Metastatic Splenic Angiosarcoma Presenting With Thrombocytopenia and Bone Marrow Fibrosis Mimicking Idiopathic Thrombocytopenic Purpura and Primary Myelofibrosis: A Diagnostic Challenge

Shimin Hu,[1] Carlos E. Bueso-Ramos,[1] Srdan Verstovsek,[2] Roberto N. Miranda,[1] C. Cameron Yin,[1] Timothy McDonnell,[1] L. Jeffrey Medeiros,[1] Pei Lin[1]

Clinical Practice Points

- The diagnosis of bone marrow metastasis of rare types of cancer can be very challenging in the absence of knowledge of the primary neoplasm. Consequently, the bone marrow changes associated with metastasis, such as fibrosis and cytopenia, can be easily attributed to a primary hematopoietic process.
- We report a case of an 83-year-old patient initially presenting with symptoms related to cytopenia. Multiple diagnoses, including refractory idiopathic thrombocytopenic purpura and primary myelofibrosis, were rendered, and a variety of treatment protocols were tried at 3 different institutions before a final diagnosis of metastatic angiosarcoma of spleen was established 4 years after the patient's initial presentation.
- To the best of our knowledge, this is the first report that a bone marrow workup can lead to a diagnosis of primary splenic angiosarcoma.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. 5, 629-33
Keywords: ITP, metastasis, myelofibrosis, splenic angiosarcoma

Introduction

Bone marrow fibrosis and consequent cytopenia are commonly associated with the advanced stage of myeloproliferative neoplasms and metastatic tumors.[1]

Splenic angiosarcoma is an extremely rare but very aggressive neoplasm with an early wide spread.[2] Here we report a case of bone marrow workup for fibrosis and cytopenia leading to establishing the previously misdiagnosed metastatic splenic angiosarcoma.

Case Presentation

An 83-year-old man with a history of prostate cancer treated with local radiation therapy 1 year earlier presented with progressive fatigue and thrombocytopenia in 2008. The initial diagnosis was idiopathic thrombocytopenic purpura (ITP), rendered at an outside institution, and the patient was treated with steroids and rituximab. Because of a lack of response to the therapy, bone marrow aspiration and biopsy were performed in November of 2009; the aspirate was a dry tap but the biopsy showed hypercellular bone marrow with increased megakaryocytes thought to be consistent with ITP. Three months later, eltrombopag an oral thrombopoietin receptor agonist, was initiated and the platelet count improved briefly, from 10 to 20 to 75 $\times$ 10^9/L, before decreasing progressively. A second bone marrow aspiration and biopsy was performed in November of 2011; again the aspirate was a dry tap and the biopsy specimen showed fibrotic changes, which was thought to be attributed to eltrombopag. The patient underwent splenectomy (920 grams) 1 month later. A diagnosis of extramedullary hematopoiesis and focal reactive angiomatous proliferation was rendered on the specimen of spleen. The patient was then treated with cyclophosphamide for presumed refractory ITP.

However, the patient continued to require red blood cell and platelet transfusions. A third bone marrow aspiration and biopsy were performed in a second hospital in January of 2012. Again, the aspirate was a dry tap whereas the biopsy specimen was interpreted

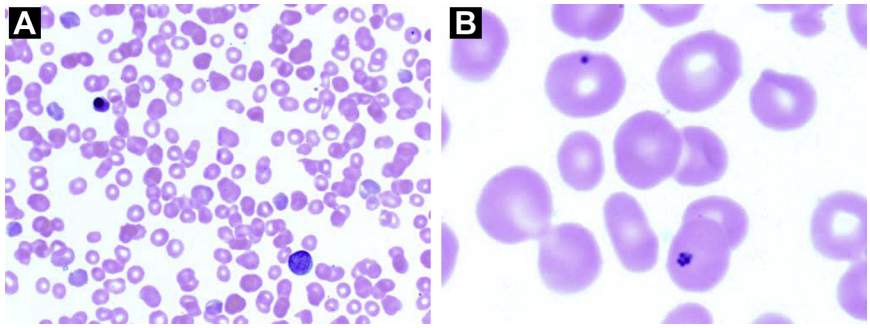
[1]Department of Hematopathology
[2]Department of Leukemia
The University of Texas M.D. Anderson Cancer Center, Houston, TX

Submitted: Nov 17, 2012; Accepted: Dec 28, 2012; Epub: Jun 22, 2013

Address for correspondence: Pei Lin, MD, The University of Texas M.D. Anderson Cancer Center, Box 72, 1515 Holcombe Blvd, Houston, TX 77030
Fax: 713-7494-1800; e-mail contact: peilin@mdanderson.org

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2012.12.013

Figure 1 (A) Peripheral Blood Smear Shows Occasional Nucleated RBCs, Blasts, and Polychromasia. (B) Peripheral Blood Smear Shows Howell-Jolly Body and Pappenheimer Body. Original Magnification, (A) ×500, and (B) ×1000



as having grade 3 myelofibrosis. At this time, the patient was given darbepoietin alfa therapy and was referred to MD Anderson Cancer Center (MDACC) for treatment options with presumed myelofibrosis. The transfusion was stopped 2 weeks before the admission as a result of alloantibodies evolving from platelet transfusions. The patient now developed petechiae throughout his body with worsening hematuria.

Pathologic Findings

A complete blood count at time of admission showed pancytopenia: white blood cell count, 2.4 × 10^9/L; hemoglobin, 8.4 g/dL; and platelet count, 4 × 10^9/L. Examination of a peripheral blood smear revealed macrocytic (MCV = 104 femtoliter) erythrocytes with moderate anisopoikilocytosis, polychromasia, occasional schistocytes, basophilic stippling, and frequent nucleated forms (Figure 1A). Howell-Jolly and Pappenheimer bodies were also observed, consistent with the patient's history of splenectomy (Figure 1B). The leukocytes were left-shifted with occasional blasts (Figure 1A) and platelets were markedly decreased with occasional giant forms. The peripheral blood picture suggested a bone marrow process such as myelofibrosis, myelophthisis or a microangiopathic process.

Serum chemistry studies revealed elevated erythropoietin at 737 mIU/mL (normal range, 5.2-25.3 mIU/mL), iron 239 ug/dL (normal range, 49-181 ug/dL), and ferritin 950 ng/mL (normal range, 30-400 ng/mL). Total bilirubin was 1.9 mg/dL (normal range, 0-1.0 mg/dL) and the serum lactate dehydrogenase level was 1149 IU/L (normal range, 313-618 IU/L). Vitamin B12, folate, thyroid stimulating hormone, and free T4 were within normal ranges, excluding their role in the patient's macrocytic anemia.

Bone marrow aspirate and biopsy was performed at MDACC. The aspirate smears showed occasional clusters of plump spindly atypical cells forming a papillary configuration (Figure 2A). These atypical cells had large round/oval nuclei, moderately condensed chromatin, occasional small nucleoli, and scant basophilic "tailed" cytoplasm. Hematopoietic cells were scant in the smear. The bone marrow biopsy specimen showed an overall hypocellular (< 10%) bone marrow with scattered islands of hematopoiesis (mainly erythropoiesis) embedded in a background of prominent fibrosis and a single focus (2 mm) of atypical vascular proliferation (Figure 2B and C). The vascular lining cells were large and plump. Some interstitial large oval/plump spindle cells were also seen. Fibrosis was marked, highlighted by reticulin and trichrome stains (Figure 2F and G, respectively). Sinusoids in the bone marrow were dilated (Figure 2E). Blasts were not increased. The morphology of megakaryocytes was unremarkable.

Immunohistochemical studies performed on the bone marrow biopsy specimen showed that the neoplastic cells were positive for CD31 and CD34, and negative for keratin and prostate cancer-associated markers, supporting endothelial origin (Figure 2D and E, respectively). Conventional cytogenetic analysis performed on bone marrow and peripheral blood specimens showed a normal karyotype. Mutational analysis of Janus kinase 2 and myeloproliferative leukemia virus oncogene and quantitative reverse transcription polymerase chain reaction for breakpoint cluster region—v-abl Abelson murine leukemia viral oncogene homolog 1 fusion transcripts were negative.

At this time, slides of the splenectomy specimen and earlier bone marrow specimens were requested from the referring institutions and reviewed. The splenic parenchyma was almost completely replaced by a vascular neoplasm with various morphologic patterns in a background of extramedullary hematopoiesis and hemorrhage (Figure 3). In some areas, the tumor cells formed interanastomosing vasoformative slit-like spaces (Figure 3A) whereas, in other areas, the tumor cells formed papillary fronds protruding into blood-filling cystic spaces (Figure 3B). A minor solid component resembling fibrosarcoma was also seen (Figure 3C). There were multiple foci of tumor necrosis and multiple vascular thrombi. The tumor infiltrates extended to perisplenic fibroadipose tissue. Immunohistochemical analysis showed that the tumor cells were positive for CD31 (Figure 3D), focal CD34 (Figure 3E), focal factor VIII (Figure 3F), and CD68 (Figure 3G), and negative for human herpes virus 8 and lysozyme (data not shown). A final diagnosis of splenic angiosarcoma was rendered.

Review of previous bone marrow biopsy specimens identified minute foci suggestive but not diagnostic of the involvement of metastatic angiosarcoma in all 3 specimens (Figure 3H). Focal erosions of bony trabeculae by the tumor cells were also seen in the