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RESEARCH ARTICLE

HEPATOSPLENIC T-CELL LYMPHOMA MASQUERADING AS CHRONIC LIVER DISEASE: A RARE CLINICAL PRESENTATION

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ABSTRACT

Hepatosplenic T-cell lymphoma (HSTCL) was first described as a distinct clinicopathologic entity in 19901 HSTCL is a rare type of non-Hodgkin lymphoma that was originally recognized by its characteristic clinical presentation, distinct histologic pattern, and expression of the ɤδ T-cell receptor (TCR)1.Recent scientific advances have allowed for better understanding of the histologic, immunophenotyping, and cytogenetic characteristics of HSTCL, including identification of HSTCL with αβ TCR expression. γδ HSTCL and αβ HSTCL are now considered immunophenotypic variants of the same disease. Despite these advances, HSTCL remains a very aggressive subset of T-cell lymphoma and confers a poor prognosis, with a reported median survival of 6–11 months2,3 .There has been no consensus to date regarding therapeutic modalities in these patients, and effective treatment of HSTCL is lacking. A review of the literature reveals the use of various treatment regimens in patients with HSTCL. The majority of these treatment modalities appear to be ineffective in most patients, although there are some case reports and case series that describe complete remissions with certain chemotherapy regimens with or without stem cell transplantation.2,4

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INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) was first described as a distinct clinicopathologic entity in 1990 (Farcet *et al*., 1990) HSTCL is a rare type of non-Hodgkin lymphoma that was originally recognized by its characteristic clinical presentation, distinct histologic pattern, and expression of the ɤδ T-cell receptor (TCR) 1. Recent scientific advances have allowed for better understanding of the histologic, immunophenotyping, and cytogenetic characteristics of HSTCL, including identification of HSTCL with αβ TCR expression. γδ HSTCL and αβ HSTCL are now considered immunophenotypic variants of the same disease. Despite these advances, HSTCL remains a very aggressive subset of T-cell lymphoma and confers a poor prognosis, with a reported median survival of 6–11 months (Falchook *et al*., 2009; Humphreys *et al*., 2008). There has been no consensus to date regarding therapeutic modalities in these patients, and effective treatment of HSTCL is lacking. A review of the literature reveals the use of various treatment regimens in patients with HSTCL.

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The majority of these treatment modalities appear to be ineffective in most patients, although there are some case reports and case series that describe complete remissions with certain chemotherapy regimens with or without stem cell transplantation (Falchook *et al*., 2009; Otrock *et al*., 2008).

Case Report

A 27 year married female, house wife by occupation, presented to JN Medical College Hospital Emergency with complaints of intermittent fever since 8 months, abdominal pain and decreased appetite for 6 months, swelling of feet and distension of abdomen since one month. Review of symptoms was positive jaundice one month back with severe left upper quadrant abdominal pain that radiated to her shoulder off & on. There was also H/0 night sweats &occasional gingival bleeding. Patient denied history suggestive of hematemesis, malena, bone pains, shortness of breath, orthopnea, PND, decreased urine output or weight loss. General Examination revealed pallor and pitting pedal edema. Physical Examination was significant for a palpable spleen 4 cm below the costal margin with hepatomegaly with a liver span of 16 cm. Fluid thrill was present.

The remainder of the physical examination was unremarkable; no lymphadenopathy was noted. Laboratory Investigations revealed the following:- Hb 9.3 gm%, TLC 2400/cu mm, Platelet Count 50,000/cu mm, ESR 58, DLC- P20L30, MCV-92 fl , MCHC- 36 g/dl, Reticulocyte Count 0.9%, Absolute Neutrophil Count 480/mm3, GBP revealed normocytic hypochromic anemia with anisopoikilocytosis. Iron Studies were normal. LFT: ALT 10 U/L, AST 12 U/L, ALP 14, T. Bil 0.9 mg%, Renal Function Test: B. Urea 32 mg%, S.Cr 0.9 mg%, HBsAg, Anti HCV & HIV 1&2 were negative.

USG Abdomen revealed altered liver echotexture (Liver span 16 cm) with dilated portal vein, splenomegaly and ascites without any mesenteric or retroperitoneal lymphadenopathy. TSPAG : Total Protein 4.8 g/dl Albumin 2.9 g/dl, Globulin 1.9g/dl, A:G 1.5, Prothrombin Time 18.4 Sec, INR 2.0,Ascitic Fluid was transudative with SAAG > 1.1 g/dl, UGI Endoscopy was WNL & KF Ring was absent on slit lamp examination. These provisional reports along with the clinical scenario led to a presumptive etiology of chronic liver disease, so a liver biopsy with copper estimation was ordered. Liver Biopsy revealed normal liver architecture and sinusoidal infiltration by a monomorphic population of small to intermediate sized lymphoid cells. Portal tracts were free of such infiltrate. These lymphoid cells were CD2, CD3 positive, TCRγδ+ and negative for CD20, CD34, CD4, CD8 and c-kit.

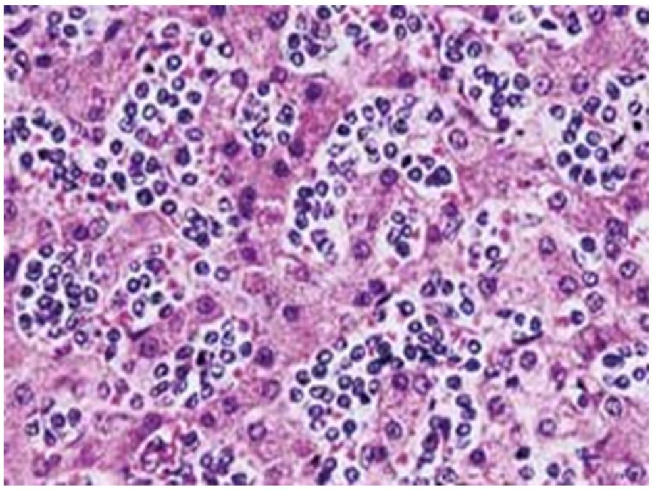

Figure 1. Liver Biopsy revealed infiltration of lymphoid cells in the hepatic sinusoids

Serum lactate dehydrogenase (LDH) was 364U/L (normal level 84–240 U/L) & serum uric acid was 9.0 mg/dL (normal level, 2.6–6.8 mg/dL) which further supported an increased turnover of tumor cells. Finally a bone marrow biopsy was undertaken which showed hypercellular bone marrow with 78% cellularity with small lymphoid aggregates approximately 30% & mild to moderate myelofibrosis with reticulin staining. Bone marrow aspirate showed clusters of medium-sized lymphocytes with irregular nuclear contours, small nucleoli and moderate minimally granular blue cytoplasm. Flow cytometry revealed tumor cells that expressed CD2, CD3, TCRγδ+ positivity, but lacked expression of CD5, CD4, and CD8 suggestive of γδ T-cell Lymphoma. The final diagnosis of the patient thus was stage IV B Hepatosplenicγδ T-cell Lymphoma and was treated with 3 cycles of CHOP chemotherapy. Treatment was well tolerated, with 1 hospitalization for neutropenic fever of unknown etiology that resolved with supportive care.

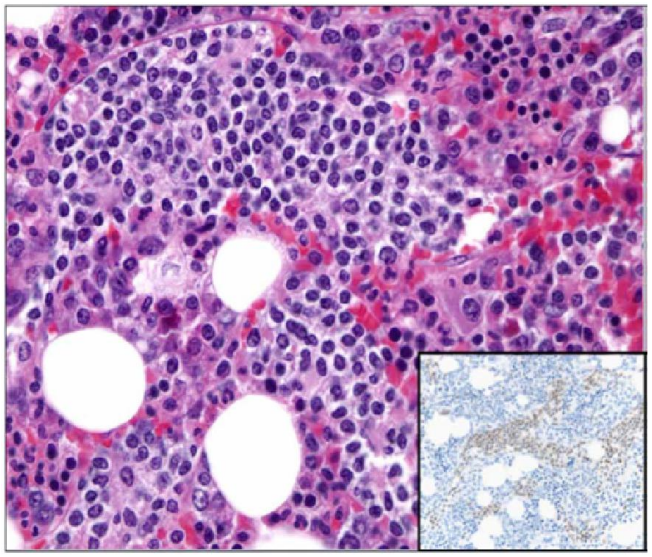

Figure 2. Bone Marrow biopsy revealed interstitial infiltrate with neoplastic lymphoid cells

Three months after diagnosis and following 3 cycles of CHOP, physical examination was remarkable for a non-palpable spleen. The patient is in regular follow up in medicine & oncology opd.

DISCUSSION

Peripheral T-cell lymphomas (PTCLs) account for 7–10% of all non-Hodgkin lymphomas in Western countries, with HSTCL identified as a rare entity within this group 5. HSTCL is a malignancy that usually affects young men inthe third or fourth decade of life, but has been reportedin patients ranging in age from 5 to 68 years (Weidmann, 2000). In approximatelyone-third of patients, HSTCL is associated with ahistory of immunosuppression, as seen in the treatment ofinflammatory bowel disease or organ transplant; it is lesscommonly associated with immunosuppression relatedto Hodgkin lymphoma or malaria (Belhadj *et al*., 2003; Rosh *et al*., 2007). It is hypothesizedthat chronic antigen stimulation in states of immunosuppressionmay contribute to the pathogenesis of HSTCL (Vega *et al*., 2007). While the possibility of an infectious connection has been explored, there is no proven association between Epstein-Barr virus (EBV) and HSTCL (Belhadj *et al*., 2003; Ohshima *et al*., 2000). Patients with HSTCL typically present with hepatosplenomegalyand constitutional symptoms, including night sweats, weight loss, and fevers (Falchook *et al*., 2009; Weidmann, 2000; Belhadj *et al*., 2003; Cooke *et al*., 1996). Lymphadenopathy is present in a minority of patients[2]. Predominant laboratory findings include cytopenias, with thrombocytopenia being a near constant finding with frequently associated anemia and/or leucopenia (Weidmann, 2000; Cooke *et al*., 1996). The severity of thrombocytopenia has been shown to correlate with disease progression (Vega *et al*., 2007). An elevated serum LDH and abnormal liver function tests may also be noted at the time of diagnosis.

HSTCL universally involves the spleen, and theliver and bone marrow have near constant involvement (Belhadj *et al*., 2003; Vega *et al*., 2007). Involvement of other sites, such as the skin, oral mucosa, and kidney, has been rarely reported (Falchook *et al*., 2009; Belhadj *et al*., 2003). Usually, the spleen is massively enlarged, with pathologic features revealing the red pulp to be diffusely infiltratedby small to medium-sized atypical lymphocytes (Farcet *et al*., 1990). Theseatypical cells are seen within the cords and sinuses of the red pulp. The liver is usually involved, as observed in liver biopsy specimens, regardless of the presence of hepatomegaly or abnormal liver function tests at the time of diagnosis (Belhadj *et al*., 2003). Liver pathology demonstrates sinusoidal infiltration by malignant cells. Bone marrow involvement is common, with findings of neoplastic cell infiltration progressing from sinusoidal involvement to interstitial involvement over time, though it may initially be difficult to recognize (Belhadj *et al*., 2003; Vega *et al*., 2007; Cooke *et al*., 1996; Vega *et al*., 2001).

Immunophenotypic features, along with cytogenetic and molecular features, aid in the diagnosis and understanding of HSTCL. The most common immunophenotypein patients with HSTCL is as follows: CD2+, CD3+,CD4–, CD5–, CD7+/–, CD8–, CD16+/–, CD 38+, and CD56+. Our patient had a common immunophenotypicprofile of CD2+, CD3+, CD4–, CD5–, CD7+, CD8– and CD56+. Neoplastic cells usually have a non-activated cytotoxic phenotype (TIA1+, granzyme B–) (Belhadj *et al*., 2003). HSTCL was first described with γδ TCR expression. While γδTCR expression is seen in the majority of patients, there are increasing reports of αβ TCR expression (Lai *et al*., 2000; Macon *et al*., 2001; Nagai *et al*., 2010). Both are now considered immunophenotypic variants of the same disease (Vega *et al*., 2007). A diagnostic approach using immunohistochemistry of bone marrow showing CD3+, CD5– lymphocytes with sinusoidal distribution is sufficient (Belhadj *et al*., 2003). Despite these criteria, a large pathologic review showed only a 72% agreement for the diagnosis of HSTCL (Vose *et al*., 2008). Certain cytogenetic and molecular features have been found in patients with HSTCL, most notably, isochromosome 7q and less commonly, trisomy 8 (Wlodarska *et al*., 2002; Jonveaux *et al*., 1996). Various treatment regimens and modalities have been reported in the literature, including splenectomy; steroids; alkylating agents;cyclophosphamide, doxorubicin,vincristine, and prednisone (CHOP) therapy; purine analogues; multi-agent approaches; and autologous or allogeneic hematopoietic SCT. While the majority of patients observed showed initial clinical improvement, very few obtained complete remissions, with the majority of patients clinically progressing until time of death. HSTCL has a poor overall survival, with the only positive prognostic factor being female sex (Falchook *et al*., 2009). The International Prognostic Indicator has no impact on outcome[16]. A history of immunocompromise is associated with a poorer prognosis (Falchook *et al*., 2009). However, treatment strategies for a sustained response are still needed. Continuing efforts to understand PTCL and actively enroll these patients in clinical trials are crucial.

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