CHAPTER 8

Familial and acquired polycythaemia

8.2 Acquired polycythaemia

Chloé James, William Vainchenker
1. Introduction

The term acquired polycythaemia, also called acquired erythrocytosis, literally defines a group of disorders characterised by an acquired increase in circulating red blood cells (RBC). Nevertheless, an increase in the number of RBC with no concomitant increase of the haematocrit level (as in thalassaemia, for example) is not considered as a polycythaemia. Therefore, polycythaemia should be suspected only when the haematocrit level exceeds the upper limit of the normal range, with the value of 51% being commonly used as a threshold. As the haematocrit level depends on the number and volume of RBC, but also on the plasma volume, the assessment of polycythaemia theoretically requires a red cell mass measurement. This isotopic investigation allows measurement of both plasma volume and red cell mass, and can discriminate between a false polycythaemia due to haemoconcentration (decreased plasma volume with normal red cell mass) and a true acquired polycythaemia (red cell mass over 125% of the predicted value). Methods based on the determination of carboxyhaemoglobin dilution may prove of value, as these would avoid the use of isotopes.

Real acquired polycythaemia can be classified as primary (commonly called polycythaemia vera), secondary and idiopathic (Table 1). In most cases of primary polycythaemia, a molecular abnormality in the JAK2 gene can be identified. Secondary polycythaemia is the consequence of a high secretion of erythropoietin (Epo), which can be appropriate (in response to chronic hypoxia) or inappropriate (in association with tumours). Idiopathic polycythaemia comprises a heterogeneous group of rare disorders with unknown aetiology.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Epo levels</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (polycythaemia vera)</td>
<td>Low</td>
<td>JAK2 V617F mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JAK2 exon 12 mutations</td>
</tr>
<tr>
<td>Secondary</td>
<td>High</td>
<td>- Chronic hypoxia (altitude, chronic obstructive lung disease, sleep apnoea syndrome, right to left cardiac shunts)</td>
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<td></td>
<td></td>
<td>- Tumours (kidney or liver tumours, cerebellar haemangioblastomas, ovarian tumours)</td>
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<tr>
<td></td>
<td></td>
<td>- Misuse of recombinant human erythropoietin</td>
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<tr>
<td></td>
<td></td>
<td>- Post transplant erythrocytosis (after kidney transplantation)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Low or high</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
2. Primary polycythaemia or polycythaemia vera

Polycythaemia vera (PV) is a clonal and acquired stem cell disease characterised by abnormal erythropoiesis, some erythroid progenitors being hypersensitive or independent from Epo. PV belongs to the family of chronic myeloproliferative neoplasms (MPN), which include haematological diseases that share clinical and biological similarities, including a haematopoietic stem cell (HSC) origin. MPN comprise PV, essential thrombocythaemia (ET), primary myelofibrosis (PMF), chronic myeloid leukaemia (CML), some types of hypereosinophilic syndrome (HES), systemic mast cell diseases (SMD) and other rare disorders. With the exception of PMF, all these disorders are characterised by increased haematopoiesis with overproduction of blood elements predominantly belonging to one myeloid lineage. In CML, the granulocytic lineage is the most hyperplastic, while the erythroblastic and the megakaryocytic lineages are predominantly involved in PV and ET, respectively. Typically, the marrow hyperplasia is not associated with any alteration in the maturation of haematopoietic cells. The most common clinical characteristics of MPN are exuberant extramedullary haematopoiesis, leading to splenomegaly, spontaneous transformation to acute leukaemia, development of marrow fibrosis at a variable rate and, above all, a high risk of thrombotic and haemorrhagic events.

PV is a rare disease with a year incidence of 2.3 per 100,000 and a prevalence of 300 cases per million in habitants.

2.1 Pathogenesis

The pathogenesis of PV has been studied for nearly four decades and the discovery of the JAK2V617F mutation in 2005 undoubtedly highlighted our understanding of the pathogenesis of this disease. Nevertheless, it is still unclear whether JAK2V617F alone is responsible for PV and PV might be a more heterogeneous disease than previously thought. We will successively summarise the major abnormal features found in PV, the insights gained by the discovery of the JAK2V617F mutation and the issues that still need to be understood.

2.1.1 What are the abnormal features of PV?

Like the other MPN, PV originates from a haematopoietic stem cell defect. Indeed, X-inactivation studies have shown that cells from the myeloid and lymphoid lineages were clonal in some female patients, demonstrating that the malignant clone was derived from one single abnormal HSC (2). Another important characteristic of PV cells is their abnormal response to cytokines. A fraction of erythroid progenitor cells (called EEC for Endogenous Erythroid Colonies) proliferates and differentiates without Epo (3). In fact, EEC formation is a very useful test used in clinical
practice for the diagnosis of PV. Nevertheless, it should be noted that the presence of EEC is not specific for PV since EEC are also found in ET, PMF and CML. Besides, PV erythroid progenitor cells are also hypersensitive to several other growth factors. Given the abnormal response of PV progenitors to cytokines, cytokine receptors and their signalling pathways have been extensively studied. No abnormality has been found in the Epo receptor (Epo-R), but interestingly, different groups reported that the Epo-R signaling pathway was activated in PV cells in the absence of Epo stimulation (4). Indeed, Bcl-xL was shown to be overexpressed, STAT3, STAT5 and AKT were found to be constitutively phosphorylated and it was shown that two major signalling pathways, the JAK/STAT and the PI3K/AKT pathways, were necessary for the Epo independency of erythroid progenitors in PV (5). In order to understand the molecular mechanisms leading to the thrombocytosis often present in PV, the group of J. Spivak studied the thrombopoietin-receptor (MPL) and its signalling pathway. Very surprisingly, these authors observed that MPL expression was reduced in platelets and megakaryocytes from PV patients, as a consequence of a defect in MPL trafficking to the cell surface (6). Finally, in 2002, the group of J. Prchal observed that 30% of PV patients showed an acquired loss of heterozygosity (LOH) on the short arm of chromosome 9 (9p24) (7). Further studies led to the demonstration that this 9pLOH was due to a mitotic recombination rather than an acquired deletion (7). Other groups also showed that a gain of 9p was frequently found in PV (8). Altogether, these studies have revealed a high frequency of cytogenetic abnormalities leading to gain of material or loss of heterozygosity at the 9p locus, suggesting the involvement of a gene that could be functionally important for the pathogenesis of PV.

2.1.2 JAK2V617F mutation explains most PV abnormalities

The molecular characterisation of PV occurred in 2005 with the discovery of the JAK2V617F mutation which is found in about 95% of the patients. While studying the mechanisms responsible for the Epo-independent growth characteristic of PV progenitors, our team discovered a mutated form of the JAK2 protein, JAK2V617F (9). Other groups came to the same conclusion after analyses of the tyrosine kinome (10), by precise mapping of the minimal 9p LOH region found in 30% of PV patients (11) or by direct sequencing of JAK2 as a candidate gene (12). This JAK2 mutation is a unique and recurrent acquired mutation encoding a JAK2 protein, in which a valine is substituted by a phenylalanine (JAK2V617F) in the auto-inhibitory JH2 (JAK Homology) domain. In the granulocytes of 30% of PV patients, sequencing shows that only the mutated allele is present. This is due to a duplication of the mutated allele by mitotic recombination as a consequence of the 9pLOH previously
mentioned. Thus these patients are “homozygous” for JAK2V617F, a very uncommon feature for a gain of function mutation. In contrast, the remaining 70% PV patients have both the mutated and normal alleles and have been called “heterozygous”. In fact, the precise status of JAK2V617F is highly complex because both normal and JAK2V617F cells, which in turn can be either heterozygous or homozygous, coexist in most patients. Indeed, analysis of individual erythroid colonies revealed that almost all PV patients display a variable proportion of homozygous progenitors. Analyses of different haematopoietic cell populations in PV patients have shown that the JAK2V617F mutation was acquired, clonal and present in HSC. Through experiments performed with murine cell lines, it was demonstrated that the mutated JAK2V617F was constitutively active and able to activate the Epo-R signalling pathway in the absence of Epo (7, 9, 10, 12). As JAK2 is a tyrosine kinase protein involved in the signalling of numerous cytokine receptors, its constitutive activation not only explains Epo independency but also hypersensitivity to other cytokines. Furthermore, the mutated protein was shown to induce genomic instability via stimulation of homologous recombination (13). This probably explains why 30% of PV patients have a 9pLOH and why some PV patients progress to secondary acute leukaemia (Figure 1).

Further confirmation of the role of JAK2V617F in the pathogenesis of PV came from animal models. Retroviral transduction of JAK2V617F in murine HSC followed by transplantation into lethally irradiated mice led to the development of a PV

The expression of MPL is diminished:
JAK2V617F can not address MPL to the membrane

STAT3 and STAT5 are constitutively phosphorylated:
JAK2V617F activates STAT

AKT is constitutively phosphorylated:
JAK2V617F activates the PI3K/AKT pathway

Del 20q and 9pLOH: JAK2V617F induces a genomic instability

Figure 1: JAK2V617F explains most of the abnormalities described in PV
phenotype, which rapidly evolved into secondary myelofibrosis, thus recapitulating the polycythaemic and the spent phases of PV (14-16). Although all these findings undoubtedly demonstrate the crucial role of JAK2V617F in the pathogenesis of PV, it is clear that this mutation is not specific for PV. Analysis of other MPN patients revealed that the JAK2V617F mutation was also found in about 50% of patients with ET and PMF, in rare patients with atypical MPNs, in myelodysplastic syndromes with thrombocytosis and even in haematologically normal patients with splanchic vein thrombosis. This intriguing observation raises the major and still unanswered question of how a unique mutation can cause different phenotypes. Several hypotheses are under investigation such as differences in the haematopoietic stem cell targeted by the mutation, host modifier polymorphisms, intensity of JAK2V617F signalling, presence of other somatic mutations or the presence of a pre-JAK2 event that may vary according to the MPN phenotype (17). Transgenic mice have already afforded some evidence that the expression level of JAK2V617F plays a major role in the disease phenotype and that the level of JAK2V617F signalling might be the major determinant accounting for disease heterogeneity (18).

2.1.3 Is PV the consequence of the sole presence of JAK2V617F?

The JAK2V617F mutation is found in the great majority of PV patients, but 5% of the patients do not carry this mutation. Scott et al showed that some of them had other mutations in JAK2, these being either point mutations, insertions or deletions. All are located in exon 12 of the gene (19). Like JAK2V617F, these mutant proteins are spontaneously active, they constitutively activate STAT5 and, when expressed in murine HSC, they induce a MPN. Interestingly, exon 12 mutations have exclusively been found in PV, and not in ET or PMF patients. In addition, PV associated with JAK2 exon 12 mutations displays a nearly pure erythrocytosis phenotype with little increase in granulocyte and platelet counts, although a trilineage proliferation is detected in the marrow. Altogether, mutations in JAK2 are thus found in almost 98% of PV patients. The molecular origin of the PV in the 2% remaining patients is yet unknown, although it is not excluded that other mutations in JAK2 might exist.

Even if animal models have unequivocally shown that introduction of JAK2V617F in multiple murine HSC leads to PV development, it is not known whether the sole presence of JAK2V617F in a single human HSC would be sufficient to induce a MPN. It seems now clear that another molecular event occurs in a HSC, before the JAK2V617F mutation, in some PV patients. For example, the analyses of leukaemic transformation in patients with JAK2V617F-positive PV show that most patients transform into a JAK2V617F-negative acute myeloid leukaemia (20). Another
example is the presence of JAK2 wild type EEC together with JAK2V617F-positive EEC in some JAK2V617F-positive PV patients (21). Finally, observation of familial cases of MPN provides the most striking evidence for the presence of a pre-JAK2 event in some patients. Firstly, within a same family, different types of MPN may occur, such as JAK2V617F-positive ET, JAK2V617F-positive PMF, JAK2 wild type mastocytosis and BCR-ABL positive CML (22). Secondly, in families with only JAK2V617F-positive MPN, there is no germline transmission of the JAK2V617F mutation since the mutation is absent from the patients T and B cells, as in sporadic MPN (22). Together, these results suggest the presence of an unknown germline event that would be a predisposing factor common to multiple forms of MPN. In “sporadic” MPN, there is evidence for an increased risk in first generation relatives supporting the hypothesis for susceptibility genes in these disorders. Recently it has been shown that some polymorphisms in the JAK2 gene predispose to the JAK2V617F mutation and may explain this increased risk. The occurrence of JAK2V617F-negative myeloid leukaemia in JAK2V617F-positive contexts and the increasing number of reports describing cases of patients with two different MPN suggest the existence of either a pre-JAK2 event leading to clonal haematopoiesis or the presence of an unknown susceptibility gene leading to the development of independent disorders.

Very recent results from our group have identified a probable tumour suppressor gene, TET2, inactivated by mutation or deletion in a fraction of PV patient (about 12%) (23). We provided evidence that this molecular event precedes the occurrence of the JAK2V617F mutation and affects HSC. The function of this gene remains to be investigated, as are the precise consequences of its inactivation. Mutations of TET2 were also found in other MPN, as well as in myelodysplastic syndromes and AML (23). It will be important to determine the frequency of TET2 inactivation in PV and other MPN.

At present, we can conclude that the pathogenesis of PV is far more complex than just the consequence of one single molecular event. It is conceivable that different molecular kinds of PV exist with (i) JAK2V617F PV, JAK2V617F being the sole molecular event causing the disease, (ii) JAK2V617F PV being associated with another preceding event, (iii) JAK2 exon 12 PV and (iv) PV still uncharacterised at the molecular level.

2.2 Diagnosis

The diagnosis of PV is often suspected after a routine blood test, as most PV patients are asymptomatic at the time of diagnosis. A few patients have symptoms or signs related to their high haematocrit level such as facial erythrosis. Signs of blood
hyperviscosity like headaches, vertigos, tinnitus or visual disorders should be looked for, as they are criteria for urgent treatment. Pruritus is sometimes reported, especially after contact with water. Thrombotic events lead to the diagnosis of PV in 30% of PV patients, and most frequently the thrombosis is arterial. Finally, some patients have splenomegaly as commonly observed in all MPN.

Before the discovery of the JAK2V617F mutation, the diagnosis of PV was based on a number of criteria defined by the World Health Organisation (WHO) and the Polycythaemia Vera Study Group (PVSG). Both these classifications used clinical and biological markers organised into major and minor criteria, allowing the diagnosis of PV when defined combinations of major and minor criteria were present. After the discovery of the JAK2V617F mutation in the majority of PV patients, it became rapidly obvious that detection of this mutation would be a major criterion for the diagnosis of PV. Nevertheless, as this molecular abnormality is also found in other MPN, it can in no way be the sole diagnostic marker for PV. In 2007, an international expert panel of pathologists and clinical investigators in MPN prepared new recommendations for the revision of the WHO diagnostic criteria for PV, and members of the Clinical Advisory Committee for the revision of the WHO Classification of Myeloid Neoplasms recommended its adoption by the WHO (24).

According to these recommendations, the diagnosis of PV would now require the presence of both major criteria AND at least one minor criterion or the presence of the first major criterion AND at least two minor criteria (Table 2).

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Haemoglobin &gt; 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume*</td>
<td>1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation</td>
</tr>
<tr>
<td>2. Presence of JAK2V617F or other functionally similar mutation such as JAK2 exon 12 mutation</td>
<td>2. Serum erythropoietin level below the reference range for normal</td>
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<tr>
<td></td>
<td>3. Endogenous erythroid colony formation in vitro</td>
</tr>
</tbody>
</table>

*Haemoglobin or haematocrit > 99th percentile of method-specific reference range for age, sex, altitude of residence or Haemoglobin > 17 g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from an individual’s baseline value that can not be attributed to correction of iron deficiency, or Elevated red cell mass > 25% above mean normal predicted value.
2.3 Evolution and complications

The clinical course of PV can be altered by a number of complications, such as arterial or venous thrombosis, evolution to myelofibrosis or transformation into secondary acute leukaemia. Analysis of the follow-up of 1,638 PV patients enrolled in the European Collaboration on Low-dose Aspirin in Polycythaemia Vera (ECLAP) study showed that the overall mortality rate is 3.7 per 100 persons per year (25). This rate resulted from a moderate risk of cardiovascular death and a high risk of death from non-cardiovascular causes (mainly haematologic transformations). In treated PV patients, the 15-year risk of evolution to myelofibrosis is estimated at 6% and the incidence is 5.1 per 1,000 persons per year.

The pathogenetic mechanisms of thrombophilia in PV and other MPN are presently still elusive. It seems that platelet and leukocyte abnormalities are particularly critical. Platelets have functional and biochemical abnormalities and granulocytes seem to be constitutively activated \textit{in vivo}. They overexpress some membrane adhesive molecules such as integrins and selectins that increase their adhesion to endothelial cells and platelets (26). These abnormal interactions between platelets and leukocytes seem important features of thrombosis in PV. This might explain why a white blood cell count above 15x10^9/L has been found to be a major risk factor for the occurrence of thrombosis (27). Finally, it is still not clear whether the presence or the burden of JAK2 V617F have an impact on the occurrence of thrombosis in PV, as many studies were during the past few years with inconsistent results. However, there are now well-recognised predictors of arterial and venous thrombosis that should guide the prescription of a treatment in PV patients (Table 3).

Post-PV myelofibrosis (MF) is one of the other complications that can occur during the clinical course of PV. After diagnosis of post-PV MF, the median survival is around 5.7 years. Very recently, Passamonti et al. reported a dynamic prognostic model for predicting survival in post-PV MF. They showed that hyperleukocytosis above 15x10^9/L at the time of PV diagnosis was a risk factor for evolution in post-PV MF. Haemoglobin level < 10 g/dL at post-PV MF diagnosis was an independent risk factor.

| Certain | Age > 65  
|         | Previous thrombotic event  
|         | Leukocyte count > 15x10^9/L |
| Uncertain | Classical cardiovascular risk factors  
|          | Factor V Leiden, hyperhomocysteinaemia  
|          | JAK2V617F presence or burden |

Table 3: Predictors of arterial and venous thrombosis in PV
for survival. They also found that a dynamic score based on haemoglobin < 10 g/dL, platelet count < 100x10^9/L and white blood cell count > 30x10^9/L could predict post-PV MF survival at any time from diagnosis of post-PV MF (28).

The last classical complication of PV is transformation into secondary acute myeloid leukaemia or myelodysplastic syndrome. Among the 1,638 PV patients enrolled in the ECLAP study, 22 were diagnosed with AML/MDS after a median of 2.5 years from recruitment in the study and a median of 8.4 years from the diagnosis of PV. Age above 65 was found to be the main independent risk factor, whereas overall disease duration failed to reach statistical significance. Exposure to 32P, busulphan and pipobroman, but not to hydroxyurea (HU) alone, had an independent role in producing an excess risk for progression to AML/MDS compared with treatment by phlebotomy or interferon (29). The burden of JAK2V617F does not seem to correlate with the risk of transformation.

2.4 Treatment

Early studies in untreated PV patients found a high incidence of thrombotic events and a life expectancy of about 18 months after diagnosis. Treatment of blood hyperviscosity by phlebotomy or chemotherapy has dramatically reduced the number of thrombotic events, even though haematologic transformation toward PMF and acute leukaemia still represent a major cause of death. Since there is a concern that myelosuppressive drugs might be implicated in transformation into acute leukaemia, current treatment recommendations should be adapted to the expected risk for thrombosis of the patient.

PV patients should therefore be classified as high, intermediate or low risk of thrombosis, according to characteristics that have been assessed in prospective studies (30) (Table 4). As leukocytosis above 15x10^9/L was recently found to be a major risk factor for the occurrence of thrombosis, it is probable that this criterion will soon be part of the risk stratification chart of PV patients (27).

In principle, all PV patients should be treated with low dose aspirin (80 to 100 mg

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Age &gt; 60 or history of thrombosis</th>
<th>Cardiovascular risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Intermediate</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>High</td>
<td>Yes</td>
<td>Not applicable</td>
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</table>
daily, as shown by the ECLAP study (31). A schedule of phlebotomy should be started as an emergency if there are any threatening signs of blood hyperviscosity, aiming to lower the haematocrit level under 45%. Phlebotomy should be continued for low and intermediate risk patients at a frequency that allows maintenance of haematocrit below 45%. Cytoreductive treatment is reserved for high-risk patients: hydroxyurea should be the first line of therapy, except for rare selected patients (age < 40, pregnancy, intractable pruritus, contraindication or intolerance to hydroxyurea) who should be treated with pegylated interferon (Figure 2). Recently Kiladjian et al. reported very promising results in PV patients treated with pegylated interferon alpha 2a who experienced complete haematologic and molecular responses (32). JAK2 inhibitors are now under development and will perhaps represent a major breakthrough for the treatment of PV in the future.

3. Secondary polycythaemia
Secondary polycythaemia is the consequence of an increased Epo synthesis which can be either appropriate (in response to chronic hypoxia) or not.

![Figure 2: Flow chart of recommended treatment for patients with PV, adapted from Finazzi et al. (30)](image)

<table>
<thead>
<tr>
<th>Diagnosis of PV</th>
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<tbody>
<tr>
<td>Phlebotomies to reach Ht &lt; 45%</td>
</tr>
<tr>
<td>Low-dose aspirin (80-100 mg/day)</td>
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<tr>
<td>Thrombotic risk stratification</td>
</tr>
<tr>
<td>Low risk</td>
</tr>
<tr>
<td>Low-dose aspirin (80-100 mg/day)</td>
</tr>
<tr>
<td>Phlebotomies to maintain Ht &lt; 45%</td>
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<tr>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Low-dose aspirin (80-100 mg/day)</td>
</tr>
<tr>
<td>Reduce to cardiovascular risk factors</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>Low-dose aspirin (80-100 mg/day)</td>
</tr>
<tr>
<td>Cytoreductive therapy</td>
</tr>
<tr>
<td>If</td>
</tr>
<tr>
<td>Poor compliance to phlebotomies</td>
</tr>
<tr>
<td>Progressive myeloproliferation</td>
</tr>
<tr>
<td>(splenomegaly, leucocytosis, thrombocytosis)</td>
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<tr>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Peg-interferon</td>
</tr>
<tr>
<td>if age &lt; 40</td>
</tr>
<tr>
<td>pregnancy</td>
</tr>
<tr>
<td>intractable pruritus</td>
</tr>
<tr>
<td>intolerance to HU</td>
</tr>
</tbody>
</table>
3.1 With appropriately high Epo level
As the oxygen sensing proteins HIF-1 and HIF-2 regulate transcription of the EPO gene, serum Epo level is increased in settings of chronic tissue hypoxia. These include chronic respiratory diseases associated with hypoxia, sleep apnoea syndrome, residence at high altitude levels and congenital heart diseases with a right-to-left cardiac shunt. Treating the cause of hypoxia will cure the polycythaemia. The risk of thrombosis in these situations is very low, but some thrombotic events were reported in patients with a right-to-left cardiac shunt.

3.2 With inappropriately high Epo level
As the kidney is the main organ that synthesises Epo, polycythaemia can be seen in patients with renal diseases such as single or multiple cysts, hydronephrosis or renal artery stenosis. Polycythaemia can be considered as a paraneoplastic syndrome when Epo is inappropriately produced either by tumour cells or by the normal parenchyma in response to hypoxia-induced tumour growth. These malignancies include renal cell carcinoma, hepatoma, uterine fibroids, cerebellar haemangioblastoma and pheochromocytomas. In the two last cases, polycythaemia may reflect mutations in the VHL pathway (see previous chapter). Erythrocytosis is reported in up to 5% of patients with renal cell carcinoma. Blood doping with recombinant human Epo should be considered especially in competitive athletes.

4. Idiopathic polycythaemia
When the diagnosis of primary and secondary polycythaemia is excluded, idiopathic erythrocytosis (IE) should be considered. To diagnose IE, the following criteria must be fulfilled: raised red cell mass and haematocrit level, no identifiable secondary cause of erythrocytosis and exclusion of PV. It seems that this group is very heterogeneous, some of these patients being reported with Epo-R or VHL or JAK2 mutations.

Acknowledgments
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References


19. Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and


Multiple Choice Questionnaire

To find the correct answer, go to [http://www.esh.org/iron-handbook2009answers.htm](http://www.esh.org/iron-handbook2009answers.htm)

1. Which is the most important risk factor for thrombosis in PV?
   a) Smoking ................................................................. [ ]

DISORDERS OF ERYTHROPOIESIS, ERYTHROCYTES AND IRON METABOLISM
b) Obesity ..............................................................

c) White blood cell count above 15x10⁹/L ..................................

d) Presence of heterozygous JAK2V617F mutation

2. In familial MPD which one of the following statements is true?
   a) The JAK2V617F mutation can be found in non-MPD patients .............
   b) The JAK2V617F mutation is found in B and T cells of JAK2V617F-positive patients ..........................................................
   c) The JAK2V617F mutation is not the primary genetic event ..................
   d) MPD usually occur in young patients .............................................

3. Which one of the following statements is true regarding JAK2 exon 12 mutations?
   a) Can be found in rare PMF patients ..............................................
   b) Are usually found in patients with a nearly pure erythrocytosis phenotype ..
   c) Are not associated with a trilineage proliferation in the marrow ..........
   d) Are never found in familial MPD ..............................................

4. Which one of the following statements is true regarding post-PV myelofibrosis?
   a) Can be cured with hydroxyurea .............................................
   b) Is always lethal within 3 years after diagnosis ..............................
   c) Is associated with a JAK2V617F burden of around 95% .................
   d) Occurs in almost all PV patients after 20 years of evolution ............

5. Which one of the following statements is true regarding interferon?
   a) Should be given to young PV patients, even if they are at low risk of thrombosis ..........................................................
   b) Is the only treatment capable of lowering the JAK2V617F burden ...........
   c) Should not be associated with aspirin ...........................................
   d) Can not be given in patients with platelets above 1.500x10⁹/L ............