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Essential thrombocythemia vs. early/prefibrotic myelofibrosis: Why does it matter

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Essential thrombocythemia (ET) and primary myelofibrosis (PMF), together with polycythemia vera (PV) are Phildelphia-negative (Ph-neg) classical myeloproliferative neoplasms (MPN). ET has been traditionally identified by thrombocytosis and absence of relevant bone marrow (BM) fibrosis, while PMF by BM reticulin or collagen fibrosis with megakaryocyte hyperplasia and dysplasia, and extramedullary hematopoiesis. These diagnostic profiles have been challenged since 2001 when the World Health Organization (WHO) has included in the domain of PMF a new category of patients, namely early/prefibrotic MF, characterized by the absence of relevant reticulin fibrosis in BM, dual megakaryocyte and granulocyte proliferation, and megakaryocyte dysplasia. This review is focused on summarizing the diagnostic uncertainties of early/prefibrotic myelofibrosis, recent advances in our understanding of the biology of the variant, and the accompanying translational implications.

Introduction

Essential thrombocythemia (ET), primary myelofibrosis (PMF), and polycythemia vera (PV) are Phildelphia-negative (Ph-neg) classical myeloproliferative neoplasms (MPN) [1]. ET has been traditionally identified by thrombocytosis and absence of relevant bone marrow (BM) fibrosis [2], while PMF by BM reticulin or collagen fibrosis with megakaryocyte hyperplasia and dysplasia, and extramedullary hematopoiesis [3]. These diagnostic profiles have been challenged since 2001 [1] when the World Health Organization (WHO) has included in the domain of PMF a new category of patients,

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namely early/prefibrotic MF, characterized by the absence of relevant reticulin fibrosis in BM, dual megakaryocyte and granulocyte proliferation, and megakaryocyte dysplasia.

Early/prefibrotic myelofibrosis: the history of an idea

The idea that PMF could be diagnosed in the presence of a non-fibrotic BM, first came in the late twentieth century, when a group of pathologists from Hannover, led by Andreas Georgii, described an entity among chronic myeloproliferative disorders (CMPD), they called chronic megakaryocytic granulocytic myelosis (CMGM) [4]. The idea was functional to the simple contention that CMPD could be classified in four categories according the dominance of proliferating myeloid lineage: granulocytic for chronic myeloid leukemia (CML), erythroid for polycythemia vera (PV), megakaryocytic for ET, and granulocytic-megakaryocytic for CMGM. As a matter of fact, they defined CMGM by the proliferation of megakaryocytic and granulocytic cell lines, atypical megakaryocyte maturation, nuclear-cytoplasmic asynchrony, nuclear inclusions and production of micromegakaryocytes.

In the first reports, CMGM was considered to be merely a variant of chronic myeloid leukemia (CML) [5]. However, CMGM was subsequently separated from CML, and positioned as an early phase of PMF. In 1996, when the group established the histopathological classification and staging of Ph-negative MPD (Hannover system), CMGM appeared as a synonym of PMF [6].

The consolidation of the seminal intuition of a non-fibrotic early stage of PMF, however, has to be attributed to Jurgen Thiele and co-workers from Cologne. From 1989 to 1999 they produced multiple retrospective analyses of an expanding and well-characterized archive of trephine biopsy specimens from patients with CMPD and thrombocytosis where the name of CMGM disappeared, but the concept of an early hyperplastic stage of PMF was set off [7–9]. Moreover, they clearly delineated the distinction between a category of patients with thrombocytosis and a BM with a proliferation of a not severely dysplastic megakaryopoiesis and a normal content of reticulin fibers, compatible with ET, and another characterized by a decline of the initially elevated thrombocyte count, and conspicuous abnormalities of megakaryocytes accompanied by a slight to moderate increase in argyrophilic fibers and a left-shifted neutrophilic granulopoiesis.

The name “prefibrotic myelofibrosis” appeared, at the best of our knowledge, for the first time in 1999 in a paper signed by a high number of European pathologists and clinicians (first author Jean Jacques Michiels from Amsterdam) [10].

Diagnosis of early/prefibrotic MF

The diagnostic histological hallmarks that allow to distinguish early/prefibrotic MF from ET [11] are those delineated from the beginning by the Hannover group, refined by the Cologne group, and formalized in the WHO histological criteria in 2001 [12] and then revised in 2008 [1] (Table 1, Fig. 1).

Table 1
Histopathology of bone marrow biopsy in early/prefibrotic myelofibrosis and essential thrombocythemia according to the WHO description [13].

Early/prefibrotic myelofibrosis	Hypercellularity by a prominent neutrophil granulocytic and megakaryocytic proliferation often associated with a concomitant reduction of nucleated red cell precursors in the absence or only minor reticulin MF, consistent with MF-0 and MF-1. Abnormalities in the megakaryocytopoietic cell lineage: these include first of all the distribution within the marrow space showing often extensive and dense clustering and translocation towards the endosteal borders. Moreover, there are markedly expressed anomalies of megakaryocyte maturation and differentiation detectable which consist of a high variability in size ranging from small to giant megakaryocytes. There are prominent aberrations of the nuclei (marked hypolobulation, condensed chromatin, and irregular foldings crating a bulbous, cloud-like aspect) and marked elevation of the nuclear-cytoplasmic ratio, as well as an increased frequency of bare (denuded) nuclei.
Essential thrombocythemia	Age-matched cellularity and a predominant megakaryopoiesis without a significant erythroid or neutrophilic myeloproliferation. In ET megakaryocytes reveal a more or less random distribution or very loose groupings within the BM space. An important feature is the large to giant cell forms with extensively folded (hyperlobulated) nuclei, surrounded by well differentiated (mature) cytoplasm. An increase in reticulin is not compatible with early stages of ET.