Philadelphia Chromosome–Negative Chronic Myeloproliferative Disease

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Abstract

Session 2 of the 2007 Workshop of the Society for Hematopathology/European Association for Haematopathology was focused on Philadelphia chromosome–negative chronic myeloproliferative diseases (Ph– MPDs), recently termed chronic myeloproliferative neoplasms. The presented and submitted cases highlighted some important issues and also impending problems associated with the diagnosis and classification. Cases included predominantly rare entities like chronic eosinophilic leukemia and related disorders, chronic neutrophilic leukemia, and others with specific genetic abnormalities that allowed molecularly targeted therapy. In this context, the distinctive role of a positive JAK2V617F mutation for the diagnosis of Ph– MPD was underscored, including entities with a low allele burden and the discrimination from reactive disorders (autoimmune myelofibrosis, reactive thrombocytosis). Although novel genetic and molecular approaches have significantly improved the way we classify Ph– MPD, a combined clinicopathologic approach, including representative bone marrow specimens, still remains the yardstick for diagnosis.

Bone Marrow Histopathology in Philadelphia Chromosome–Negative Chronic Myeloproliferative Diseases: The New WHO Classification

The wealth of new data and molecular discoveries in the past years have raised the need for a significant revision of the current World Health Organization (WHO) diagnostic criteria for Philadelphia chromosome–negative chronic myeloproliferative diseases (Ph– MPDs). Several international working groups cooperated to propose new diagnostic guidelines to the steering committee of the WHO. In this context, intentions were not only driven by considering the JAK2V617F mutation, which is specific for MPD, although expressed at different levels in the various entities, but also other genetic abnormalities focusing on their molecular pathogenesis. As a consequence, myeloid neoplasms with molecularly characterized clonal eosinophilia, previously classified under eosinophilic leukemia/hypereosinophilic syndrome, are now removed from this section and assembled into a new category of their own. Another aim was to enhance clinicopathologic correlations including progression to myelofibrosis and leukemia. Finally, the focus was on prodromal stages and dynamics of the disease process and on a more accurate differentiation of thrombocytemic disorders.

The new WHO proposals for classification, which take all these considerations into account and attempt a synoptic approach to categorizing the Ph– MPDs according to their clinical, morphologic, and molecular manifestations, are listed in Table 1. In the revised 2008 classification system, the phrase “disease” is replaced by “neoplasm,” implying that MPD is now replaced by the term myeloproliferative neoplasm, or MPN. In addition to the already mentioned changes regarding
the eosinophilic disorders, mast cell diseases, or mastocytosis, have been included in the MPN category. It should be noted that these revisions and new terminology (Ph+ MPN) emphasize the neoplastic nature of these disorders and molecularly distinct categories among patients.

Concerning the different subtypes of MPNs as outlined in Table 1, paragraphs of this review are arranged according to the frequency of cases submitted to session 2 of the 2007 Workshop of the Society for Hematopathology/European Association for Hematopathology in Indianapolis, IN.

### Chronic Eosinophilic Leukemia Not Otherwise Specified

Chronic eosinophilic leukemia (CEL), not otherwise specified (NOS), is defined as a clonal proliferation of eosinophilic precursors that results in a sustained increase in the numbers of this cell lineage in blood, bone marrow, and peripheral tissues. Differential diagnosis includes the idiopathic hypereosinophilic syndrome (HES), which is characterized as eosinophilia (eosinophil count, ≥1,500/µL [1.5 × 10⁹/L]) persisting for at least 6 months for which no clonality or underlying cause can be detected and that is accompanied by organ involvement and systemic disease.

### Blood and Bone Marrow Findings

The most conspicuous feature of CEL in the blood is eosinophilia (eosinophil count, ≥1,500/µL [1.5 × 10⁹/L]) predominantly consisting of mature eosinophils. There may be some cytologic anomalies observed, including decreased granulation generating clear areas, cytoplasmic vacuolation, nuclear hypersegmentation or hyposegmentation, and enlarged size. Unfortunately, all of these changes may also be encountered in HES. Accordingly, the bone marrow is hypercellular with prevalence of the eosinophil lineage, maturation is usually orderly, and Charcot-Leyden crystals are often present. Reticulin fibers may be increased in some cases of CEL. No single or specific cytogenetic or molecular aberration has been identified.

### Clinical Findings

In a number of cases, eosinophilia is an incidental finding in asymptomatic patients. Severe organ damage may be generated by the leukemic infiltrates or the release of cytokines, enzymes, or other mediators from the eosinophils. Patients may complain of a variety of constitutional symptoms, but the most serious findings are related to endomyocardial fibrosis causing occasionally restrictive cardiomyopathy, and scarring of the valves may lead to regurgitation and intracardial thrombosis with fatal embolism. Peripheral neuropathy, pulmonary symptoms, and rheumatologic findings may be other manifestations. Prognosis is very variable, with a 5-year survival rate up to 80%.

### Workshop Cases of CEL, NOS

About one third of the 33 cases submitted in the category Ph– MPD were originally discussed as disease entities associated with eosinophilia or CEL and related disorders. Following the panel evaluation and discussion, only 4 cases were finally considered consistent with CEL, NOS. Of these cases, one should be presented in more detail: the case of a 12-month-old girl in whom hepatosplenomegaly and leukocytosis were incidentally identified (case 18). The admission WBC count was 208,000/µL (208 × 10⁹/L) with 2% neutrophils (0.02), 58% mature eosinophils (0.58), and fewer than 1% blasts. A bone marrow aspirate revealed gross hypercellularity without blasts and a myeloid/erythroid (M/E) ratio of 7.2:1 and marked eosinophilia (35%) with left-shifting Image 1A. In a course of a month, the infant developed pulmonary insufficiency, rash, and diffuse lymphadenopathy due to dense eosinophilic tissue infiltrates Image 1B. Cytogenetics showed a normal female karyotype without evidence of BCR-ABL1, FIP1L1-PDGFRα, or PDGFRβ-TEL. The clonality was demonstrated by using the human androgen-receptor gene assay, supporting the diagnosis of CEL, NOS in the absence of increased blasts or cytogenetic anomalies. Therapy included hydroxyurea and imatinib mesylate with incomplete response. However, recently, the infant received corticosteroids, resulting in a dramatic response. It is noteworthy that CEL, NOS is extremely rare in children, and differentiation from HES may be difficult unless molecular or cytogenetic markers are in keeping with an MPN as demonstrated in this unusual case.

### Myeloid and Lymphoid Neoplasms Associated With Eosinophilia and Abnormalities of PDGFRα, PDGFRβ, or FGFR1

Myeloid and lymphoid neoplasms frequently manifesting with eosinophilia and rearrangement of PDGFRα, PDGFRβ, or FGFR1 reveal a number of remarkable features associated with variable degrees of eosinophilia. The underlying pathogenetic mechanism is the formation of a fusion...
gene encoding an aberrant tyrosine kinase. Because MPNs with rearranged PDGFRα and PDGFRβ are susceptible to imatinib and related tyrosine kinase inhibition therapy, their recognition is important.45-50

Myeloid and Lymphoid Neoplasms Associated With PDGFRα Rearrangement

Among these generally rare MPNs, the most common entity is that associated with FIP1L1-PDGFRα rearrangement generated by a cryptic del(4)(q12)10,11 or t(4;10)(q12;p11).40 The clinical picture most often resembles CEL but may also resemble acute myeloid leukemia (AML), T-lineage lymphoblastic lymphoma, or both simultaneously.41 The peripheral blood eosinophil count is significantly increased, there is no BCR-ABL1 gene detectable, and there are fewer than 20% blasts in the blood and bone marrow in cases in which no AML or transformation to acute leukemia is detectable.42

Blood and Bone Marrow Findings

As mentioned, the most remarkable feature is eosinophilia consistent with CEL. There may be some cytologic anomalies, including clear areas of cytoplasm or clumping of granules, immature granules, and disturbed nuclear segmentation.10,42 The bone marrow is hypercellular with strikingly increased eosinophils, including precursors. In only a minority of cases is an aberrant maturation observed. Necrosis, cell debris, and Charcot-Leyden crystals can be found. Bone marrow mast cells may be slightly increased and show anomalies11,43 that resemble mastocytosis. However, this diagnosis may be established only if all criteria are present, including the demonstration of a KIT mutation.

Clinical Findings

Patients with CEL and FIP1L1-PDGFRα have a multisystem disorder and usually complain of constitutional symptoms, including pruritus, or cardiorespiratory and gastrointestinal distress.10,42,44 The peripheral blood eosinophil count is significantly elevated, up to 1,500/µL (1.5 × 109/L) or more.42 Most patients have splenomegaly, but the fatal feature may be endomyocardial fibrosis causing restrictive cardiomyopathy by scarring of the valves and formation of intracardial thrombi generating emboli. Pulmonary involvement is restrictive and related to fibrosis, resulting in dyspnea. There may be some increase in the serum tryptase and serum vitamin B12 levels.42 Because of the wide spectrum of clinical and morphologic manifestations, broader testing for this translocation is recommended. The prognosis seems to be favorable following the introduction of tyrosine kinase inhibitors.10,43 Resistance may, however, develop as a result of a T674I mutation,10,45,46 but alternative inhibitors may be efficient.47,48 Even patients with AML or T-lymphoblastic lymphoma may achieve remission.41

Workshop Cases of CEL With PDGFRα Rearrangement

Of the 3 cases with CEL-like manifestations and the FIP1L1-PDGFRα fusion gene, data for case 67 were particularly well documented. The routine examination of a 78-year-old woman revealed eosinophilia with bilateral axillary and inguinal lymphadenopathy but no increase in spleen or liver size. The WBC count was 77,000/µL (77.0 × 109/L) with 56% eosinophils (0.56). The peripheral blood smear showed eosinophils with coarse granules, areas of cytoplasmic clearing, and/or nuclear hypersegmentation and a shift to immaturity in the neutrophil lineage.

**Image 1** (Case 18) Chronic eosinophilic leukemia. A, Sample from a female infant showing an abundance of mature coarsely granulated eosinophils in the bone marrow aspirate smear (Wright). B, Liver tissue with dense infiltrates of eosinophils (H&E). Contributed by M. Bayerl and colleagues.
Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1 (A and B, Case 67; C, D, and E, Case 81; F, Case 69). A, PDGFRA rearrangement with peripheral blood smear showing eosinophils with coarse granules and conspicuous cytoplasmic clearance (Wright). B, Bone marrow biopsy reveals hypercellularity with predominance of mature eosinophils (H&E). Contributed by T. Isaacson and W. Finn. C, PDGFRB rearrangement with prevalence of mature neutrophils in the peripheral blood smear (Wright). D, Prominent neutrophilia and hypercellularity in the bone marrow biopsy (H&E).

The bone marrow biopsy revealed conspicuous hypercellularity with expansion of neutrophils and eosinophils. Megakaryocytes appeared normal with a slight increase in number. Cytogenetic analysis was consistent with a normal female karyotype and negative for BCR-ABL1 fusion transcripts; fluorescence in situ hybridization (FISH) studies showed FIP1L1-PDGFRA rearrangement. The patient was successfully treated with a regimen of low-dose imatinib with subsequent normalization of her peripheral blood cell counts, including the eosinophilia, as described in relevant clinical studies.¹⁰,⁴²

Myeloid and Lymphoid Neoplasms With PDGFRB Rearrangement

This distinctive type of MPN is characterized by a rearrangement with t(5;12) and formation of an ETV6-PDGFRB fusion gene.¹²,⁴⁹ There may be variants with generation of other genetic anomalies, but the common result is a synthesis of an aberrant activated tyrosine kinase. The clinical manifestations mimic chronic myelomonocytic leukemia, CEL, or unclassifiable MPN with eosinophilia.³⁷,⁵⁰ Most noteworthy is that MPNs with PDGFRB abnormalities respond to tyrosine kinase inhibitor treatment.⁵¹-⁵³
Blood and Bone Marrow Findings

Usually the WBC count is elevated, and there is a variable increase in neutrophils, eosinophils, and monocytes, including precursors. The bone marrow is hypercellular with predominant neutrophilic granulopoiesis and eosinophilia. In addition, an increase in spindle-shaped mast cells and increased reticulin fibers may also be found.

Clinical Findings

Frequently, patients have splenomegaly and only a few have associated hepatomegaly. Skin infiltrates and cardiac damage with cardiac failure may be observed. The serum tryptase level may be mildly or moderately elevated. Patients with PDGFRB-rearranged MPNs do not necessarily have eosinophilia or monocytosis, and, therefore, a proper genetic and molecular workup is warranted for therapeutic implications. The prognosis is likely to improve when cases are recognized and appropriate therapy with a tyrosine kinase inhibitor is started.

Workshop Cases of CEL With PDGFRB Rearrangement

The 2 submitted cases with MPN and PDGFRB expression showed a number of interesting features because many of the blood and bone marrow findings in this 38-year-old man with the major complaint of neck pain resembled chronic myeloid leukemia (case 81). There had been a remote splenectomy in 1970 for unknown cause. The WBC count revealed leukocytosis (68,300/µL [68.3 × 10^9/L]) and mild anemia with thrombocytopenia. The differential showed neutrophilia (67% [0.67]), 4.0% monocytes (0.04), and 4.5% eosinophils (0.045) Image 2C. The bone marrow biopsy was hypercellular with a prominent neutrophilic proliferation but no significant increase in eosinophils or monocytes Image 2D. On the other hand, mild reticulin fibrosis was present Image 2E. Cytogenetic analysis failed to show a BCR-ABL1 fusion gene, but FISH identified PDGFRB-TEL fusion. The patient was treated with tyrosine kinase inhibitors and achieved a complete hematologic and cytogenetic remission.

Myeloid and Lymphoid Neoplasms With FGFR1 Abnormalities

A variety of translocations with an 8p11 breakpoint may be encountered in this entity and related to the partner chromosome, and different fusion genes incorporating part of the FGFR1 are generated. The clinical manifestations are strikingly heterogeneous, usually including an MPN, frequently in blastic transformation, AML, T- or B-lineage lymphoblastic leukemia/lymphoma, or bilineage acute leukemias.

Blood and Bone Marrow Findings

As mentioned, the spectrum of features includes CEL, AML, and precursor-T/B lymphoblastic leukemia/lymphoma. Noteworthy is that cases with AML may exhibit a bilineage appearance and that in CEL, a transformation into AML and myelosarcoma may be observed. Patients in chronic phases of this entity usually have eosinophilia and neutrophilia and, occasionally, monocytosis. It has to be emphasized that the eosinophils belong to the neoplastic clone similar to lymphoblasts and myeloblasts in cases that transform into AML.
Clinical Findings

A number of patients have systemic symptoms such as fever, weight loss, night sweats, and a lymphoma-like picture, whereas others show MPN-like findings, including splenomegaly and features consistent with AML. The prognosis is generally unfavorable because, in contrast with the other categories, there is no established tyrosine kinase inhibitor treatment available, although interferon has induced cytogenetic remission in several patients.60,62

Workshop Cases of Myeloid and Lymphoid Neoplasms With FGFR1 Abnormalities

Case 69 was a 57-year-old woman with a few months’ history of dyspnea who had hypercellular bone marrow with a prevalence of myeloid and lymphoid blasts. The diagnosis of bilineage leukemia was established, and cytogenetic analysis revealed the sole aberration as 46,XX,t(6;8)(q27;p11.2), consistent with so-called 8p11 myeloproliferative syndrome. The patient underwent induction and consolidation chemotherapy, but 5 months later, overt leukemia developed, with a WBC count of 294,000/µL (294 × 10^9/L) including 89% neutrophils (0.89) and 6% lymphocytes (0.06). The findings in bone marrow aspirates were in keeping with this finding, and, again, an 8p11 aberration was detectable. After transplantation, this constellation recurred about 29 months posttransplantation, including left-shifted myelopoiesis and eosinophilia Image 2F. However, a complete hematologic and cytogenetic remission occurred approximately 44 months posttransplantation. An unusual feature of this case is that it apparently initially manifested with bilineage AML and not as a transformation of an MPN.37,60

Chronic Neutrophilic Leukemia

It is mandatory that the diagnosis of chronic neutrophilic leukemia (CNL) requires exclusion of reactive neutrophilia and other MPNs.63-65 In up to 20% of cases, the neutrophilia is associated with a neoplastic disorder, usually multiple myeloma.66-68 However, until now, there has been no clear evidence that, in cases with accompanying neoplasia, in particular multiple myeloma, a clonal transformation has been convincingly demonstrated in the neutrophils by molecular techniques.69 Therefore, there is an ongoing discussion that in such cases, the neutrophil proliferation is not autonomous but represents cytokine-mediated growth caused by the neoplastic plasma cells.68 Cytogenetic studies are normal in about 90% of cases of CNL, but in the remaining cases, clonal karyotypic anomalies may include +8, +9, +21, del(20q), del(11q), and del(12p).21,65,70 No Ph chromosome or BCR-ABL1 fusion gene is found. Occasionally, patients with a JAK2 mutation have been described.71,72

Blood and Bone Marrow Findings

Usually the WBC count exceeds 25,000/µL (25 × 10^9/L), showing well-segmented neutrophils and a conspicuous increase in band forms. Immature granulocytes account for fewer than 10%,63,65,73,74; however, myeloblasts are almost never observed. Granulocyte dysplasia is not detectable, but the granules may be coarse (toxic). Bone marrow specimens reveal hypercellularity with a striking neutrophil proliferation, shifting the M/E ratio up to 20:1 or more. Blasts or promyelocytes are not increased in number in the beginning, and dysplasia and reticulinfibrosis are not evident.65,74

Clinical Findings

The most frequently found feature in addition to the increase in the WBC count is splenomegaly, often accompanied by hepatomegaly.63,73 Some patients have a history of bleeding from the gastrointestinal tract.73,75 CNL is regarded as a relatively slowly progressive disease; survival is unpredictable and ranges from about 6 months to more than 20 years. Progressive neutrophilia associated with anemia and a decrease in the platelet count has been reported, as has transformation into myelodysplasia and AML.73,75

Workshop Cases of CNL

Of the 33 cases submitted in the Ph– MPD category, 5 cases were originally discussed as manifesting as CNL. Two of these cases should be described in more detail. Case 169 involved a 70-year-old man with clinical suspicion of MPN. The WBC count was 49,000/µL (49.0 × 10^9/L) with marked mature neutrophilia and a proportion of neutrophils showing prominent (toxic) granules Image 3A, a hemoglobin level of 13.3 g/dL (133 g/L), and a platelet count of 339 × 10^9/L (339 × 10^9/L). The bone marrow biopsy sample was markedly hypercellular with a left-shifted maturation, mostly neutrophils, but no dysplasia Image 3B. Cytogenetics showed 40,XY,del 20(q12), but no BCR-ABL1 translocation. The molecular analysis revealed a JAK2VA617F mutation. There are only a few reports about cases with CNL positive for a JAK2 mutation,71,72 and this has been rarely found to be homozygous.72 Complete cytogenetic remission with imatinib therapy was achieved in a patient with t(15;19), thus implicating the possibility of an unidentified fusion gene.76

Case 208 involved a 66-year-old woman with a 3.5-year history of an elevated WBC count in the range of 40,000 to 60,000/µL (40-60 × 10^9/L) consisting nearly entirely of mature neutrophils. About 18 months earlier, the WBC count increased to 80,000 to 90,000/µL (80-90 × 10^9/L) Image 3C in association with a decrease in the hemoglobin level from 12.2 to 11.9 g/dL (122 to 119 g/L). Because of the worsening leukocytosis, she received hydroxyurea, but weight loss and severe fatigue subsequently developed. Bone marrow karyotyping was normal, and no BCR-ABL1 translocation was found.
Image 3 | Chronic neutrophilic leukemia (A and B, Case 169; C, D, and E, Case 208). A, Marked mature neutrophilia in peripheral blood smear showing occasionally coarse (toxic) granulation (Wright). B, Prominent neutrophilia in the bone marrow biopsy specimen with left-shifting and medium-sized megakaryocyte (H&E). Contributed by W. Chen and colleagues. C, Peripheral blood smear with prevalence of mature neutrophils (Wright). D, Bone marrow aspirate smear showing prominent (mature) plasma cells intermingled with neutrophils (Wright). E, Immunohistochemical identification of a monoclonal plasma cell population (\(\lambda\) light chain restriction) (\(\lambda\) light chain immunostaining). Contributed by L. Novoa-Takara and S. Kroft.
Serum immunoglobulin quantification revealed a significantly increased IgA fraction (3,116 mg/dL [31,160 mg/L]), whereas the IgG and IgM levels were almost within the normal range. The bone marrow aspirate was highly cellular with a predominance of segmented neutrophils, besides metamyelocytes and bands and more than 13% plasma cells showing large, distinctive nucleoli [Image 3D]. In the core biopsy specimen, a comparable finding was present, with a large number of interstitial plasma cells. Immunohistochemical analysis revealed a light chain restriction of the plasma cells [Image 3E].

Considering relatively frequent reports of CNL in association with multiple myeloma, the bone marrow specimens have to be scrutinized for plasma cell neoplasms. Moreover, it may be advisable before establishing a diagnosis of CNL to prove the clonality of the neutrophil lineage by proper cytogenetic and/or molecular examinations.

**Polycythemia Vera**

The diagnosis of polycythemia vera (PV) requires the recognition of autonomous RBC production that is acting independently of the mechanisms that normally regulate erythropoiesis. The majority of patients have a JAK2 mutation that results in a proliferation of not only the erythroid cell lineage but also granulocytes and megakaryocytes, consistent with pancytosis and, occasionally, also borderline to mild reticulin fibrosis [Table 2]. The disease evolution of PV includes a low incidence of transformation into myelofibrosis with myeloid metaplasia and a myelodysplastic phase and/or AML.

### Blood and Bone Marrow Findings

The peripheral blood shows a mild to overt excess of normochromic, normocytic RBCs. Neutrophilia and, rarely, basophilia may be present. Occasional immature granulocytes may be detectable in the overt polycythemic phase, but circulating blasts are generally not observed. Because of prominent thrombocytosis, up to 15% of cases of early-phase PV may clinically mimic essential thrombocythemia (ET); but such cases eventually evolve into an overtly polycythemic stage. In the original and updated criteria of the Polycythemia Vera Study Group (PVSG), bone marrow findings are not mentioned and in the proposal for the revision of the WHO classification, they are considered a minor criterion for substantiating the diagnosis. The major reason why bone marrow morphologic examination has been neglected as a useful tool is that the disease has been traditionally defined by clinical, laboratory, and biologic parameters, which are generally assumed to be sufficient for the establishment of the diagnosis. In the era of JAK2V617F, it should be emphasized that about 95% of patients with PV have this mutation, and, for this reason, in addition to the relevant laboratory and clinical markers, bone marrow morphologic examination seems to be a minor issue in the total setting of diagnostic procedures. On the other hand, in correlation to clinical findings, a clear pattern of histopathologic features emerges and can be used to confirm the diagnosis in cases without clear-cut hematologic and molecular genetic data.

One should be aware that PV, as other MPNs, represents an evolving disease process, and it is not surprising that in the beginning, a number of cases do not fulfill all of the required diagnostic criteria, particularly with regard to the RBC mass or the required hemoglobin and hematocrit values. These cases have often been reported to exhibit “latent, occult PV” or “benign, idiopathic erythrocytosis” and are regarded as a heterogeneous group that may eventually develop overt polycythemic PV. It is emphasized that some of the patients have an initial or early prodromal phase of PV that is accentuated by thromboembolic episodes as the first manifestation of the disease, but a diagnosis is not possible using conventional criteria.

The histopathology of prepolyctic and full-blown PV is characterized by hypercellular bone marrow due to a trilineage proliferation (panmyelosis) of erythroid and granulocytic precursors in variable proportions, associated with megakaryocytic proliferation of cells displaying distinctive morphologic features. Some of these findings are more significant than others in establishing the diagnosis of PV and in distinguishing it from reactive or secondary polycythemia (SP) and from other types of MPN.

| Table 2 | Relative Incidence (%) of Borderline to Marked Reticulin and/or Collagen Myelofibrosis in Initially Performed Bone Marrow Biopsies Derived From About 1,300 Specimens With Philadelphia Chromosome–Negative Chronic Myeloproliferative Neoplasms Diagnosed According to the World Health Organization Classification

<table>
<thead>
<tr>
<th>Grade of Myelofibrosis</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia vera</td>
<td>94</td>
<td>15</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Primary myelofibrosis</td>
<td>27</td>
<td>38</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Essential thrombocythemia</td>
<td>99</td>
<td>1</td>
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In PV, the usual small and rounded islets of nucleated erythroid precursors show conspicuous enlargement and a tendency to merge into sheets. Although these changes are significantly more pronounced in PV, they may also be present in a few cases with severe SP, and, therefore, this feature alone may not serve as a reliable diagnostic parameter, especially in an early stage of the disease. A similar situation may be observed regarding the neutrophil lineage because an increase in

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in promyelocytes and metamyelocytes (left-shifting) is frequently displayed in PV and may also be prominent in SP. On the other hand, megakaryocytes reveal a variety in sizes, often large to giant, that are not found in SP.100,103

The most common pattern of disease progression is postpolycythemic myelofibrosis (post PV-MF)104 accompanied by myeloid metaplasia (MM), which is characterized by a leukoerythroblastic blood smear, poikilocytosis with teardrop-shaped RBCs, and splenomegaly due to extramedullary hematopoiesis (EMH) [Table 3].78,104,105 The morphologic hallmark of this stage of the disease is overt reticulin and collagen fibrosis of the bone marrow.95,100,104,106,107 The cellularity varies in this terminal stage, but hypocellular specimens are common. Clusters of megakaryocytes, often with hyperchromatic and very dysmorphic nuclei, are prominent. Erythropoiesis and granulopoiesis are decreased, and erythrocytes and granulocytes are sometimes found, along with megakaryocytes, lying within dilated narrow sinusoids.100

Osteosclerosis may also occur.95,106 An increase in the number of immature cells may be observed in these stages, but the finding of more than 10% blasts in the blood or bone marrow or the presence of significant myelodysplasia is unusual and most likely signals transformation to an accelerated phase and/or a myelodysplastic syndrome (MDS). Cases in which 20% or more blasts are found are considered AML.77,81,100,107

Clinical Findings

Most clinical findings in PV are related to hypertension or vascular abnormalities caused by the increased RBC mass. In nearly 20% of cases, an episode of venous or arterial thrombosis, such as deep venous thrombosis, myocardial ischemia, or stroke, is documented in the medical history79 and may be the first manifestation of PV.77,79,108,109 Mesenteric, portal, or splenic vein thrombosis and the Budd-Chiari syndrome should always lead to consideration of PV as an underlying cause and may precede the onset of an overt polycythemic phase.79,110 Headache, dizziness, visual disturbances, and paresthesias are major complaints, and pruritus, erythromelalgia, and gout are also common. In the full-blown polycythemic stage, physical findings usually include plethora and palpable splenomegaly in 70% and hepatomegaly in 40% of cases.77,111

Clinical laboratory findings that aid in confirmation of the diagnosis of PV include subnormal erythropoietin levels,112,113 endogenous erythroid colony formation,114 and detection of the JAK2 V617F or functionally similar mutations, eg, JAK2 exon 12 mutations.128,82 Occasionally, patients may have clinical symptoms suggestive of PV but a hemoglobin level and/or red cell volume not sufficiently elevated to substantiate the diagnosis. The patients may be in the prepolycythemic phase, which was previously referred to by some authors as “latent PV” or as “pure idiopathic erythrocytosis.”88,90,103,109,115 The detection of a low erythropoietin level, a JAK2 V617F or functionally similar mutation, and/or an endogenous erythroid colony formation, in combination with the typical morphologic features, will allow the diagnosis of this phase of PV.91,103,112-114

Median survival times longer than 10 years are commonly reported following currently available therapeutic regimens,77,89,116,117 although controversy persists about the risk factors other than older age.108,117,118 Most patients die of thrombosis or hemorrhage, but up to 20% die of MDS or AML.77,79,108

Workshop Cases of PV

Of the 3 cases with PV submitted to the workshop, 2 represented a terminal stage of the disease. In case 219, a 68-year-old woman with a history of PV since 1985 was initially treated with phlebotomy only. Since 1996, increasing anemia developed, and post PV-MF and MM with splenomegaly were diagnosed. She received hydroxyurea and had a splenectomy 2 years later. Bone marrow aspirates showed 11% blasts, and conventional cytogenetic analysis demonstrated del(20q)/+8, del(20q). Therapy continued with interferon-alfa for about 8 years, and the blast count decreased to 5%. In 2006, her peripheral WBC count was 9,800/µL (9.8 × 10⁹/L) with 73% neutrophils (0.73) and 9% blasts. Molecular studies revealed a JAK2 V617F mutation (80.4% with the mutation according to the polymerase chain reaction product), and conventional cytogenetic analysis revealed 47,XX,+8,der(17)t(1;17)(q11;1p13),del(20)(q13.1). The bone marrow biopsy revealed mild osteosclerosis and extensive reticulin fibrosis and variable cellularity (70%-100%). Megakaryocytes were increased and occasionally clustered and exhibited variable sizes and shapes with maturation defects [Image 4A]. Immature cells were detectable in patchy distribution [Image 4B].
In summary, 21 years after the diagnosis of (JAK2+) PV, post PV-MF with MM developed (Table 3). Progression was characterized by an increasing blast count (10% blasts before the diagnosis of AML). A chromosomal anomaly, del(20q), was detected as the sole aberration when PV transformed into post PV-MF and was in combination with +8 and der(17) at progression to AML. Noteworthy is that the incidence of MDS and AML transformation is only 2% to 3% in patients who have not been treated with cytotoxic agents but increases to 10% or more following certain types of chemotherapy.\(^{80,81,108,116,118}\)

**Primary Myelofibrosis**

The disease entity of primary myelofibrosis (PMF),\(^{119}\) formerly termed chronic idiopathic myelofibrosis or agnogenic myeloid metaplasia, is characterized by a stepwise evolution from an initial prefibrotic phase\(^1\) revealing hypercellular bone marrow with absent or minimal reticulin fibrosis and development into an overt fibrotic phase with marked reticulin or collagen fibrosis in the bone marrow, often with accompanying osteosclerosis. There is a proliferation of predominantly megakaryocytes and granulocytes in the bone
megakaryopoiesis, which is characterized not only by a disturbance of bone marrow histologic topography (extensive clustering of megakaryocytes with loose to dense groupings with abnormal localization of these toward the endosteal borders) but also by the striking abnormalities in their morphologic features and maturation. Significant anomalies of megakaryocytes include a high degree of cellular pleomorphism with variations in size that range from small to giant forms and, in particular, abnormal nuclear foldings and an aberration of the nuclear/cytoplasmic (N/C) ratio created by large bulbous and hyperchromatic cloud-shaped nuclei. Furthermore, apart from their disorganized nuclear lobulation, there are many so-called naked (bare) megakaryocytic nuclei observable.

Overall, the megakaryocytes in PMF are characterized by a more pronounced degree of cytologic atypia (megakaryocytic dysplasia, dysmegakaryopoiesis) than in any other subtype of MPNs, in particular, ET.

Blood and Bone Marrow Findings

There has been a consensus, based on the PVSG\textsuperscript{120} and also the Italian guidelines,\textsuperscript{121} that criteria applied to the diagnosis of so-called myelofibrosis with myeloid metaplasia or (advanced stage) PMF should include leukoerythroblastic blood smear morphologic features with teardrop poikilocytosis, splenomegaly due to EMH or MM, and anemia of varying degrees, all in the presence of relevant fibrosis of the bone marrow.\textsuperscript{122,123} However, some investigators have recognized that in many cases, a striking variability in hematologic findings may be observed at the time of initial examination.\textsuperscript{99,122,124-127} These wide ranges of clinical data are paralleled by significant heterogeneity of bone marrow features, occasionally revealing only a minimal or mild increase in reticulin fibers, the so-called hypercellular phase.\textsuperscript{94,125,126,128-130} PMF initially manifests with hypercellular bone marrow characterized by prominent granulocytic and megakaryocytic myeloproliferation with a concomitant reduction and maturation arrest of the nucleated erythroid precursors in the absence of bone marrow reticulin fibrosis or with only a borderline to mild degree of reticulin fibrosis. Fiber content is consistent with grades 0 and 1 according to the guidelines of a recently established consensus scoring system for bone marrow fibrosis (Table 2).\textsuperscript{78} This scoring system tries to improve the so-called Manoharan score.\textsuperscript{105,130} Most conspicuous is the abnormal megakaryopoiesis, which is characterized not only by a disturbance of bone marrow histologic topography (extensive clustering of megakaryocytes with loose to dense groupings with abnormal localization of these toward the endosteal borders) but also by the striking abnormalities in their morphologic features and maturation. Significant anomalies of megakaryocytes include a high degree of cellular pleomorphism with variations in size that range from small to giant forms and, in particular, abnormal nuclear foldings and an aberration of the nuclear/cytoplasmic (N/C) ratio created by large bulbous and hyperchromatic cloud-shaped nuclei.

Furthermore, apart from their disorganized nuclear lobulation, there are many so-called naked (bare) megakaryocytic nuclei observable.\textsuperscript{92,95,126,128,129,131-133} Overall, the megakaryocytes in PMF are characterized by a more pronounced degree of cytologic atypia (megakaryocytic dysplasia, dysmegakaryopoiesis) than in any other subtype of MPNs, in particular, ET.\textsuperscript{131,134-142} Megakaryocytic dysplasia is, thus, one of the most important features discriminating prefibrotic-early stage PMF (ie, false ET) from true ET, a concept that is also stressed by the WHO classification system.\textsuperscript{1} As it has been elucidated in different studies,\textsuperscript{143-146} there is a more than 65% probability of progression from a prefibrotic-early stage to a full-blown disease associated with clinical signs and symptoms of MM conforming to the classic diagnostic criteria.\textsuperscript{120-123,147} In contrast with the initial prefibrotic or early (reticulin fibrotic) stages of PMF, the more advanced fibro-osseosclerotic phases of disease (conforming to classical myelofibrosis with myeloid metaplasia/agnogenic myeloid metaplasia) are characterized by a significant amount of reticulin deposition...
and the appearance of coarse bundles of collagen fibers in the bone marrow. According to a previously quoted semiquantitative fiber scoring system, these stromal changes are consistent with grades 2 and 3 of myelofibrosis (Table 2). Additional features that indicate an advanced to terminal stage include plaque to bud-like osteosclerosis (endophytic bone formation), which is often associated with patchy hematopoiesis, replaced by adipose tissue, ie, progressive hypoplasia. Similar to the prodromal stages, atypical megakaryopoiesis remains a most prominent feature, including the presence of numerous naked nuclei of megakaryocytes. Dilated marrow sinuses with intraluminal hematopoiesis, especially megakaryocytes, are also among the prominent bone marrow findings.

Clinical Findings

About 30% of patients may be asymptomatic at the time of diagnosis, and the disease is by detection of splenomegaly during a routine physical examination or when a routine blood cell count discloses anemia, leukocytosis, and/or thrombocytosis. Less commonly, the diagnosis results from the finding of unexplained leukoerythroblastosis or an increased lactate dehydrogenase level. It should be stressed that in the very initial prefibrotic phase of PMF, the only relevant finding may be marked thrombocytosis, mimicking ET, and borderline anemia and/or splenomegaly. Therefore, sustained thrombocytosis cannot, by itself, discriminate between prefibrotic PMF and ET. Constitutional symptoms may include fatigue, dyspnea, weight loss, night sweats, low-grade fever, and bleeding episodes. Splenomegaly of varying degrees is detected in many patients and may be massive; nearly 50% have hepatomegaly. The W617F mutation can be found in about 50% of patients in the fibrotic phase; its incidence in the prefibrotic stage has not been well studied. Although helpful in distinguishing PMF from reactive conditions that may result in bone marrow fibrosis, the mutation is not specific for PMF but is found in PV and ET as well. The overall prognosis depends on the stage in which PMF is first diagnosed. The median survival time is approximately 3 to 7 years when the disease is diagnosed in the fibrotic stage, which contrasts with 10- and 15-year relative survival rates of 72% and 59%, respectively, when diagnosed in the early prefibrotic phase.

Workshop Cases of PMF and Reactive Myelofibrosis

Concerning initial-early PMF or currently undetermined disorders, the case of a 55-year-old previously healthy man with acute cerebral infarction was presented. There were no known cardiovascular risk factors, and there was no organomegaly; radiographic studies failed to find any source of the embolism, and the cranial vessels appeared to be normal. On the other hand, molecular analysis showed a JAK2V617F mutation. No BCR-ABL1 gene was detectable. The peripheral blood findings were inconspicuous, and there was no increase in the WBC or platelet count. The peripheral blood smear displayed no gross abnormalities, and, in the bone marrow aspirates, a subset of megakaryocytes were large with hyperlobulated nuclei and increased N/C ratios. Pathology of the megakaryocytes was more evident in the bone marrow biopsy sample, which showed megakaryocytic proliferation, an increase in megakaryocyte size, and loose and dense clusters of nuclear features consistent with spatial and cytologic abnormalities. There was no increase in reticulin density.

This case of a latent MPN in a patient with a cryptogenic stroke as the initial clinical feature raises a number of questions. Although occult MPN is uncommon in cerebral arterial thrombosis, a significant proportion of JAK2+ cases associated with abdominal vein thrombosis will evolve to overt MPN. A problem is the exact subtyping of this MPN at this point; although peripheral blood findings were not remarkable, bone marrow morphologic features were certainly aberrant, and an early initial (prefibrotic) stage of PMF has to be discussed according to similar findings reported in the literature.

In contrast with the preceding case, which definitely needs follow-up before establishing clear-cut subtyping, case 148 involves a 51-year-old woman in whom recurrent skin and mouth infections developed in 2000. Peripheral blood showed neutropenia. Since 2002, the patient has required granulocyte colony-stimulating factor support. Approximately 2 years ago, thrombocytopenia, anemia, and mild splenomegaly were noted, and she became transfusion-dependent. The first bone marrow biopsy showed marked age-matched hypocellularity with prominent lymphoid aggregates. The subsequently performed trephine biopsies demonstrated increasing cellularity under cytokine-stimulating therapy and reticulin fibrosis. Although there was some increase in megakaryocytes, they revealed no gross disturbances of maturation. The multiple lymphoid aggregates contained predominantly T cells (CD4+ and a few CD8+ lymphocytes). No monotypic B-cell or abnormal T-cell population was detectable.

This well-documented case raises the differential diagnosis of PMF or MDS with fibrosis and bone marrow involvement by lymphoma. Morphologic features of the megakaryocytes and only slight splenomegaly after 6 years are not consistent with PMF, and the lack of dysplastic appearance of the hematopoiesis (including megakaryocytes) speaks against MDS. On the other hand, autoimmune (reactive) myelofibrosis is a distinct clinicopathologic entity that may occur as isolated (idiopathic) disease or in conjunction with a systemic and/or an organ-specific autoimmune disorder.
Essential Thrombocythemia

In this MPN, the megakaryocyte lineage is primarily characterized by sustained thrombocytosis with a platelet count of more than 450 × 10^9/L (450 × 10^9/L). Clinically, there are frequent episodes of thrombosis and/or hemorrhage, and prodromal stages have been described.167

Blood and Bone Marrow Findings

Marked and sustained thrombocytosis is the hallmark of ET. The platelets often display anisocytosis, ranging from tiny forms to atypical, large to giant platelets that may reveal bizarre shapes, pseudopods, and agranularity. The WBC count and leukocyte differential are usually normal, although a borderline elevation in the neutrophil lineage may occur.168-171

In ET, according to the histologic guidelines of the WHO classification,1,136,151 neither a relevant increase in cellularity nor a significant left-shifted neutrophil granulopoiesis is observable. Any case with a mild to moderate granulocytic and erythroid growth pattern (panmyelosis) and an erythropoietin level below the reference range is “suspicous” for occult (prepolycythemic) PV mimicking ET.83,91

Regarding megakaryopoiesis, gross disturbances of the histologic topography (significant abnormal localization and/or extensive dense clustering of these cells) are not seen. These cells show a more or less random distribution within the bone marrow, with scattered forms or a few loose clusters. In true ET, a predominance of large to giant mature megakaryocytes with extensively folded (staghorn-like) nuclei107,131,134-141,151 surrounded by correspondingly mature cytoplasm is found. These features are clearly distinguishable from prefibrotic early PMF because, in the latter, megakaryocytes show extensive dense clustering and hypolobulated (cloud-like) and hyperchromatic nuclei with striking maturational defects.95,131,136-141,151 which result in a marked anomaly of the N/C ratio.

Finally, at diagnosis, there is no substantial increase in reticulin fibers, and collagen fibrosis is never observable in true ET (Table 2), a finding that contrasts with the allowance of some degree of fibrosis according to the criteria of the PVSG.172 The lack of significant reticulin fibrosis has been reported in a large series of cases in which minimal to slight reticulin fibrosis was described in only 3%.95,142,173

Clinical Findings

In many asymptomatic patients, a markedly elevated platelet count is found fortuitously at the time of a routine blood cell count.167-171 The remaining patients have some manifestation of vascular occlusion or hemorrhage.165,166 Microvascular occlusion may lead to transient ischemic attacks, digital ischemia with paresthesias, and gangrene.165-167,174,175

Thrombosis of major arteries and veins also occurs, and ET may be a cause of splenic or hepatic vein thrombosis as in the Budd-Chiari syndrome. Bleeding occurs most commonly from mucosal surfaces, such as the gastrointestinal tract or upper airway passages.161,171,172,176 If the criteria established by the PVSG for ET are applied, mild splenomegaly is present in approximately 50% of patients at diagnosis and hepatomegaly in 15% to 20%.168-172 However, when the WHO classification is used and patients with thrombocytosis associated with the prefibrotic stage of PMF are excluded, splenomegaly is seen in only a minority of patients with ET.117

No molecular genetic or cytogenetic abnormality specific for ET is known at present. Approximately 40% to 50% of cases have the JAK2V617F or a functionally similar mutation.1 ET is an indolent disorder characterized by long, symptom-free intervals interrupted by occasional life-threatening thromboembolic or hemorrhagic episodes.117,168-172 Although after many years a few patients with ET may develop marrow fibrosis,1 Table 478,104,105 associated with MM,104 such progression is uncommon.95,128,143,173

Workshop Cases of ET vs PMF and Reactive Thrombocytosis

The first case (case 94) demonstrates the difficulties in discriminating true ET according to the WHO classification1 from initial-early PMF with accompanying thrombocytosis (false ET). A 37-year-old woman had complaints of cold-induced pain and discoloration of the fingers starting in April 1999. A borderline increase in the WBC count (11,000/µL [11.0 × 10^9/L]) and thrombocytosis (platelet count, 1,974 × 10^9/µL [1,974 × 10^9/L]) were well controlled with hydroxyurea following the diagnosis of ET. Cytogenetic analysis demonstrated a normal 46,XX karyotype. In 2005, AML developed. The former bone marrow biopsy sample from 1999 was reviewed by the panel and revealed, in addition to gross (age-matched) hypercellularity, diffuse granulocytic

<table>
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<th>Table 4</th>
<th>Criteria for Post–Essential Thrombocythemia Myelofibrosis as Proposed by the International Myelofibrosis Working Group104</th>
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<tr>
<td>Required criteria</td>
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<tr>
<td>1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the World Health Organization criteria</td>
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<td>2. Bone marrow fibrosis grade 2 or 3 (on 0-3 scale)78 or grade 3 or 4 (on 0-4 scale)106</td>
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<td>Additional criteria (2 are required)</td>
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<tr>
<td>1. Anemia or a ≥2-g/dL decrease from baseline hemoglobin level</td>
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<td>2. A leukoerythroblastic peripheral blood picture</td>
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<td>3. Increasing splenomegaly defined as an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly</td>
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<td>4. Increased lactate dehydrogenase level (above reference level)</td>
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<td>5. Development of ≥1 of 3 constitutional symptoms: &gt;10% weight loss in 6 mo, night sweats, unexplained fever (&gt;37.5°C)</td>
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and prominent megakaryocytic proliferation with clustering and defects of megakaryocyte maturation [Image 5A] not compatible with the WHO diagnostic guidelines of ET but with initial PMF.\textsuperscript{129,139-141} Remission of AML was achieved following induction chemotherapy, but the disease relapsed [Image 5B] and showed a conspicuous t(9;22) translocation with a \textit{BCR-ABL1} fusion gene by FISH analysis. It is remarkable that this secondary appearance of a Ph chromosome in a Ph– MPN points to an inherent genetic instability and/or a therapy-related cause.\textsuperscript{177,178}

For many years, the recognized “gold standard” criteria for diagnosing ET have been those outlined by the PVSG, which are based on the separation of ET from other thromboctyemic MPNs, particularly chronic myelogenous leukemia and overt PV or PMF.\textsuperscript{116,170,172,179} A critical reevaluation of these diagnostic guidelines, which up to now have been entered into all relevant clinical trials, revealed that they do not allow for a clear-cut distinction of ET from the prodromal stages of PMF or PV, which are often associated with thrombocytosis.\textsuperscript{131,137-141,151} As a consequence of the inclusion of
histopathology in the current WHO classification, serious diagnostic discrepancies are encountered when bone marrow specimens derived from patients with the clinical diagnosis of ET based on the PVSG criteria are evaluated by hematopathologists using the WHO classification. Because of the impact of bone marrow histology for the clear-cut classification of MPNs, discussion and controversy persist regarding reproducibility of morphologic features. As with the diagnosis and classification of malignant lymphomas and AML subtypes, studies conducted by many groups have demonstrated that the recognition of discriminating histologic patterns is dependent on the experience of the investigator. This issue is particularly evident in the differentiation between ET and the precursor stages of PMF with associated thrombocytosis, clinically often mimicking ET. A blinded study among 3 hematopathologists questions the reproducibility and validity of distinguishing so-called true ET according to the WHO classification from prefibrotic PMF. However, it should not be overlooked that the results of this study are greatly impaired by a number of significant inconsistencies, including, among others, a missing training set for standardization and a clear definition of certain parameters (dysplastic or pyknotic megakaryocytes and others). Moreover, there is failing correspondence between description of megakaryocyte features and accompanying figures, small biopsy specimens (less than the required 1.5 cm), the inability to reach a sufficient level of consensus on basic features such as erythroid cellularity, and no self-assessment (intraobserver evaluation). Finally, in an undisclosed fraction of specimens, moderate to gross (grades 3 and 4) bone marrow fibrosis and new bone formation (osteosclerosis) were described. This unusual finding comprising about 20% of the patients was reiterated in a recent article, including most of this cohort. It must be emphasized that these findings hardly characterize ET at onset, but are more in keeping with PMF.

The second case (case 175) involves a 60-year-old man with no significant medical history and no medications but with complaints of mild fatigue. The only remarkable laboratory finding was normocytic anemia with moderate anisocytosis (hemoglobin level, 10.3 g/dL [103 g/L]) and thrombocytosis (platelet count, 614 × 10^9/L [614 × 10^9/µL]). Bone marrow aspirates showed an M/E ratio of 2:1, a slight increase in eosinophils was observed, and there was an orderly matura-
tion of all cell lineages, including megakaryocytes. The biopsy sample was hypercellular for age, revealing an increase in erythroid precursors, neutrophils, and eosinophils and no evidence of reticulin fibrosis. Cytogenetic studies showed a 46,XY karyotype and no BCR-ABL1 gene. Molecular analysis revealed JAK2V617F in the bone marrow cells, but only at the level of 0.5% mutated alleles. There are 2 remarkable issues in this case: one point is the diagnostic dilemma in a patient with clinical features that may be suspicious for a Ph– MPN but no characteristic bone marrow morphologic features, and the other point is the very low JAK2 mutation burden. Concerning morphologic features, discrimination of ET from reactive thrombocytosis may be easily accomplished because there is no predominance of large to giant megakaryocytes with nuclear hyperlobulation detectable, and often a granulocytic and/or eosinophilic proliferation associated with various degrees of inflammatory bone marrow reactions may be present. The critical question is whether such a low-level positivity of the JAK2 mutation is sufficient to establish an occult MPN with predominant thrombocytosis at this time. According to the current literature, mutation ranges in ET are very variable, and percentages between 1% and 100% (median, 6%-9%) were reported. The very low level of JAK2 mutation may be very rarely found in normal and reactive diseases. Altogether, data derived from this case are not sufficient for a diagnosis of MPN. At least the bone marrow morphologic features are more consistent with reactive thrombocytosis associated with anemia. For this reason, this patient requires close follow-up, including repeated bone marrow examination.

It is not surprising that the submitted and/or presented workshop cases were characterized by a selection of mostly very rare entities (CNL, CEL, and related disorders) and/or cases with conspicuous genetic anomalies that allowed molecularly targeted treatment. The distinctive role of a positive JAK2 mutation status and an allele burden for the diagnosis of MPN were repeatedly underscored. All of these cases highlighted important issues and difficulties in relation to the diagnosis and classification of Ph– MPNs.

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References


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