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The investigation and management of erythrocytosis and thrombocytosis

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ABSTRACT Erythrocytosis and thrombocytosis are among the most common reasons for referral to haematology outpatients. Most cases are identified on routine blood counts as part of the investigation of non-specific symptoms. Erythrocytosis is a term used to describe a group of conditions with an increase in circulating red cell concentration leading to an increase in haematocrit and often an increase in haemoglobin concentration (polycythaemia). True erythrocytosis is commonly seen in isolation but may also be associated with thrombocytosis and leukocytosis in the myeloproliferative disease polycythaemia vera (PV). Isolated erythrocytosis may also be a manifestation of myeloproliferative disease but is commonly seen as a secondary response to elevated erythropoietin levels, most frequently because of chronic hypoxia. Recently, an acquired point mutation in the gene Janus kinase 2 (*JAK2*) has been identified in approximately 95% of cases of PV, and this is a significant development in terms of diagnosis and as a future target for therapy. Persistent thrombocytosis is the hallmark of another myeloproliferative disease: essential thrombocythaemia (ET). The same acquired point mutation in *JAK2* is identified in approximately 40–50% of cases of ET. Transient reactive thrombocytosis (days to months) is a common response to a wide range of conditions including acute and chronic blood loss, iron deficiency, malignancy, sepsis, chronic inflammation and temporal arteritis. The identification of the myeloproliferative forms of erythrocytosis and thrombocytosis is important as appropriate therapy will reduce the lifetime risk of arterial and venous thromboembolic disease.

KEYWORDS Erythrocytosis, *JAK2V617F*, management, polycythaemia, thrombocytosis

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ERYTHROCYTOSIS

Erythrocytosis is an increase in red cell concentration leading to an increase in haematocrit and often an increase in haemoglobin concentration. Patients with a persistently raised venous haematocrit (>0.52 in males, >0.48 in females for more than two months) should be further investigated. Such patients may have a true erythrocytosis (an absolute increase in red cell mass) or a relative erythrocytosis (a normal red cell mass and decreased plasma volume). However, males with a venous haematocrit above 0.6 and females above 0.56 can be assumed to have an absolute erythrocytosis.

Symptoms and signs

A majority of patients will be symptom free or have non-specific symptoms, including fatigue and headache. Patients with myeloproliferative disease (MPD) may have hypercatabolic symptoms of excess sweating, weight loss and gout. Generalised pruritis, sometimes aquagenic (brought on by water and heat), also occurs in polycythaemia vera (PV). Occasionally such patients present with overt arterial thrombosis, including stroke or transient ischaemic attack (TIA), or venous thrombosis. Patients with a secondary erythrocytosis may have symptoms from the underlying cause for the elevation in their erythropoietin (EPO), most commonly hypoxia. Rarely, patients will have documented haematuria from an underlying EPO-secreting renal cell carcinoma. In all patients with a true erythrocytosis it is crucial to take a detailed history of other risk factors for thrombosis, including past history of vascular events, hypertension, diabetes mellitus, smoking and alcohol consumption.

On examination patients may be plethoric. Patients with a high haematocrit and haemoglobin concentration are more likely to demonstrate peripheral cyanosis. If PV is the cause then patients may demonstrate loss of weight and splenomegaly. Evidence of underlying cyanotic heart disease, chronic pulmonary disease or renal cell tumour (other EPO-secreting tumours such as cerebella haemangioblastomas are exceptionally rare) should be looked for.

Investigations

During 2005 several groups reported a mutation, *JAK2V617F*, within the Janus kinase 2 gene in approximately 95% of cases of PV. This and other rarer mutations in *JAK2* are highly specific for MPD and have changed the approach to the investigation of erythrocytosis. The initial investigations are in Table 1.

TABLE 1 Initial investigations

- History and examination
- Full blood count and film
- Arterial oxygen saturation (hypoxic causes if O_2 sats <92%)

If no obvious secondary cause such as hypoxia then proceed to:

- *JAK2V617F* mutation analysis
- Serum ferritin
- Renal and liver function

TABLE 2 Further tests

- Urine dipstick (microscopic haematuria)
- Abdominal ultrasound (renal or hepatic tumours)
- Serum erythropoietin level (increased in hypoxia and EPO-secreting tumours)
- If all the above tests are negative then consider a bone marrow aspirate, trephine and cytogenetics to identify *JAK2*-negative PV

If the patient has a raised haematocrit as defined above and has a *JAK2* mutation, then the diagnosis of PV is confirmed. The serum ferritin will help identify iron-deficient cases of PV, which are relatively common because of excess iron use and an increase in incidence of gastrointestinal (GI) bleeding. Such patients have a high red cell count, low mean corpuscular volume (MCV) and near normal or even reduced haemoglobin concentration.

If the *JAK2* test is negative the history and examination may identify an obvious secondary cause. If not, the next test is a blood volume measurement to distinguish patients with a true erythrocytosis from those with a relative erythrocytosis. If the red cell mass is above 25% of that predicted based on body surface area, then true erythrocytosis is confirmed and clarification of the cause should be sought by the tests in Table 2.

JAK2-negative PV is diagnosed if the red cell mass is >25% above predicted or the haematocrit is >0.60 in men and >0.56 in women, there is no secondary cause identified and any two additional features of myeloproliferation are present.

Management of erythrocytosis

The management of erythrocytosis depends on the cause. If the patient has a relative erythrocytosis secondary to low plasma volume then management is based on lifestyle advice in relation to known associations with low plasma volume: stopping smoking, reducing alcohol, losing weight, increasing exercise and controlling blood pressure without diuretics. The mainstay of treatment for secondary erythrocytosis is to treat the cause, if possible. The role of venesection in relative and secondary erythrocytosis remains unclear and most haematologists employ a trial of venesection only if the patient has symptoms such as fatigue and headache or has suffered a recent vascular event.

Patients with confirmed PV are at increased risk of arterial and venous thromboses. Such patients should be regularly venesected to keep the haematocrit below 0.45 and started on aspirin at 75–150 mg per day. Other risks for arterial thrombosis should be managed aggressively. The additional risk from a raised platelet count in PV remains controversial. However, it is reasonable to reduce the platelet count to within the normal range with hydroxycarbamide, especially in patients with additional risk factors for thrombosis. The natural history of PV includes progression to myelofibrosis or acute myeloid leukaemia, and cytoreductive agents may increase the leukaemia risk.

THROMBOCYTOSIS

Thrombocytosis is a persistent increase in the platelet count above normal (400–450 x 10^9/L). The differential diagnosis lies between the myeloproliferative disease essential thrombocythaemia (ET) and a wide range of reactive causes and some rarer haematological disorders, such as chronic myeloid leukaemia (CML), which occasionally presents with isolated marked thrombocytosis, and occasional forms of myelodysplatic syndromes (MDS), which will generally be detected by their particular morphological features on blood film examination.

Essential thrombocythaemia, like PV, is a clonal stem cell disorder and the principal feature of the disease is an increased risk for arterial and, to a lesser extent, venous thrombosis. The *JAK2V617F* mutation has been identified in approximately 40–50% of cases of ET and such cases tend towards higher haematocrits, suggesting a close pathophysiological link between *JAK2*-positive PV and ET. The risk of thrombosis in ET is greater when patients are above 60 years of age or have a history of previous vascular events or additional risks for vascular disease. An interesting group of patients are those presenting with unexplained intra-abdominal venous thrombosis and a normal full blood count. A proportion of these, including 50% of cases of unexplained Budd-Chiari syndrome (hepatic vein thrombosis), have been shown to harbour the *JAK2V617F* mutation, and this represents occult MPD.

Symptoms and signs

Again, the majority of patients are asymptomatic. Patients with ET may have evidence of arterial thrombosis including TIA or digital ischaemia. Erythromelalgia (burning finger and toe pain) is a relatively common symptom in ET. Some patients also describe migraine-type headaches. Patients with ET and a very high platelet count (>1,000 x 10^9/L) may present with bleeding. The history and examination should cover potential reactive causes as listed in the abstract.

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Investigations

Once a persistent increase in the platelet count is identified the investigations are aimed at confirming or excluding ET and identifying a reactive cause. The initial screening tests in Table 3 are a practical approach.

TABLE 3 Initial screening tests for thrombocytosis

- Blood film: a wide variation in platelet size, including giant platelets, supports a diagnosis of ET. Reactive thrombocytoses tend to be of uniformly small platelets
- *JAK2V617F* mutation analysis
- *BCR/ABL* rearrangement (if very high platelets and *JAK2* negative, to exclude CML)
- Ferritin
- Renal and hepatic biochemistry, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and immunoglobulins as markers of inflammation
- Bone marrow trephine (*JAK2*-negative MPD)

Management

If the patient is *JAK2*-negative with no obvious reactive cause, less than 60 years old, asymptomatic and with no significant additional risks for thrombosis, then it is appropriate to watch and wait. Some will have *JAK2*-negative ET defined by exclusion and persistence, and in others the platelet count will settle. In patients with an obvious reactive cause the treatment is aimed at alleviating the underlying cause. The risk of thrombosis in reactive thrombocytosis is considered minimal and rarely would cytoreduction be considered.

Patients with ET (*JAK2*-positive or negative) who are over 60 years of age or of any age with significant additional vascular risk factors, including current or previous vascular events, should receive aspirin and cytoreduction with hydroxycarbamide. Reducing the platelet count to within the normal range reduces the risk of vascular events in ET. Very young patients can often be managed with aspirin alone even with high platelet counts. Patients who are resistant to, or intolerant of, hydroxycarbamide should receive the drug anagrelide. The MRC Primary Thrombocythaemia 1 study confirmed that patients with ET and a high risk of thrombosis were less likely to reach a composite endpoint of thromboses, bleeding or death when treated with hydroxycarbamide than with anagrelide, hence the second-line use of anagrelide. As with PV, patients with ET can progress to myelofibrosis or acute myeloid leukaemia.

KEY POINTS

- Erythrocytosis with haematocrits above 0.52 in males and 0.48 in females or persistent thrombocytosis above 450 x 10^9/L are appropriate reasons for investigation.
- The acquired genetic mutation *JAK2V617F* is a key feature of myeloproliferative disease and occurs in 95% of cases of polycythaemia vera and 40–50% of cases of essential thrombocythaemia. This test is now the first-line investigation in cases of non-hypoxic erythrocytosis.
- Patients with polycythaemia vera should have their haematocrit kept below 0.45 by regular venesection to reduce the risk of vascular events.
- Patients with essential thrombocythaemia aged over 60 years or of any age with additional risk factors for arterial disease or vascular symptoms should have their platelet count normalised with hydroxycarbamide.
- The role of venesection in secondary erythrocytosis and relative erythrocytosis remains unproven.

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