK for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-PV myelofibrosis, or post-essential thrombocythaemia myelofibrosis.[12]

- Intermittent long-term phlebotomy to maintain the haematocrit below 45% (lower target level may be appropriate for women). Phlebotomy may cause progressive and sometimes severe thrombocytosis and iron deficiency. Splenomegaly and pruritus may persist despite control of the haematocrit by phlebotomy.[13]
- Low-dose aspirin produces a small reduction in thrombotic events, including myocardial infarction and stroke, whilst not increasing the risk of haemorrhage.[14] [15]
- If it is not possible to control thrombotic events with phlebotomy alone then myelosuppression must be considered. However, this is not without risk and increases the risk of leukaemic transformation. Risks and benefits have to be balanced.
- Chemotherapy options include:[3]
- - Cytoreductive therapy is recommended for people at high risk of thrombosis (aged over 60 years, or history of thrombosis).
  - The first-line drug is usually hydroxycarbamide, with interferon alfa or ruxolitinib as possible alternatives where hydroxycarbamide is contra-indicated, not tolerated, or ineffective.
  - Pharmacological cytoreductive therapy may also be considered if:
    - Platelet count is abnormally high.
    - There is evidence of disease progression - eg, weight loss or night sweats.
    - Splenomegaly progresses or becomes symptomatic.
    - There is poor tolerance of venesection.

- Pruritus can be disabling:
    - Taking baths or showers at lower temperatures and patting the skin dry, to avoid rubbing, may help.
    - Antihistamines, including H_2-receptor antagonists (H2RAs), are useful in refractory cases.
    - Selective serotonin reuptake inhibitors (SSRIs) - eg, paroxetine or fluoxetine.
- Elevated uric acid may require allopurinol.
- It may be necessary to consider splenectomy when there is painful splenomegaly or there are repeated episodes of splenic infarction.

Prognosis [3] [16]

- Currently available drugs for PV have not been shown to prolong survival or alter the natural history of the disease and are instead indicated primarily for prevention of thrombosis. [17]
- Median survival is about 14 years (24 years for younger patients). Risk factors for survival include advanced age, leukocytosis and thrombosis.
- Leukaemic transformation rates at 20 years are estimated at less than 10% but fibrotic transformation rates are slightly higher.

- High risk for recurrent thrombosis is defined by the presence of age over 60 years or presence of thrombosis history; low risk is defined by the absence of both of these two risk factors.
- The most common causes of death are ischaemic stroke and myocardial infarction. Other life-threatening complications may include:
    - Pulmonary embolism.
    - Progression to myelofibrosis or acute myeloid leukaemia.
    - Increased risk of gastrointestinal haemorrhage.

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