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Limitations of fibrosis grade as diagnostic criteria for post polycythemia vera and essential thrombocytosis myelofibrosis

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ABSTRACT

Background: The clinical phenotype of patients with myeloproliferative neoplasms (MPNs) including primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocytosis (ET) whom manifest WHO grade 1 marrow fibrosis is poorly defined. Current IWG-MRT criteria require 2+ marrow fibrosis for diagnosis of post PV/ET myelofibrosis (MF). In contrast, the 2008 WHO definition of PMF does not require a minimum fibrosis threshold.
Methods: We retrospectively analyzed the clinical characteristics of 91 MPN patients with 1+ marrow fibrosis. We compared the clinical phenotype of sub threshold fibrosis PV/ET with that manifested by PMF. We applied the IWG-MRT criteria for post-PV/ET MF with the fibrosis component omitted and evaluated for percentage of criteria fulfillment.
Results: When IWG-MRT criteria were applied to the PV/ET group, 38/58 (66%) of patients fulfilled criteria for diagnosis of post-PV/ET myelofibrosis except for the 2+ fibrosis requirement. Comparison of sub threshold fibrotic PV/ET clinical phenotype to PMF revealed similar characteristics including heavy symptomatic burden (57% and 52%), presence of splenomegaly (43% and 55%), leukoerythroblastic blood smear (38% and 45%), and median hemoglobin (12.8 g/dL and 11.1 g/dL).
Conclusion: MPN progression represents a biological spectrum and definitions of progression in ET/PV may benefit from criteria not restricted by degree of fibrosis.

1. Introduction

The myeloproliferative neoplasms (MPNs) are a group of disorders characterized by clonal proliferation of myeloid hematopoietic elements that include polycythemia vera (PV), essential thrombocytosis (ET), and primary myelofibrosis (PMF). PV/ET may evolve into the clinical and pathologic diagnosis of myelofibrosis (MF) [1], known as post-PV/ET MF, and may subsequently progress to acute myeloid leukemia [2]. In 2008, the WHO and IWG-MRT set forth a list of criteria for both PMF and post-PV/ET MF (Tables 1 and 2) [3,4]. For patients to fulfill criteria for post PV/ET MF WHO grade 2 fibrosis must be identified on bone marrow evaluation. In clinical practice, a subgroup of patients with PV/ET exist whom manifest grade 1 marrow fibrosis and concurrently possess a phenotype that overlaps that of PMF however; these patients fail to meet IWG-MRT 2008 criteria. Importantly, these patients may be excluded from clinical trial participation given their sub-threshold fibrosis despite their phenotypic manifestation being closer to that of PMF.

In this study we propose MPN progression represents a biologic spectrum and definitions of progression in ET/PV may benefit from other criteria not restricted by degree of fibrosis. We evaluate the clinical phenotypes of both PMF and PV/ET with 1+ fibrosis, perform a comparison analysis, and lastly apply IWG-MRT criteria minus the fibrosis component to the sub threshold PV/ET population.

2. Methods

MPN patients with WHO grade 1 (scale 0–3) fibrosis [5], either primary or secondary, within two institutional databases were identified between 2005 and 2013. The clinical and laboratory characteristics were collected retrospectively including information regarding symptom burden and the presence of splenomegaly on physical exam. Symptom burden was assessed as the presence of constitutional symptoms such as fatigue, weight loss, and fever at time of last patient follow up. Data were then compared between PMF and PV/ET patients focusing on elements also present in IWG-MRT criteria including laboratory findings, presence of splenomegaly, and

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Table 1
World Health Organization (WHO) diagnostic criteria for primary myelofibrosis [7].

Major criteria	(1) Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular phase disease (2) Not meeting criteria for PV, Chronic myeloid leukemia, myelodysplastic syndrome, or other myeloid neoplasm (3) Demonstration of the JAK V617F or other clonal marker, or in the absence of clonal marker, no evidence the underlying fibrosis is due to underlying inflammatory or other neoplastic process
Minor criteria	-Leukoerythroblastosis -Increased LDH -Anemia -Palpable splenomegaly

Diagnosis requires all 3 major criteria AND 2 minor criteria.

presence of a leukoerythoblastic blood smear. 2008 IWG-MRT criteria were applied to PV/ET patients with exclusion of fibrosis component and percentage of those with sub threshold fibrosis PV/ET who met criteria was calculated.

Descriptive statistics were used to summarize the two groups, PMF and PV/ET. Data were compared between groups by chi-square test for categorical data and the non-parametric Wilcoxon rank-sum test for continuous data. SAS version 9.3 (Cary, NC) was used for analysis.

3. Results

3.1. The 1+ fibrosis phenotype

Within the two participating academic centers, 91 MPN patients with WHO grade 1 fibrosis were identified. The primary diagnosis was PMF in 33 patients (36%), PV in 37 patients (41%), ET in 20 patients (22%), and MPN-unclassified in 1 patient (1%). The 1+ clinical and laboratory characteristics are reported in Table 3. The median hemoglobin for the PMF group was 11.1 g/dL (range 7.9–16.4) and similar in the PV/ET group at 12.8 g/dL (range 8.0–19.8). Surprisingly, the PMF group had a higher median WBC at 15.0×10^9 (range 1.3–188) while the PV/ET group median was 8.9×10^9 (range 3.5–51.3), $p = 0.02$. A higher incidence of a leukoerythoblastic blood smears was seen in PMF patients (45%) than PV/ET patients (38%). The majority (55%) of patients exhibited one or more symptoms including weight loss, night sweats, early satiety, bone pain, and/or fatigue. The presence of symptomatic disease was similar between groups, with 52% PMF versus 57% PV/ET exhibiting at least one symptom. When DIPSS risk score was applied to each group, risk was higher in the PMF group with DIPSS risk of intermediate 2 or higher being present in 39% (PMF) versus 29% (PV/ET). Erythrocyte transfusion dependence occurred in a small percentage of overall population (9%), and was seen primarily in the PMF group (6/8 patients). Incidence and severity of splenomegaly was higher in the PMF group, with 55% having splenomegaly versus 43% of the PV/ET group. Two or more prior medical therapies were utilized in 45/90 (49%) of patients, with the most common prior therapies including hydroxyurea (71%), pegylated interferon (28%), anagrelide (18%), Jak inhibitor (13%), lenalidomide (4%), and prednisone (4%).

3.2. IWG-MRT criteria analysis for post polycythemia vera and essential thrombocytosis myelofibrosis

When IWG-MRT criteria for post PV/ET MF were applied to the PV/ET group, 38/58 (66%) of patients fulfilled criteria for diagnosis of post-PV/ET myelofibrosis (except for the 2+ fibrosis requirement).

Table 2
2008 IWG-MRT diagnostic criteria for post-PV/ET MF [16].

Required criteria	(1) Documentation of a previous diagnosis of ET or PV as defined by WHO criteria (2) Bone marrow fibrosis grade 2/3 (on a 0–3 scale or grade 3/4 (on a 0–4 scale)
Additional criteria	
Post-PV MF	(1) Anemia or sustained loss of requirement for either phlebotomy or for cytoreductive treatment (2) Leukoerthryoblastic peripheral blood smear (3) Increasing splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or appearance of new splenomegaly (4) Development of ≥1 of 3 constitutional symptoms: >10% weight loss, night sweats, or unexplained fever >37.5 °C
Post-ET MF	(1) Anemia and a 2 mg/ml decrease from baseline hemoglobin level (2) Leukoerythroblastic peripheral blood smear (3) Increasing splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or appearance of new splenomegaly (4) Increased lactate dehydrogenase (above reference level) (5) Development of ≥1 of 3 constitutional symptoms: >10% weight loss, night sweats, or unexplained fever >37.5 °C

Diagnosis requires presence of required criteria and 2 additional criteria.

When evaluating those with PV who met criteria for post-PV/ET MF (27 patients), 14 patients (52%) met 2 of the criteria, 7 patients (26%) met 3 of the criteria, and 6 patients (22%) met 4 elements of the diagnostic criteria. In those afflicted with ET who met criteria (11 patients), 8 patients (73%) met 2 criteria, 2 patients (18%) met 3 criteria, and 1 patient (9%) met 4 of the diagnostic criteria (Table 4). The most common diagnostic criteria met were the presence of symptoms.

4. Discussion

Within the spectrum of MPNs, the clinical manifestations of disease and symptomatic burden vary dramatically. Patients afflicted with PMF exhibit splenomegaly, cytopenias, risk of leukemic transformation, and oftentimes a heavy symptomatic burden [6]. PV/ET patients tend to be less symptomatic, have hyperproliferative blood smears, and increased thrombotic and hemorrhagic risk [7,8]. Diagnostic strategies have changed significantly in the last decade, with a molecular revolution beginning with the discovery of the *JAKV617F* mutation in 2005 [1,9]. Since this discovery, multiple subsequent clonal markers have been identified [10–17]. Despite the molecular renaissance that has occurred in MPNs, the diagnosis remains largely histologically based with a bone marrow biopsy being the gold standard diagnostic procedure [18]. The role of histology in diagnosis of myelofibrosis is indisputable however; the clinical manifestations of disease play an integral role and may be underemphasized in the diagnosis of post PV/ET MF.

The treatment for PV/ET and PMF and/or post PV/ET MF differs profoundly. The goal in therapy for PV/ET patients is primarily that of cytoreduction, with subsequent thrombotic and hemorrhagic risk reduction employing agents such as hydroxyurea, anagrelide, or pegylated interferon [19–22]. In contrast, treatment of MF primarily focuses on symptom control and spleen reduction with the utilization of JAK inhibitors, such as the FDA approved agent ruxolitinib, as well as other therapies [23–26]. The only potentially curative option in intermediate to high risk MF is allogeneic stem cell transplant [27]. Given the diversity in therapeutic options, the therapeutic armamentarium changes as disease progresses from PV/ET to post-PV/ET MF. It is of the utmost clinical importance to

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