ABC of clinical haematology

Polycythaemia, primary (essential) thrombocythaemia and myelofibrosis

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Primary polycythaemia (polycythaemia rubra vera), primary (or essential) thrombocythaemia, and myelofibrosis are all clonal disorders originating from a single aberrant neoplastic stem cell in the bone marrow. They are generally diseases of middle or older age and have or may develop common features including a small potential for transforming to acute leukaemia. Myelofibrosis may arise *de novo* or result from progression of primary polycythaemia or primary thrombocythaemia. Treatment of primary polycythaemia and primary thrombocythaemia can greatly influence prognosis, hence the importance of diagnosing these rare disorders. They need to be distinguished from other types of polycythaemia (secondary polycythaemia, apparent polycythaemia) and other causes of a raised platelet count (secondary or reactive thrombocytosis), whose prognosis is different.

Polycythaemia

The packed cell volume, rather than the haemoglobin concentration, is the indicator of polycythaemia. A raised packed cell volume (> 0.51 in males, > 0.48 in females) needs to be confirmed on a specimen taken without venous occlusion. Patients with a persistently raised packed cell volume should be referred to a haematologist for measurement of red cell mass by radionuclide labelling of the red cells. Red cell mass is best expressed as the percentage difference between the measured value and that predicted from the patient's height and weight (derived from tables).

Red cell mass more than 25% above the predicted value constitutes real or absolute polycythaemia, of which there are two types: primary and secondary. When the packed cell volume is raised but the red cell mass is not, the condition is known as apparent polycythaemia.

Primary polycythaemia

Presentation can be incidental but is classically associated with a history of occlusive vascular lesions (stroke, transient ischaemic attack, ischaemic digits), headache, mental clouding, facial redness, itching, abnormal bleeding, or gout.

Initial laboratory investigations—A raised white cell count ($> 10 \times 10^9/l$ neutrophils) or a raised platelet count ($> 400 \times 10^9/l$) suggest primary polycythaemia, especially if both are raised in the absence of an obvious cause, such as infection or carcinoma. Serum ferritin concentration should be determined as iron deficiency may mask a raised packed cell volume, resulting in a missed diagnosis.

Specialist investigations—Red cell mass should be determined to confirm absolute polycythaemia, and secondary polycythaemia should be excluded. Most patients with primary polycythaemia have a low serum erythropoietin concentration. If the spleen is not palpable then splenic sizing (ultrasonography) should be performed to look for enlargement. Bone marrow chromosomal analysis may show changes that establish clonality which would be in favour of a primary marrow disorder such as primary polycythaemia. Erythroid colony growth in culture from peripheral blood can support the diagnosis.

Classification of the polycythaemias.

Symptoms and signs of primary polycythaemia

- Stroke
- Transient ischaemic attack
- Digital ischaemia
- Headache
- Mental clouding
- Facial plethora
- Pruritus
- Bleeding (including gastrointestinal tract)
- Gout

Palpable splenomegaly is present in less than half of patients with primary polycythaemia, but when present it reliably distinguishes primary polycythaemia from the other polycythaemias

Aims of treatment of primary polycythaemia

- To reduce packed cell volume to < 0.45 (by regular venesection)
- To reduce platelet count to $< 400 \times 10^9/l$ (by daily hydroxyurea)

Facial redness in patient with primary polycythaemia.

Treatment—Traditional treatment using the marrow suppressant effect of radioactive phosphorus (^{32}P) has been largely superseded because of the additional risk of inducing malignancies such as acute leukaemia in later life. It is still useful, however, in elderly people and when venous access or patient attendance or compliance is poor. Repeated venesection to maintain the packed cell volume at < 0.45 has become the mainstay of treatment. At this volume the risk of thrombotic episodes is much reduced. Venesection has to be frequent at first but is eventually needed only every six to 10 weeks in most patients. Concurrent cytotoxic therapy to control the platelet count ($< 400 \times 10^9/\text{L}$) is necessary. Hydroxyurea (0.5–1.5 g daily) is recommended for this purpose and is not thought to have a pronounced leukaemogenic potential. Low dose intermittent oral busulphan is often more convenient in elderly people, in whom potential side effects may be more acceptable.

Progression—Long survival (> 10 years) of the treated patient has revealed a 20% incidence of transformation to myelofibrosis and about 5% to acute leukaemia. The incidence of leukaemia is further increased in those who have transformed to myelofibrosis and those treated with ^{32}P or high dose cytotoxic agents.

Secondary polycythaemia

Many causes of secondary polycythaemia have been identified, the commonest being hypoxaemia (arterial saturation $< 92\%$) and renal lesions. Investigations are designed to determine the underlying cause to which the polycythaemia is secondary.

Causes of secondary polycythaemia

- Hypoxaemia—for example, chronic lung disease, cyanotic congenital heart disease, and sleep apnoea
- Renal—for example, hypernephroma, polycystic kidney disease, and post renal transplant
- Miscellaneous—for example, hepatoma, cerebellar haemangioma, raised oxygen affinity haemoglobin

Treatment is aimed at removing the underlying cause when practicable. In hypoxaemia—in which the risk of vascular occlusion is much less pronounced than in primary polycythaemia—venesection is usually undertaken only in those with a very high packed cell volume. Reduction to packed cell volume 0.50–0.52 may result in an improvement of cardiopulmonary function. At this level the harmful effects of increased viscosity no longer outweigh the oxygen carrying benefits of a raised packed cell volume. In polycythaemia associated with renal lesions or other tumours, the packed cell volume should generally be reduced to < 0.45 .

Apparent polycythaemia

In apparent polycythaemia red cell mass is not increased, and there is no evidence of primary or secondary polycythaemia. Some association exists with smoking, increased alcohol intake, obesity, diuretics, and hypertension.

The need for treatment is uncertain. Lowering the packed cell volume by venesection is undertaken only in patients who have increased risk of vascular occlusion for other reasons, or whose packed cell volume is > 0.54 . On follow up one third of patients revert spontaneously to normal packed cell volume.

Since some patients with apparent polycythaemia may be at an early stage of progression to absolute polycythaemia, investigations for primary or secondary polycythaemia are relevant even when the red cell mass is normal.

Packed cell volume versus incidence of thrombotic events.

Median survival in primary polycythaemia

- Untreated patients—18 months, death being due mainly to vascular occlusion (especially strokes)
- Treated patients—10 to 15 years

Angiogram in patient with hypernephroma leading to secondary polycythaemia.

Investigations in suspected secondary polycythaemia

Routine

- Arterial oxygen saturation (pulse oximetry)
- Renal, hepatic, and splenic ultrasound

Specialist

- Serum erythropoietin
- Oxygen affinity haemoglobin (p50)
- Sleep study (if clinically indicated)

Apparent polycythaemia

This supersedes older nomenclature including terms such as:

- Pseudo, spurious, or relative polycythaemia
- Stress erythrocytosis
- Gaisbock's syndrome

Primary (essential) thrombocythaemia

Like primary polycythaemia and myelofibrosis, primary thrombocythaemia is one of the group of conditions known as the myeloproliferative disorders.

A persisting platelet count $> 600 \times 10^9/l$ is the central diagnostic feature. But other causes of raised platelet count need to be excluded before a diagnosis of primary thrombocythaemia can be made.

Exclusion requirements for diagnosing primary thrombocythaemia

- Reactive thrombocytosis—History and general clinical examination may reveal underlying conditions such as infection or malignancy to which the raised platelet count may be secondary
- Primary polycythaemia should be suspected if the packed cell volume is raised (or the rise is masked by coexisting iron deficiency)
- Myelofibrosis (teardrop red cells, nucleated red cells and immature white cells—for example, myelocytes—in the peripheral blood, marrow fibrosis on trephine). A raised platelet count may be an early feature
- Myelodysplasia (dysplastic peripheral blood and bone marrow cells, abnormal karyotype). Some patients have a raised platelet count

Laboratory investigations

Investigations may reveal other causes of raised platelet count. Apart from a full blood count and blood film they should also include erythrocyte sedimentation rate, serum concentrations of C reactive protein and serum ferritin; bone marrow aspirate; and trephine and cytogenetic analysis (this is generally normal, but abnormalities may favour a diagnosis of myelodysplasia, and, very occasionally, the Philadelphia chromosome is present).

Presentation and prognosis

Thirty to fifty per cent of patients with primary thrombocythaemia have microvascular occlusive events—for example, burning pain in extremities or digital ischaemia—major vascular occlusive events, or haemorrhage at presentation. These are most pronounced in elderly people in whom the risk of cerebrovascular accident, myocardial infarction, or other vascular occlusion is very high in untreated patients. The risk in young patients is lower, though major life threatening events have been described. Transformation to myelofibrosis or acute leukaemia may occur in the long term in a minority of patients.

Treatment and survival

All patients should receive daily low dose aspirin, unless contraindicated because of bleeding or peptic ulceration. This reduces the risk of vascular occlusion but may increase the risk of haemorrhage, particularly at very high platelet counts.

Reduction of the platelet count by cytotoxic agents (daily hydroxyurea or intermittent low dose busulphan in elderly people) reduces the incidence of vascular complications and appreciably improves survival in older patients (from about three years in untreated to 10 years or more in treated patients). Newer drugs, such as anagrelide or interferon alfa, are under investigation.

The value of these cytotoxic agents in young patients is uncertain—particularly in the face of a possible leukaemogenic risk made worse by the prospect of many years of treatment. Clinical trials comparing the effects of different cytotoxic agents and looking at the possibility of not lowering the platelet count in young asymptomatic patients are planned.

Differential diagnosis of a raised platelet count

- Reactive thrombocytosis due to:
 - Infection
 - Malignancy
 - Chronic inflammatory bowel disease
 - Hyposplenism
 - Bleeding
- Primary thrombocythaemia
- Primary polycythaemia
- Myelofibrosis
- Myelodysplasia

If there is palpable splenomegaly a raised platelet count is much more likely to be due to primary thrombocythaemia than to reactive thrombocytosis

Gangrene of the toes in the presence of good peripheral pulses and a raised platelet count strongly suggests primary thrombocythaemia

Toe gangrene in patient with essential thrombocythaemia.

The risk of occlusive vascular lesions is very small in reactive thrombocytosis but high in primary thrombocythaemia

Idiopathic myelofibrosis (primary)

The main features are bone marrow fibrosis, extramedullary haemopoiesis (that is, production of blood cells within organs such as the spleen), splenomegaly, and leucoerythroblastic blood picture (immature red and white cells in the peripheral blood). Good evidence exists that the fibroblast proliferation is secondary (reactive) and not part of the clonal process. Idiopathic myelofibrosis needs to be distinguished from causes of secondary myelofibrosis.

Presentation

Idiopathic myelofibrosis (primary) may have been present for many years before diagnosis. Patients could have had previous undiagnosed primary polycythaemia or thrombocythaemia. The absence of an easily palpable spleen is rare. The main presenting features are abdominal mass (splenomegaly), weight loss (hypermetabolic state), anaemia, fatigue, and bleeding.

Laboratory investigations

The blood count is variable. In the initial "proliferative phase" red cell production may be normal or even increased. About half of presenting patients may have a raised white cell count or platelet count (absence of Philadelphia chromosome will distinguish from chronic myeloid leukaemia). As the bone marrow becomes more fibrotic, the classic "cytopenic phase" supervenes.

Progression and management

Survival varies, with a median of two to four years. It may be much longer in patients who are asymptomatic at presentation.

Supportive blood transfusion may be needed for anaemic patients. Cytotoxic agents may be useful in the proliferative phase to suppress the bone marrow. Splenectomy will improve the quality of life (though not the prognosis) by reducing the need for transfusion and thrombocytopenia. Operative morbidity and mortality can be high when the splenomegaly is gross.

Low dose irradiation of the spleen may be helpful in frail patients. Death can be due to haemorrhage, infection, cardiac failure, or transformation to acute leukaemia. Portal hypertension with varices, iron overload from blood transfusion, and compression of vital structures by extramedullary haemopoietic masses may also contribute to morbidity.

We thank Monica Nestor for secretarial help. The graph was adapted, with permission, from the *Lancet* (Pearson TC *et al.* Vascular occlusive episodes and venous haematocrit in primary proliferative polycythaemia. 1978;ii:1219-22). The photographs of facial plethora and splenomegaly are reproduced with permission from *Clinical Haematology Illustrated* (A V Hoffbrand, J E Pettit), Edinburgh: Churchill Livingstone, 1987.

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Massive splenomegaly in patient with myelofibrosis.

Laboratory investigations of idiopathic myelofibrosis (primary)

Peripheral blood

- Normochromic anaemia (teardrop red cells)
- Nucleated red cells and immature neutrophils
- Thrombocytopenia and large abnormal platelets

Bone marrow examination

- "Dry" or "blood tap" on aspiration
- Biopsy (trephine) shows increased fibrous tissue, with variable amounts of cellular marrow in between (megakaryocytes prominent)

Indications for splenectomy in myelofibrosis

- Frequent blood transfusion
- Troublesome thrombocytopenia
- Large painful spleen

Secondary myelofibrosis

This is not a clonal myeloproliferative disorder but a reaction to other diseases. The diagnosis is based on discovering associated disease:

- Primary marrow malignancy—for example, myelodysplasia, myeloma
- Secondary metastatic carcinoma
- Chronic infections—for example, tuberculosis

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