

Primary Splenic Lymphoma Associated with Hemophagocytic Lymphohistiocytosis Complicated with Splenic Rupture

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Primary splenic lymphoma (PSL) is a rare disease with ambiguous definition, comprising less than 1% of non-Hodgkin's lymphoma. Even rarer is PSL combined with hemophagocytic lymphohistiocytosis (HLH), which has presentations of fever, cytopenia, hepatosplenomegaly, hyperferritinemia, and phagocytosis of hematopoietic cells in the reticuloendothelial system. We report the case of a 77-year-old man who presented with HLH initially. Refusing diagnostic splenectomy, he received chemotherapy. Spontaneous splenic rupture occurred after chemotherapy. In the following emergency operation, PSL was diagnosed. He received another 5 courses of chemotherapy with the R-CNOP regimen (rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisolone). Now he has no residual or relapsed disease. Diagnostic splenectomy for adult HLH patients without definite etiologies may play an important role. [*J Chin Med Assoc* 2008;71(4):210–213]

Key Words: hemophagocytic lymphohistiocytosis, primary splenic lymphoma, splenic rupture

Introduction

Although primary splenic lymphoma (PSL) is ambiguously defined, it probably comprises less than 1% of non-Hodgkin's lymphoma (NHL).¹ Abdominal discomfort from spleen enlargement is the most common presentation. Das Gupta et al² adopted a restrictive definition of PSL as a lymphoma involving only the spleen and splenic hilar lymph nodes, but PSL tends to be asymptomatic until the disease spreads. Without altering the primariness of the disease, Falk and Stutte³ defined PSL as generalized lymphoma localized in the spleen with minimum liver and bone marrow involvement.

Hemophagocytic lymphohistiocytosis (HLH) is a rare and fatal disorder; patients usually present with fever, cytopenia, liver dysfunction, hepatosplenomegaly, hypertriglyceridemia and hyperferritinemia.⁴ It is characterized by accumulation, in the reticuloendothelial system, of activated macrophages showing

phagocytosis of hematopoietic cells. Despite HLH possibly being associated with infections, autoimmune diseases and solid malignancies, T cell lymphoma is still the leading cause of adult HLH.^{5,6} Here, we report the case of a 77-year-old man with diffuse large B cell PSL, who presented with HLH complicated by spontaneous splenic rupture after chemotherapy. His PSL was diagnosed in the subsequent emergency splenectomy.

Case Report

A 77-year-old man presented with intermittent fever up to 39°C of 3 weeks' duration. Infection surveys including blood culture, urine culture and stool culture were all negative. Splenomegaly with infarction was found by computed tomography (Figure 1). Complete blood count revealed leukocytosis (white blood count, $10.4 \times 10^9/L$), anemia (hemoglobin,



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Figure 1. Computed tomography of the abdomen shows an enlarged spleen with multiple irregular and attenuated density lesions.

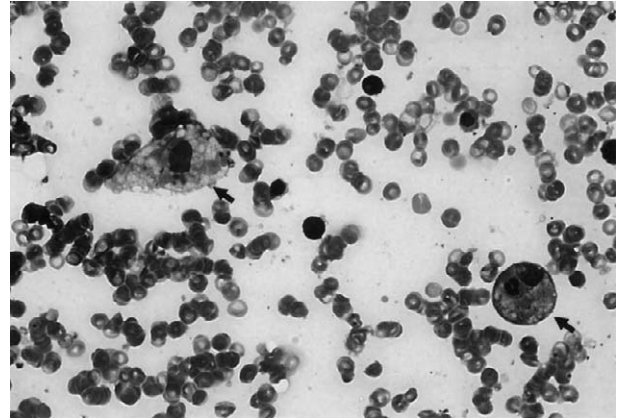


Figure 2. Bone marrow aspiration smear reveals activated macrophages (arrows) with phagocytosis of hematopoietic cells, including mature red blood cells, neutrophils and platelets (Wright and Giemsa stain, 400 \times).

7.4 g/dL) and thrombocytopenia (platelet count, $109 \times 10^9/L$). Serum biochemistries, including aspartate aminotransferase (40 U/L; normal, 8–40 U/L), alanine aminotransferase (12 U/L; normal, 4–44 U/L), alkaline phosphatase (167 U/L; normal, 50–190 U/L), total bilirubin (0.8 mg/dL; normal, 0.1–1.2 mg/dL), blood urea nitrogen (18 mg/dL; normal, 5–25 mg/dL) and serum creatinine (0.9 mg/dL; normal, 0.7–1.4 mg/dL) were all within normal limits, except for lactate dehydrogenase which was elevated at 418 U/L (normal, 120–140 U/L). Coagulopathy was also noted (prothrombin time, 14.0/10.5; international normalized ratio, 1.33; activated partial thromboplastin time, 50.4/32.7).

Tests for autoimmune disease, including antinuclear and anticardiolipin antibodies, as well as rheumatoid factor, were negative. Serum triglyceride level (394 mg/dL; normal, 20–200 mg/dL), ferritin (4,690 ng/mL; normal, 6–81 ng/mL) and soluble interleukin-2 receptor (7,402 pg/mL; normal, < 880 pg/mL) were elevated. Bone marrow examinations revealed marked hemophagocytosis without evidence of malignancy (Figure 2). The diagnosis of HLH was made according to the following criteria: fever, cytopenia, elevated lactate dehydrogenase, hyperferritinemia, hepatosplenomegaly, and bone marrow hemophagocytosis.⁴ The patient's fever and general condition responded only fairly to 5 mg methasone every 8 hours and 2 consecutive days of 100 mg etoposide. Low grade fever persisted for 2 weeks. At the end of this time, a second bone marrow examination revealed minimal large atypical lymphocyte aggregation and profound hemophagocytosis.

Under the suspicion of lymphoma-associated HLH, splenectomy was suggested for further diagnosis, but

the patient refused this treatment. As malignant lymphoma is the leading cause of adult HLH, the patient underwent chemotherapy for lymphoma with the CNOP regimen (cyclophosphamide 750 mg/m², mitoxantrone 10 mg/m², vincristine 1.4 mg/m², prednisolone 40 mg/m² for 5 days). Four days after initiation of chemotherapy, the patient suffered from acute left upper abdominal pain and received urgent splenectomy because of spontaneous splenic rupture with internal bleeding and hypovolemic shock. Pathologic examination of the spleen confirmed the diagnosis of NHL, diffuse large cell, B phenotype with positive CD20 stain (Figure 3). Intraoperative liver biopsy disclosed hemosiderosis, but no evidence of lymphoma cell infiltration.

The patient's fever subsided after chemotherapy, and he recovered from the splenic rupture. He received another 5 courses of chemotherapy with the R-CNOP regimen (rituximab 375 mg/m², cyclophosphamide 750 mg/m², mitoxantrone 10 mg/m², vincristine 1.4 mg/m², prednisolone 40 mg/m² for 5 days), and was released in a stable condition. Over a follow-up period of 12 months, there was no residual disease or relapse.

Discussion

As a delicate filter to clear the blood of particulate matter and senescent blood cells, the spleen is commonly involved in hematologic malignancies. For example, half of all patients with Hodgkin's disease and a third of those with NHL have splenic involvement,⁷ which greatly increase the difficulty in diagnosing true PSL. Splenic involvement can be part of a

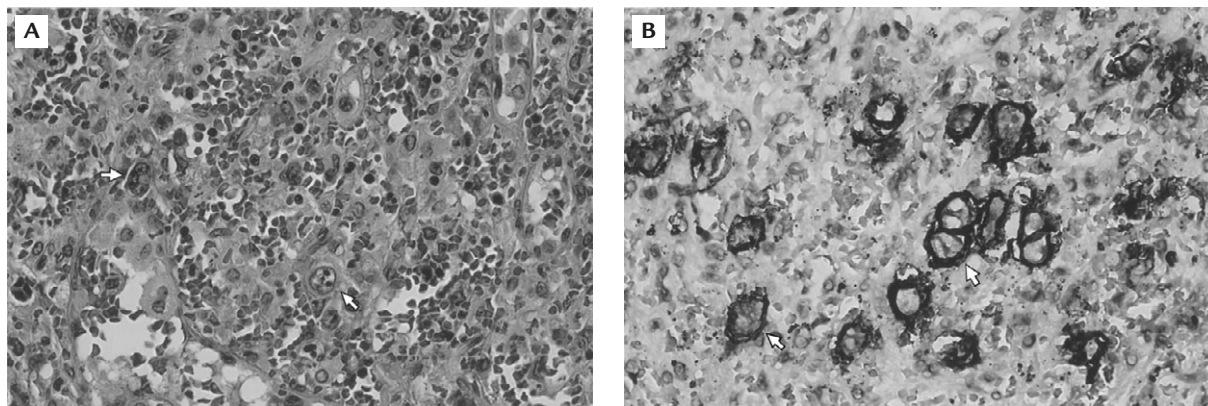


Figure 3. Histologic examination of the splenectomy specimen reveals: (A) diffuse and large atypical lymphocyte aggregations (hematoxylin & eosin, 400 \times); (B) positive CD20 staining (arrows) (400 \times).

diffuse dissemination of the lymphoma, however, the spleen itself may be the primary site. Das Gupta et al² restrictively defined PSL as a lymphoma involving only the spleen and the splenic hilar lymph nodes, but not the liver or other sites. Six months or more between detection of splenic involvement and appearance of lymphoma elsewhere is also required.² Two less restrictive definitions of PSL have also been proposed. Skarin et al⁸ suggested diagnosis of PSL for any lymphoma with splenic involvement and splenomegaly as a predominant feature. Kraemer et al⁹ further defined PSL as lymphoma, presenting with splenomegaly, at least bicytopenia, and in the absence of peripheral adenopathy. Regardless of the definition, PSL is rare, probably comprising less than 1% of NHL.¹ Our patient was diagnosed as having PSL by fulfilling the criteria proposed by Skarin et al and Kraemer et al.

The most common presentation of PSL is splenomegaly. Constitutional symptoms such as weight loss, fever and night sweating are often noted.¹⁰ Diagnosis of PSL, however, is not easy. A study by Kraus et al¹¹ evaluated the diagnostic yield of splenectomy in patients with unexplained splenomegaly or splenic mass. Although malignancy, especially NHL, is the most common diagnosis, splenectomy is seldom used as a diagnostic maneuver because of its invasiveness and patients' rejection of the treatment. Some studies¹² documented safe use of alternatives: splenic fine needle aspiration and splenic core biopsy for patients with splenomegaly or splenic mass, but these procedures frequently result in splenic rupture with fatal consequences. Inadequate specimens are another concern. Even so, splenectomy is still the cornerstone of diagnosis, remaining the main treatment modality for PSL.

PSL shares similar clinical presentations with HLH, including fever, splenomegaly, cytopenia, and elevated

lactate dehydrogenase, but they rarely occur together. The presence of HLH greatly increases the difficulty of diagnosing PSL. Eradication of the underlying disease is definitely the cornerstone of HLH treatment.⁵ Since NHL is still the leading cause of adult HLH,⁵ Takahashi et al¹³ have suggested that without definite etiology, HLH should be treated as lymphoma when it is refractory to steroids.

After our patient's refusal of diagnostic splenectomy, we followed Takahashi et al's suggestion and treated him as an NHL-associated HLH patient with systemic chemotherapy. Unfortunately, spontaneous splenic rupture occurred soon after chemotherapy began. Immediate splenectomy saved the patient's life and provided an accurate diagnosis of PSL. Spontaneous splenic rupture is a rare condition. According to the criteria described by Orloff and Peskin in 1958,¹⁴ spontaneous rupture of a diseased spleen is categorized as a pathologic rupture. Hematologic malignancies, especially NHL, are the most common underlying diseases.¹⁵ Congestion of the splenic parenchyma by tumor cells, coagulation disorders, and splenic infarction may explain the rupture.¹⁵ Our patient had all of these risk factors.

Treatments for PSL include splenectomy, local radiotherapy, and systemic chemotherapy. Splenectomy is the most popular choice because it provides both correct diagnosis and effective treatment. Local radiotherapy is an option for patients diagnosed with PSL if splenectomy is not feasible.¹⁶ Morel et al¹⁷ stated that early splenectomy can improve survival for patients tolerating adjuvant chemotherapy who recover from cytopenia after surgery. Survival of PSL patients significantly correlates to the stage of the disease,¹⁸ but Xiros et al¹⁹ documented that median survival after diagnostic splenectomy was 24 months regardless of disease stage or adjuvant chemotherapeutic regimen.

It is not clear whether splenectomy or systemic chemotherapy is the better choice for initial PSL treatment when PSL is combined with HLH. The efficacy of adding rituximab to conventional chemotherapeutic agents has not been proven either. Pathologic spontaneous splenic rupture, however, is a potential risk. Our case constitutes a successful experience in using monoclonal antibodies and chemotherapeutic agents to treat PSL combined with HLH. Long-term observations of survival are still needed.

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