Nontuberculous mycobacterial infection in a patient with myelofibrosis: case report and concise review

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Key Clinical Message
A 70-year-old patient having massive refractory ascites in the course of idiopathic myelofibrosis was diagnosed of peritoneal extramedullary hematopoiesis and developed an overwhelming nontuberculous mycobacterial infection. The case describes this unusual infection and highlights the need for additional studies to confirm the etiology of ascites in primary myelofibrosis.

Keywords
Extramedullary, hematopoiesis, mycobacteria, myelofibrosis, peritoneal.

Introduction
Primary myelofibrosis (PM) is a myeloproliferative disorder characterized by unexplained fibrosis in the bone marrow and osteosclerosis, extramedullary hematopoiesis with marked splenomegaly, and a leukoerythroblastic anemia. Other manifestations include abdominal fullness associated with the mass effect of splenomegaly, esophageal varices, and ascites caused by portal hypertension in 2–10% of patients [1, 2]. More rarely, ascites may result due to peritoneal extramedullary hematopoiesis [3, 4]. We describe an unusual case of myelofibrosis in a splenectomized patient presenting with massive ascites, and peritoneal extramedullary hematopoiesis; that developed nontuberculous mycobacterium infection.

Case Report
An 70-year-old Moroccan man was admitted to our hospital with fever, abdominal fullness, and general fatigue. He gave a previous history of splenectomy, diabetes, and hypertension. He had otherwise been well until 2–3 months before entry, when he began to note fever, poor appetite, and progressive painful abdominal fullness. He was treated in his country for suspected myelofibrosis with hydroxyurea. Because his symptoms responded poorly to therapy he decided to ask for a second opinion. On physical examination, he appeared pale and cachectic. A distended abdomen with an obvious fluid wave was noted. Pretibial ulcer was present. No leg edema, icterus, or lymphadenopathy was noted.

Initial laboratory data were as follows: white-cell count 3.6 × 10³/µL; hemoglobin 10.1 g/dL, platelet count 108 × 10³/µL. Lactate dehydrogenase was 1092 U/L. The results of all liver function test, including bilirubin, serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase, and ammonium were within normal limits. Serologic tests for hepatitis B surface antigen, hepatitis C antibody, and HIV ELISA were negative. Tuberculin skin test was negative. JAK-2V617F was negative.

Diagnostic paracentesis yielded yellow-colored ascites that contained 824 cells/mm³, with 70% lymphocytes. The serum protein was 3.5 g/dL, and adenosine-deaminase was 9.6 U/L. Smear and cultures for bacteria, and tuberculosis were all negative.
A computed tomographic (CT) scan of the abdomen showed massive ascites, hepatomegaly, with no evidence of the thrombosis of the portal vein, and nodular thickening and enhancement of the peritoneum (Fig. 1). A right lower lobe consolidation on chest CT scan was observed. Urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila* were negatives. Bronchoscopy with bronchoalveolar lavage was performed. Although the lavage fluid results were unrevealing, smear and cultures for bacteria, nocardia/actinomyces, and fungi were all negative. Mycobacterium culture was positive for *Mycobacterium avium* complex (MAC) in bronchoalveolar lavage and urine.

A biopsy specimen of the peritoneum showed foci of extramedullary hematopoiesis and fibrous tissue. Most of the cells were described as megakaryocytic.

A biopsy specimen of the bone marrow showed decreased hematopoietic cells, fibrosis, and thickening and distortion of the bony trabeculae (osteosclerosis). Flow cytometry of bone marrow aspirate showed 6% of myeloid blasts (CD45\textsuperscript{low}, CD13+, CD133\textsuperscript{low}, CD34+, HLA-DR\textsuperscript{+}, CD5\textsuperscript{low}, CD38+, CD117\textsuperscript{low}, CD71\textsuperscript{low}) compatible with a chronic myeloproliferative neoplasm and transformation to Acute Myeloid Leukemia.

We administered hydroxyurea and corticosteroid to reduce extramedullary hematopoiesis, but he was refractory to the treatment. He received treatment with Azithromycin, Rifampicin, Ethambutol, and decided to go back to his country where he was admitted to a hospital. Finally he died after 10 days of progression of his disease. An autopsy was not performed.

**Discussion**

Extramedullary hematopoiesis refers to the production of blood cells outside the bone marrow and is a compensatory mechanism for bone marrow dysfunction. Because the bone marrow reserve does not necessarily correlate with its metastatic potential, a presentation resembling metastasis of unknown origin in an otherwise asymptomatic patient with PM is possible [5].

Patients with symptomatic massive ascites caused by peritoneal extramedullary hematopoiesis have been reported previously, but are limited in number [5–10].

Symptomatic ascites in PM is rare and is often attributed to portal hypertension accompanied by ectopic hematopoiesis in the liver and spleen, and in some cases thrombosis of the portal vein [11]. In the previously reported cases, ascites occurred after splenectomy, as initial manifestation, or from 2 months to 17 years after the diagnosis of myelofibrosis was established [1, 5, 9].

Peritoneal extramedullary hematopoiesis as the cause of ascites remains uncommon [12–14]. We have not found more than nine case reports in MEDLINE (See Table 1).

**Table 1. Case reports of ascitis related to EMH on peritoneum confirmed by peritoneal biopsy.**

| References | Year | Age (years) | Sites of EMH | Ascites with megakaryocytes |
|------------|------|-------------|--------------|-----------------------------|
| [12]       | 1969 | 45          | Peritoneum   | Yes                         |
| [13]       | 1983 | 60          | Peritoneum   | Yes                         |
| [10]       | 1985 | 45          | Spleen, liver, heart, lungs, peritoneum, and pleura | Yes |
| [1]        | 1991 | 61          | Peritoneum   | Yes                         |
| [14]       | 1991 | 66          | Liver and peritoneum | No  |
| [9]        | 1993 | 44          | Spleen, liver, peritoneum and pleura | Yes |
| [5]        | 1999 | 83          | Peritoneum   | Yes                         |
| [8]        | 1999 | 33          | Peritoneum and pleura | Yes |
| [4]        | 2003 | 55          | Peritoneum   | Yes                         |

EMH, extramedullary hematopoiesis.
A CT scan sometimes shows the mass of extramedullary hematopoiesis [15]. Peritoneal extramedullary hematopoiesis is usually proven by peritoneal biopsy. Peritoneal biopsy is the gold standard method as a diagnostic procedure for the peritoneal hematopoiesis, but additional cytogenetic analysis of the cells in the ascites might be useful. Megakaryocytes are rarely found in peritoneal fluid and it seems to be suggestive of peritoneal extramedullary hematopoiesis [8].

There is no effective treatment for refractory ascites in patients with PM. There is a report about the use of busulfan and hydroxyurea for treating ascites [9]. Corticosteroid has been used for pleural effusion [16]. TIPS may be considered as rescue management for refractory ascites secondary to portal hypertension [17].

Leukemic transformation occurs in approximately 20% of patients during the first 10 years after the onset of the disease, as our case [18].

Nontuberculous mycobacterial infection can cause four clinical syndromes: pulmonary disease, superficial lymphadenitis, skin/soft tissue infection, and disseminated disease in severely immunocompromised patients like our case. Disseminated MAC disease may complicate MAC pulmonary disease through local multiplication and entry into the bloodstream with seeding of other organs and tissues [19]. Isolation in urine culture is rare and should be specifically collected in special media, different from the media used in standard bacterial blood cultures. In a series of 15 patients with genitourinary infections by nontuberculous mycobacteria, only two patients had disseminated infection not related to hematologic malignancy [20]. To the best of our knowledge, this is the first report of MAC associated to PM. Tuberculous peritonitis and extramedullary hematopoiesis has been reported previously [8]. The treatment regimen for M. avium complex pulmonary and disseminated infection includes simultaneous use of three oral antibiotics: a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin), for at least 1 year [22, 23]. Monotherapy is never advised in the treatment of MAC because of the concern for developing resistance. Successful treatment of disseminated MAC relies on recovery of the immune system, in case of HIV patients [24, 25].

**Conclusion**

This case demonstrates that refractory ascites caused by peritoneal implants of myeloid tissues may be a manifestation of myelofibrosis. Extramedullary hematopoiesis should be included in the differential diagnosis of ascites. Nontuberculous mycobacterial disseminated infection should be included in the differential diagnosis of fever in PM patients.

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**Conflict of Interest**

None declared.

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