Bone Marrow Histopathology in Myeloproliferative Disorders—Current Diagnostic Approach

Juergen Thiele, a Hans Michael Kvasnicka, a and Attilio Orazib

Current diagnostic issues in chronic myeloproliferative disorders (MPDs) include the differentiation of essential thrombocythemia (ET) from its mimics: early (prefibrotic) stages of chronic idiopathic myelofibrosis (CIMF) and early polycythemia vera (PV), both of which can be associated with thrombocytosis. Applying a systematic evaluation of bone marrow histopathology, in accordance with the current World Health Organization (WHO) classification system, it is possible to identify cases of true ET as opposed to false ET, usually early-stage CIMF accompanied by an excess of platelets. This distinction is important because the frequency of complications such as progression to overt myelofibrosis, blastic crisis, and overall prognosis are significantly different in the two conditions. The diagnostic criteria of the Polycythemia Vera Study Group (PVSG) do not adequately define the initial stages of PV, nor do they distinguish PV with thrombocytosis from ET. Differentiation of the two is possible by bone marrow histopathology, which also is highly predictive (96%) in distinguishing PV from secondary polycythemia. In conclusion, bone marrow biopsy is an important diagnostic tool for distinguishing specific subtypes of MPD and should be a mandatory step for entry evaluation and follow-up of patients enrolled in prospective studies and/or clinical trials.

Semin Hematol 42:184-195 © 2005 Elsevier Inc. All rights reserved.

The development of novel therapeutic strategies for the treatment of chronic myeloproliferative disorders (MPDs)1-4 has reawakened interest in the precise diagnosis and objective distinction of the different MPD subtypes. Several recent investigations have drawn attention to the dynamics of the disease process in MPDs by identifying its prodromic stages and documenting its clinical as well as bone marrow evolutive patterns.5-11 In addition, the important issue of thrombocytemia in MPDs12 continues to be a controversial topic, especially in relation to the diagnosis of true essential thrombocytemia (ET) and its discrimination from the other MPD subtypes that may be accompanied by an excessive platelet count.7,9,13-16

A reasonable diagnostic approach in cases of MPDs includes careful evaluation of bone marrow morphology, within the context of clinical findings. This implies that all MPDs should be diagnosed and classified according to the World Health Organization (WHO) criteria.17 In this context, follow-up data, including bone marrow biopsy examinations and outcome, are in keeping not only with the diagnosis but also with the exact subtyping of the MPDs or related reactive conditions. The present review addresses some of the previously mentioned diagnostic issues. We describe how histopathology can help to establish a set of positive diagnostic criteria for ET, by providing for the objective identification of diagnostic findings in early stages of chronic idiopathic myelofibrosis (CIMF) and polycythemia vera (PV), and by distinguishing between reactive and neoplastic bone marrow lesions that may assist in the recognition of a MPD.

Differentiation of MPDs With Thrombocytemia

Controversies about how to establish reliable diagnostic guidelines for the diagnosis of ET have existed for many years and there is a general awareness of the difficulties in discriminating this entity from the other subtypes of MPDs when they present with an excess of platelets.4,18-22 The study of biomarkers, such as clonality, cell culture studies, and erythropoietin (Epo) expression, suggested that the various diseases are often heterogeneous.19 For this reason, according to the criteria of the Polycythemia Vera Study Group (PVSG), which are still accepted as the gold standard and generally...
used in clinical studies.\textsuperscript{1,4} ET is considered a diagnosis of exclusion.\textsuperscript{21-23} Moreover, bone marrow features that were only marginally taken into consideration by the original PVSG system (only evaluation of fibrosis was included) and even the updated PVSG criteria\textsuperscript{23} are not stringent enough to discriminate between ET and the early (hypercellular) stages of chronic idiopathic myelofibrosis (CIMF), since some degree of fibrosis is allowed in both conditions. A number of authors have criticized the PVSG criteria for their obvious shortcomings, predominantly related to bone marrow morphology, and challenged the proposed heterogeneity of ET.\textsuperscript{13,19,16,20,24,25}

**Figure 1** (a) ET with normally arranged and developing erythropoiesis and granulopoiesis, accompanied by dispersed large to giant megakaryocytes. (b) Prefibrotic CIMF with striking hypercellularity and conspicuous granulocytic and megakaryocytic growth revealing dense clustering and abnormal dislocation to the endosteal border. (c) Clustering of megakaryocytes with naked nuclei (arrows) and a streaming aspect of cells in later stages of CIMF with reticulin fibrosis. (d) Early-stage PV with hypercellularity and trilineage proliferation including many megakaryocytes.
Histologically, only a fraction of patients clinically considered to have ET show no relevant increase in age-matched cellularity or left-shifting of myeloid precursors, and/or lack a prominent increase in granulopoiesis or erythropoiesis and/or alteration in their marrow topographical distribution (Fig 1a). The major pathologic feature in these cases is the proliferation of randomly dispersed or loosely clustered megakaryocytes with a prevalence of large to giant cells (Fig 2a) revealing no gross maturation defects.13,15,20,24 According to the WHO classification, which emphasizes bone marrow...
histopathology as a major discriminating parameter, only these cases represent true ET.26

In contrast, other cases that are also considered to represent ET by clinical criteria reveal an increased preponderance of less mature myeloid precursors and granulocytic and megakaryocytic proliferation associated with a remarkable disturbance of histotopography, including, in particular, clustering and paratrabeicular (endosteal) dislocation of megakaryocytes (Fig 1b). These features may be even more pronounced in later stages, exhibiting a streaming aspect of hematopoiesis, probably due to evolving slight reticulin fibrosis (Fig 1c). In these cases, megakaryopoiesis is abnormal, with atypical forms characterized by the presence of hypolobulated, bulbous, or cloud-shaped, highly pleomorphic, hyperchromatic nuclei due to defects in maturation (Fig 2b) as well as naked nuclei (Fig 1c). The reticulin content is variable, ranging from normal to a mild increase (Fig 3a and b). On the basis of their histologic features, this second group

Figure 3 Grading of myelofibrosis in CIMF (compare with Table 4). (a) Prefibrotic stage (CIMF-0). (b) Early fibrotic stage (CIMF-1). (c) Manifest fibrosis (CIMF-2). (d) Advanced fibro-osteosclerotic stage (CIMF-1).
of “ET” cases best fits a diagnosis of prefibrotic and early-stage CIMF with accompanying thrombocythemia, that is, false ET. It is therefore not surprising that significant discrepancies are seen when comparing cases classified according to the PVSG and WHO (Table 1). The inadequacy of the PVSG criteria on their own for identifying “true” ET may account at least partially for the disturbing heterogeneity of clinical findings and outcomes seen in these patients.4,19,21

Standardized histologic features determined by semiquantitative grading are helpful to recognize bone marrow patterns associated with different MPDs and can facilitate the distinction between true and false ET (Table 2). The presence of an even slightly increased degree of reticulin fibrosis is rare in true ET, while it is commonly observed in early CIMF with thrombocythemia, where the reticulin content may approach a moderately increased degree (Table 3). The risk of developing myelofibrosis and blastic crisis, while relatively low in true ET, is higher in prefibrotic CIMF.5,8,11,29,43 In true ET, evolution into manifest myelofibrosis was found in less than 3% of cases after a mean follow-up of more than 5 years including sequential bone marrow biopsies. However, because myelofibrosis is defined on the basis of bone marrow morphology, this does not necessarily imply a significant increase in splenomegaly, anemia, or the presence of an overt leukoerythroblastic blood smear consistent with extramedullary hematopoiesis or myeloid metaplasia (MM). Therefore, current literature reports of a 5% to 24% risk of myelofibrotic transformation in ET must be viewed critically (Fig 4), in particular, when one considers that the diagnosis was often based on clinical symptoms consistent with the presence of overt MM.21,31 Similarly, using the PVSG criteria, blastic crisis including transformation into acute megakaryocytic leukemia was found in 3% to 7% of patients.21,32,33 In contrast, bone marrow blastic transformation (blast counts exceeding 30%) was an extremely rare event in true ET after an observation time of almost 6 years.10,29

Within the category of false ET lies a group of patients who may present with the clinical features presumptive of this condition, but who later develop overt erythrocytosis and polycythemic PV.21,34-36 It is reasonable to discuss whether these patients belong to a cohort of initial PV cases who, at the beginning of their disease course, did not fulfill the diagnostic

| Table 1 Re-evaluation of 564 Patients With a Platelet Count > 600 × 10^9/L and the Clinical Diagnosis of ET According to the PVSG Criteria by Following the WHO Classification |
|---------------------------------|----------------|----------------|----------------|----------------|
| ET | CIMF-0 | CIMF-1 | CIMF-2 | PV With Thrombocytemia |
| No. of patients | 158 | 174 | 135 | 71 | 26 |
| (%) | 28.0 | 30.9 | 23.9 | 12.6 | 4.6 |

Abbreviations: ET, essential thrombocythemia; CIMF, chronic idiopathic myelofibrosis (grading of myelofibrosis, see Tables 3 and 4); PV, polycythemia vera.

| Table 2 Diagnostic Impact of Certain Standardized Histologic Bone Marrow Features in 297 Patients Following Discriminant Analysis and Clinical Diagnosis According to the WHO Classification |
|---------------------------------|----------------|----------------|----------------|----------------|
| Clinical Diagnosis (WHO classification) | PV (n = 52) | ET (n = 90) | CIMF-0 (n = 118) | CIMF-1 (n = 37) |
| Megakaryopoiesis Maturation defects | ○ | ○ | ● | ● |
| Nuclear lobulation | ● | ● | ○ | ○ |
| Myeloid stroma Reticulin fibers | ○ | ○ | ○ | ● |
| Erythropoiesis Left shifting | ● | ○ | ○ | ○ |
| Megakaryopoiesis Naked nuclei | ○ | ○ | ● | ● |
| Small forms | ● | ○ | ● | ● |
| Erythropoiesis Quantity | ● | ○ | ○ | ○ |
| Granulopoiesis Left shifting | ● | ○ | ○ | ○ |
| Megakaryopoiesis Giant forms | ● | ● | ● | ● |
| Cellularity | ● | ○ | ● | ● |
| Megakaryopoiesis Bulbous nuclei Clusters | ○ | 72 | ● | ● |

NOTE. Relative incidence of histologic features displaying a discriminating effect: ○, ≤10%; ●, ≥80%. Statistical analysis: predicted group membership: ET 299 of 319 of original grouped cases correctly classified (93.6%).
criteria of the PVSG\textsuperscript{22,37} or WHO,\textsuperscript{38} especially hemoglobin level and/or red cell mass. These conditions, variously termed “latent PV” or “idiopathic erythrocytosis,”\textsuperscript{22,36,39,40} may be accompanied by a platelet count greater than 600 $\times$ 10\textsuperscript{9}/L, mimicking ET, at least at disease onset.\textsuperscript{41} Histopathology in these early PV cases is characterized by a trilineage proliferation, including a prominent megakaryopoiesis without gross maturation defects (Fig 1d) exhibiting a remarkable degree of cellular pleomorphism (Fig 2c). Those patients with initial early PV that fails to conform to the conventional PVSG diagnostic criteria\textsuperscript{20,41} are nevertheless clearly distinguishable by their specific bone marrow histopathologic pattern (Table 2).

Retrospective studies also have shown that bone marrow histopathology with identification of megakaryocyte morphologic anomalies (dysplasia) and presence of increased reticulin is clearly associated with a worsening of survival.\textsuperscript{42} These results agree with our original description of early CIMF associated with thrombocythemia,\textsuperscript{24,43} confirmed by recent studies based on much larger databases.\textsuperscript{15,44} Thus, it must be emphasized that the distinction between false and true ET bears a significant prognostic impact by greatly reducing the heterogeneity of outcomes generally seen in ET patients (Fig 5).

Myelofibrosis Developing in MPDs

There is general agreement that the increase in the density of reticulin fibers, the presence of collagen fibrosis, and the osteosclerotic changes in the trabecular bone that frequently occur in MPDs are secondary phenomena caused by fibrogenic cytokines produced by abnormal megakaryocytes or other cells.\textsuperscript{45-47} Since myelofibrosis per se is not diagnostic of MPDs, particularly CIMF, a large variety of myeloid neoplastic diseases associated with the development of myelofibrosis has to be taken into account for the purpose of differential diagnosis. These entities usually comprise fibrotic subtypes of myelodysplastic syndromes and acute myeloid leukemia; the latter group includes the so-called acute panmyelosis with myelofibrosis.\textsuperscript{48,49} Conventional criteria applied for the diagnosis of CIMF include a leukoerythroblastic blood smear with teardrop poikilocytosis, splenomegaly due to extramedullary hematopoiesis (also known as MM), anemia of varying degree, and bone marrow fibrosis. This represents the characteristic clinicopathologic picture seen only in advanced cases of CIMF, such as myelofibrosis with myeloid metaplasia (MMM).\textsuperscript{2,18,50-53} However, several investigators have repeatedly emphasized that in larger series of patients with adequate follow-up, striking variations of hematologic findings are observed.\textsuperscript{17,18,20,52,54-56} These wide ranges of clinical results were associated with a remarkable heterogeneity of bone marrow features observed at the time of diagnosis. In particular, the degree of myelofibrosis ranged from a minimal to a mild increase in reticulin fibers, the so-called hypercellular phase (Fig 1b and c, Fig 3a and b), to overt reticulin (Fig 3c) and collagen fibrosis and osteosclerosis, seen in the more advanced disease stages (Fig 3d). In the last two decades, accurate clinicopathologic investigations based on a careful comparative analysis of sequential bone marrow biopsy specimens have significantly elucidated the dynamics of the disease process in CIMF.\textsuperscript{5,8,29,55} According to the results derived from these studies, progression of CIMF is stepwise and, thus, the spectrum of clinical changes observed in the patient is paralleled by the evolving features seen in the bone marrow biopsy—above all, the differences in the amount and quality of...
myelofibrosis (Table 3). A scoring system of four grades has been used in several studies to assess quantity and quality (reticulin vs collagen) of the bone marrow fiber content and to document the progression of disease in CIMF. This grading approach was recently validated in an international consensus meeting of bone marrow biopsy experts (Table 4) 30. Table 5 shows the relation between the extent of myelofibrosis (reticulin/collagen) and corresponding clinical data, as observed at disease onset. Approximately 25% of patients with CIMF initially present in CIMF-0, a hypercellular stage characterized by a prominent granulocytic and megakaryocytic proliferation accompanied by a reduction and/or partial maturation arrest of erythroid precursors, with no or only a borderline increase in the amount of reticulin (Fig 1b and Fig 3a). 6,8,10,11,29,43,57,58 However, even in (prefibrotic) CIMF-0, the megakaryopoiesis is conspicuously abnormal, being characterized not only by a disturbance of bone marrow histotopography (loose to dense clustering and translocation to the endosteal borders), but also by striking abnormalities of cell maturation (Fig 1b and Fig 2b). These deviations include an extreme degree of size variability (pleomorphism) with giant as well as small megakaryocytes, and also aberrations of the nuclear cytoplasmic ratio marked by bulbous and hyperchromatic (cloud-like) nuclei (Fig 2b). In addition to the disorganized nuclear lobulation pattern, there are many naked (bare) nuclei detectable. 7,10,17,29,36-58 Overall, the megakaryocytes in CIMF exhibit an atypical (dysplastic) appearance more consistently than in any of the other MPDs. Although progression of CIMF is somewhat unpredictable, there is some indication that an increase in the degree of megakaryocyte dysplasia has predictive value regarding the evolution into myelofibrosis.

Clinical findings in cases of CIMF-0 often demonstrate only borderline to slight leukocytosis, therapy-refractory mild anemia, minimal to modest splenomegaly, and often mild to marked thrombocytopenia (Table 5), mimicking ET. Nucleated erythroid precursor cells, teardrop red blood cells, and immature granulocytes in the peripheral blood are usually infrequent in the early stages of CIMF. 8,43 As has been repeatedly demonstrated, 5,7,8,11,43 there is a significant probability of progression from a prefibrotic-early stage (Fig 3a and b) to full-blown CIMF (Table 6), the latter conforming to the classical diagnostic criteria for MMM. 2,50,52,54 In this context, clinical parameters that indicate evolution of myelofibrosis and therefore progressive disease in these early stages of CIMF (including increasing anemia, splenomegaly, and the development of a leukoerythroblastic blood picture) do occur in about 30% of cases in the first 5 years of observation (Fig 6).

The manifest (classical) grossly fibrotic stages are associated with a pronounced increase in reticulin (CIMF-2) and collagen (CIMF-3), and in these stages (Fig 3c and d) bone marrow cellularity becomes more variable, with areas of patchy hematopoiesis that may be separated by fatty marrow (Fig 2d). These advanced stages of disease usually show coarse bundles of collagen fibers with variable focal osteosclerosis (Table 4). 5,8,10,11,29,36,59,60 Additional histologic findings seen in the advanced cases include the presence of dilated marrow sinuses 53,55,61 with a prominent intraluminal hematopoiesis, which includes megakaryocytes (Fig 2d). Similar to the initial-prefibrotic stages, atypical megakaryopoiesis with megakaryocytes arranged in sizable clusters surrounded by (residual) left-shifted granulopoiesis and small groups of erythroid precursors (Fig 2d) presents a morphologic hallmark. Even in cases without previous history of cytoreductive therapy, myelodysplastic changes, usually of mild to moderate severity, may be seen as the disease progresses. 60

### Table 4: Grading of Myelofibrosis as Adapted From a Consensus of European Experts 30

<table>
<thead>
<tr>
<th>Grading</th>
<th>Description*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF-0</td>
<td>Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow</td>
</tr>
<tr>
<td>MF-1</td>
<td>Loose network of reticulin with many intersections, especially in perivascular areas</td>
</tr>
<tr>
<td>MF-2</td>
<td>Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis</td>
</tr>
<tr>
<td>MF-3</td>
<td>Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis</td>
</tr>
</tbody>
</table>

Abbreviation: MF, myelofibrosis.

*Fiber density should be assessed in hematopoietic (cellular) areas.

### Table 5: Characteristic Clinical Data in 865 Patients (median values) First Presenting With Various Stages of CIMF According to Their Bone Marrow Fiber Content

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>CIMF-0</th>
<th>CIMF-1</th>
<th>CIMF-2</th>
<th>CIMF-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.9</td>
<td>13.7</td>
<td>12.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Leukocytes (× 10^9/L)</td>
<td>10.8</td>
<td>11.2</td>
<td>10.1</td>
<td>9.7</td>
</tr>
<tr>
<td>Thrombocytes (× 10^9/L)</td>
<td>854</td>
<td>825</td>
<td>593</td>
<td>276</td>
</tr>
<tr>
<td>Peripheral blasts (%)</td>
<td>0</td>
<td>0</td>
<td>1.6</td>
<td>2.7</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>263</td>
<td>303</td>
<td>333</td>
<td>492</td>
</tr>
<tr>
<td>Splenomegaly (cm below costal margin)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

NOTE: Degree of myelofibrosis (MF; see also Table 4 for scoring system)
Abbreviation: LDH, lactate dehydrogenase.
In these late stages of CIMF (consistent with MMM), significant collagen fibrosis of the bone marrow is a constant finding (Table 4). The peripheral blood typically shows leukoerythroblastosis and poikilocytosis with many teardrop-shaped erythrocytes accompanied by anemia and pronounced splenomegaly (Table 5), corresponding with full-blown CIMF or MMM.2,18,51,54,62 The presence of between 10% and 20% blasts in the peripheral blood smear should prompt a diagnosis of acceleration, and, if blast number exceeds this threshold, blast crisis has to be assumed.17 Transformation of CIMF to (secondary) acute myeloid leukemia occurs in 5% to 20% of patients63 and, as in allied MPDs, may be partially related to myelosuppressive therapy.64 However, it is still controversial whether or not splenectomy plays a role in this transformation.55

### Reactive Lesions Versus MPDs

Considering the diagnostic criteria for ET of the PVSG,21-23 concern has been repeatedly expressed regarding their value in separating ET from reactive thrombocytosis. However, evaluation of bone marrow specimens in these cases clearly revealed features that are specific and allow such a distinction.9,24,28 In reactive thrombocytosis (Fig 7a), in contrast to ET (Fig 7b), there is a random distribution throughout the marrow cavity of small to medium megakaryocytes lacking the extensive, staghorn-like nuclear hyperlobulation seen in ET. In addition, reactive granulocytic hyperplasia is usually only predominant in reactive thrombocytosis. Thus, histologic analysis allows for an easy distinction between reactive and autonomous thrombocytosis (Table 7) and represents a valuable tool for improving diagnostic accuracy.

### Latent and Early (initial) Stages of PV

Neither the original nor the updated PVSG criteria,22,23,37 as well as the diagnostic guidelines of the WHO classification,38 consider the latent and early (initial stages) of PV.20,41,66 The majority of these cases, termed idiopathic (latent, pure) erythrocytosis, are characterized by a mild increase in the hemoglobin/hematocrit level, normal or borderline increase in the red cell mass, normal leukocyte count, and the lack of splenomegaly in the absence of any cause of secondary polycythemia.20,22,36,67 In contrast to the non–histology-based PVSG criteria,22,23 the WHO classification of PV recognizes bone marrow histopathology only as one of the minor diagnostic criteria, together with thrombocytosis, low Epo level, and increased white blood cell count.38 In contrast, a recent clinicopathologic study suggested that histopathology should be considered as one of the main tools for diagnosing PV.20 On the other hand, a rather critical attitude concerning the value of bone marrow examinations for discriminating PV from other subtypes of MPDs, as well as from reactive erythrocytosis or secondary polycythemia, has been expressed.37 Historical studies are of limited value in addressing this problem,22,37 since former investigations of histologic bone marrow features in PVSG patients resulted in relatively nonspecific descriptions.14,68,69 Moreover, it has been emphasized that in order to use histopathology as a reliable criterion,70 a more accurate definition of standardized objective parameters of discriminating impact would be necessary.22,71 Finally, the results of morphologic studies are ambiguous and not easily reproducible, because, at least until now, no investigation has proven the validity of histopathology for PV in a blinded fashion.71,72 This problem has been circumvented by independently performed clinicopathologic investigations testing the discriminating power of morphology in a large series of patients presenting with mild to significant erythrocytosis.56,73 This study resulted in an overall discrepancy to differentiate between PV and secondary polycythemia of about 4%. According to clinical data and follow-up examinations in this series of patients, secondary polycythemia was prevalent in males and caused in the majority (about 80%) by heavy smoking associated with recurrent bronchopulmonary infection and could be further related to rare conditions as metastasizing malignant tumors, kidney cysts, hydronephrosis, and hepatomas.70 Referring to the issue of failing standardized features to emphasize the sensitivity and reproducibility of histologic patterns in erythrocytosis, Table 8 lists the relevant ranking of distinctive parameters separating both entities.28,66,73 These studies support previous data describing specific bone marrow features in PV.10,11,29

Although erythropoiesis (extensive groupings of nucleated erythroid precursors) is always a prominent feature in PV...
marrows, histopathology of bone marrow biopsy specimens reveals important differences in regard to the other marrow constituents: hematopoiesis and myeloid stroma. In addition to the constant finding of increased (age-matched) marrow cellularity, PV is characterized by a trilineage proliferation (panmyelosis) involving granulopoiesis, erythropoiesis, and megakaryopoiesis (Fig 1d), which contrasts the normocellular or slightly hypercellular marrow seen in secondary polycythemia (Fig 7c). Megakaryocytes exhibit striking differences in appearance and size between the two conditions.

Figure 7 (a) In reactive thrombocytosis there may be a slight hypercellularity with left-shifted hematopoiesis and prominent small to medium normal megakaryocytes. (b) In ET, mature megakaryocytes are large to giant and present correspondingly developed nuclei as a most characteristic feature. (c) Secondary polycythemia is characterized by a prominent granulopoiesis and erythropoiesis, but usually lacks a conspicuous megakaryocytic proliferation (compare with Fig 1d). (d) Many iron-laden macrophages are observable in secondary polycythemia. (e) Secondary polycythemia usually shows a marked perivascular plasmacytosis and surrounding eosinophils (arrows). (f) Small interstitial assemblies of cell debris (arrows) may be observed frequently in secondary polycythemia.

J. Thiele, H.M. Kvasnicka, and A. Orazi
In secondary polycythemia, small megakaryocytes dispersed in a random fashion throughout the marrow are prevalent, whereas the megakaryocytes in PV display a marked degree of pleomorphism, including the presence of small as well as giant to large forms. These cells are often arranged in loose clusters without evidence of a significative maturation defect (Fig 2c).11,20,29,70,73 Finally, the conspicuous alterations of the bone marrow stroma characterizing secondary polycythemia (Fig 7d-f) have not, at least until now, been well documented.70,73 The presence of iron-laden macrophages (Fig 7d), although not an absolute diagnostic criteria in favor of secondary polycythemia, is nevertheless a reliable indicator of a reactive cause. Even patients with PV and concomitant inflammatory disorder show at most a slight to moderate positive staining in about 6% of bone marrow specimens on admission without preceding phlebotomies.68-70,73 Moreover, in secondary polycythemia, reactive plasma cells lining the vessel walls and surrounded by eosinophils are a prominent feature (Fig 7e), as are deposits of cell debris (Fig 7f). The incidence of reticulin fibrosis at presentation is less than 20%,11,29,34,70 in contrast to data from the PVSG that suggested a significantly higher frequency of 36%, including collagen fibrosis.69,74 It is tempting to speculate whether this discrepancy is due to the stage of disease (that is, the time of performing the bone marrow biopsy), because the natural cause of PV includes evolution into myelofibrosis—post-polycythemic MM.10,11,20,74

In conclusion, cumulative insight has been gained into the natural history of MPD by the mutual relationships between clinical data and histopathology. The latter technique is most valuable in the diagnostic work-up of MPDs when specimen processing and histopathologic evaluation are performed by experienced pathologists trained to identify specific histologic patterns that have been shown to be of discriminatory value in these conditions.
myeloid metaplasia (AMM) - correlation of bone marrow lesions with laboratory data: A longitudinal clinicopathological study on 114 patients. Hematol Oncol 7:327-343, 1989


