



## A Patient with Abdominal Pain, Vomiting and Splenomegaly

Eyal Reinstein MD PhD<sup>1</sup>, Rachel Pauzner MD<sup>2</sup>, Haim Mayan MD<sup>2</sup> and Gina Schiby MD<sup>3</sup>

Departments of <sup>1</sup>Medicine B, <sup>2</sup>Medicine E and <sup>3</sup>Pathology, Sheba Medical Center, Tel Hashomer, Israel

IMAJ 2006;8:435-438

### Case Presentation

#### R. Pauzner and H. Mayan

A 54 year old woman, married with four children, was admitted in November 2004 because of splenomegaly and abdominal pain. Her medical history included: hypertension, well controlled with ramipril 2.5 mg/day, hypothyroidism treated with thyroxine, and repair of an inguinal hernia 2 years earlier. In January 2003 she was admitted, for the first time, to a surgical ward because of abdominal pain from which she had been suffering for the previous 6 months. The pains occasionally appeared after a meal and were located in the right lower quadrant and epigastric area. The evaluation revealed mild splenomegaly, gallbladder stones, and a suspected intrauterine mass. A proton pump inhibitor was prescribed, but it did not provide relief and the patient was referred to the hematology and gastroenterology clinics.

A repeated abdominal computerized tomography scan confirmed the presence of splenomegaly (16 cm) without hepatomegaly or a uterine mass. Liver scan did not show any signs of portal hypertension. Both gastroscopy and colonoscopy were normal. Laboratory tests revealed: white blood cells  $3 \times 10^3$  K/ $\mu$ l, hemoglobin 11 g/dl, platelets  $140 \times 10^3$  K/ $\mu$ l. Teardrop cells were observed in the blood smear. Immunoelectrophoresis of the blood and urine were negative for a monoclonal gammopathy. Other abnormal findings included low complement levels and B12 116 pg/ml (normal 180–1050). The patient refused to undergo a bone marrow aspiration, and was lost to follow-up for 6 months.

She was hospitalized in the Internal Medicine ward in March 2005 because of worsening abdominal pain, accompanied by vomiting and weight loss of 4 kg. On physical examination, her blood pressure was 105/85, pulse 75/minute, there was no lymphadenopathy, breath sounds were normal, a systolic murmur 1-2/6 was heard all over the precordium, and a firm spleen was palpated 6 cm below the rib cage. Laboratory tests showed sedimentation rate of 6/16, WBC  $2.4 \times 10^3$  K/ $\mu$ l, hemoglobin 9.7 g/dl, platelets  $110 \times 10^3$  K/ $\mu$ l, lactate dehydrogenase 200 IU/L (normal 100–260), aspartate aminotransferase 62 IU/L (normal 7–40), alanine aminotransferase 76 IU/L (normal 7–45), and alkaline phosphatase 178 IU/L (normal 45–115). Haptoglobin was normal, ferritin 85  $\mu$ g/L (normal 50–200), transferrin 266 mg/dl (normal 193–378), antinuclear factor positive, anti-DNA negative, anticardiolipin

immunoglobulin G 7.2 U/ml (normal 0–15), anticardiolipin IgM >140 IU/ml (normal 0–15), circulating anticoagulant 1.94 (normal 0.9–1.3), circulating anticoagulant-partial thromboplastin time 2.81 (normal 0.9–1.55). Markers for malignancy and serology for hepatitis C and B were negative. Abdominal CT-angiography did not demonstrate any arterial occlusions. Doppler ultrasound showed normal flow in the portal system and splenic vein. Repeated gastroscopy was normal and gastric scan showed normal gastric evacuation. Bone marrow biopsy was normal. The patient was discharged for further evaluation in the outpatient clinic.

Endoscopic ultrasound demonstrated an enlarged lymph node anterior to the pancreas and two hypoechoic findings at the head of the pancreas. Endoscopic retrograde cholangiopancreatography examination revealed two filling defects in the choledochus, and two small gallstones were removed. Laparoscopic cholecystectomy was performed in July 2005. The gallbladder contained many small stones, the enlarged lymph node was resected, and the histologic finding was a necrotizing granulomatous, sarcoid-like inflammation. For 5 months the patient felt well.

She was readmitted to the Internal Medicine ward in November 2005 because of severe left abdominal pain radiating to the left shoulder. On physical examination the patient looked ill and pale, and a huge tender hard spleen of 20 cm was palpated. Abdominal CT showed an enlarged spleen with hypodense areas in the upper and lower poles, and sub-capsular fluid. Laboratory findings included: sedimentation rate 70/80, hemoglobin 7.5 g/dl, LDH 700 IU/L. The patient received blood and was referred to the surgical ward for a diagnostic procedure.

### Differential Diagnosis

#### E. Reinstein

This patient presented with abdominal pain, splenomegaly and mild pancytopenia without peripheral lymphadenopathy. The causes of splenomegaly fall into three main categories: a) due to *increased demand for splenic function*, such as in infectious diseases (including infectious mononucleosis, chronic malaria and leishmaniasis), autoimmune diseases (systemic lupus erythematosus, Felty's syndrome), and hemolytic conditions (thalassemia, hemoglobinopathies, hereditary spherocytosis, etc). b) Secondary

WBC = white blood cells

Ig = immunoglobulin  
LDH = lactate dehydrogenase

to *portal hypertension*, such as in liver cirrhosis and hepatic and splenic vein obstructions. c) *infiltrative diseases*, such as Gaucher's disease and hematologic diseases, including myeloproliferative and lymphoproliferative disorders.

In the current case, the first category can be ruled out for the following reasons: no evidence of exposure to infection in areas where these diseases are endemic; absence of fever, peripheral lymphadenopathy and abnormalities in the differential blood count; no symptoms indicative of rheumatic disease in the patient's clinical history; and finally, no abnormalities in the patient's blood smear, laboratory tests or family history that suggest a hemolytic disease. The findings of normal blood flow in the portal and splenic venous systems on ultrasonography make the diagnosis of splenomegaly secondary to portal hypertension unlikely as well. In the third category, Gaucher's disease is implausible in this case, since the disease usually presents at a younger age with bone pain and a characteristic bone marrow. The presence of pancytopenia with splenomegaly suggests a hematologic disorder, and I shall focus my discussion on diseases in that category.

#### **Hematologic disorders causing massive splenomegaly**

Massive splenomegaly associated with pancytopenia in a 54 year old patient can be caused by a variety of hematologic disorders. The most common hematologic causes are myelo- and lymphoproliferative disorders such as chronic myeloid leukemia, myelofibrosis, polycythemia vera, chronic lymphocytic leukemia, hairy cell leukemia and lymphoma. The first four conditions are associated with significant distinctive alterations in blood count, peripheral blood picture and bone marrow, which this patient does not appear to have, and therefore are very unlikely in this case.

##### **• Chronic myeloid leukemia**

Patients with CML usually present with fatigue, night sweats and low grade fever that is related to hyper-metabolism secondary to overproduction of leukocytes. The spleen is enlarged in most patients. The hallmark of CML is a marked elevation of the white blood cell count and the peripheral blood is characteristic – i.e., the myeloid series is left shifted and this shift is also seen in the bone marrow.

##### **• Myelofibrosis**

Patients with myelofibrosis most commonly present with fatigue due to anemia or abdominal fullness and pain secondary to massive splenomegaly. Fibrosis of the bone marrow leads to extra-medullary and liver hematopoiesis and to portal hypertension. The peripheral blood smear is characteristic with teardrop poikilocytosis, leukoerythroblastic blood picture and giant abnormal platelets.

##### **• Polycythemia vera**

Patients with polycythemia vera have symptoms related to expanded blood volume and increased blood viscosity such as headache, dizziness and blurred vision. Splenomegaly is

usually not massive at the time of presentation, and the hematocrit is high, sometimes greater than 60%. The bone marrow is hypercellular with hyperplasia of all hematopoietic elements.

##### **• Chronic lymphocytic leukemia**

Many patients with CLL will be incidentally discovered to have lymphocytosis; most others present with fatigue. Peripheral lymphadenopathy is present in 80% of patients and hepatosplenomegaly in up to 50%. The hallmark of CLL is isolated lymphocytosis, usually higher than 20,000/ $\mu$ l but it may be elevated to several hundred thousand. The malignant lymphocytes are indistinguishable from normal lymphocytes on a blood smear, thus immunophenotyping is essential for diagnosis. The bone marrow is variably infiltrated with lymphocytes.

##### **• Hairy cell leukemia**

Although occurring mainly in men (> 85%), the diagnosis of hairy cell leukemia should be kept in mind when confronting a woman presenting with splenomegaly and pancytopenia. In this case, however, there were no hairy cells in both blood smear and bone marrow biopsy (hairy cells exhibit a characteristic tartrate-resistant acid phosphatase staining), arguing against the diagnosis of hairy cell leukemia.

##### **• Lymphoma**

In a patient with a large spleen, pancytopenia, normal differential blood count and weight loss, the diagnosis of lymphoma heads the differential diagnosis list. The absence of peripheral lymphadenopathy combined with normal gastroscopy and colonoscopy point to primary lymphoma of the spleen. Primary splenic lymphoma can be defined in patients with splenomegaly, cytopenia of at least two hematologic cell lines, and absence of peripheral lymphadenopathy at the time of presentation. Patients may have solitary or multiple mass lesions that mimic primary or metastatic carcinoma, thus producing a diagnostic challenge. Although splenic involvement is common in advanced stages of both Hodgkin's disease and non-Hodgkin's lymphoma, primary lymphoma of the spleen is unusual and comprises only 1% of malignant lymphomas. Symptoms of primary splenic lymphoma include weakness, weight loss, fever, and left upper quadrant pain or discomfort from splenomegaly. Other symptoms are induced by direct invasion to adjacent organs such as the pancreas, colon and stomach. Diagnostic imaging may demonstrate hypodense lesions on CT and hypochoic lesions on sonography. Imaging studies that suggest the diagnosis of primary splenic lymphoma are usually followed by either core biopsy of the spleen or splenectomy. During or after surgery, a staging evaluation is performed to determine the extent of the disease. The staging is as follows: stage I refers to patients with tumor only in the spleen, stage II patients have disease that involves lymph nodes in the splenic hilum, while stage III patients have involvement of the liver or distant lymph nodes. Treatment of primary splenic

CML = chronic myeloid leukemia

CLL = chronic lymphocytic leukemia

lymphoma includes splenectomy, which also serves as a diagnostic tool [1,2].

The finding of a sarcoid-like granuloma in a pancreatic lymph node may suggest other diagnoses as well. However, neither tuberculosis nor sarcoidosis – both of which are granulomatous diseases that may produce similar symptoms – would be expected to induce such a profound splenomegaly as in the present case. In addition, these diseases would probably be associated with other imaging and hematologic changes, such as adenopathy and peripheral monocytosis, respectively. The presence of a granuloma in a lymph node biopsy is not specific to sarcoidosis, as sarcoid-like granulomas can be found in chronic inflammatory, infectious and neoplastic diseases, including non-Hodgkin's lymphoma and Hodgkin's disease. The pathogenic mechanism responsible for the development of a granuloma is elusive, but it may be related to an immune response to lymphoma antigen [3,4].

Finally, patients with lymphoma exhibit several autoimmune features, including antiphospholipid antibodies (anticardiolipin and lupus anticoagulant), immune thrombocytopenia, autoimmune hemolytic anemia, and antinuclear antibodies. In particular, antiphospholipid antibodies, usually in low titers, have been detected in about 2% of patients with lymphoma. However, this presence is not associated with clinical symptoms and thromboembolic disease and is usually transitory [5,6]. During the patient's most recent hospitalization, the hemoglobin concentration decreased to 7.5, the LDH and ESR, which were normal initially, increased rapidly. The CT scan demonstrated findings consistent with spleen infarction and formation of hemorrhoids. These findings may indicate an autoimmune hemolytic crisis, which was followed by a diagnostic procedure.

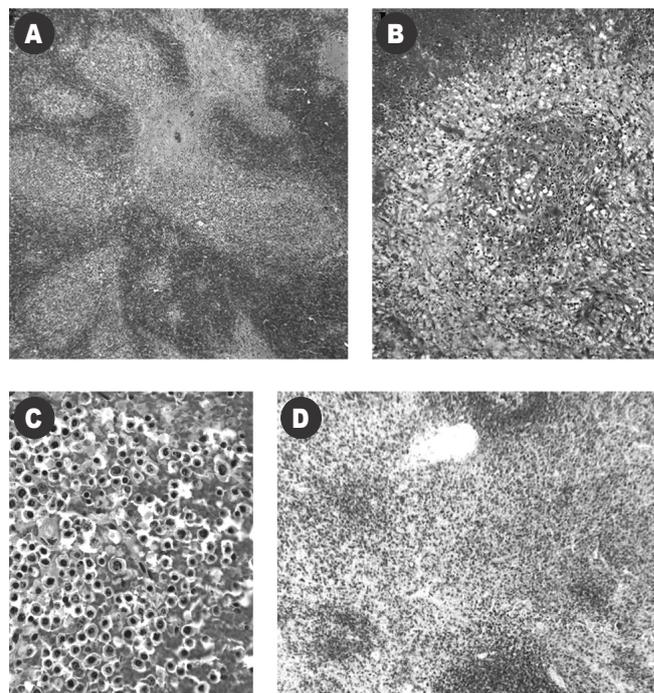
I believe that this patient had primary splenic lymphoma with antiphospholipid antibodies and splenic infarcts, but the final step in the diagnosis would have to be a spleen biopsy or splenectomy.

## Pathologic Discussion

### G. Schiby

The first biopsy was taken from the stomach. It showed a chronic active gastritis but no atrophic changes. The bone marrow biopsy demonstrated the presence of a few small well-circumscribed lymphoid nodules. Though the B cells in these nodules were numerous in comparison with the T cells, the polymerase chain reaction molecular study indicated polyclonality and a reactive nature of the B cells. The gallbladder, which was removed a few months later, contained a few stones. A lymph node from the anterior aspect of the pancreas showed numerous non-necrotizing epithelioid granulomata. Neither a foreign body nor infectious agents were identified. Finally, splenectomy was performed. The spleen weighed 2307 g, the capsule was rough, and in the cut sections the parenchyma showed diffuse granularity with a few large yellowish areas but no masses.

The microscopic examination revealed a hyperplastic and



**Figure 1.** Splenic lymphoma. **[A]** Hyperplastic and irregular white pulp (hematoxylin & eosin x400). **[B]** Hemorrhagic infarct (right upper corner) with organization. **[C]** The lymphoma cells show clear and eosinophilic cytoplasm resembling monocytoid cells (H&E x400). **[D]** Lymphoma cells positive for the B cell marker CD20 (immunostain x200)

irregular white pulp, a severely congested red pulp and numerous organizing hemorrhagic infarcts [Figure 1A and B]. Uniform small lymphoid cells with slightly irregular nuclei and prominent clear or eosinophilic cytoplasm replaced the peripheral zones of the white pulp follicles. Some of them showed a plasmacytoid pattern [Figure 1C]. Many of these cells colonized the follicles completely and many extended into the red pulp. The immunohistochemical stains revealed expression of the B cell marker CD20, with lambda light chain predominance and lack of the CD10, CD5, CD23, cyclin D1, DBA 44 and TRAP for hairy cells [Figure 1D]. The Ki67 proliferation marker was positive in about 20% of the cells. The PCR molecular study confirmed the presence of a monoclonal B cell population. The fluorescence *in situ* hybridization study revealed trisomy of chromosome 3 in about 50% of the B cells but absence of trisomy 18, t(11;14), t(11;18) and t(4;14).

In summary, this is a low grade B cell lymphoma of the spleen, involving the white pulp and extending into the red pulp. The cell morphology – with most of the cells resembling monocytoids, and their distribution, together with the immunohistochemical results and the presence of trisomy of chromosome 3 – favor the diagnosis of marginal zone lymphoma.

## Pathologic Diagnosis

Splenic marginal zone lymphoma

ESR = erythrocyte sedimentation rate

PCR = polymerase chain reaction

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**Correspondence:** Dr. E. Reinstein, Dept. of Medicine B and Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer 52621, Israel.  
Phone: (972-3) 530-2652  
Fax: (972-3) 535-2855  
email: eyalr@mit.edu