Bone marrow fibrosis reversal after use of hydroxyurea in a patient with myelofibrosis

Mohamad A. Cherry, MD,[1] Samer A. Srour, MB ChB,[1] William Kern, MD,[2] and Aref Al-Kali, MD[3]

[1]Department of Medicine, Hematology/Oncology Section, [2]Department of Pathology, The University of Oklahoma Health Sciences Center, Oklahoma City; [3]Division of Hematology, Mayo Clinic, Rochester, Minnesota

Myeloproliferative neoplasms represent a variety of neoplasms that are characterized by proliferation of one or more hematopoietic lineages, which leads to myeloid cell expansion in the peripheral blood. There has been considerable progress in the last decade in understanding the molecular pathogenesis of these entities. *JAK2* and *MPL* mutations are now incorporated in the classification of MPNs and may play a role in prognosis, especially in regard to venous thromboembolism, overall survival, and leukemic transformation. Several new drugs, especially those that target *JAK1/2* enzymes, show promising results in the management of MPN.[1,2] Hydroxyurea still plays a cornerstone role in the management of MPN because of its good control of peripheral blood count and its relatively safe profile. It has been studied in the prevention of cardiovascular complications in patients with polycythemia vera (PV) and essential thrombocythemia (ET), but there is scant literature on its effect on the bone marrow environment. We report an interesting case in which hydroxyurea was able to reverse bone marrow fibrosis (BMF).

Case presentation

A 50-year-old white man was seen at the University of Oklahoma Health Sciences Center in September 2002 for thrombocytosis. His past medical history was significant for hypertension and post-trauma splenectomy in 2000. His white blood cell count (WBC) was 10×10^9/L; hemoglobin level, 15.5 g/dL; and platelet count, $1{,}542 \times 10^9$/L. A bone marrow biopsy in 2002 showed hypercellular marrow with increased megakaryocytes and marked fibrosis (Figure 1A, B). The overall impression was of myeloproliferative disorder, most consistent with cellular phase of primary myelofibrosis (PMF). The patient was started on anagrelide 500 mg twice daily and the dose was increased gradually until the platelet count stabilized at 1 g orally 3 times daily. His platelet count dropped gradually until it was less than 400×10^9/L within 4 months. He stayed under good control with anagrelide until March 2008 when he presented with left-sided hemiparesis and light-headedness. A computed tomography scan of his head showed an acute right middle cerebral artery infarct for which he was given activated tissue plasminogen. A complete work-up showed that this patient had a patent foramen ovale and chronic anticoagulation with coumadin was initiated. At his second presentation, his WBC was 10.6×10^9/L; hemoglobin level, 12.2 g/dL; and platelet count, 749×10^9/L. He was referred to the hematology clinic for further recommendations.

Further blood work-up showed that his LDH was 1.5 times higher than normal and that his B_{12}/folate levels were normal. An ultrasound of his abdomen confirmed the history of splenectomy. A polymerase chain reaction assay for *BCR-ABL* RNA transcripts performed on the peripheral blood came back negative. A *JAK2 V617F* mutation analysis revealed a wild-type *JAK2* genotype. Hydroxyurea was restarted at 500 mg

Manuscript received June 19, 2012; accepted November 1, 2012.
Correspondence Mohamad A. Cherry, MD, Department of Medicine, Department of Medicine, Hematology/Oncology Section, The University of Oklahoma Health Sciences Center, 800 NE 10th Street, Oklahoma City, OK 73012 (mohamad-cherry@ouhsc.edu).
Disclosures None of the authors has any disclosures to make.

Commun Oncol 2013;10:58-61

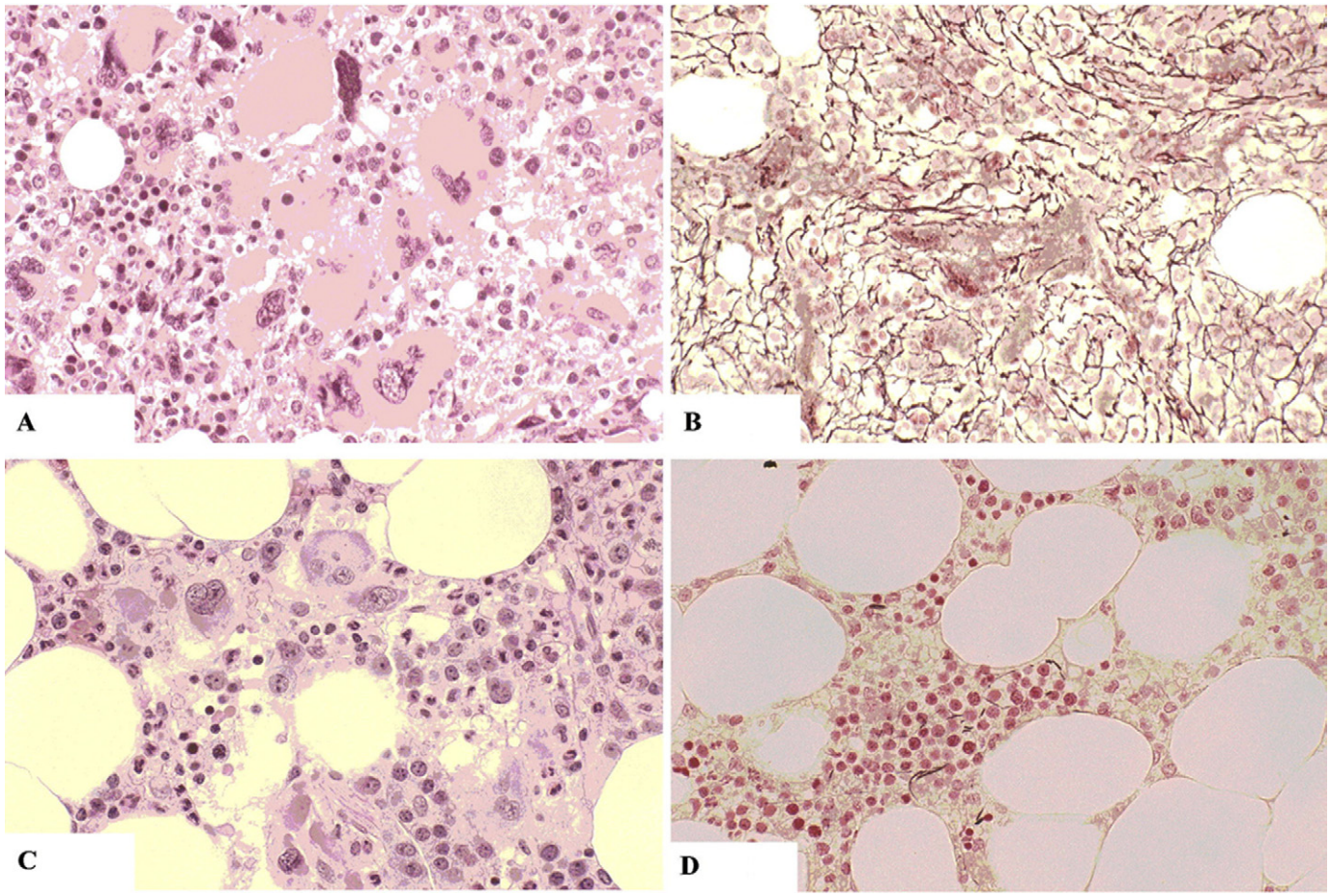

FIGURE 1 Bone marrow biopsy prior to hydroxyurea: Markedly hypercellular bone marrow with increased, clustered and dysplastic megakaryocytes (A; H&E stain, original magnification ~400x) and reticulin stain showing marked increase in number and density of reticulin fibers (B; original magnification ~400x). Bone marrow biopsy after treatment with hydroxyurea: Normocellular marrow with trilineage hematopoiesis; decreased megakaryocyte number and clustering (C; H&E stain, original magnification ~400x) and reticulin stain showing marked decrease in number, thickness and density of reticulin fibers compared with the first bone marrow biopsy (D; original magnification ~400x).

orally daily and was increased to 1,500 mg orally twice daily. His complete blood count showed a gradual drop in his counts, including those for hemoglobin and white blood cells. In August 2008, the patient was seen again because he had developed pancytopenia. His WBC was 2.4×10^9/L; hemoglobin level, 7.6 g/dL; and platelet count, 101×10^9/L. Hydroxyurea was then stopped and a bone marrow biopsy was repeated because of concerns of transformation into acute leukemia (Figure 1C, D). The biopsy showed normocellular marrow with trilineage hematopoiesis and a remarkable decrease in fibrosis. Within 2 months of stopping the hydroxyurea, the patient's counts went back to his baseline except for high platelet count. His WBC was 6.3×10^9/L; hemoglobin level, 11.4 g/dL; and platelet count, $1{,}091 \times 10^9$/L. The patient decided to transfer care to another State and lost further follow ups.

Discussion

Myeloproliferative neoplasms encompass a range of neoplasms. The 2008 World Health Organization classification changed the terminology from myeloproliferative disorders to myeloproliferative neoplasms.[3] MPNs currently include chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis (PMF), chronic eosinophilic leukemia, hypereosinophilic syndrome, chronic neutrophilic leukemia, mast cell disease, and MPN unclassified. Chronic myelogenous leukemia is a prototype for an entity that is driven by a specific translocation t(9;22)(q34;q11) and has excellent targeted therapy represented by the tyrosine kinase inhibitors imatinib, nilotinib, and dasatinib.

PV, ET, and PMF share in common the finding of *JAK2 V617F* mutation, which is present in 50% of ET

and PMF patients and in 95%-97% of PV patients.[4-7] The *MPL W515k/L* mutation has been reported in ET and PMF, but not in PV and it is less prevalent than the *JAK2 V617F* mutation.[8] Drugs such as hydroxyurea, anagrelide, and aspirin are commonly used in these neoplasms. Interferon is another medicine that is used but it is poorly tolerated in patients with PV.[9,10]

Hydroxyurea is a ribonucleotide reductase inhibitor that works through many mechanisms.[11] It interferes with the synthesis of DNA during the S-phase of cell division and prevents the conversion of ribonucleotides to deoxynucleotides. The adverse side effects of hydroxyurea include cytopenias, chronic mucocutaneous ulcers, fluid retention, congestive heart failure, and questionable mutagenicity. It has been studied in MPN in several large studies in preventing cardiovascular complications. In a study reported by Finazzi and colleagues in which ET patients were randomized to receive hydroxyurea or placebo, the overall survival was similar between the 2 groups, but there was a significant decrease in the rate of thrombosis in the hydroxyurea group compared with the placebo group (9% vs 45%, respectively; $P < .0001$).[12] In a UK-based trial in which patients with ET were randomized to receive low-dose aspirin plus hydroxyurea or anagrelide, the rates of arterial thrombosis, serious hemorrhage, and transformation to myelofibrosis were lower among patients who received hydroxyurea plus aspirin.[13]

Many previous studies have linked anagrelide with progression of bone marrow fibrosis in patients with MPNs.[14-16] A phase 2 study compared the bone marrow fibrosis of 53 patients with MPNs (36 ET, 16 PV, and 1 PMF) before and after 2 years of treatment with anagrelide. The reticulin scores and bone marrow cellularity were significantly higher after treatment ($P = .02$ and $P = .014$, respectively). The investigators concluded that treatment with anagrelide indicated progression of fibrosis.[14] Another study that evaluated the effects of bone marrow fibrosis in patients with ET showed significantly greater increases in reticulin grade in patients assigned to anagrelide compared with those allocated to hydroxyurea ($P = .0003$), and 4 patients who developed increased bone marrow reticulin on anagrelide showed regression of fibrosis when switched to hydroxyurea.[15] Additionally, a small prospective study of 20 patients treated with anagrelide for a median of 2 years showed that megakaryocytic staining intensity for transforming growth factor beta and platelet-derived growth factor was not affected by treatment.[16] For these reasons, we think that the reversal of BMF is not likely related to the previous anagrelide therapy in our case.

Aside the small study[15] that showed regression of fibrosis when some patients were switched from anagrelide to hydroxyurea, very little information exists regarding hydroxyurea's effect on BMF. Löfvenberg et al reported a similar observation 20 years ago.[17] In a recent paper by Martinez-Trillos et al, 40 patients with myelofibrosis who were treated with hydroxyurea yielded response rates of 100% in bone pain, 82% in constitutional symptoms, 40% in splenomegaly, and 71% in thrombocytosis. No information was provided regarding the fibrosis response.[18]

Several papers have been published on using newer therapies in patients with PMF. There was a decrease in fibrosis rate in patients who received lenalidomide but not in patients who received azacitidine or etanercept.[19-21] Interestingly, Sirhan et al reported that the presence of *JAK2 V617F* mutation in patients with PMF predicts chemosensitivity to hydroxyurea but no information was provided regarding its effect on BMF.[22]

In our case, the bone marrow fibrotic changes were reversed by a short course of treatment with hydroxyurea. Previous reports revealed that hydroxyurea has a direct favorable effect against *JAK2 V617F* allele burden in ET and PV,[23] and the presence of this mutation might as well predict chemosensitivity to hydroxyurea.[22] Despite the absence of *JAK2 V617F* mutation, our patient had a dramatic response to hydroxyurea as we have described. Though many emerging novel therapies are being investigated recently, our report highlights the need for better understanding of hydroxyurea effects as it may lead to complete bone marrow fibrosis reversal in a subset of MPN patients. Our case highlights as well the importance of incorporating bone marrow evaluation for fibrosis assessment in all MPN therapy protocols.

References

1. Santos FP, Kantarjian HM, Jain N, et al. Phase 2 study of CEP-701, an orally available JAK2 inhibitor, in patients with primary or post-polycythemia vera/essential thrombocythemia myelofibrosis. *Blood*. 2010;115:1131-1136.
2. Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med*. 2010;363:1117-1127.
3. Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. *Leukemia*. 2008;22:14-22.
4. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet*. 2005;365:1054-1061.
5. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature*. 2005;434:1144-1148.
6. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell*. 2005;7:387-397.
7. Zhao R, Xing S, Li Z, et al. Identification of an acquired JAK2 mutation in polycythemia vera. *J Biol Chem*. 2005;280:22788-22792.
8. Pikman Y, Lee BH, Mercher T, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. *PLoS Med*. 2006;3:e270.

9. Silver RT. Long-term effects of the treatment of polycythemia vera with recombinant interferon-alpha. *Cancer*. 2006;107:451-458.
10. Quintas-Cardama A, Kantarjian H, Manshouri T, et al. Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol*. 2009;27:5418-5424.
11. Yarbro JW. Mechanism of action of hydroxyurea. *Semin Oncol*. 1992;19:1-10.
12. Finazzi G, Ruggeri M, Rodeghiero F, Barbui T. Second malignancies in patients with essential thrombocythaemia treated with busulphan and hydroxyurea: long-term follow-up of a randomized clinical trial. *Br J Haematol*. 2000;110:577-583.
13. Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med*. 2005;353:33-45.
14. Hultdin M, Sundstrom G, Wahlin A, et al. Progression of bone marrow fibrosis in patients with essential thrombocythemia and polycythemia vera during anagrelide treatment. *Med Oncol*. 2007; 24:63-70.
15. Campbell PJ, Bareford D, Erber WN, et al. Reticulin accumulation in essential thrombocythemia: prognostic significance and relationship to therapy. *J Clin Oncol*. 2009;27:2991-2999.
16. Yoon SY, Li CY, Mesa RA, Tefferi A. Bone marrow effects of anagrelide therapy in patients with myelofibrosis with myeloid metaplasia. *Br J Haematol*. 1999;106:682-688.
17. Lofvenberg E, Wahlin A, Roos G, Ost A. Reversal of myelofibrosis by hydroxyurea. *Eur J Haematol*. 1990;44:33-38.
18. Martinez-Trillos A, Gaya A, Maffioli M, et al. Efficacy and tolerability of hydroxyurea in the treatment of the hyperproliferative manifestations of myelofibrosis: results in 40 patients. *Ann Hematol*. 2010;89:1233–1237.
19. Quintas-Cardama A, Tong W, Kantarjian H, et al. A phase II study of 5-azacitidine for patients with primary and post-essential thrombocythemia/polycythemia vera myelofibrosis. *Leukemia*. 2008;22:965-970.
20. Steensma DP, Mesa RA, Li CY, Gray L, Tefferi A. Etanercept, a soluble tumor necrosis factor receptor, palliates constitutional symptoms in patients with myelofibrosis with myeloid metaplasia: results of a pilot study. *Blood*. 2002;99:2252-2254.
21. Tefferi A, Cortes J, Verstovsek S, et al. Lenalidomide therapy in myelofibrosis with myeloid metaplasia. *Blood*. 2006;108:1158-1164.
22. Sirhan S, Lasho TL, Hanson CA, Mesa RA, Pardanani A, Tefferi A. The presence of JAK2V617F in primary myelofibrosis or its allele burden in polycythemia vera predicts chemosensitivity to hydroxyurea. *Am J Hematol*. 2008;83:363-365.
23. Girodon F, Schaeffer C, Cleyrat C, et al. Frequent reduction or absence of detection of the JAK2-mutated clone in JAK2V617F-positive patients within the first years of hydroxyurea therapy. *Haematologica*. 2008;93:1723-1727.