should identify drugs that may have to be stopped. Some individuals are particularly sensitive to the usually mild anticoagulant effect of aspirin. A single episode of abnormal surgical bleeding may not be readily explained, but this should be taken into consideration at times of future surgery so that mechanical rather than pharmacological thromboprophylaxis is used and any antiplatelet therapy stopped.

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Myeloproliferative disorders

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Myeloproliferative diseases are clonal stem cell disorders characterised by proliferation of one or more of the erythroid, granulocytic or megakaryocytic cell lines resulting in increased numbers of red blood cells, granulocytes or platelets in the peripheral blood. Extramedullary haemopoiesis may also occur in the liver and spleen. The major non-leukaemic myeloproliferative disorders are polycythaemia vera (PV), essential thrombocythaemia (ET) and myelofibrosis.[1] These conditions overlap, with the potential for further clonal evolution to either myelofibrosis or acute myeloid leukaemia (AML) (Fig 1).[2]

Polycythaemia

The term polycythaemia refers to a number of conditions where the haemoglobin and haematocrit are excessively raised. Patients with a persistently raised haematocrit will usually require a red cell mass estimation to confirm whether there is a genuine or absolute increase in red cell volume. A diagnosis of absolute erythrocytosis can be assumed, however, if the haematocrit exceeds 0.60 in men or 0.56 in women.

The classification of polycythaemia has proved confusing in the past, with the use of terms such as secondary, relative or apparent polycythaemia. The term 'relative polycythaemia' or erythrocytosis should be reserved for states of dehydration, and 'apparent polycythaemia' where there is a raised haematocrit but the red cell mass is within the normal range. The causes and classification of absolute polycythaemia are shown in Table 1.

Clinical features

The median age of presentation is 55–60 years, with an equal sex incidence. Vascular occlusive events are a common presenting feature but there may also be haemorrhage and, in about two-thirds of patients, an enlarged spleen. A useful clinical pointer is the presence of aquagenic pruritus when patients complain of intense itching after a hot bath or shower. Increased uric acid production is not uncommon. The natural history includes progression to myelofibrosis in about 30% of individuals and the development of AML in about 10%.

Key Points

- **The non-leukaemic myeloproliferative disorders are clonal stem cell disorders and have considerable overlap**
- **All these disorders can undergo further clonal evolution to develop either myelofibrosis or acute myeloid leukaemia**
- **Venesection is the standard initial therapy of patients with a raised haematocrit**
- **Essential thrombocythaemia remains a diagnosis of exclusion in the absence of a single confirmatory test**
- **The role of hydroxyurea in increasing the risk of acute leukaemia is still far from clear**
- **Further randomised controlled trials are required to define the indications for and the timing of treatment**

KEY WORDS: clonal evolution, extramedullary, haematocrit, leuco-erythroblastic, leukaemogenesis, non-leukaemic, transplantation

Investigations

The blood count may show a rise in neutrophils in about two-thirds of patients and a thrombocytosis in 50%. The erythropoietin (EPO) level is characteristically low in PV and bone marrow examination will usually reveal a hypercellular marrow with reduced iron stores. Cytogenetic abnormalities are seen in about 20% of patients, the most frequent being deletions of chromosomes 1 and 20. Those patients who go on to develop acute leukaemia invariably have a karyotype abnormality.

Confirmation of an enlarged spleen may be obtained with abdominal ultrasound. Other baseline investigations should include:

- arterial oxygen saturation
- serum ferritin
- renal and liver function tests, and
- chest X-ray.

Sleep studies and lung function tests may be indicated in those patients with a history of snoring or daytime somnolence.

Treatment

The natural history of PV may be assumed from a report by Chievitz[3] in a study of 250 patients of whom 50% were dead within 18 months, the majority due to thrombosis. The primary aim of treatment therefore is to reduce the haematocrit levels to below 0.45 in order to reduce the thrombotic tendency.[4]

The early experience of the Polycythaemia Vera Study Group observed a high incidence of leukaemia with the use of chlorambucil. Treatment with the alkylating agent busulphan and with radioactive phosphorus both also carry a higher risk of acute leukaemia.[5] There is considerable debate about possible increased leukaemogenesis with hydroxyurea (hydroxycarbamide) but the present evidence is inconclusive.[6] Based on a number of trials, the current recommendations are to maintain a haematocrit below 0.45 with venesection and to administer aspirin 75 mg daily unless there is some contraindication.[7]

Cytoreductive therapy should be considered if venesection is poorly tolerated or if there is other evidence of disease progression or significant thrombocytosis. Agents available for cytoreduction are interferon (IFN)-α, hydroxyurea, anagrelide or radioactive phosphorus. For patients under the age of 40 years, first-line therapy should be IFN. There are no randomised controlled trials (RCTs) with IFN and it is poorly tolerated, but it is known to be safe in pregnancy. Alternatively, hydroxyurea may be used; this is useful in preventing thrombosis and possibly in preventing myelofibrosis. Radioactive phosphorus can be useful in individuals over the age of 75.[8]

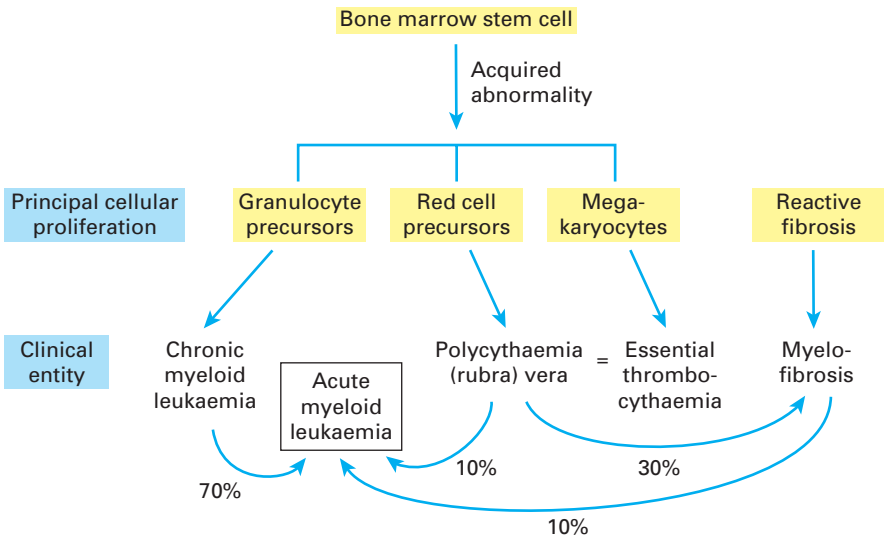

Fig 1. Diagram showing the natural history of and overlap between the myeloproliferative disorders (reproduced, with permission, from Ref 2).

Table 1. Classification of absolute polycythaemia.

Polycythaemia vera	
Secondary polycythaemia:	
(a) Congenital	High oxygen-affinity haemoglobin
	EPO receptor-mediated
(b) Acquired (EPO-mediated)	Chronic respiratory disease
	High altitudes
	Sleep apnoea
	Cardiovascular disease
	Carbon monoxide poisoning
	Smoker's erythrocytosis
	Renal disease (hydronephrosis, renal cysts)
(a) Tumours producing EPO	Hypernephroma
	Hepatocellular carcinoma
	Uterine leiomyoma
	Cerebellar haemangioblastoma

EPO = erythropoietin.

Apparent polycythaemia

Patients with a haematocrit that is slightly elevated or in the high normal range have an increased risk of cardiovascular mortality. There are no RCTs to confirm the beneficial effects of lowering the haematocrit, but it seems reasonable to correct known risk factors for an apparent polycythaemia such as obesity, smoking and hypertension.[9] If the haematocrit remains above 0.54 for more than three months, venesection should be considered to lower the haematocrit to the 0.45 target.

Table 2. Essential thrombocythaemia, diagnostic criteria.

Diagnostic criteria	
Positive criteria	Platelet count >600 x 10^9/l for at least 2 months Clustering of megakaryocytes on trephine biopsy
Negative criteria	Absence of a reactive cause (inflammatory process, iron deficiency, acute blood loss, post-splenectomy, malignancy) No Philadelphia chromosome No fibrosis on trephine biopsy

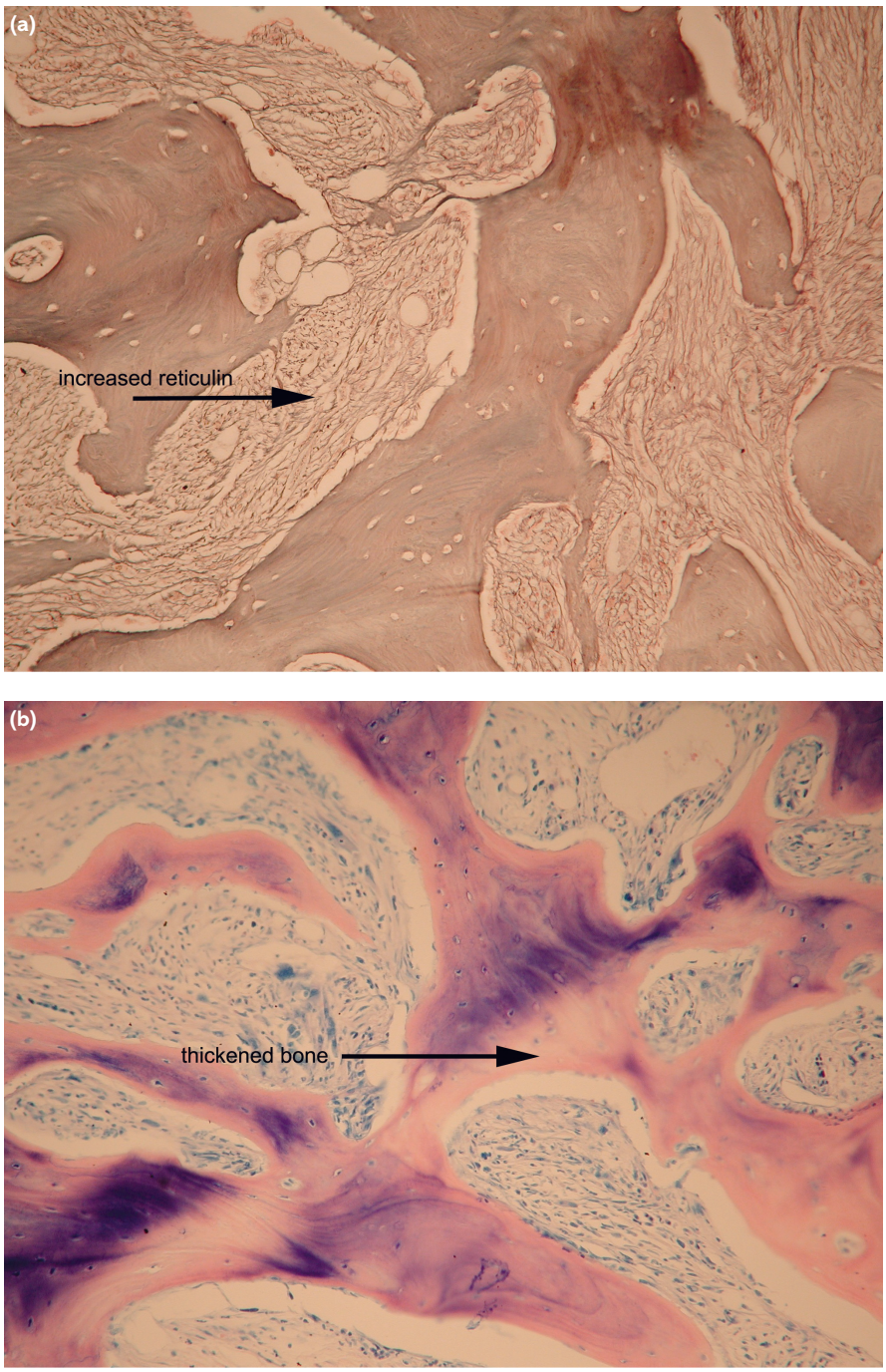

Fig 2. Low power trephine biopsy sections in myelofibrosis showing (a) increased reticulin and (b) thickened bony trabeculae (haematoxylin and eosin stain).

Essential thrombocythaemia

The condition of ET carries the best outlook as it is frequently stable for periods of 10–20 years. The diagnosis is often difficult to confirm as there is no single diagnostic test (Table 2).[10]

Clinical features

Most patients are asymptomatic, but thrombotic and haemorrhagic complications may develop in the longer term. Younger patients are generally monitored without treatment as the risk of thrombosis is relatively low. Thrombotic complications include transient ischaemic attacks, erythromelalgia and Budd-Chiari syndrome. Paradoxically, bleeding complications are usually seen in patients with extremely high platelet counts. Leukaemic transformation is rare in ET, occurring in about 2% of patients.

Treatment

Low-dose aspirin may be used (but not until the very high counts have fallen below 1,000 × 10^9/l). IFN is also effective. Anagrelide is a specific inhibitor of megakaryocyte maturation,[11] but in the recent Medical Research Council (MRC) trial it carried increased risks of haemorrhage and fibrosis.[12]

Prognosis

Recent evidence suggests that many patients previously diagnosed as ET are really early cases of myelofibrosis. This may mean that the risk of progression to myelofibrosis in thrombocythaemia is much lower than has been appreciated.[8]

Myelofibrosis

Previously described as myelosclerosis or agnogenic myeloid metaplasia, myelofibrosis is a condition with reactive fibrosis in the bone marrow secondary to proliferation of abnormal megakaryocytes. The fibroblasts are stimulated by a variety of growth factors produced by megakaryocytes and platelets.[13]

Clinical features

Most patients (90%) have an enlarged spleen and many have abdominal discomfort or even splenic infarction. Constitutional symptoms (weight loss, night sweats) are common and haemorrhagic problems may occur from platelet dysfunction.

Laboratory findings

A mild normocytic anaemia is usual and in the early stages the white cell and platelet counts may be raised. The blood film usually shows leuco-erythroblastic change with characteristic teardrop poikilocytes. Other diagnostic features are marked bone marrow fibrosis, extramedullary haemopoiesis and splenomegaly. The bone marrow is usually difficult to obtain by aspiration; trephine biopsy may show an obvious increase in reticulin fibres (Fig 2(a)). Increased megakaryocytes are frequently seen and some cases show thickened bony trabeculae (manifest radiologically as sclerotic bones) (Fig 2(b)).

Prognostic factors

Haemoglobin less than 10 g/dl and white cell count below 4×10^9/l or above 30×10^9/l identify different risks groups (Lille criteria) (Table 3).

Treatment

Some patients will require supportive blood transfusions and folic acid supplements to maintain a reasonable haemoglobin. Hydroxyurea may be useful where there is myeloproliferation and allopurinol is indicated because of the high uric acid levels. Splenectomy may be considered for patients with high transfusion requirements or splenic infarction, but this carries a high operative risk.[14] Splenic irradiation can sometimes be used to reduce splenomegaly, but the improvement is generally transient.

Anti-angiogenic drugs such as thalidomide have a role by acting against cytokines (vascular-endothelial growth factor) and doses of 50–100 mg daily improve anaemia and thrombocytopenia, but there is a high incidence of side effects (generally neuropathy). Androgens, IFN and EPO therapy may have a role.

Younger patients with a poor prognosis may be suitable for allogeneic transplantation, but this is high risk with transplant-related mortality of about 30%. Recently, reduced-intensity transplantation has been introduced as an option for high-risk patients over the age of 45.

Table 3. Myelofibrosis, prognostic factors. Each prognostic factor scores 1, giving the median survival.

Prognostic factors:	
Anaemia	Hb <10 g/dl
Low white cell count	$<4 \times 10^9$/l
High white cell count	$>30 \times 10^9$/l
Median survival (months):	
low-risk (no factors)	93
intermediate risk (one factor)	26
high-risk (two or more factors)	13

Hb = haemoglobin.

Indications for cytoreductive therapy

There is a dearth of RCTs to direct when to start treatment and what agent to use. In polycythaemia, venesection therapy remains the standard initial measure to lower the haematocrit to 0.45. Hydroxyurea will be the first-line cytoreductive agent for most patients, even though doubts remain about its possible leukaemogenicity. The recent MRC trial on primary thrombocythaemia is a welcome addition to the evidence base for therapeutic decisions.[12] It remains a matter of debate whether the trial was halted prematurely, but there is now good evidence both for the efficacy and the complications of treatment with hydroxyurea and anagrelide.

In myelofibrosis, better recognition of the new diagnostic entity 'prefibrotic myelofibrosis' will lead to reclassification of many patients previously labelled as ET and should provide better understanding of the natural history.

New agents such as imatinib mesylate (Glivec®) have resulted in a major change in the management of chronic myeloid leukaemia. The use of Glivec® and similar agents is now being explored in other myeloproliferative conditions.

There is unlikely to be a shortage of choices for treatment in these conditions but potential toxicity will always be a consideration. Guidance on such choices may come from RCTs or from expert opinion such as Mae West with her immortal words:

> *When faced with a choice between two evils I always like to take the one I haven't tried before.*

Conflict of interest

None.

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Bone marrow failure syndromes

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Bone marrow failure syndromes: what they comprise

Bone marrow failure syndromes are characterised by the primary failure to produce one or more blood cell lineages. Secondary causes of marrow failure such as chemotherapy or radiotherapy, marrow infiltration or peripheral autoimmune destruction of blood cells are excluded. Marrow failure may occur at the level of the haemopoietic stem cell resulting in aplastic anaemia or at a later developmental stage of haemopoiesis affecting a single lineage. Single lineage marrow failure disorders may later progress to aplastic anaemia. Bone marrow failure syndromes are most commonly acquired but there are rare congenital forms.[1]

In aplastic anaemia, there is overlap with clonal disorders such as paroxysmal nocturnal haemoglobinuria (PNH) and myelodysplastic syndromes (MDS, pre-leukaemia). Previously, abnormal cytogenetic clones were thought to indicate MDS, but it is now clear that abnormal clones as well as PNH clones may be present in aplastic anaemia or arise during the course of the illness and then disappear.[2]

Aplastic anaemia

Definition, disease severity and causes

Aplastic anaemia is defined by:

- pancytopenia
- hypocellular bone marrow where normal haemopoietic cells are replaced by fat cells and there is no increase in reticulin or fibrosis (Fig 1), and
- absence of abnormal cells in the bone marrow.

There are three grades of severity of aplastic anaemia, as defined by peripheral blood counts and the degree of marrow hypocellularity. In non-severe aplastic anaemia the neutrophil count is $>0.5 \times 10^9$/l, in severe aplastic anaemia $<0.5 \times 10^9$/l, and in very severe aplastic anaemia $<0.2 \times 10^9$/l.[3]

Aplastic anaemia is a rare idiosyncratic disorder, with an incidence in the West of 1–2 per million population per annum. It is 2–3 times more common in the Far East. The disease is idiopathic in many cases but may be drug-induced or occur following an episode of acute viral hepatitis (Table 1).

Pathogenesis

Aplastic anaemia is characterised by a defect in the haemopoietic stem cell compartment, with both deficiency and

Key Points

Aplastic anaemia is a potentially life-threatening disorder, but treatment outcomes with bone marrow transplantation and immunosuppressive therapy have improved considerably with time

In many patients there is evidence of an autoimmune basis for acquired bone marrow failure disorders

The genetic basis of congenital forms of bone marrow failure is now more clearly understood

KEY WORDS: amegakaryocytic thrombocytopenia, aplastic anaemia, cyclic neutropenia, pure red cell aplasia, severe congenital neutropenia