Journal of Gastrointestinal & Digestive System

Mehta et al., J Gastrointest Dig Syst 2015, 5:3
DOI: 10.4172/2161-069X.1000283

Case Report Open Access

T-Cell/Histiocyte-Rich Large B-Cell Lymphoma Masquerading as Autoimmune Hepatitis with Clinical Features of Hemophagocytic Lymphohistiocytosis

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Rec date: Mar 14, 2015, **Acc date:** Apr 16, 2015, **Pub date:** Apr 28, 2015

Abstract

We report the case of a 20-year-old male who presented with acute hepatitis resembling autoimmune hepatitis, but subsequently found to be T-Cell Rich/Histiocyte Rich Large B-Cell Lymphoma. Our patient was mistakenly diagnosed with autoimmune hepatitis based on liver histology demonstrating a pronounced lobular and portal infiltrate comprised predominately of polyclonal T cells, in the setting of negative serologic testing. This conclusion was reinforced by a compelling biochemical response to standard immunosuppressive therapy. The correct diagnosis of T/HRBCL subsequently was established by bone marrow biopsy (and confirmed by lymph node biopsy) when the patient presented with clinical features of HLH. In conclusion, our case elucidates a unique clinical spectrum of T/HRBCL. This patient initially presented with acute hepatitis, before mistakenly being diagnosed with autoimmune hepatitis and finally exhibited clinical features of HLH, which led to the diagnosis of T/HRBCL. It is critical to consider lymphoma in the differential for acute hepatopathy and clinical features of HLH.

Keywords: Autoimmune hepatitis; T-Cell/Histiocyte-rich large B-cell lymphoma; Hemophagocytosis

Case Report

A 20-year-old man was seen for evaluation of abnormal liver tests. Six months previously, the patient presented to an outside facility with new onset jaundice and dark urine following a 2-week prodrome of malaise, fatigue, and abdominal discomfort. Serologic analysis was notable for ALT (alanine transaminase) 2338 U/L, AST (aspartate transaminate) 2129 U/L, alkaline phosphatase 267 U/L, total bilirubin 8.4 mg/dL, direct bilirubin 6.5 mg/dL, albumin 3.7 g/L, and INR 1.4. Testing for hepatitis A, B, C, EBV (Epstein-barr virus), and CMV (cytomegalovirus) was negative. His symptoms gradually abated over several weeks. At two months follow-up, the patient reported feeling well. Physical examination was notable for splenomegaly. Serologic testing revealed: ALT 197 U/L, AST 120 U/L, alkaline phosphatase 162 U/L, total bilirubin 1.7 mg/dL, albumin 4.2 g/L, INR 1.5, WBC (white blood cells) 4.4, hemoglobin 13.9, platelets 118. Serum ceruloplasmin, ANA, anti-smooth muscle antibody, total IgG, anti-LKM (liver-kidney-muscle) antibody, alpha-1-antitrypsin, iron saturation, and ferritin were normal. A subsequent transjugular liver biopsy demonstrated histologic findings that were consistent with autoimmune hepatitis (Figure 1). Oral prednisone 40 mg and azathioprine (2 mg/kg) daily were initiated, resulting in prompt biochemical improvement: ALT 40 U/L, AST 47 U/L, AP 127 U/L, total bilirubin 1.2 mg/dL, INR 1.2, WBC 4.4, hemoglobin 11.4, platelets 132.

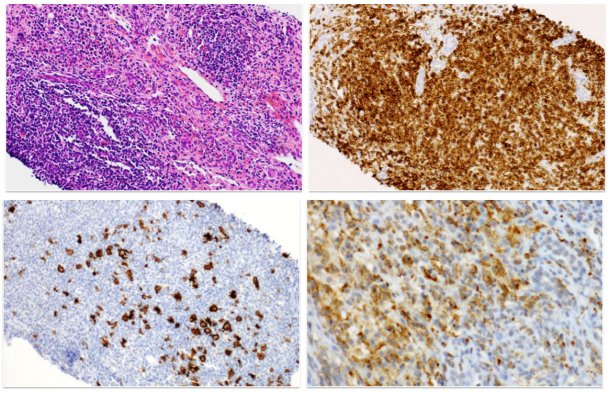

Figure 1: Liver histology. Panel A depicts an H&E stained liver section (200X) demonstrating a dense portal inflammatory infiltrate comprised predominantly of lymphocytes with scattered plasma cells and marked interface activity. Significant lobular inflammation with focal necrosis also is noted. Immunohistochemical staining reveals infiltrates to be comprised predominantly of CD3+ T-cells (Panel B; 200X), with scattered CD20+ large B-cells (Panel C; 200X) and an abundance of CD68+ histiocytes (Panel D; 400X).

One month later, the patient presented with acute onset malaise, fatigue, fever (102°F), and pancytopenia: WBC 1.1, hemoglobin 8.5, platelets 56, ferritin 5290 ng/mL, TG 223. Soluble IL2 receptor (sIL-2R) level was markedly elevated at 31,000 U/mL. The diagnosis of hemophagocytic lymphohistiocytosis (HLH) was entertained. Bone

marrow biopsy revealed a hypercellular marrow diffusely infiltrated by sheets of small lymphocytes that stained positive for CD3, CD5, CD7 and CD45 and were interspersed with scattered large atypical lymphocytes that were positive for CD20 and PAX-5 and negative for CD15, ALK-1, and CD30. The histologic findings were indicative of T-cell/Histiocyte rich large B-Cell lymphoma (T/HRBCL). A PET scan demonstrated diffuse lymph node uptake (Figure 2A), and the diagnosis was confirmed by jugular lymph node biopsy (Figure 2B). Retrospective immunohistochemical staining of the patient's liver biopsy was consistent with T/HRBCL (Figure 1B-1D).

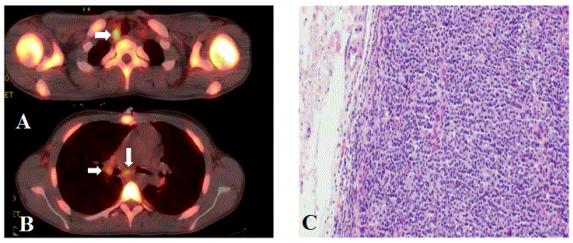

Figure 2: PET images and lymph node histology. PET scan images demonstrating uptake in a right supraclavicular lymph node and sub-carinal and hilar lymph nodes (panel A) are shown. Panel B displays an H&E stained section of a left jugular lymph node demonstrating partial effacement by a mixed population of small lymphocytes and histiocytes interspersed with scattered large atypical B-cells (200X).

Discussion

This patient was initially thought to have autoimmune hepatitis based on liver histology and a compelling biochemical response to immunosuppressive therapy. The correct diagnosis of T/HRBCL subsequently was established by bone marrow biopsy after the patient presented with clinical features of HLH, the diagnostic criteria for which include at least five of the following eight findings: fever >38.5°C, splenomegaly, peripheral blood cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis (in bone marrow, spleen, lymph node, or liver), low or absent NK cell activity, ferritin >500 ng/mL, and elevated sIL-2R (also termed soluble CD25) [1]. Hematological malignancies, particularly non-Hodgkin lymphoma, are the most common underlying disease in adults who present with the hemophagocytic syndrome [2,3]. Moreover, the patient manifested a level of sIL-2R >5000 U/ml and an sIL-2R/ferritin ratio (>2.0) that have been strongly associated with lymphoma [4].

T/HRBCL is a rare subset of Diffuse Large B-Cell Lymphoma (DLBCL). It occurs predominately in middle-aged men, and more commonly involves the liver, spleen, and bone marrow than does DLBCL [5-7]. Typical clinical manifestations of T/HRBCL include generalized fatigue, varying degrees of abnormal liver tests, and organomegaly [8-11]. T/HRBCL is characterized histologically by the presence of fewer than 10% neoplastic B cells interspersed within a robust inflammatory response comprised of small T-lymphocytes, with or without histiocytes [12]. Liver involvement is characterized by infiltration of the portal tracts with large numbers of small, reactive lymphocytes and histocytes, the confluence of which can lead to a "geographic map" appearance [9]. Because the T-cell infiltrate is polyclonal, interface activity is not uncommon, and the scattered neoplastic B cells are easily overlooked, the histologic features seen on liver biopsy can be difficult to distinguish from autoimmune hepatitis. Further confounding the diagnosis in our patient was the excellent biochemical response to immunosuppressive therapy. Khan et al. described eight cases of T/HRBCL presenting as liver disease, one of which was mistakenly diagnosed with "chronic active hepatitis" [11]. Notably, only a single patient in that series was suspected of having lymphoma on the basis of liver histology. In additional small series [10,13], liver disease initially was ascribed to acute hepatitis B, alcoholic hepatitis, choledocholithiasis, primary biliary cirrhosis, or granulomatous hepatitis. A number of these patients succumbed to their illness in short order, highlighting the critical importance of awareness of the diagnosis. Our patient presently remains in remission after receiving 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (RCHOP), along with intrathecal methotrexate.

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