Prolonged fever with pancytopenia and massive hepatosplenomegaly

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ABSTRACT

Prolonged fever with pancytopenia and hepatosplenomegaly is a clinical entity frequently encountered by physicians. The diagnosis of such cases is challenging due to the diversity of differential diagnoses. Hepatosplenic T-cell lymphoma is a rare and aggressive type of non-Hodgkin lymphoma that can present with massive hepatosplenomegaly, pancytopenia and prolonged fever. Most of the patients are young men and the majority are associated with chronic immunosuppression. We report a 40-year-old immunocompetent woman with prolonged fever and pancytopenia due to hepatosplenic T-cell lymphoma.

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INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive type of lymphoma that represents <1% of non-Hodgkin lymphoma and 1.4% of all T-cell lymphomas.[1,2] HSTCL is characterized by infiltration of malignant T-cells within the red pulp of the spleen, sinusoids of the liver and sinuses of bone marrow leading to hepatosplenomegaly and pancytopenia.[3] Most HSTCL occur in young men (M:F of 9:1) and 20% are associated with chronic immunosuppression.[4–6] The prognosis is poor as the clinical course is aggressive, with a certain fatal outcome and a median survival of 6–11 months.[5]

THE CASE

A 40-year-old woman was referred to us from a peripheral hospital with complaints of low-grade fever for 10 months along with progressive abdominal distention, early satiety and easy fatigability. She had a history of multiple blood transfusions in the past 10 months. She also had a history of non-quantified weight loss associated with decreased appetite with drenching night sweats. There was no history of any chronic medical condition, diabetes mellitus, high-risk behaviour, organ transplantation or the use of any immunosuppressive medications. On examination, her vitals were normal. She was thin built with pallor and the liver was enlarged 6 cm below the right costal margin and there was a massive spleen palpated till the right iliac fossa. There was no lymphadenopathy or skin rashes. The rest of the systemic examination was normal.

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Her initial laboratory work-up showed pancytopenia with haemoglobin 6.0 g/dl, white cell count 2×103/μL and platelets 60×103/μL. RBC indices were normal; corrected reticulocyte count was 2%. Peripheral smear was suggestive of pancytopenia with anisopoikilocytosis. No blast or atypical cells were seen in the peripheral smear. The aspartate aminotransferase was 30 i.u., alanine aminotransferase was 29 i.u. and alkaline phosphatase was 50 i.u.. The coagulation profile (prothrombin time 15 seconds, activated partial prothrombin time 32) was normal. Kidney function tests, serum electrolytes, including calcium, serum angiotensin-converting enzyme, lactate dehydrogenase and uric acid levels, were normal. Based on the above presentation, differential diagnosis of chronic infection, autoimmune disease, haematological malignancy or any infiltrative pathology was considered.

Screening tests for malaria, leishmania, HIV, hepatitis B and C and histoplasma were negative. The Mantoux test was negative. The antinuclear antibody, anti-smooth muscle antibody, anti-liver-kidney microsomal antibody were negative. Serum ceruloplasmin and serum ferritin were normal. Fibroscan measured median liver stiffness of 12.1 kPa. Upper gastro-intestinal endoscopy was normal. Contrast-enhanced computed tomography (CECT) of the chest was normal while CECT of the abdomen showed hepatomegaly (20 cm) and splenomegaly (27 cm) with portal hypertension. Bone marrow aspiration and biopsy were done in peripheral hospitals at the initial presentation and were suggestive of hypercellular bone marrow with trilineage hyperplasia.

Because of a high suspicion of haematological malignancy, a repeat bone marrow biopsy was done in our centre, which was suggestive of diffuse infiltration of mature lymphocytes in the bone marrow along with areas of trilineage haematopoiesis. In immunohistochemistry, atypical cells were positive for CD5 and leucocyte common antigen. Liver biopsy was done after consent and platelet transfusion, which showed lymphoid aggregates in lobular parenchyma with CD3 positivity and CD2 and CD 30 negativity—suggestive of T-cell lymphoproliferative disorder. The cytogenetic analysis could not be done due to financial constraints. Therapeutic and diagnostic splenectomy was done because of massive splenomegaly with hypersplenism and persistent pancytopenia. The patient was vaccinated for *Streptococcus pneumoniae*, *Haemophilus influenza* and *Neisseria meningitis* 2 weeks before the surgery. The procedure was uneventful. The gross specimen of the spleen was congested, measuring 18×16×14 cm and weighing 1.5 kg. Histopathology showed marked expansion of the red pulp with intervening areas of white pulp replaced by sheets of small lymphocytes focally admixed with foci of extramedullary haematopoiesis. The infiltrating tumour cells were strongly positive for CD3 and CD8 while negative for CD4, CD5 and CD23, which was suggestive of HSTCL (Fig. 1). The final diagnosis of HSTCL (Ann Arbor stage IV) was made. The patient showed clinical improvement with therapeutic splenectomy followed by six cycles of cyclophosphamide, doxorubicin, vincristine and prednisone. She was under regular follow-up at our hospital for 6 months post-chemotherapy (January 2020) without any evidence of recurrence but then was lost to follow-up.

DISCUSSION

Patients presenting with massive hepatosplenomegaly with pancytopenia require a detailed history, physical examination

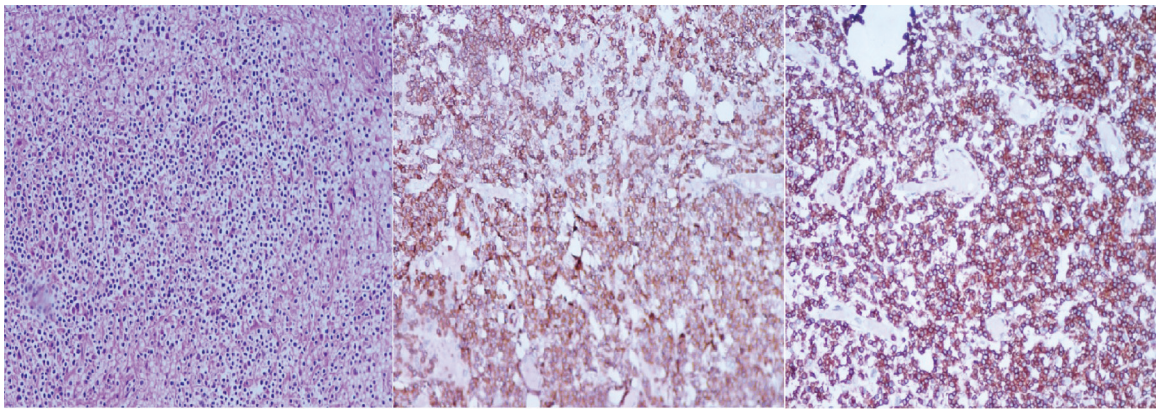

FIG 1. (a) ×100 magnified view of haematoxylin and eosin stain of spleen showing sheets of small lymphocytes; (b) immunohistochemistry showing CD3 positivity; and (c) CD5 positivity

and work-up. The diagnosis of HSTCL is challenging and requires a high degree of clinical suspicion. Most patients of HSTCL present with hepatosplenomegaly and pancytopenia with bone marrow involvement.3 Patients described earlier were young men with underlying chronic immunosuppression.[4,7,8] In contrast, our patient was a 40-year-old immunocompetent woman.

HSTCL remains an aggressive type of T-cell lymphoma with a median survival of 6–11 months, the 5-year overall survival rate of 7%, and a 5-year failure-free survival rate of 0%.1,6 However, our patient got diagnosed with HSTCL after 10 months of progressive symptoms and responded to therapeutic splenectomy and chemotherapy and was doing well for 6 months post-chemotherapy. This less aggressive nature of the disease in our patient could be related to her immunocompetent status and female sex. Falchook *et al*. reported that overall survival for women was 25 months, compared with 8 months for men and female gender is the only positive prognostic factor for HSTCL.[6]

Clonal rearrangement of the g gene of T-cell receptor, isochromosome 7q and trisomy 8 on cytogenetics are typically seen in cases of HSTCL. The cytogenetic analysis could not be done for the patient, and is a major limitation.

There are limited data on the treatment of HSTCL and no standard therapy exists. The majority of patients of HSTCL have initial clinical improvement, but few obtained complete remission. Autologous or even allogeneic transplantation can be considered in patients who achieve complete remission.

Although rare, the diagnosis of HSTCL should be considered along with other common haematological malignancies in a patient presenting with massive hepatosplenomegaly with pancytopenia and B symptoms.

Conflicts of interest. None declared

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