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Discrepancy in diagnosis of primary myelofibrosis between referral and tertiary care centers

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ABSTRACT

Primary myelofibrosis (PMF) is myeloproliferative neoplasm whose diagnosis is based on a combination of clinical and pathology criteria. We evaluated 560 consecutive patients who were diagnosed with PMF upon a referral to our center and evaluated the frequency of and reasons for diagnostic discordance. Discordance in the diagnosis was found in 70 (12.5%) patients. Discordant cases had a significantly lower grade of bone marrow fibrosis (grade 0–1), more likely to be JAK2V617F-mutation negative, and have no peripheral blood blasts, possibly explaining the difficulty in making a proper diagnosis and underscoring the need for a complete evaluation at a tertiary center.

1. Introduction

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by clonal expansion of abnormal hematopoietic cells, resulting in secondary bone marrow (BM) fibrosis and osteosclerosis, angiogenesis and extramedullary hematopoiesis [1–3]. Patients develop significant cytopenia, enlarged spleen and liver, and experience significant deterioration in their quality of life, with weight loss and decreased performance status. Diagnosis of PMF is based on a BM examination for morphology, cytogenetics, and molecular abnormalities that must not meet criteria for other chronic myeloid diseases, such as chronic myelogenous leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PV), or myelodysplastic syndrome (MDS), and fibrosis should not be reactive in nature [4,5]. Diagnostic criteria also include findings of abnormalities in peripheral blood as well as in serum chemistry. An accurate diagnosis is important for correct therapeutic considerations and prognostication [5]. The aim of this study was to evaluate the frequency of and reasons for diagnostic discordance in patients who were diagnosed with PMF upon a referral to a tertiary center.

2. Methods

We performed a retrospective analysis of 560 consecutive adult patients referred to The University of Texas MD Anderson Cancer Center (MDACC) between January 2007 and December 2011 with a confirmed diagnosis of PMF at MDACC. The research was based on a chart review protocol approved by the institutional review board. We compared the pathology report from the referring institution with the final pathology report at MDACC. Complete diagnostic evaluation of all patients at MDACC included BM biopsy, clot section and aspirate smear. Usually at least 3 independent pathologists are involved in diagnostic evaluation at our center. Pathologist 1 releases in the laboratory information system a report on the bone marrow differential from a 500-cell count of cellular bone marrow aspirates and/or touch imprints. Pathologist 2 releases a final bone marrow pathology report, including peripheral blood film, core biopsy, clot section, and aspirate smears. He/she also reviews outside specimens, if any are available. Pathologist 3 reviews all new leukemia department cases with clinicians at the weekly leukemia planning conference, with integrated molecular and genetic data. The final report therefore reflects a team effort. We reviewed the BM slides from the referring institution when available. Diagnosis of PMF required meeting all 3 major and 2 minor criteria according to the 2008 WHO classification system for chronic MPNs [6]. The major criteria included (1) presence of megakaryocyte proliferation and atypia, with either reticulin and/or collagen fibrosis, or increased marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis; (2) not meeting WHO criteria for PV, *BCR-ABL*+CML, MDS, or other myeloid neoplasms; (3) demonstration of JAK2V617F or other clonal marker (e.g. MPL W515K/L), or no evidence of reactive fibrosis. The minor criteria included (1) leukoerythroblastosis, (2) increased serum lactate dehydrogenase (LDH), (3) anemia, and (4) splenomegaly. Demographic and clinical information were compiled from patients' medical records. Comparisons between non-discordant and discordant groups for categorical variables were calculated using the Chi-square test. All patients were assigned a Dynamic International Prognostic Scoring System-plus (DIPSS-plus) score for prognostic stratification of PMF. Overall survival (OS) was calculated from the date of presentation to MDACC until death from any cause or date of last follow-up using the Kaplan–Meier method.

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3. Results

Discrepancy between the diagnoses made by the referring institution and MDACC was documented in 70 of 560 (12.5%) cases (Table 1). Of the discordant cases, 31 (44%) were diagnosed at community hospitals, 26 (37%) at commercial laboratories and 13 (19%) at university hospitals. We first examined whether standard diagnostic criteria were present in discordant cases to explain the difficulty in making a proper diagnosis. We did not find significant differences in spleen size or LDH levels between the two groups, but low grade (0–1) BM fibrosis was significantly more frequent in the discordant group ($p < 0.0013$). In the non-discordant group, 381 (78%) of patients carried the JAK2V617F mutation compared with 46 (66%) in the discordant group ($p < 0.027$). Peripheral blood blasts ≥1% were present in 378 (77%) of patients in the non-discordant group and 36 (51%) in the discordant group ($p < 0.001$). These results suggest that the absence of several established criteria for PMF, namely advanced-grade BM fibrosis, the JAK2V617F mutation, and peripheral blood blasts, possibly contributed to difficulties referring physicians had in making a correct diagnosis of PMF (Table 2).

In addition, all patients were evaluated by the DIPSS-plus for prognostic stratification [7]. Median time from diagnosis to presentation at MDACC was 3.4 months (0–46 years); 59% of patients were seen at MDACC within 6 months of diagnosis and 70% within 1 year. Differences in DIPSS-plus score among the two groups were not evident, suggesting that the aggressiveness of the disease did not have an influence on the diagnostic process. After a median follow up of 32 months, there were 136 (28%) deaths in the non-discordant group and 21 (30%) in the discordant group. Projected median OS from presentation at MDACC in non-discordant and discordant groups were 44.6 and 36.6 months, respectively ($p = 0.07$).

4. Discussion

We found a discordance rate between the referring and final diagnoses of 12.5%. Unclassified MPN (MPN-U) was the most common referring diagnosis followed by MDS/MPN-unclassified (MDS/MPN-U). MPN-U and MDS/MPN-U are diagnoses of exclusion, and per WHO classification these patients do not fulfill criteria for a specific MPN subtype. Most cases of MPN-U likely fall in the categories of early-stage MPN before pathology characteristics have fully developed [6]. A survival analysis done in Sweden demonstrated that patients with MPN-U had a significantly reduced life expectancy likely related to late diagnosis and progression to myelofibrosis [8]. A prognostic scoring system has been recently proposed for MDS/MPN-U, highlighting a need for diagnostic accuracy [9]. MDS/MPN-U is grouped in the category of MPN variants, and exhibits features of MDS and MPN [10]. Currently, no specific molecular or chromosomal abnormalities for this condition have been identified, and the diagnosis is generally made based on morphologic and clinical assessment [11].

De Lima et al. [12] reported a cross-sectional study of 409 patients referred to MDACC in 1995 for whom BM examinations performed by the referring physician and MDACC were available. The overall concordance rate was 73%. Major discordance rates were 2% for chronic lymphocytic leukemia and 5% for CML, but 29% for AML, 43% for acute promyelocytic leukemia, 19% for acute lymphocytic leukemia, 57% for hairy cell leukemia, and 23% for MDS. Diagnostic criteria and evaluations have improved since that study, and a more recent study [13] reported a 12% discordance rate in 915 MDS patients who were referred to MDACC between September 2005 and December 2009; patients were reclassified as having higher-risk disease by French–American–British (67%) or by International Prognostic Scoring System (77%), with implications for therapy selection and prognosis calculation.

One limitation of our study is the assumption that the diagnosis of PMF made at MDACC is correct. Distinguishing PMF from other chronic myeloid diseases is inherently difficult due to the subjective process of grading BM fibrosis, absence of the JAK2V617F mutation in half of the cases, and variations in peripheral blood counts, such as white blood cell and platelet counts, blast percentage, and hemoglobin and LDH levels. Furthermore, patients referred to a tertiary center are often those with disease that is more difficult to classify. Thus, concordance rates may vary even among tertiary institutions. In everyday practice, in order to reduce discrepancies in diagnoses, we strongly suggest that the initial bone marrow biopsy material be reviewed at the time of evaluation at the tertiary center. Another potential bias of our study is the pattern of referrals to our institution. The very short time period between the initial diagnosis and presentation to MDACC in our cohort of patients, as well as their relatively short survival time after presentation, highlights the fact that the patients we see are usually those with advanced features. Therefore, the diagnostic discordance rated in other clinical settings with more patients presenting with early-phase disease might be more than the 12.5% we found in our patient population.

The appropriate diagnosis of PMF is very important for prognostication and therapeutic planning. For example, early/prefibrotic PMF may often be confused with ET, but patients with this entity have increased risk for progression to overt myelofibrosis, bleeding and thrombotic events [14]. Thiele et al. [15] found a concordance rate of 83% between 2 groups of expert hematopathologists in 2 European clinical centers in distinguishing early/prefibrotic PMF from ET. Buhr et al. [16] reported on the efforts by 6 hematopathologists from 5 European countries in re-classifying 102 non-fibrotic BM trephines obtained because of sustained thrombocytosis: consensus on histological classification (early/prefibrotic PMF vs. ET), defined as at least 4 identical diagnoses, was reached for 63% of the samples. The percentage of MPN-U rose from 2% to 23% when minor criteria for PMF were taken into account. In contrast, the frequency of PMF dropped from 23% to 7%, indicating that the majority of patients with a histological diagnosis of PMF did not fulfill complete criteria for this disease. Thus, over 50% of cases in their series either could not be reproducibly classified or fell into the category of MPN-U. This is an important clinical problem and the input of an outside hematopathologist not necessarily from a tertiary cancer center might be helpful. One may envision that in the future, with the development of the proper lines of communication, a review of

Table 1
Discordance between referral diagnoses and final diagnoses at MDACC.

Primary myelofibrosis discordant group, $N = 70$ (12.5%)			
Referring diagnosis			
WHO classification	Diagnosis	*N*	%
MPN	MPN-unclassifiable	18	26
	Polycythemia vera	12	17
	Essential thrombocythemia	7	10
	CML	5	7
MDS/MPN	MDS/MPN unclassified	15	21
	Atypical CML (BCR/ABL negative)	2	3
	CMML	2	3
MDS	RCMD	3	4
	RARS	1	1
	RAEB-1	2	3
	RAEB-2	2	3

Among 560 patients with confirmed diagnosis of primary myelofibrosis, 70 were referred to MD Anderson with different diagnosis, as outlined in this table.
MPN: myeloproliferative neoplasm; MDS/MPN: myelodysplastic syndrome/myeloproliferative neoplasm; CML: chronic myeloid leukemia; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndrome; RCMD: refractory cytopenia with multilineage dysplasia; RARS: refractory anemia with ring sideroblasts; RAEB: refractory anemia with excess blasts.