Human Pathology: Case Reports (2016) 3, 6–11

ELSEVIER

Human PATHOLOGY Case Reports

http://www.humanpathologycasereports.com

Concomitant *BCR-ABL1* positive chronic myelogenous leukemia emerging in a patient with *MPL* W515L associated primary myelofibrosis☆,☆☆

Juan C. Gomez-Gelvez MD, Elena Ivan MD, Bryan L. Betz PhD, Megan S. Lim MD, PhD*

Department of Pathology, University of Michigan Medical School, 1301 Catherine Street, Ann Arbor, MI 48109, USA

Received 23 June 2015; revised 19 September 2015; accepted 24 September 2015

Keywords:
Myeloproliferative neoplasms;
Chronic myelogenous leukemia;
Primary myelofibrosis;
BCR-ABL1;
MPL W515L

Abstract Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by proliferation of one or more cell lineages in the bone marrow. At present, the main criterion in the 2008 World Health Organization classification of MPNs is the presence of an underlying genetic abnormality. These mutations are generally mutually exclusive except for rare reports in the literature. We report for the first time a detailed analysis of the clinical, histologic and cytogenetic/molecular features of a patient who initially presented with *MPL* W515L positive primary myelofibrosis and over the course of five years developed an MPN associated with both *BCR-ABL1* and *MPL* W515L mutation. We discuss the diagnostic challenges and therapeutic implications of concomitant *BCR-ABL1* translocation with *MPL* W515L mutation. Multiple genetic alterations may simultaneously coexist in patients exhibiting features of myeloproliferative disorders.

1. Introduction

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by proliferation of myeloid, erythroid and/or megakaryocytic lineages in the bone marrow. The 2008 World Health Organization (WHO) classification of MPNs is currently based on the presence of an underlying genetic abnormality [1]. MPNs can be classified into *BCR-ABL1* positive MPNs, representing chronic myelogenous leukemia (CML); and *BCR-ABL1* negative MPNs, which include polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). Among the *BCR-ABL1* negative MPNs, the most common gene mutation is *JAK2* V617F seen in 95% of PV patients and 50%–60% of ET or PMF [2]. This is followed by the recently described mutations in *CALR* exon 9, which are present in 20%–25% of ETs or PMFs [3,4]. Additionally, *MPL* W515L/K mutations are found in approximately 5-10% of patients with ETs or PMFs [5,6]. Rare cases of coexisting *BCR-ABL*1 and *JAK2* V617F mutation have been reported [7–9]. These cases may present with overlapping clinical or histopathological features that can complicate their diagnosis, classification, therapy and prognosis. Although considered mutually exclusive, herein, we report the first case of a *BCR-ABL1* positive CML emerging in a patient with previous *MPL* W515L associated PMF.

☆ Conflict of interest: The authors declared no conflict of interest.
☆☆ Funding disclosure: The authors received no financial support.

* Corresponding author at: Department of Pathology and Laboratory Medicine, University of Pennsylvania, Room 6.060 Founders, 3400 Spruce Street. Tel.: +1 215 614 0978 (office); fax: +1 215 662 7529.
E-mail address: Megan.Lim@uphs.upenn.edu (M.S. Lim).

http://dx.doi.org/10.1016/j.ehpc.2015.09.004

2. Case report

A 79 year old female patient with past medical history of well differentiated mucinous lung adenocarcinoma (remote, surgically resected) and anemia of chronic disease secondary to stage III chronic renal disease, presented to her primary care physician complaining of fatigue. Physical examination revealed splenomegaly with no other organomegaly. There was no evidence of lymphadenopathy. The initial work-up revealed moderate normocytic normochromic anemia and mildly increased platelets (PLTs). A complete blood count showed; white blood cells (WBCs): 6.1 k/μL, hemoglobin (HGB): 9.5 g/dL, MCV: 96.8 fL, PLTs: 504 k/μL; with 76% neutrophils, 11.5% lymphocytes, 8.0% monocytes, 0.5% eosinophils, 2.0% metamyelocytes and 2.0% myelocytes. Examination of the peripheral smear demonstrated left shifted granulocytic maturation and frequent dacrocytes. The platelets displayed unremarkable morphology. A bone marrow biopsy revealed a hypercellular marrow (60% cellularity) with preserved myeloid to erythroid ratio (M:E ratio 2:1). The megakaryocytes were markedly increased displaying obvious clustering and significant atypical features including large size with hyperlobated and hyperchromatic nuclei. There was increased reticulin fibrosis with focal bundles (fibrosis grade 2/3) as well as collagen fibrosis (Fig. 1A–C). The myeloid and erythroid lineages were adequate in number with no evidence of dysplasia. There was no increase in blasts. Flow cytometric and cytogenetic studies were unremarkable. Molecular studies for *JAK2* mutations (including both V617F and exon 12) were negative. No other ancillary tests were performed at the time. These findings were highly suggestive of an MPN, and likely representing PMF.

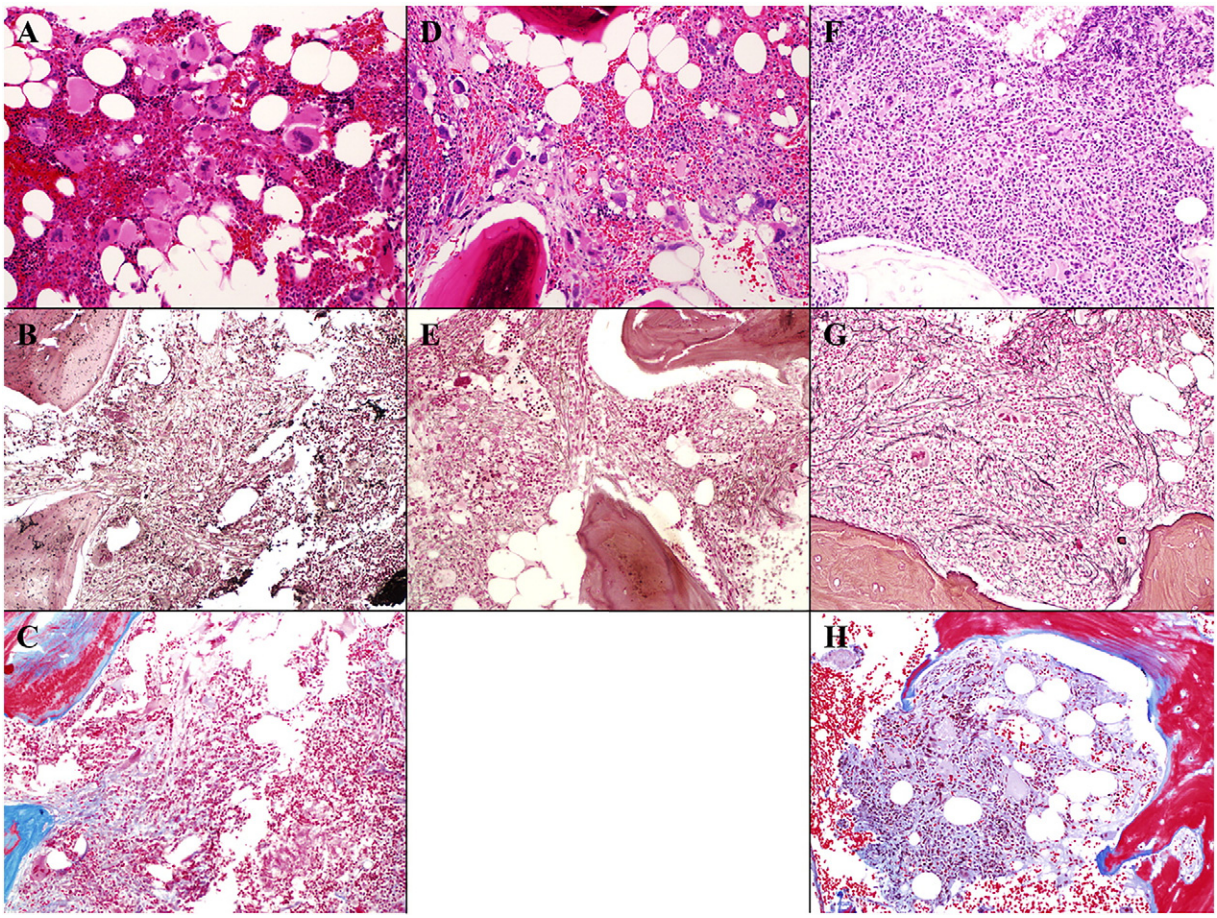

Fig. 1 Histological findings of bone marrow biopsies. (A) The first bone marrow core biopsy illustrates a hypercellular marrow with clusters of markedly atypical megakaryocytes showing large size, hyperlobated and hyperchromatic nuclei (H&E, 200×). (B) Reticulin stain shows bundle formation (grade 2/3) (200×). (C) Trichrome stain demonstrates mild collagen fibrosis (200×). (D) The second bone marrow core biopsy illustrates a persistently hypercellular bone marrow with increased and markedly atypical megakaryocytes showing similar morphologic features as in the previous biopsy (H&E, 200×). (E) Reticulin stain demonstrates increased fibrosis and osteosclerosis of bone trabeculae (fibrosis grade 3/3) (200×). (F) The third bone marrow core biopsy illustrates a hypercellular bone marrow with persistent clusters of atypical megakaryocytes, showing similar morphologic features as in the previous biopsies, and prominent myeloid hyperplasia (H&E, 200×). (G) Reticulin stain demonstrates progression of fibrosis and osteosclerosis (fibrosis grade 3/3) (200×). (H) Trichrome stain demonstrates marked collagen fibrosis (200×).