New Onset Ascites Secondary to Extramedullary Hematopoiesis as an Initial Manifestation of Myelofibrosis: A Case Report

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A 57-year old male presented with new onset ascites, lower extremity edema and splenomegaly. Cytological analysis of the ascitic fluid revealed multinucleated giant cells consistent with megakaryocytes suggestive of extramedullary hematopoiesis. Liver biopsy confirmed the presence of extramedullary hematopoiesis. Bone marrow biopsy revealed myelofibrosis. The patient was treated conservatively for symptom relief. Ascites in myelofibrosis is most often attributed to portal hypertension and is considered a late presentation of the disease. After careful workup, the ascites in this case was attributed to be secondary to peritoneal implants of hematopoietic stem cells and extramedullary hematopoiesis secondary to myelofibrosis. As such extramedullary hematopoiesis should be considered under the differential diagnosis of ascites.

INTRODUCTION

Myelofibrosis also known as agnogenic myeloid metaplasia is a disorder of multipotent hematopoietic stem cell of unknown etiology characterized by bone marrow fibrosis, splenomegaly, extramedullary hematopoiesis, and myeloid metaplasia with a leukoerythroblastic blood smear. Most patients are asymptomatic in the early phases of the disease and are diagnosed after further evaluation for incidentally detected splenomegaly on physical exam. Some patients may present with the hematological manifestations of the disease, or with abdominal symptoms related to the mass effect of an enlarged spleen (1), or with symptoms of a hypercatabolic state such as weight loss, fatigue, night sweats and low grade fever (2).

Others with myelofibrosis may present with ascites and esophageal varices attributed to be secondary to portal hypertension (1). Rarely myelofibrosis may present as ascites secondary to seeding of the peritoneum by myelometaplastic cells.

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CASE REPORT

A 57-year-old male was admitted to the Cleveland Clinic Foundation in March 2001 with new onset ascites. He was in his usual state of health until December 2000 when he started complaining of increased abdominal girth, lower extremity edema, and generalized weakness. He denied any history of fever, night sweats, nausea, vomiting, melena or rectal bleeding. He had no prior history of blood transfusion, alcohol intake, or exposure to tubercular disease. He stopped smoking twenty years ago. He reported no family history of cancer, hematological, or liver diseases.

On physical exam, he had stable vital signs and was afebrile. He had non-icteric sclera. Heart and lung exam were unremarkable. His abdomen was tensely distended with positive fluid shift, with superficial venous collaterals, but no spider angiomata. He had evidence of splenomegaly at 15 cm below left subcostal margin, but he had no palpable liver. Neurological exam was grossly non-focal.

Blood chemistry revealed the following: White blood cell count 10.39 K/uL with 12% metamyelocytes, 3% blasts, 5% nucleated red blood cells. Hemoglobin 9.2gm/dL, platelet count 113k/uL. Blood smear showed neutrophilic leukocytosis with left shift, leukoerythroblast changes, thrombocytopenia. His basic metabolic profile and liver function test were within normal limits. He had negative viral serology.

An abdominal paracentesis was done and six liters of ascitic fluid were drained. Analysis of the ascitic fluid revealed the following:

- Red blood cells: 3900, white blood cells: 900 (neutrophils 15%, lymphocytes: 35%, monocytes: 42%, reactive 5%, rare megakaryocytes, reactive lymphocytes).
- Proteins: 2.8 g/dL, Glucose 160 mg/dL, LDH: 454 u/L, albumin: 1.2, Serum albumin ascitic gradient (SAAG) = 1.7.
- Cytology: Negative for malignant cells, however there was evidence of multinucleated giant cells consistent with megakaryocytes (Figure 1); findings suggestive of extramedullary hematopoiesis.
- Cultures (including bacterial, fungal and mycobacterial) were negative.

Echocardiogram was within normal limits. Ultrasound of the abdomen showed patent hepatic vasculature, large volume ascites, and a normal liver texture and size. The spleen was enlarged with sagittal dimensions estimated at 26–27 cm. Computerized tomography scan of the abdomen (Figure 2) revealed ascites, splenomegaly, and evidence of mesenteric stranding and peritoneal nodularity consistent with peritoneal carcinomatosis Trans-jugular liver biopsy with pressure measurements showed the following results: right atrium pressure: 12 mmHg, IVC: 14 mmHg, right hepatic venous pressure: 12 mmHg, wedge hepatic venous pressure: 20 mmHg, corrected wedge/gradient: 8 mmHg; findings not consistent with portal hypertension. The right hepatic vein was widely patent. Liver biopsy revealed normal hepatic parenchyma without evidence of fibrosis and clusters of cells infiltrating the sinusoids compatible with extramedullary hematopoiesis (Figure 3). Peripheral smear, bone marrow aspirate and biopsy were diagnostic of myelofibrosis (Figure 4).

The patient was managed conservatively with diuretic therapy and large volume paracentesis. After discussing various palliative measures, he elected not (continued on page 37)
to have radiation therapy or any other therapy at this point of time.

**DISCUSSION**

Around 10% of patients with myelofibrosis may present with ascites, and a similar percentage of patients may present with portal hypertension and evidence of esophageal varices as a complication of their disease (3).

Symptomatic ascites as the initial presentation of myelofibrosis is rare (1). Multiple theories have been proposed to explain ascites in the setting of myelofibrosis. Portal hypertension as an etiology was considered. One of the contributing factors for the portal hypertension can be the increased blood flow through the portal system, so called "forward hypertension" (1). The increased blood flow may be due to splenomegaly, where flow in the splenic vein may increase to 3000 mL/minute from a normal value of 100 mL/minute as the size of the spleen increases (4). However this alone cannot entirely account for the ascites especially that ascites occurs even in splenectomized patients with myelofibrosis (5). On the other hand, portal pressure measurements before and after splenectomy suggested a major role of enlarged spleen and hence increased blood flow as a factor in the development of portal hypertension (6,7).

Another theory is portal hypertension secondary to portal vein thrombosis or Budd Chiari syndrome which may occur more frequently in patients with myelofibrosis given their increased clotting tendency, hence increasing resistance to splanchnic blood flow (8). However several case reports of patients with ascites and myelofibrosis including our case did not show evidence of venous thrombosis (9).

A third theory for portal hypertension has been proposed suggesting that extensive portal zone infiltration by primitive hematopoietic cells might cause intrahepatic perisinusoidal obstruction and secondary hypertension (10). However in those cases described, the wedge hepatic venous pressure was normal but intrasplenic pressure was increased.

More rarely, widespread thrombotic occlusions can cause oblitative portal venopathy secondary to smaller portal vein radical involvement, eventually leading to a nodular regenerative hyperplasia on pathology, causing increased portal outflow resistance and sinusoidal hypertension (11).

Myelofibrosis is characterized by extramedullary hematopoiesis mostly of the reticuloendothelial organs such as spleen, liver and lymph nodes causing the hepatosplenomegaly (12). However organs such as kidney, pancreas, adrenals, heart retroperitoneum, stomach, epididymus, gall bladder, ovaries, skin as
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Figure 4. A+B: Peripheral smear showing megakaryocyte, tear drop RBC’s, reactive lymphocytes. C+D+E: Bone marrow biopsy H&E/ trichome stain showing marrow spaces extensively replaced by fibrous tissue with associated osteosclerosis and panhypoplasia consistent with myelofibrosis.

well as pleura and omentum can also be involved (13). Hence extramedullary hematopoiesis and ectopic implants in the peritoneum can explain ascites formation. The occurrence of such condition is rare and more rarely is the occurrence of ascites from extramedullary hematopoiesis as the initial presentation of myelofibrosis (1,14).

Some reports suggested the peritoneal involvement could be as a result of minute spontaneous splenic ruptures (5). Silverman, et al described ectopic multi-centric myeloid metaplasia of the omentum in patients with intact splenic capsule (12). Others described these foci as “metastatic lesions”(1), causing ascites by obstruction of lymphatic ducts by extra medullary foci, or by increased permeability of the capillaries (1). However, in order to explain the characteristic and diagnostic cytological findings of ascites secondary to extramedullary hematopoiesis, Silverman, et al also suggested that the most likely mechanism of ascites formation is desquamation or exfoliation of the myeloid and megakaryocyte cells into the peritoneum.

Megakaryocytes in the peritoneum and the ascitic fluid are rarely found, and are highly suggestive of peritoneal extramedullary hematopoiesis (5). As described previously, in almost 5000 peritoneal and pleural fluid samples, only 5 had megakaryocytes among which 3 had myelofibrosis, 1 had lymphoma, and 1 had chronic myelogenous leukemia (5). As such, cytological analysis should be performed in all cases of ascites and myelofibrosis.

Based on the above-proposed mechanisms, it is evidently very important to determine the factors contributing to the ascites in myelofibrosis because different etiologies are usually treated differently.

Several treatment options were used to treat the myelofibrosis and its complications, but usually most of the treatment for myelofibrosis is only supportive and palliative. Splenectomy, in good surgical candidates, was used for refractory anemia, symptom control, and the relief from symptomatic splenomegaly and portal hypertension, yet this modality was not very effective (15). Some, however, contributed the increased aggressiveness of myelofibrosis to splenectomy (2). Alkylating agents such as hydroxyurea or busulfan were used for hematologic control of disease as well as symptom control and ascites formation, yet none was really effective (1,16).

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Hematopoietic tissues, whether in bone marrow or at extramedullary sites, are highly sensitive to radiation therapy. Radiation therapy may be very useful in treating symptomatic non-hepatosplenic extramedullary hematopoiesis, such as patients with spinal cord compression, or even with pleural or peritoneal involvement (2,5,16–18).

In one study, 23 patients with myelofibrosis and myeloid metaplasia, splenic irradiation resulted in transient reduction in size of spleen in more than 90% of patients, for a mean duration of six months, yet 26% had severe myelosuppression (2). They reported that 62% of patients treated with radiotherapy for symptomatic hepatomegaly, with or without ascites, became cytopenic and 2 patients died as a consequence. The objective response was not always present although the majority of patients had subjective relief; these symptoms were short lived, for a median of 3 months without affecting survival favorably (2). On the other hand, this study did not evaluate the role of radiotherapy in earlier stages of myelofibrosis with peritoneal implants and secondary ascites. One reported case of intractable ascites in myelofibrosis was successfully treated with a Leveen shunt (19). Others reported a case of ascites secondary to extramedullary hematopoiesis of the peritoneum with rapid symptomatic relief after treatment with intraperitoneal Ara-C (14). Lukie, et al described resolution of ascites and gastroesophageal varices in a patient with myelofibrosis and myeloid metaplasia with intractable ascites following splenectomy (20).

Until now, no specific and effective treatment has been shown to have a sustained response and favorable effect on survival for patients with ascites secondary to myelofibrosis.

CONCLUSION

Our patient presented with new onset ascites, which is an unusual initial manifestation of myelofibrosis. There was no evidence of liver, heart or kidney disease. Cytological analysis of the ascitic fluid suggested extramedullary hematopoiesis. Liver biopsy confirmed the presence of extramedullary hematopoiesis. Bone marrow biopsy revealed myelofibrosis. The patient was treated conservatively for symptom relief. This demonstrates the need to include extramedullary hematopoiesis under the differential diagnosis of patients presenting with ascites, although it is rare in this context.

References
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