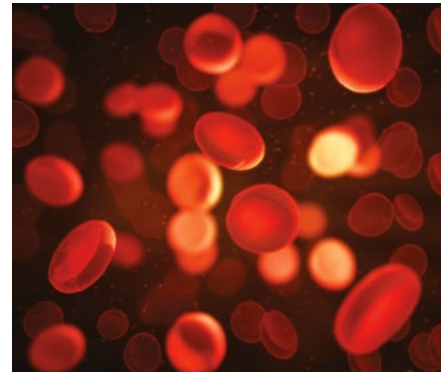


Myeloproliferative neoplasms

Classifications and an approach to diagnosis

CPD 

Richard Lin, Yi Ling Tan

Background

Myeloproliferative neoplasms (MPNs) are a group of illnesses that share a tendency to transform into myelofibrosis and acute leukaemias. Their initial presenting symptoms may be non-specific, which can make diagnosis difficult without a structured approach.

Objective

The aim of the article is to provide general practitioners (GPs) insight into the classification and clinical approach to diagnosis of MPNs.

Discussion

An elevated peripheral blood cell count is often among the first presenting features of an MPN. Although MPNs are rare illnesses, the GP is well placed to identify suspicious features and initiate investigations and referral. It is therefore important for GPs to have an approach to differentiating between reactive and neoplastic causes of elevated blood cell counts.

THE MYELOPROLIFERATIVE NEOPLASMS (MPNs) are a group of disorders that share overlapping clinical, pathological and genetic features that result in abnormal proliferation of mature myeloid cell lineages and a predisposition to developing bone marrow fibrosis and acute myeloid leukaemia.^{1,2} MPNs are uncommon, with incidence rates quoted as 2–6 per 100,000 per year.^{3,4}

The four classic MPNs, which will be discussed in this article, include polycythaemia vera, essential thrombocytosis, primary myelofibrosis (PMF) and chronic myeloid leukaemia (CML).⁵

Approach to diagnosing myeloproliferative neoplasms

Full blood examination interpretation

Most MPNs are associated with persistent abnormalities on full blood examination (FBE). The haemoglobin, white cell count (WCC) or platelet count is usually elevated in polycythaemia vera, CML and essential thrombocytosis, respectively, although more than one parameter can be elevated in each diagnosis. For example, thrombocytosis can be seen in approximately 50% of patients with polycythaemia vera and CML.^{6,7} Myeloproliferative disorders have a normal

spectrum of maturation but exaggerated proliferation, in contrast to other causes of clonal haematopoiesis, such as myelodysplasia (MDS), where there is an abnormal maturation of cells that often leads to cytopenias. Uncommonly, there are diseases that overlap between MDS and MPNs, but this is beyond the scope of this article.

Polycythaemia

The definition of polycythaemia is an increase in haemoglobin >165 g/L in men or >160 g/L in women or a haematocrit >49% in men or >48% in women.⁸

Box 1 outlines the causes of polycythaemia. If absolute polycythaemia is identified, Table 1 highlights investigations that should be performed to differentiate between primary and secondary causes of absolute polycythaemia.

Leucocytosis

Leucocytosis is defined as a WCC above $11 \times 10^9/L$. The first step would be to look at the WCC differential. It is important to rule out benign causes of leucocytosis such as infection/inflammation, glucocorticoid use, splenectomy or smoking.⁹

In CML, there is often a neutrophilia with left shift (presence of immature myeloid precursors – myeloblasts, myelocytes and,

metamyelocytes). Other common features are basophilia and eosinophilia.¹⁰

PMF may present with various combinations of elevated (white) cell counts or cytopaenias, with anaemia being a common feature. Typical findings on a blood film are leucoerythroblastosis and teardrop erythrocytes.¹

Thrombocytosis

Thrombocytosis is defined as a platelet count >450 × 10⁹/L. Common secondary aetiologies of thrombocytosis include infection/inflammation, iron deficiency and bleeding.¹¹

Essential thrombocytosis should be suspected with a persistent thrombocytosis of >450 × 10⁹/L in the absence of secondary causes.⁸ Large and giant platelets can be seen on a blood film.

Molecular testing

Patients with CML have a *BCR-ABL1* fusion gene (Philadelphia chromosome). This is a reciprocal translocation of

chromosomes 9 (*ABL1*) and 22 (*BCR*), producing an abnormal chromosome that confers abnormal cellular survival and loss of apoptotic ability.¹⁰ Testing for the *BCR-ABL1* gene should be strongly considered in patients with left shifted leucocytosis as outlined previously, and also considered in cytosis of other lineages.

Essential thrombocytosis, polycythaemia vera and PMF are Philadelphia chromosome negative and are often thought of as a continuum, seen in their shared genetic mutations and tendency of polycythaemia vera and essential thrombocytosis to progress to secondary myelofibrosis.¹² Mutations of Janus kinase 2 (*JAK2*), calreticulin (*CALR*) and the myeloproliferative virus oncogene mutation (*MPL*) are considered the most specific mutations for the classical MPNs; however, their absence does not exclude the diagnosis.¹³

Those with *CALR* mutations tend to be of younger age and have more extreme

thrombocytosis and a lower thrombotic risk when compared with those with *JAK2/MPL* mutations. Patients with *MPL* mutations are also thought to be at higher risk of progression to fibrosis.¹⁴

Table 2 provides a list of mutations and their relative incidences.

Bone marrow testing

Bone marrow biopsy is performed to confirm the diagnosis with morphology and genetic testing. Common features include varying hypercellularity due to proliferation of granulocytic, erythroid and megakaryocytic cell lines. The bone marrow is also used to assess for the degree of reticulin fibrosis.¹⁵

Other investigations

Other tests commonly performed at initial work-up for MPNs are lactate dehydrogenase and urate. These are commonly elevated in patients with MPNs because of increased cell turnover; however, they are not specific for the disease.

Box 1. Causes of polycythaemia

- Relative (reduced plasma volume)
 - Dehydration
- Absolute (increase in red cell mass)
 - Primary (acquired or germline/inherited mutations)
 - Acquired
 - Polycythaemia vera
 - Other myeloproliferative disorders
 - Inherited
 - High affinity haemoglobinopathies
 - Erythropoietin (EPO) receptor mutations
 - Secondary (caused by elevated serum EPO)
 - Appropriate physiological response to tissue hypoxia
 - Chronic lung diseases
 - Obstructive sleep apnoea
 - Right to left cardiac shunt
 - High altitude
 - Inappropriate EPO production
 - EPO-producing tumours (eg renal cell carcinoma, hepatocellular carcinoma, cerebellar haemangioblastoma)
 - Supplementation
 - Androgen use

Table 1. Investigations for absolute polycythaemia

Upfront investigations	Selective investigations dependent on history/clinical examination findings
<ul style="list-style-type: none"> • Full blood examination; electrolytes, urea and creatinine; liver function tests • Iron studies • Oxygen saturations • EPO level 	<ul style="list-style-type: none"> • <i>JAK2 V617F</i> mutation* • <i>CALR/MPL</i> mutation* • <i>BCR-ABL1</i> fusion gene* • Bone marrow biopsy • Sleep study (secondary polycythaemia) • Arterial blood gas (evaluating for hypoxia and carboxyhaemoglobin) • US abdomen/CT abdomen, pelvis, brain (EPO-secreting tumours) • Transthoracic echocardiography • Chest X-ray for chronic lung pathologies • Haemoglobin electrophoresis – high-affinity haemoglobin • EPO receptor mutations • FSH/LH and total testosterone

*Currently, the Medicare Benefits Schedule (MBS) in Australia offers a rebate for *JAK2*, *MPL* and *CALR* gene testing in the diagnostic work-up by, or on behalf of, a specialist physician for patients with clinical and laboratory evidence of polycythaemia vera, essential thrombocytosis and primary myelofibrosis. The MBS also offers a rebate for *BCR-ABL1* gene testing in the diagnosis and monitoring of chronic myeloid leukaemia that does not specify restrictions on qualifications of ordering physicians.²⁸ CT, computed tomography; EPO, erythropoietin; FSH, follicle stimulating hormone; LH, luteinising hormone; US, ultrasonography

Clinical manifestations of myeloproliferative neoplasms

The clinical manifestations of MPNs can be broadly categorised as disease related or complications.

Disease related

CML is typically classified into three phases: chronic, accelerated and blast. The majority (90%) of patients are diagnosed in the chronic phase and present with few symptoms. Symptoms usually relate to disease-related anaemia and splenomegaly. Uncommonly, patients may present with leucostasis manifesting as pulmonary (dyspnoea, hypoxia) or neurological (visual changes, headaches, dizziness) symptoms.^{1,10}

In polycythaemia vera, microvascular-related symptoms such as headaches, dizziness, visual disturbances, plethora, erythromelalgia and aquagenic pruritus may be evident. Erythromelalgia can be described as episodic intense erythema and burning pain in response to heat stimuli. Aquagenic pruritus is the characteristic syndrome of generalised pruritus experienced after exposure to water, typically during a hot bath.¹⁵

Patients with essential thrombocytosis are typically asymptomatic and identified on routine testing. Symptoms, if present, are similar to polycythaemia vera and may include headaches, visual disturbances, dizziness and erythromelalgia.^{1,13}

PMF is a presentation of myelofibrosis without a preceding diagnosis of polycythaemia vera or essential thrombocytosis, in contrast to secondary myelofibrosis, in which there is a transformation of disease. Constitutional symptoms, such as fatigue, fevers, weight loss and night sweats, are common. Extramedullary haematopoiesis due to marrow fibrosis accounts for the remaining clinical features, including hepatosplenomegaly and bone pain.¹⁶

Complications

The major complications of MPNs are thrombosis, haemorrhagic events and disease transformation to acute myeloid leukaemia or myelofibrosis.²

Patients with thrombotic events in unusual sites should be screened for MPNs.¹⁶ In one large study, the prevalence of MPNs in Budd-Chiari syndrome and portal vein thrombosis was 40.9% and 31.5%, respectively.¹⁷ Patients with extreme thrombocytosis may also experience bleeding due to acquired von Willebrand's syndrome.¹⁶

Patients with MPNs are also predisposed to disease transformation to acute leukaemia or myelofibrosis. Transformation to acute myeloid leukaemia occurs in approximately 5–10% of all MPN cases after 10 years and is associated with a poor prognosis.¹⁸

Timing of referral

It is recommended that GPs consider referral to a haematologist if there is:

- persistent cytosis on peripheral blood count without a clear alternative cause
- unexplained arterial or unusual site venous thrombosis regardless of FBE parameters
- evidence of elevated blood counts or anaemia with constitutional symptoms.

Performing genetic testing for driver mutations such as *BCR-ABL1* and *JAK2* while awaiting haematology review may help in expediting the diagnosis.

Management

Chronic myeloid leukaemia

The management of CML has been revolutionised with tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib and nilotinib, which target the *BCR-ABL1* oncogene. More than three-quarters of those taking TKIs achieve a major molecular response, and 10-year survival rates currently exceed 83.3% for patients on imatinib. For patients who do not respond to imatinib or develop medication resistance, second-generation TKIs such as dasatinib and nilotinib can be used with demonstrated haematological and cytogenetic responses.¹⁰ Newer generation TKIs are also in development, and phase I studies have shown efficacy in patients with CML who have had exposure to at least three TKIs.¹⁹

Although allogeneic stem cell transplants remain the only curative therapy, in the era of TKIs they are now reserved for patients with refractory or accelerated/blast phase CML to minimise associated morbidity and mortality.¹⁰

Polycythaemia vera

Management of polycythaemia vera is aimed at preventing thrombotic complications through a combination of phlebotomy, aspirin and cytoreduction.

Phlebotomy is used to maintain a haematocrit <0.45 in patients with polycythaemia vera to reduce the risk of cardiovascular disease and major thrombosis, as demonstrated in the cytoreductive therapy in polycythaemia vera (CYTO-PV) trial.²⁰

Table 2. Genetic mutations associated with myeloproliferative neoplasms^{1,12,13}

2016 World Health Organization classification of myeloproliferative neoplasms

	Genetic mutation
Chronic myeloid leukaemia	<i>BCR-ABL1</i> (99%)
Polycythaemia vera	<i>JAK2</i> (99%) <i>JAK2V617F</i> (>95%) <i>JAK2</i> exon 12 (3%) <i>CALR</i> (<1%)
Primary myelofibrosis	<i>JAK2</i> (50–60%) <i>CALR</i> (25–30%) <i>MPL</i> (5–10%)
Essential thrombocythaemia	<i>JAK2</i> (50–60%) <i>CALR</i> (20–25%) <i>MPL</i> (5–10%)

Low-dose aspirin (100 mg/day) is used in all patients with polycythaemia vera who do not have any contraindications. The European collaboration on low-dose aspirin in polycythemia vera (ECLAP) study showed a significant benefit for aspirin in reducing nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes by 60%.²¹

Cytoreductive therapy is considered in high-risk patients (age ≥ 60 years or history of thrombosis) and those with progressive splenomegaly, leucocytosis or thrombocytosis, or poor tolerance of venesection.^{15,22} Hydroxyurea, an oral antimetabolite that prevents DNA synthesis, is the most commonly used therapy because of ease of use and safety profile. Side effects include myelosuppression, leg ulcers and gastrointestinal toxicity.²² Interferon is an alternative that is non-leukaemogenic and non-teratogenic, making it a preferred choice for younger patients as well as during pregnancy. Its use is limited by significant side effects, with discontinuation rates of up to 30% reported.^{12,15} Pegylated interferon alfa-2a can be used and is associated with lower toxicity and reduced frequency dosing when compared with conventional interferon, with demonstrated haematological and molecular responses.²³

Median survival for patients with polycythaemia vera is relatively long, measuring up to 27 years.² Approximately

12–21% of cases evolve into post-polycythaemia vera myelofibrosis, and approximately 7% transform into acute myeloid leukaemia within 20 years.²⁴

Essential thrombocytosis

Antithrombotic and cytoreductive treatment of essential thrombocytosis is also risk stratified and largely mirrors polycythaemia vera, as outlined in Table 3.^{11,14}

Cytoreductive therapy for high-risk patients with essential thrombocytosis is titrated to a platelet count of $<450 \times 10^9/L$, with hydroxyurea the most commonly used agent. In patients <40 years of age, where the theoretical leukaemogenicity of hydroxyurea is a concern, or in women of childbearing potential, pegylated interferon alfa-2a can also be considered as an alternative. Anagrelide is shown to be non-inferior to hydroxyurea in preventing thrombotic events; however, its use is limited by its cardiotoxicity.¹¹

Primary myelofibrosis

The prognosis and management of patients with PMF is dependent on the risk of illness, which can be assessed using the Dynamic International Prognostic Scoring System Plus (DIPSS-Plus), as outlined in Table 4.²⁵

Allogenic stem cell transplant remains the only curative treatment; however, because of significant morbidity and mortality, this is reserved for high-risk patients.²

Patients with predominant anaemia can be treated with androgens, prednisone, thalidomide/lenalidomide or danazol.¹³ Other supportive/symptom-directed

options include transfusions, splenectomy, hydroxyurea and splenic irradiation.²⁶

Ruxolitinib is a selective JAK1/2 inhibitor therapy for patients at intermediate-1 risk refractory to current therapy or patients at intermediate-2 risk. The controlled myelofibrosis study with oral JAK inhibitor treatment (COMFORT) studies using ruxolitinib showed positive results in reducing spleen size, myelofibrosis-related symptoms and overall survival.²⁷

Appendix 1 (available online only) summarises four classic presentations of MPNs alongside assessments, investigations and management.

Conclusion

MPNs are a group of disorders with abnormal myeloid lineage proliferation. They commonly presents with persistent and unexplained elevated FBE parameters. The majority of MPNs, except CML, lack disease-modifying therapy. Early diagnosis and ongoing follow-up can help to manage and monitor for complications of illness, which may help to reduce the burden of the illness. It is recommended that GPs consider this group of illnesses in the differential diagnosis of persistent cytosis and refer for haematologist review.

Key points

- The four classical MPNs include polycythaemia vera, essential thrombocytosis, PMF and CML.

Table 3. Approach to management of essential thrombocytosis by risk group^{11,13}

	Very low risk	Low risk	Intermediate risk	High risk
Characteristics	Age ≤ 60 years No history of thrombosis <i>JAK2V617F</i> mutation absent	Age ≤ 60 years No history of thrombosis <i>JAK2V617F</i> mutation present	Age >60 years No history of thrombosis <i>JAK2V617F</i> mutation absent	Age >60 years <i>JAK2V617F</i> mutation present OR History of prior thrombosis
Management	Aspirin 100 mg daily**		Aspirin 100 mg daily†	Aspirin 100 mg daily† Cytoreductive therapy recommended

*Observation alone may be considered in those with absent cardiovascular risk factors.

†Aspirin should not be used in patients with a platelet count of $>1000 \times 10^9/L$ and a history of bleeding given the possible diagnosis of acquired von Willebrand's disease.

Table 4. Dynamic International Prognostic Scoring System Plus (DIPSS-Plus)^{25,29}

- Age >65 years (1 point)
- Leucocyte count >25 × 10⁹/L (1 point)
- Haemoglobin <100 g/L (2 points)
- Circulating blast cells ≥1% (1 point)
- Constitutional symptoms (1 point)
- Platelet count <100 × 10⁹/L (1 point)
- Anaemia requiring transfusion (1 point)
- Unfavourable karyotype (1 point)

DIPSS-Plus interpretation

Score	Category	Median survival	Treatment
0	Low risk	15.4 years	Observation or supportive/symptom-directed therapy*
1	Intermediate-1 risk	6.5 years	Supportive/symptom-directed therapy* Clinical trial JAK1/2 inhibitor in patients with severe disease-related symptoms that are resistant, refractory or intolerant to available therapy
2-3	Intermediate-2 risk	2.9 years	JAK1/2 inhibitor +/- allogeneic stem cell transplant
4-6	High risk	1.3 years	

*Examples of supportive or symptom-directed therapy include transfusions, prednisone, hydroxyurea, danazol, pegylated interferon alfa-2a, splenic irradiation and splenectomy.

- MPNs should be suspected on the basis of a persistently elevated and unexplained cell count on the FBE, and referral to haematology sought.
- Genetic testing for the Philadelphia chromosome (*BCR-ABL1*) should be performed in patients with suspected CML.
- Mutated genes common in polycythaemia vera, essential thrombocytosis and PMF patients are *JAK2*, *CALR*, and *MPL*.
- MPNs carry a significant risk of arterial and venous thrombosis, with the predisposition of transformation into myelofibrosis and acute leukaemia.

Authors

Richard Lin BMed, MD, MPH, FRACGP, General Practitioner, Sydney, NSW

Yi Ling Tan MBBS, MMed (Clin Epi), FRACP, FRCPA, Clinical and Laboratory Haematologist, Nepean Hospital, Kingswood, NSW

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Correspondence to:

richard.jia.lin@gmail.com

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correspondence ajgp@racgp.org.au