Case Report

Primary Hepatic Diffuse Large B-Cell Lymphoma in a Patient with Scleroderma

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ABSTRACT

Primary Hepatic Lymphoma (PHL) is rare and possibly associated with viral hepatitis and autoimmune diseases. Scleroderma could exceptionally be complicated by lymphoma. We describe PHL occurring in a 52-year-old female suffering scleroderma for eight years, with no history of cytotoxic or high-dose glucocorticoid therapy. CT scan, performed to work-up abdominal discomfort, constipation, and elevated alkaline phosphatase, showed a liver mass. Following left hepatic lobectomy, diffuse large B-cell lymphoma was diagnosed by pathological evaluations. Shortly after operation, chemotherapy began. The patient is alive and free of disease eight years after diagnosis of primary hepatic lymphoma. To the best of our knowledge, this is the first case of Primary Hepatic Lymphoma occurring in the setting of long-standing scleroderma. The fact that our patient had no history of immunosuppressive/ high-dose glucocorticoid therapy may indicate that similar immunologic abnormalities have pathogenetic role in both scleroderma and non-Hodgkin's lymphoma.

Key words: Liver, Lymphoma, Systemic Scleroderma

Introduction

Although the liver is often secondarily involved in the late stages of Hodgkin's and non-Hodgkin's lymphomas, primary hepatic lymphoma (PHL) accounts for less than 1% of all extra nodal lymphomas (1). Several cases of PHL, with preexisting chronic hepatitis or liver cirrhosis due to hepatitis B or C virus infection have been described (2). In addition, previous studies have suggested that PHL could evolve in patients with acquired immune deficiency syndrome (AIDS) or autoimmune diseases (2-6). It is also known that scleroderma could be complicated by lymphoma

early in the course of the disease; however, this is not a common occurrence (7, 8). Moreover, no relationship has ever been reported between scleroderma and primary hepatic lymphoma.

The case of PHL presented here had occurred in a patient suffering scleroderma for eight years who had no history of previous immunosuppressive/cytotoxic treatment. This is peculiar because lymphoma usually complicates scleroderma within the first two years (8). Furthermore, lack of immunosuppressive treatment in the patient may suggest some pathogenetic relationship between lymphoma and scleroderma.

Here we present an scleroderma patient diagnosed with primary diffuse large B-cell lymphoma of liver, review the clinical and radiological features, pathological findings, natural history and prognosis of PHL, and discuss etiologic and pathogenetic theories.

Case Report

A 52-year-old woman, diagnosed with scleroderma in 1991, was referred to us in 1999 with weakness, anorexia, significant weight loss, diaphoresis, facial numbness, constipation, arthralgia and Reynaud's phenomenon.

The diagnosis of scleroderma had been made regarding typical clinical presentation, high titer of ANA and skin biopsy. The patient's history was significant for hypothyroidism and depression treated with levothyroxin and imipramin.

Physical examination showed thin shiny skin and sclerodactyly. The abdomen was soft and nontender; no palpable liver mass was identified. No lymphadenopathy or splenomegaly was detected. Neurological examination was normal.

Laboratory findings included ESR: 58 mm/hr, C-reactive protein: 2+, Anti-nuclear antibody: 1/1280 (within reference range), normal C3 and C4 levels, negative LE test and RPR and normal CBC. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total protein, and bilirubin levels were normal; however, alkaline phosphatase (ALP) was significantly elevated (1165 U/L, normal: 20-130 IU/L). Serology was negative for HIV, HBV,

and HCV. Thyroid function tests were also within normal limits.

Abdominal sonography revealed a multiloculated hypoechoic mass, measuring 97 x 40 mm in the left lobe of liver. Spiral CT scan showed a large hypodense mass in the left lobe with mild peripheral enhancement following contrast injection, without enhancement of the central lesion in delayed images. Spleen appeared normal and no abdominal lymphadenopathy was detected. Upper GI endoscopy revealed moderate deformity of the duodenal bulb. ERCP showed a filling defect in the left hepatic duct with evidence of erosion; right hepatic duct and common bile duct were unremarkable. Liver scan by Tc-RBC with planar and SPECT methods revealed homogeneous perfusion and blood pool in the liver, excluding the diagnosis of hemangioma.

With probable diagnoses of primary hepatic tumor (e.g. hepatic adenoma, hepatocellular carcinoma, including fibrolamellar carcinoma) or secondary lesions (e.g. metastatic carcinoma) laparotomy was carried out. A mass was detected in the left lobe of liver. No perihepatic or para-aortic lymphadenopathy was identified. Spleen was normal in size and appearance. Hepatic left lobectomy and cholecyctectomy were done.

The submitted specimen for pathologic evaluation consisted of the left lobe of liver measuring 12x8x5 cm^3, containing a nonencapsulated multiloculated mass, composed of yellow-white fleshy nodules with diameters ranging from 1cm to 4 cm. Other parts of the liver as well as gall bladder showed no gross pathologic changes.

Histologic sections of the nodules (Fig. 1 and 2) showed monotonous sheets of densely packed large centroblast-like cells, with a thin rim of pink cytoplasm and enlarged vesicular nuclei with one to two small nucleoli. Several mitotic figures and occasional apoptotic bodies were evident. There were only few reactive infiltrating lymphocytes. No necrotic area was seen. The tumor was well demarcated from the nonneoplastic liver.

Immunostaining of the tumor cells showed positive reaction for LCA and CD20 (Fig. 3 and 4) and negative reaction for CD3, Cytokeratin, EMA, CEA, AFP and NSE.
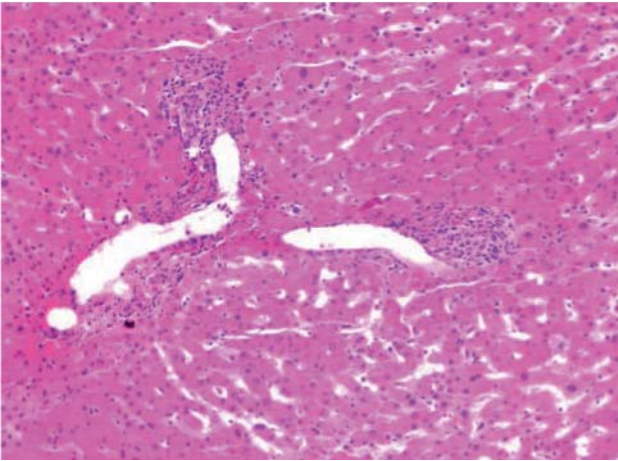
Fig.1: Sheet of malignant lymphoid cells with abrupt transition to adjacent liver tissue (Hematoxylin-Eosin ×100)
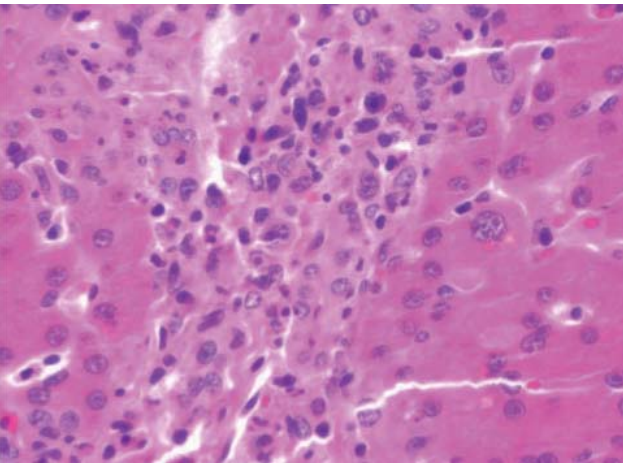

Fig. 2: Densely packed lymphoid cells with enlarged vesicular nuclei, prominent nucleoli and thin rim of pink cytoplasm (Hematoxylin-Eosin ×400)
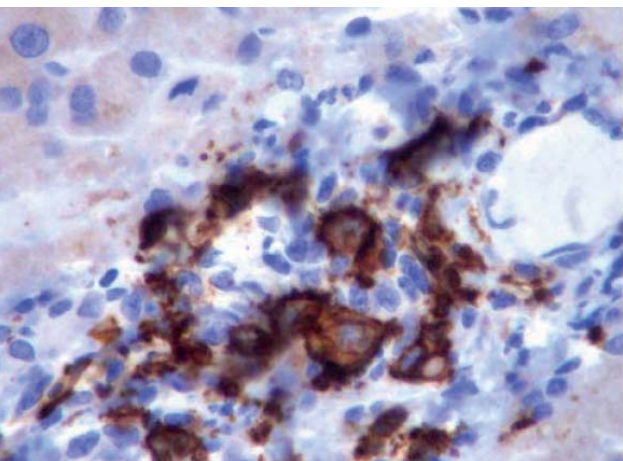

Fig. 3: Immunohistochemical staining for Leukocyte Common Antigen. The tumor cells show marked peripheral (membranous) staining (Immunoperoxidase ×400)
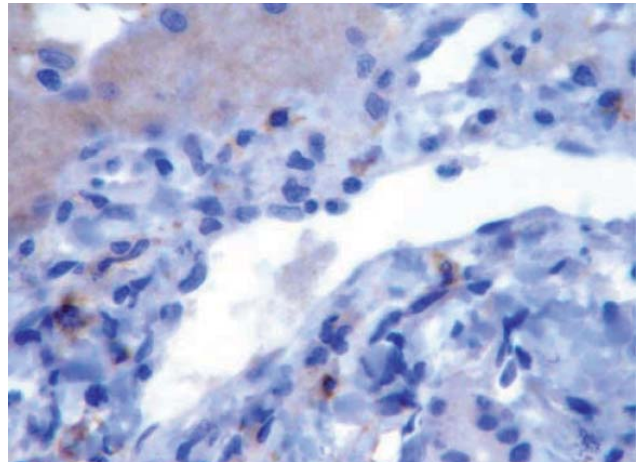

Fig. 4: Positive immunohistochemical staining of the tumor cells for CD20 (Immunoperoxidase ×400)

Bone marrow aspiration and biopsy showed normocellular marrow with no evidence of lymphomatous involvement. Thus, the patient was diagnosed with primary hepatic large B-cell lymphoma; stage IE. Regarding the constitutional symptoms, she underwent eight cycles of chemotherapy with CHOP (Cyclophosphamide, vincristin, doxorubicin and prednisone) regimen.

Fever and diaphoresis of the patient resolved after treatment, and she regained weight. Interestingly, her sclerodactyly also improved dramatically after chemotherapy. Currently, eight years after diagnosis of lymphoma, she is doing well, without any laboratory or clinical evidence of relapse.

Discussion

Primary hepatic lymphoma (PHL), defined as an extranodal lymphoma confined to the liver, accounts only for less than 1% of all extranodal lymphomas, and is reported most frequently in middle-aged men (1, 2, 9). PHL is most commonly of large B-cell type; however, other types of primary lymphoma have been reported in the liver (1).

The diagnosis is clinically suggested by right upper quadrant or epigastric pain or discomfort, fatigue, lethargy, hepatomegaly and systemic symptoms of lymphoma and/or jaundice (10).

Liver function tests are typically abnormal. Elevation of LDH and ALP, accompanied by normal

serum alpha-fetoprotein and CEA, is an important diagnostic feature (1). Although no radiological finding appears to be diagnostic of PHL, it mostly presents as a single well-defined hepatic lesion that is hypoechoic on ultrasonography, shows hypo-attenuation on CT with rim enhancement after contrast administration, and may appear hypo and hyper-intense respectively on T1 and T2-weighted MR imaging (11).

According to Caccamo *et al.*, PHL is diagnosed clinically if lymphoma remains confined to the liver six months after detection, this limitation being confirmed by CT scan and peripheral blood and bone marrow examinations (2). Thus, our case meets the criteria for the diagnosis of PHL.

The clinical course of PHL is variable. It is usually a slow growing tumor (12, 13). However, PHL could mimic acute fulminating hepatic failure in its course, followed by a rapidly fatal outcome (14).

Generally, PHL is thought to have a relatively favorable prognosis if detected in an early stage (15). Nevertheless, the prognosis of PHL is still a matter of debate. Many authors believe that in the majority of the patients with smoldering disease, good results could be obtained with a reasonable treatment (12). Others claim that the outcome is generally poor even after early diagnosis and use of the best treatment modalities (16). Many treatment options are available including chemotherapy, surgery, and radiation therapy (1).

The etiology and pathogenesis of PHL are unclear at present; however, evidence suggests that chemical carcinogens (e.g. petrol, propane, or chromium) and viruses such as HBV, HCV, HIV, or EBV could be possible etiologic factors (2).

PHL has also been reported in immunosuppressed individuals following organ transplantation (17). Some authors have proposed that chronic persistent immunogenic stimulation causes development of lymphoma in the setting of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Primary Biliary Cirrhosis, Sjogren's syndrome, sclerosing cholangitis and autoimmune thyroid disease (3-6).

Systemic sclerosis (SSc) is characterized by vascular abnormalities, immune system activation, and fibrosis of the skin and internal organs (6). There are reports of association of SSc with malignancies other than lymphoma and with lymphomas of solitary organs other than the liver (7). One study has shown a prevalence of 1.38% for lymphoma in diffuse cutaneous form of SSc, developing within two years after the onset of the disease (8).

Reported cases of NHLs occurring in SSc patients, were either systemic or confined to lymph-nodes, lung, pleura, heart, kidney, pancreas, transverse colon, stomach, jejunum, spleen, muscles, bones, soft tissue, tongue, salivary glands, dura and orbital region, and were mainly of B-cell subtype (7). Liver lymphoma has only been reported as part of multiple organ involvement (7).

The major reported risk factors of development of NHL and other malignancies in SSc are female gender, old age, diffuse cutaneous involvement, and early disease (7, 18).

Higher incidence of cancer, particularly B-cell malignancies in SSc may be explained by B cell malfunction (19). Altered B cell homeostasis in SSc is manifested by increased naïve cells, decreased but activated circulating memory B cells, and defective natural killer cell activity (7, 20, 21). It has also been postulated that the increased risk of NHL among patients with scleroderma may be due to the use of cytotoxic drugs (22).

The primary hepatic lymphoma described here, had unique features. First, developed in a patient with known history of scleroderma. To our knowledge, no such relationship has been reported in literature before. Second, our case of primary hepatic diffuse large B-cell lymphoma occurred 8 years after the diagnosis of scleroderma, which is in contrast to the usual early occurrence of lymphoma in the course of scleroderma. Moreover, our patient had no history of immunosuppressive/ high-dose glucocorticoid therapy, just like the twelve SSc cases presented and reviewed in the study of Vettori *et al*. (7). This fact may indicate that there are similar immunologic abnormalities which have pathogenetic role in both SSc and NHL.

In conclusion, as NHL is a possible complication of scleroderma, during the diagnostic workup of a liver mass in a patient with this autoimmune disease, primary hepatic lymphoma should always be considered.

The authors declare that they have no conflicts of interest.

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