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Hepatosplenomegaly and Bone Marrow Fibrosis in Primary Myelofibrosis: A Case Report

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Abstract

Primary myelofibrosis is a spontaneous neoplastic disorder of the bone marrow that results in fibrosis and disruption of myeloid cell lines. Progression of this disease results in marrow fibrosis and production compensation in other organs. In this case report, a 69-year-old woman with JAK2+ myelofibrosis presents with left sided abdominal pain and gastrointestinal complications likely due to her disease. We review images demonstrating hepatosplenomegaly and osteosclerosis, both common findings in patients with myelofibrosis. We also noted that although a rare finding, extramedullary hematopoiesis may occur in the bowel and can present with symptoms of gastrointestinal complications. Further examination would be required to confirm the suspicion in this patient.

Introduction

Primary myelofibrosis is one of the chronic myeloproliferative disorders characterized by abnormal proliferation of hematopoietic stem cells within the bone marrow that results in progressive fibrotic replacement of the bone marrow [1]. Bone marrow fibrosis eventually leads to extramedullary hematopoiesis which can affect bones and internal organs like the spleen and liver [1,2]. The most common presenting symptom in patients with myelofibrosis is severe fatigue, followed by abdominal pain, weight loss, and constitutional symptoms [3]. Lab abnormalities can include anemia of less than 10 g/dL seen in about half of patients with myelofibrosis [2]. White blood cell and platelet count are variable in these patients, with marked thrombocytopenia occurring later in the disease [4]. Most patients with primary myelofibrosis contain a JAK2 mutation, a cytoplasmic tyrosine kinase associated with several cytokines involved in the growth and proliferation of hematopoietic and immune cells [4]. The predominant radiographic feature of myelofibrosis is osteosclerosis [5]. Bone marrow imaging with magnetic resonance can demonstrate a change in signal consistent with the conversion of fatty marrow to fibrotic marrow.

Case

A 69-year-old Caucasian female presents to the clinic as a referral for follow up of diarrhea associated with myelofibrosis. Several years prior to this encounter, the patient reported some fatigue, night sweats, pruritus, weight loss, chronic constipation and diarrhea, headaches, and left upper quadrant pain that occurred about once a week. Examination showed elevated liver function tests and she underwent a liver biopsy which excluded cirrhosis and hepatitis. Patient history at the time included mild thrombocytopenia with episodes of ecchymoses, hyperlipidemia, and Vitamin D deficiency.

The patient was subsequently referred to a hematologist/oncologist who performed a bone marrow biopsy of the left ilium which was consistent with JAK2+ pre-fibrotic myelofibrosis. Complete blood count showed thrombocytopenia, reticulocytosis with decreased red blood count and high red cell distribution width (RDW), neutrophilia, and elevated lactate dehydrogenase. Patient was observed at this time.

Three years after a myelofibrosis diagnosis, computed tomography (CT) showed extensive diffuse patchy sclerosis throughout the entire bony pelvis and proximal femurs (**Figure 1**). Findings were consistent with diffuse pathologic marrow infiltration or depletion seen with myelofibrosis. An incidental 4 cm isolated sclerotic chondroid bone lesion within the left intertrochanteric region demonstrated well defined borders, no aggressive features and stability over time, consistent with a benign cartilaginous lesion.

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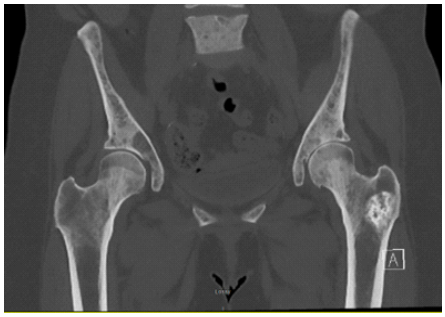

Figure 1: *Noncontrast CT of the pelvis, coronal view: diffuse osteosclerosis consistent with myelofibrosis. There is an isolated chondroid bone lesion in the left intertrochanteric region. Mild joint space narrowing, and osteophytosis of the left hip.*

Magnetic resonance imaging (MRI) of the hip was performed. Imaging showed diffusely heterogenous bone marrow signal with decreased T1 and T2 signal intensity consistent with reported history of myelofibrosis (**Figure 2**). Radiographs taken for templating purposes showed patchy hyperdensity of the osseous structures throughout the pelvis and femora consistent with myelofibrosis (**Figure 3**).

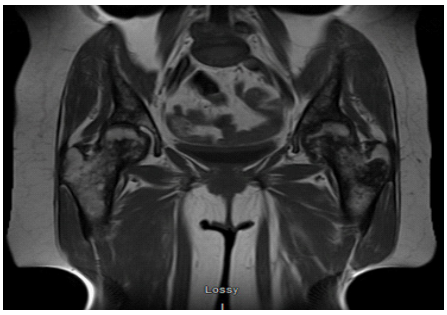

Figure 2: *T1 weighted MRI coronal view of the pelvis showing heterogenous decreased bone marrow signal in the proximal femora and pelvis.*

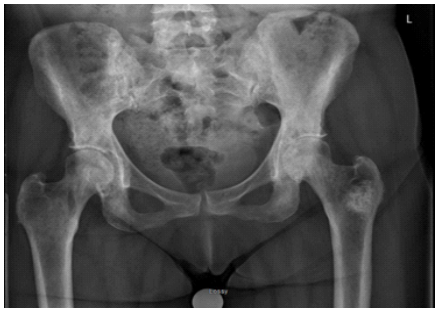

Figure 3: *Plain radiograph of the pelvis demonstrating diffusely sclerotic bone marrow throughout the pelvis and femurs.*

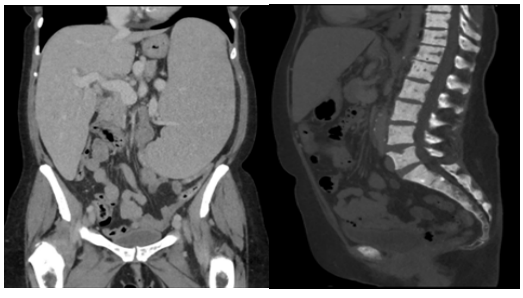

Figure 4: *CT of the abdomen with contrast, coronal (a) and sagittal (b) views, reveals massive hepatosplenomegaly (a) and diffuse osteosclerosis of the vertebral bodies (b).*

The patient would later come to the clinic with current findings of left-sided abdominal pain, worsening bowel issues, early satiety, and weight loss. Labs demonstrated thrombocytopenia (55 K/µL), macrocytic anemia [Hemoglobin: 11.1 g/dL, mean corpuscular volume (MCV): 101.2 fL], decreased erythrocyte count (3.38 cells/µL) with increased RDW (18.6%), increased LDH (848 U/L), and hyperuricemia (7.9 mg/dL). White blood count differential showed neutrophilia (7.44 K/µL) with an increase in metamyelocytes and myelocytes. LFTs and coagulation studies were within normal range. Gastrointestinal issues were worked up with fecal calprotectin which was elevated. Fecal elastase was normal. A CT of her abdomen and pelvis showed massive splenomegaly with hepatomegaly and diffuse osseous sclerosis (**Figure 4a** and **4b**).

Discussion

Patients with primary myelofibrosis often present with nonspecific systemic symptoms, splenomegaly, hepatomegaly, anemia, and either high or low platelet and white blood cell count. However, it is important to note that some patients are asymptomatic in which myelofibrosis is discovered incidentally. In our case, a 69-year-old woman presented to the clinic after worsening diarrhea and was found to have marked hepatosplenomegaly and thrombocytopenia associated with her preexisting myelofibrosis. Primary myelofibrosis is a neoplastic disease of the older population primarily affecting patients over the age of 50, the median age being 64 years old [2]. Current criteria for primary myelofibrosis, as determined by the World Health Organization, includes fibrosis of bone marrow, demonstration of JAK2 mutation, increased serum LDH, palpable splenomegaly, anemia, and leukoerythroblastosis; all of which were observed in our patient (**Table 1**) [6].

Table 1: *World Health Organization (WHO) diagnostic criteria for primary myelofibrosis. Notes: The diagnosis requires all three major criteria and two minor criteria to be met.*

Major Criteria	1. Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis, or in the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis (ie, prefibrotic PMF)
	2. Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
	3. Demonstration of JAK2V617F or other clonal marker or no evidence of reactive bone marrow fibrosis
Minor Criteria	1. Leukoerythroblastosis
	2. Increased serum LDH
	3. Palpable splenomegaly
	4. Anemia

Genetic mutations are seen in about 90% of patients with myelofibrosis, the most common being the JAK2 mutation which occurs in up to 65% of cases [2]. In short, a mutation that substitutes valine to phenylalanine in the JAK2 gene results in a constitutive activation of the tyrosine kinase function leading

to overactivation of downstream signaling pathways [6]. The overproduction of cells ultimately leads to fibrosis of the bone marrow. This fibrosis impedes proper hematopoietic and immune cell production as is reflected in these patient's labs.

Although there is no gold standard in diagnosing primary myelofibrosis, bone marrow biopsy is a major criterion required for diagnosis. In this patient, bone marrow biopsy early in the disease showed moderate hypercellularity with slightly increased erythroid precursors and moderately increased pleomorphic megakaryocytes. Reticulin fibers were moderately increased, classified as a grade 2 (of 3) myelofibrosis. Decreased marrow cellularity is expected with disease progression [5].

The most common imaging findings in patients with myelofibrosis are osteosclerosis, hepatosplenomegaly, and lymphadenopathies. Osteosclerosis is the predominant feature seen in radiographs and is most evident in the axial skeletal bones including the ribs, scapulae, vertebrae, pelvis, and the metaphysis of the femur, humerus, and tibia [5]. In the case of our patient, multiple radiographs and CT imaging showed diffuse patchy sclerosis in the spine, pelvis, and femurs consistent with the pattern seen in myelofibrosis. Magnetic resonance imaging (MRI) is very sensitive to changes in signal intensity of bone marrow making it a useful imaging modality to evaluate stage and progression of the disease [5]. High signal intensity, best seen on T1-weighted images, is a result of the fatty marrow indicating healthy bone. When this fatty bone marrow begins to fibrose, the intensity is attenuated and appears heterogenous. Complete fibrosis appears as a homogenous, hypointense area. Therefore, the degree of the intensity correlates with the progression of fibrosis. In this case, MRI showed diffuse heterogenous bone marrow signal indicating the gradual replacement of the marrow with fibrotic tissue.

When bone marrow cannot keep up with the demands of cellular production, extramedullary hematopoiesis occurs for compensation. The spleen is one of the extramedullary sites where cell production takes place and results in splenomegaly, the most common finding at physical examination and observed in approximately 94% of patients. Infarction of the spleen is not uncommon. The liver is a prominent location of extramedullary hematopoiesis as well with hepatomegaly affecting nearly 70% of myelofibrosis cases. Moreover, portal hypertension may develop. In such cases, CT imaging is indicated for evaluation [5]. In our patient, a key symptom was gastrointestinal issues. Although rare, infiltration of the small or large intestines by hematopoietic tissue may contribute to these complaints. In an earlier case, a 78-year-old woman with myelofibrosis presented with an acute small bowel obstruction due to thickened bowel from hematopoietic infiltration [7]. CT imaging and possible colonoscopy and biopsy may be indicated in these patients to establish the presence and extent of such tissue in the bowel [5]. Further work-up in this patient would be necessary to confirm this possible disease progression.

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