Human Pathology (2014) **45**, 498–503

ELSEVIER

Human PATHOLOGY

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Original contribution

Clinicopathologic characteristics of prefibrotic–early primary myelofibrosis in Chinese patients☆,☆☆

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Received 3 June 2013; revised 15 August 2013; accepted 21 August 2013

Keywords:
Prefibrotic–early primary myelofibrosis;
Essential thrombocythemia;
Megakaryocytes

Summary The clinicopathologic features of patients with prefibrotic–early primary myelofibrosis (PEPMF) are still uncertain, and the characteristics of PEPMF in Asian patients are rarely reported. This study analyzed the clinicopathologic characteristics of 42 Chinese patients with PMF newly diagnosed according to the 2008 World Health Organization criteria. Some clinical and laboratory features of the patients differed significantly from those of the predominantly white patients in Western countries. Chinese patients with PEPMF were more often male (1.28:1) and younger, less likely to have higher median hemoglobin concentrations (126 g/L), less frequently had palpable spleens (35.7%), and had longer median times between prefibrotic–early and classical PEPMF (64 months). On bone marrow trephine sections, Chinese patients were more likely to have increased granulopoiesis (78.6%) and less frequently had balloon-like megakaryocytes (61.9%), giant and staghorn megakaryocytes (35.7%), or megakaryocytes with hyperchromatic and dysplastic nuclei (40.4%). In conclusion, some clinicopathologic characteristics of PEPMF in Chinese patients in China differ substantially from those seen in predominantly white patients in Western countries, and more clinicopathologic studies involving different ethnic populations and geographic regions of the world should help unfold the characteristics of this disease.

1. Introduction

Philadelphia-negative classical myeloproliferative neoplasms (MPNs) include polycythemia vera, essential thrombocythemia (ET), and primary myelofibrosis (PMF) [1-3]. The diagnosis of MPNs, according to the revised Polycythemia Vera Study Group (PVSG) criteria established in the

☆ Disclosure: No conflicts of interest to declare.

☆☆ Funding: This work was supported by the National Natural Science Foundation of China (No. 81070420), Health Bureau of Zhejiang Province (2012KYA099, 2012ZHA005).

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http://dx.doi.org/10.1016/j.humpath.2013.08.021

late 1990s, is one of exclusion, and bone marrow (BM) histopathologic features are not regarded as specific clues to diagnosis [4,5]. In 2001, the World Health Organization (WHO) published its criteria for the diagnosis of MPNs [6]. This classification scheme was based on BM pathology, and the concept of "prefibrotic myelofibrosis" and "true ET" as distinct disorders was introduced. The recently revised 2008 WHO classification [2,3] still emphasizes the diagnostic value of BM histopathology examination and adds somatic Janus kinase 2 (*JAK2*) V617F mutation testing as an invaluable diagnostic criterion.

PMF is the rarest of the MPNs and the most obscure with regard to its pathophysiology [2]. The early phases of PMF (PMF-0/1), also named "prefibrotic myelofibrosis" or "prefibrotic–early PMF" (PEPMF), share many morphologic characteristics with ET. Some investigators claim that approximately 40% to 50% of patients with ET based on PVSG criteria in fact have PEPMF and that this entity needs to be distinguished from true ET [7-10]. In contrast to the minimal disease development in patients with true ET on long-term follow-up, there is at least mild and sometimes severe fibrosis in patients with PEPMF. Furthermore, there is an apparent reduction in life expectancy in PEPMF compared with true ET [2,11]. Consequently, reliably distinguishing PEPMF from ET is important because of the worse survival rate in PEPMF compared with ET, which is associated with a normal life expectancy.

Most reports of clinical and laboratory features of patients with PEPMF were written predominantly about white patients from Western countries [7-10,12,13], whereas reports of Asian (such as Chinese) patients are rare. This study analyzed the clinicopathologic characteristics of 42 patients from the east of China who had PEPMF diagnosed by the revised 2008 WHO criteria [2]. The findings were compared with those reported for predominantly white patients with PEPMF.

2. Materials and methods

2.1. Study population

The study was approved by the ethics committees of the Institute of Hematology and the Second Affiliated Hospital, School of Medicine, Zhejiang University, according to the guidelines of the Declaration of Helsinki.

Between July 1994 and April 2012, patients 18 years or older with a new presumptive clinical diagnosis of either ET or early PMF were recruited from 9 institutions in the east of China (The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou; Zhejiang Center for Clinical Laboratories, Hangzhou; The 117 Hospital of People's Liberation Army, Zhejiang; Traditional Chinese Medical Hospital, Hangzhou; People's Hospital of Cixi City, Ningbo; Anji Traditional Chinese Medical Hospital, Huzhou; The First Affiliated Hospital of Wenzhou Medical College, Wenzhou; People's Hospital of Qingyun City, Lishui; Wenzhou Central Hospital, Wenzhou), which cover a population of more than 45.9 million.

Our approach in asymptomatic patients was to wait until disease progression. Symptomatic persons typically received single-drug oral therapy, mainly with hydroxyurea, but also in some cases with busulfan, 6-mercaptopurine, and thioguanine. Other therapies included androgenic steroids, erythropoiesis-stimulating drugs, prednisone, interferon-α, and thalidomide.

2.2. BM biopsies

A total of 367 BM trephine biopsies of at least 0.8 cm were available. Most specimens were formalin fixed, decalcified in EDTA, and paraffin embedded. The tissues were then stained with hematoxylin and eosin, hematoxylin-Giemsa-fuchsin, Giemsa, periodic acid–Schiff reagent, Prussian blue, and Gomori silver impregnation to identify reticulin/collagen fibers [14].

2.3. Assessment of BM sections and clinical data

Without knowledge of the clinical findings, except for age and sex (for evaluation of age-matched cellularity), 3 hematopathologists experienced in MPNs independently reassessed all trephine sections. An initial diagnosis was made. In discordant cases, a discussion was held on a multiheaded microscope to reach agreement. In addition, available immunohistochemical data and clinical outcome helped to define the correct diagnosis.

To reflect the clinicopathologic characteristics of PEPMF and to avoid the subjectivity of histomorphologic diagnosis, cases of PEPMF analyzed in this study had the following characteristics: (1) a histopathologic diagnosis of PEPMF (MF-0/1) was made strictly according to the revised 2008 WHO criteria [2], with the specimens not meeting the WHO criteria for ET, *BCR-ABL1*–positive chronic myelogenous leukemia, and other myeloid neoplasms, and (2) transformation to overt BM fibrosis (MF-2/3) during follow-up between July 1994 and April 2012. Meanwhile, 91 cases of ET, selected consecutively based on the WHO classification [2], were used for comparison with cases of PEPMF.

2.4. *JAK2* V617F mutation analysis

Genomic DNA was obtained using different extraction kits according to the type of material. The QIAamp DNA minikit (QIAGEN, Hilden, Germany) was used for whole blood or BM aspirate and the QIAamp DNA FFPE Tissue Kit (QIAGEN) for formalin-fixed, paraffin-embedded BM tissue, according to the manufacturer's instructions. The purity and quantity of each DNA sample were determined by Nanodrop spectrophotometry [15]. The presence of the *JAK2* V617F mutation was assessed using a highly sensitive allele-specific real-time quantitative *Taq*Man assay