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Polycythaemia/Erythrocytosis

Insight – March 2018

- An elevated haemoglobin or haematocrit is not an uncommon incidental finding on routine blood tests.
- It is most important to distinguish between primary polycythaemia and that which is secondary to another medical condition.
- Management is focused on reducing potential complications and addressing the underlying cause; venesection may be used in some cases.

Polycythaemia or erythrocytosis refers to an elevation of the haemoglobin or haematocrit (haemoglobin >16.0 g/dL in women or >16.5 g/L in men; haemocrit >48% in women or 49% in men) or increased red cell mass (>25% above the mean normal predicted value). An initial concerning result on routine testing should always be confirmed by a second measurement in a non-fasting state.

Definition

Relative Polycythaemia

Relative polycythaemia is secondary to a decreased plasma volume (without an increased red cell mass). This is generally the consequence of intravascular fluid depletion, which may be due to dehydration (including that induced by diuretics and caffeine), movement of fluid into the third-space, tobacco smoking and ovarian hyperstimulation syndrome (IVF).

Absolute Polycythaemia

Absolute polycythaemia is a true increase in red cell mass resulting in an elevated haemoglobin, haematocrit or red blood cell count. It is clinically significant and can arise as a primary or secondary phenomenon.

Primary polycythaemia manifests when a congenital or acquired disorder leads to abnormal erythropoiesis. The most commonly encountered condition is polycythaemia vera (PV), a clonal myeloproliferative neoplasm (MPN) almost invariably accompanied by the JAK2 V617F mutation and frequently by a low serum erythropoietin (EPO). Table 1 outlines the recently updated World Health Organisation (WHO) diagnostic criteria for this disorder.

Secondary polycythaemia is caused by exogenous stimulation of erythropoiesis. It is generally associated with an elevated EPO level, which may be physiologically appropriate (stimulated by hypoxia) or inappropriate (in the absence of hypoxia).

Major Criteria
1. Haemoglobin >16.5 g/dL in men or >16.0 g/dL in women, or Haematocrit >49% in men or 48% in women, or Increased red cell mass (>25% above mean normal predicted value)
2. 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)
3. Presence of JAK2 V617F or JAK2 exon 12 mutation
Minor Criteria
Subnormal serum EPO level

Table 1 – WHO Criteria For PV

Requires all three major criteria or the first two major criteria and the minor criterion.

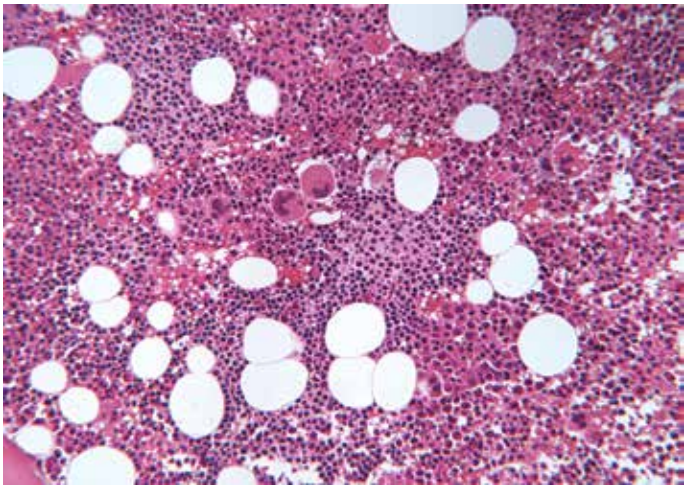

Figure 1 – PRV bone marrow

Causes

Relative Polycythaemia
Dehydration
Third-spacing
Tobacco
Absolute Polycythaemia
Secondary Polycythaemia
Physiologically inappropriate increase in EPO
▪ EPO-producing neoplasms including renal cell carcinoma, hepatocellular carcinoma, cerebellar haemangioblastoma, parathyroid carcinoma/adenomas, uterine leiomyomas, pheochromocytoma and meningioma
▪ EPO-producing renal lesions such as renal artery stenosis, end-stage renal failure, polycystic kidney disease and hydronephrosis
Physiologically appropriate increase in EPO
▪ Hypoxia due to high altitude, chronic pulmonary disease, right-to-left cardiac shunts, sleep apnoea, massive obesity, high altitude and red cell abnormalities
Primary Polycythaemia
▪ Polycythaemia vera (JAK2 mutation)
▪ High oxygen affinity haemoglobins
▪ Congenital methemoglobinaemia
▪ Idiopathic familial polycythaemia
▪ 2,3 bisphosphoglycerate (BPG) mutase deficiency
▪ Rare gene mutations such as those involving prolyl hydroxylase domain 2 (PHD2), HIF2-α, von Hipple-Lindau (VHL), erythropoietin receptor (EPOR)

Table 2. Major causes of polycythaemia

Erythropoiesis and JAK2

Erythropoiesis is primarily regulated by the hormone EPO. EPO is produced by the kidney and liver; its release is triggered by a reduction in oxygen delivery.

The erythropoietin receptor (EPOR) facilitates the action of EPO on erythroid progenitors, via phosphorylation of the Janus 2 tyrosine kinase (JAK2).

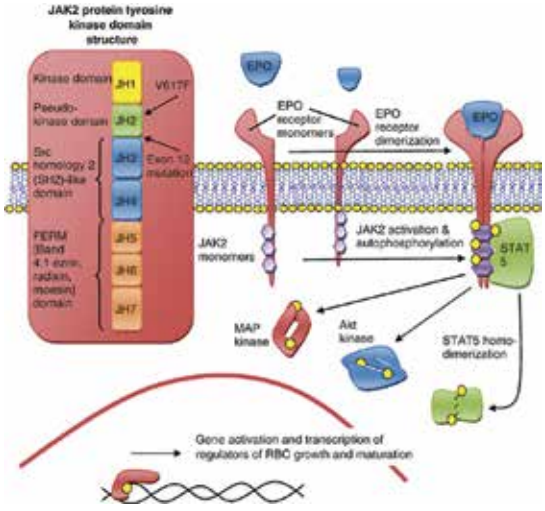

Figure 2. Erythropoietin Receptor Signalling

In polycythemia vera, there is constitutive hyperactivatity of this pathway by a 'gain-of-function' JAK2 mutation[1].

Diagnostic approach

Diagnosis involves the use of clinical and laboratory findings to establish whether there is a true polycythaemic state (absolute versus relative) and if present, whether it is primary or secondary in nature. Figure 3 provides a diagnostic algorithm.

History and examination should include a search for cardiorespiratory, renal and liver disease as well as complications of hyperviscosity. Familial conditions, occupational risks, smoking, snoring and medication exposures (such as diuretics, androgens, anabolic steroids and erythropoietin therapy) should all be considered.

Common symptoms of hyperviscosity of any cause include cardiocerebral compromise (chest pain, transient ischaemic attack, headache, fatigue, blurred vision). Symptoms more specific to PV include itch, erythromelalgia, gout or splenic discomfort.

Erythromelalgia is a rare condition that primarily affects the feet and, less commonly, the hands (extremities). It is characterised by intense, burning pain of affected extremities, severe redness (erythema), and increased skin temperature that may be episodic or almost continuous in nature.

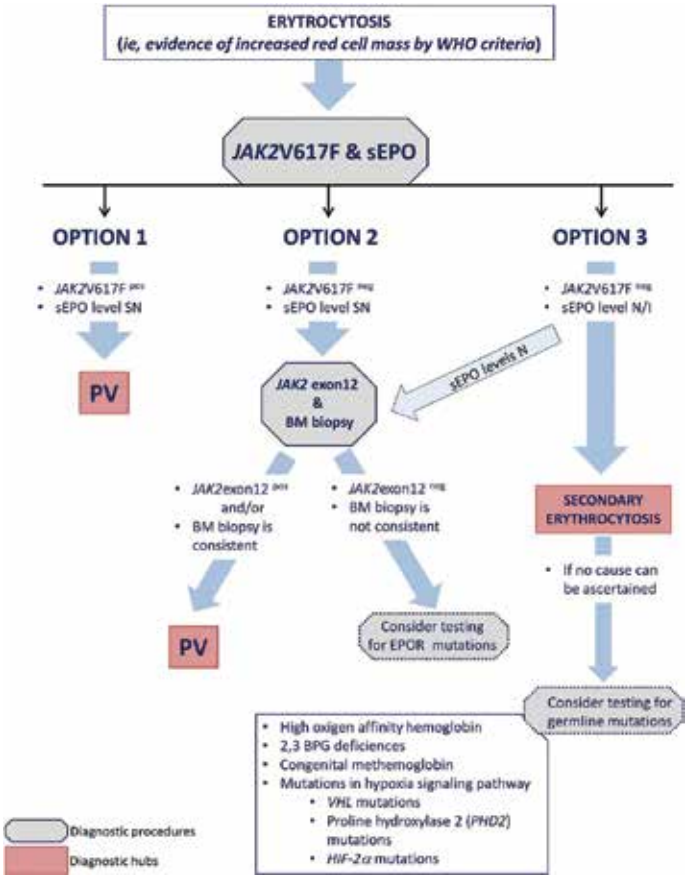

Figure 3. Erythrocytosis Diagnostic Approach

Diagnostic procedures indicated with a dotted border require a high level of suspicion and, preferably, reasonable evidence of familial history. These genetic tests are complex, costly and should be performed in a specialised laboratory.[2]

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Investigations

- Full blood examination (FBE) and film:
  Additional findings of microcytosis and/or thrombocytosis suggest PV
- Urea/electrolytes and urine dipstick:
  Renal disease
- Liver function tests:
  Cirrhosis
- Iron studies:
  Iron deficiency common in PV
- Vitamin B12, urate and lactate dehydrogenase:
  Increased in myeloproliferative disorders
- Oxygen saturation:
  Cardiorespiratory disease
- Carboxyhaemoglobin level:
  Smokers
- Chest radiograph
- Abdominal ultrasound (liver, spleen and kidneys)
- Lung function tests
- Sleep study

In the absence of an established diagnosis referral to a clinical haematologist is recommended for:

- JAK2 V617F mutation:
  Medicare rebate available
- Serum erythropoietin level:
  No medicare rebate available
- Bone marrow biopsy

If the diagnosis remains elusive, haemoglobin studies for high affinity haemoglobin (p50, haemoglobin electrophoresis, methaemoglobin) and low incidence mutation analysis (JAK2 exon 12, erythropoietin receptor gene) may be required.

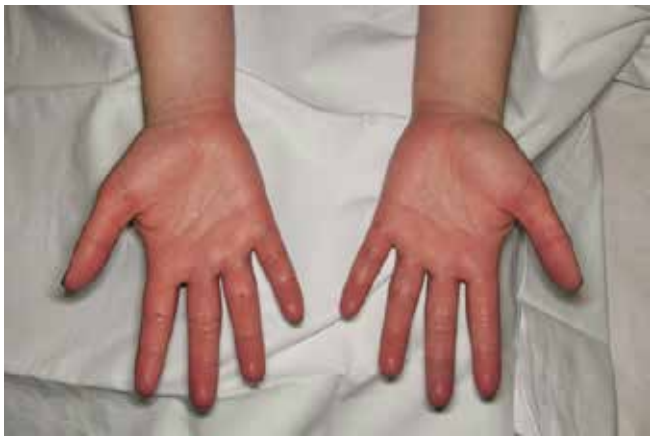

Figure 4. Erythromelalgia in hands

Image courtesy: Uptodate 2017[3].

A thorough examination must also exclude the presence of hypertension, cardiac murmurs, clubbing, hepatosplenomegaly and dilated retinal vessels.

Complications

Haemorrhage and thrombosis can complicate both primary and secondary cases of polycythaemia, however the risk of progression to marrow fibrosis or leukaemia is exclusive to PV. It is vital to ensure correct diagnosis so that appropriate therapy can be instituted.

Management

Secondary Polycythaemia

Strategies include:

- Reduction or elimination of precipitating factors
- Limited phlebotomy considered in those symptomatic from hyperviscosity or with risk factors for thrombosis
- Disease-specific therapies such as in renal transplantation

Polycythaemia vera

Patients are stratified into risk survival groups based on their age, leucocyte count and history of prior thrombosis to define the treatment approach. **Therapies comprise:**

- Aspirin
  100 mg daily to reduce thrombosis and cardiovascular risk, unless there is a specific contraindication
- Phlebotomy/venesection aiming for a haematocrit of:
  <45% in men
  <42% in women
  <37% in late pregnancy
- Cytoreduction:
  Hydroxyurea or pegylated interferon (IFN) may be used in symptomatic and high-risk cases
- JAK2 Inhibitors:
  Ruxolitinib is appropriate in those with resistance or intolerance to hydroxyurea
- Venesection

Melbourne Pathology provides a therapeutic venesection program to patients that have been deemed medically unsuitable to donate at the Australian Red Cross Blood Service (ARCBS).

Further information regarding this service is available via the Melbourne Pathology website and the enrolment form can be assessed from the following link:

http://www.mps.com.au/media/3305262/tv_info_and_referral_may13_final.pdf

Table 16-11 PV risk (3 groups) survival

Age, years	>67 (5 points)
	57-66 (2 points)
	<57 (0 points)
Leukocytes	$>15 \times 10^9$/L (1 point) vs. $<15 \times 10^9$/L
Prior thrombosis	Yes (1 point) vs no (0 points)
Risk group point cutoffs/survival	Sum above points. Median survival:
	Low risk (0 points): 27.8 years
	Intermediate risk (1-2 points): 18.9 years
	High risk (≥3 points): 10.9 years

Adapted from Tefferi A, et al. *Leukemia.* 2013;27:1874-1881.

Table 3. PV Risk Groups

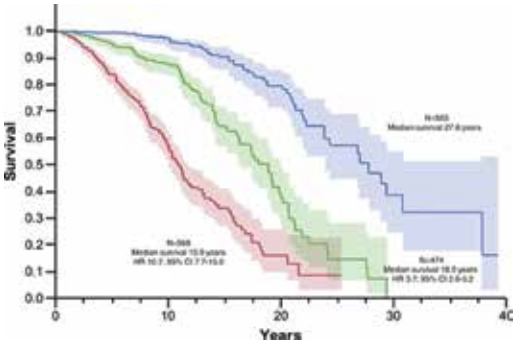

Figure 5. PV Risk-Stratified Survival in 1545 patients with polycythaemia vera[4].

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3. BPG, erythrocyte 2,3-biphosphoglycerate; EPO-R, erythropoietin receptor; HIF-2a, hypoxia-inducible factor 2a; N/I, normal/increased; PDH2, prolyl hydroxylase domain protein 2; SN, subnormal; VHL, von Hippel-Lindau. Vannucchi AM.(2014). How I treat polycythemia vera. Blood 2014;124:3212-20.
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Dr Liesl Butler

MBBS (Hons)

Dr. Butler graduated from Monash University in 2010 and has trained in haematology at St. Vincent's Health, Peter MacCallum Cancer Centre, Melbourne Health and Melbourne Pathology. She is completing a dual fellowship with the Royal College of Pathologists Australasia and the Royal Australasian College of Physicians, and will commence her final year of training in 2018 at Western Health.

With an avid interest in laboratory haematology, Dr Butler hopes to be pursue research and educational opportunities, and eventually work in the area.

Dr Ellen Maxwell

MBBS, FRACP, FRCPA

Medical Director & Director of Haematology

Dr Maxwell is a University of Melbourne graduate who completed combined fellowships with the College of Physicians and the College of Pathologists in 1997.

She trained initially at the Austin and Repatriation Medical Centres and later the Alfred Hospital where she developed a keen interest in coagulation and transfusion medicine.

Dr Maxwell is a current member of the Victorian Blood User Group, the National Blood Transfusion Committee, The Australian Red Cross Blood Service Advisory Committee and the Serious Transfusion Incident Reporting Working Group (DHS Victoria). She has been an active member of many committees for the RCPA and ANZSBT. Dr Maxwell was appointed Medical Director at Melbourne Pathology in September 2009.