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Hepatosplenic T-Cell Lymphoma in an Immunocompetent Young Female: A Diagnostic Challenge

Dr. Rachana Singh[1*], Dr. Ravindra Votterry[2*], Dr. Milap[1], Dr. Seema Afroz[1]

[1]Department of Laboratory Medicine, Yashoda Hospitals, India
[2]Department of Medical Oncology, Yashoda Hospitals, India

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***Corresponding author:** Dr. Rachana Singh
Department of Laboratory Medicine, Yashoda Hospitals, India

Abstract **Case Report**

Hepatosplenic T-cell lymphoma (HSTCL) is a rare T-cell neoplasm, most commonly arises from a small subset of γ/δ T-cell receptor–expressing lymphocytes and forms less than 1% of all non-Hodgkin's lymphomas. HSTCL is more common in adolescent and young adults and has a rapidly progressive clinical course and poor outcome due to its refractoriness to conventional chemotherapy regimens. The rarity of this disease, along with lack of nodal involvement and presenting symptoms that mimic different entities including infectious aetiologies, makes this lymphoma a significant diagnostic challenge. To place emphasis on the challenges encountered in establishing the diagnosis, here in, we present a case of a 29-year-old-female who presented with asymptomatic pancytopenia and massive splenomegaly. After an elaborate workup, and extensive investigations, which all turned out to be negative, a combination of morphologic finding of atypical lymphoid cells in the bone marrow, typical immunophenotypic profile on flow cytometry and the pattern of involvement of the bone marrow biopsy, were a key in diagnoses. The report of this case is an effort to emphasize the high index of suspicion for timely detection of such a rare entity.

Keywords: Hepatosplenomegaly, Malignancy, T-Cell Lymphoma.

I. INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a rare subtype of peripheral T-cell lymphoma (PTCL), first described in 1981 [1], the term "Hepatosplenic T-cell lymphoma" was first used in 1990 [2], and has been adopted to describe this neoplasm in the World Health Organization (WHO) classification [3]. HSTCL is characterized by a proliferation of small-medium–sized mature T cells infiltrating the sinusoids of liver and spleen as its name indicates. Clinical presentation, histologic features, and molecular findings make this disease a unique entity among other PTCLs. Although lymphocytosis is uncommon, a small population of atypical lymphocytes can be detected by flow cytometry in ~50% of patients. As the presentation and blood work resemble those of other benign and malignant hematologic conditions, the diagnosis requires a high level of suspicion and is confirmed by a combination of clinical findings with histologic and immunophenotypic analysis of the tissue biopsy [2]. HSTCL is more common among young males in their teenage years and in young adulthood [2, 3]. It exhibits a rapidly progressive clinical course and a poor response to currently available therapies, with a 5-year survival rate of 7% 4. Herein, we report a case of this rare disease from our institute, highlighting the clinicopathologic features of this uncommon T cell Non-Hodgkin Lymphoma (NHL) and emphasizing a combination of clinical findings, histologic features, flowcytometry and immunohistochemistry (IHC) in detecting this unique entity.

II. CASE REPORT

This is a case of 29 yr young female who presented with pancytopenia and abdominal discomfort, investigated elsewhere at three other corporate hospitals/ centers and came for fourth opinion at our center with history of weight loss 10kg in 4 months, easy fatiguability, fever low grade and occasional bone pains. She is married for 9 yrs., has regular menstrual cycles, and has one child. On examination, pallor, moderate hepatomegaly, massive splenomegaly were discerned. She is vaccinated for covid.

The blood work showed anaemia (Haemoglobin 7.4g/dl) with thrombocytopenia (Platelet count 54000/cmm). Total leucocyte count was markedly decreased (710 cells/µl); however, there were no significant abnormalities on the peripheral smear.

The other abnormal findings were moderately raised liver enzymes, LDH and C-reactive protein were increased. Coagulation profile, renal function tests, viral markers (for hepatitis B, hepatitis C and Human Immunodeficiency Virus), autoimmune profile [Antinuclear antibodies (ANA, DsDNA negative) and Anti-neutrophil cytoplasmic antibodies (ANCA)] were unremarkable. Uric acid was 5.1.

Bone marrow done outside was dilute and marrow biopsy was cellular with no increase in reticulin and no identified abnormal or atypical cells. Serum electrophoresis done showed no M band and Flowcytometry for PNH showed minor PNH clone.

Ultrasonography confirmed massive splenomegaly 20cm and spleniculi 2.6cm with moderate hepatomegaly. As part of radiological investigations, the triphasic CT abdomen revealed no shunts or ascites. PET CET findings were suggestive of hepatosplenomegaly with multiple spleniculi with diffuse marrow and spleen uptake.

Based on the above clinical details a Provisional clinical diagnosis of massive splenomegaly with Pancytopenia and the possibilities considered were IMF (idiopathic myelofibrosis), SMZL (splenic marginal zone lymphoma), HCL (Hairy Cell Leukemia).

In view of the severe pancytopenia, bone marrow aspiration and biopsy were repeated at our center. Bone marrow aspiration showed a cellular marrow infiltrated by abnormal small to medium sized lymphoid cells (20%), having a high N: C ratio, round to oval nuclei, clumped chromatin and scant to moderate cytoplasm along with trilineage haematopoiesis.

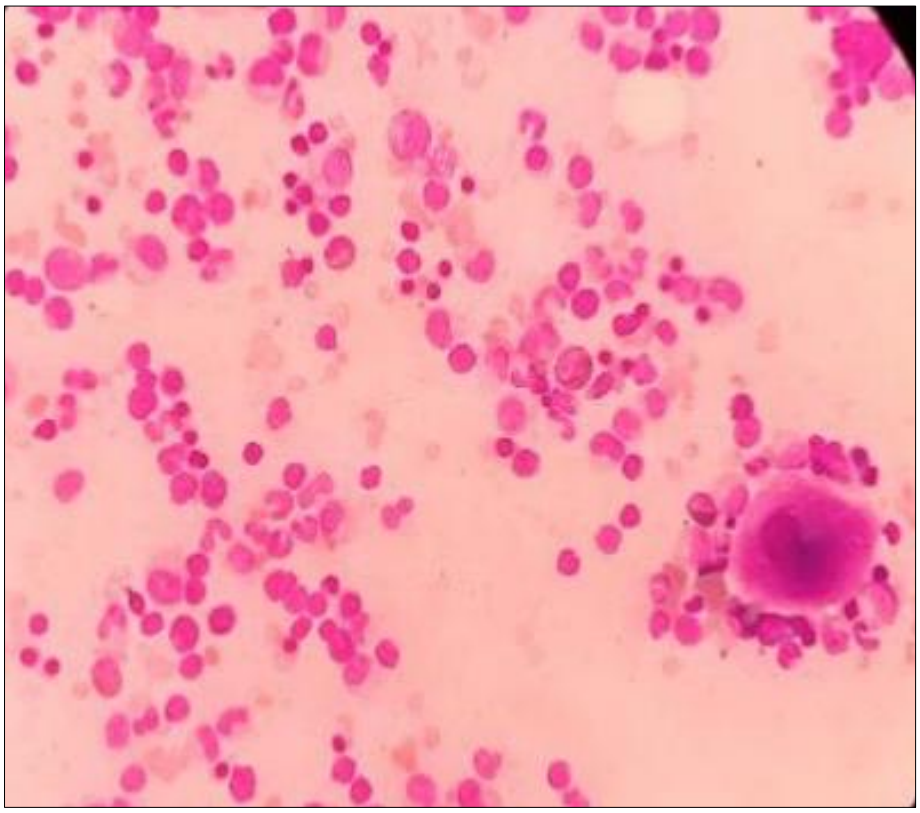

Fig. 1: Bone marrow aspirate showing infiltration by atypical lymphoid cells [Leishman stain]

Flow cytometric analysis was performed on the marrow aspirate sample using a comprehensive panel. The sample was processed by standard lyse-wash procedure and data was analysed using the FACS diva soft ware in the eight-colour Becton Dickinson (BD) FACS CANTO flow cytometer.

The lymphoid cell cluster was gated on CD45, Forward Scatter and Side Scatter which comprised 14to15% of total leukocyte population showed T cell proliferation (CD3+CD7+ CD 2+) with loss of CD5, CD4 and CD8. These cells were negative for CD 34, Terminal deoxynucleotidyl transferase (TdT) and CD1a. A scant B cell population identified with B cell markers (CD 19, CD 20, CD 10, CD 79a) with no evidence of clonality (negative for kappa, lambda) and myeloid markers (CD 33, HLA-DR, CD 13, MPO) were negative. [All antibodies from BD Biosciences, San Jose, CA, USA]. The T cell receptor analysis (γδ) was performed - *Negative for TCR gamma delta*. The immunophenotype suggested a T cell NHL infiltrating the marrow, with the possibility of HSTCL, considering the clinical and the radiological findings. Negativity of the atypical cells for TdT and CD 34 did not favour a leukemic disease.

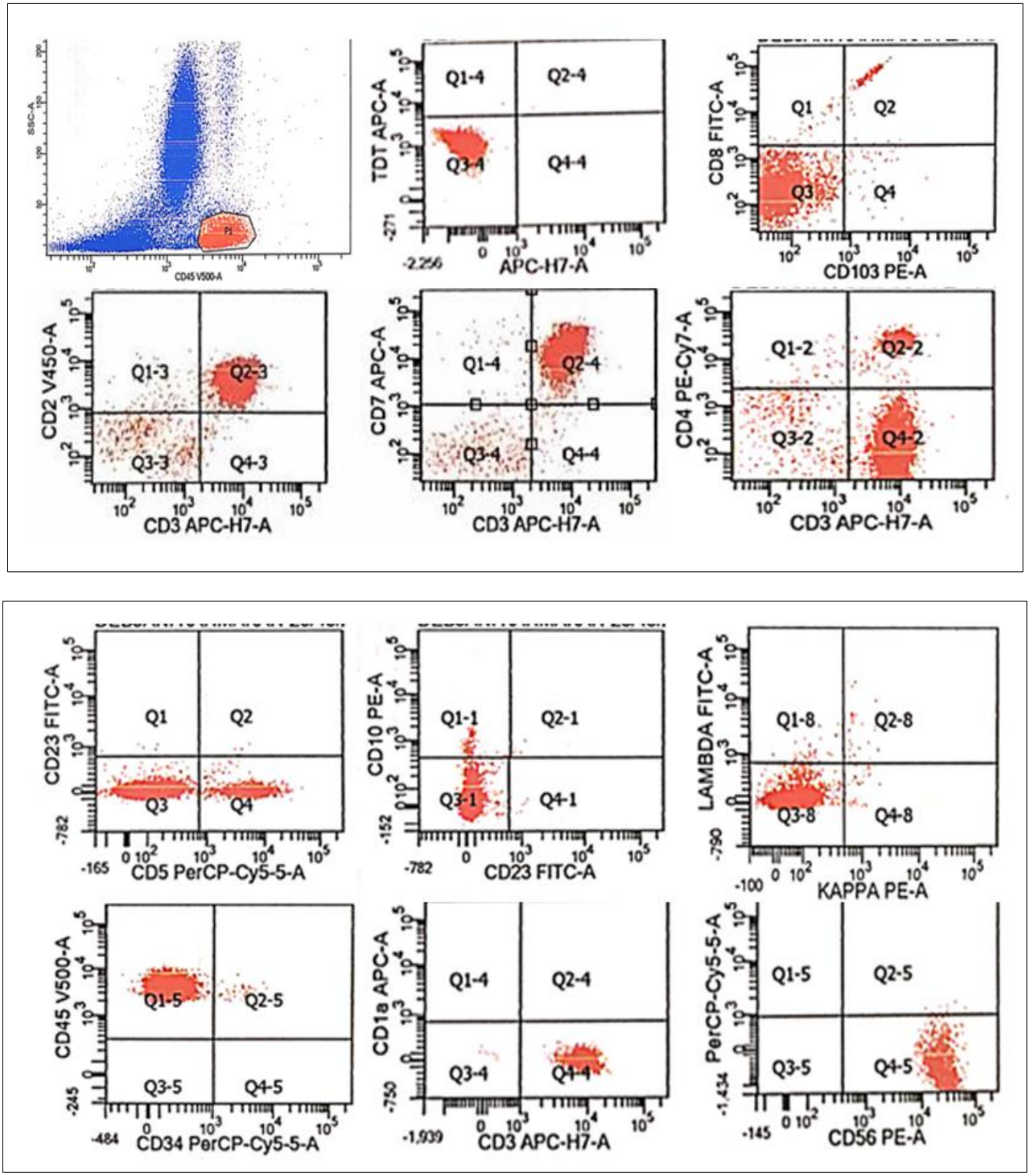

Fig. 2: Flow cytometric analysis exhibiting predominance of the lymphoid population which was gated on the CD45 vs Side Scatter plot. The gated events demonstrate positivity for cytoplasmic & surface CD3, CD7 and CD56, while negative for CD4, CD8 CD34, CD103, TdT, CD10, CD5, CD23, CD1a, kappa &lambda and CD19.

III. Biopsy Morphology

The bone marrow biopsy shows increased cellularity for the age of the patient.

The M: E ratio appears normal. Granulopoiesis shows sequential maturation. Erythropoiesis is normoblastic. megakaryocytes that are normal in number and morphology. Bone marrow core biopsy showing sinusoidal expansion by medium-sized lymphoid cells was noted.

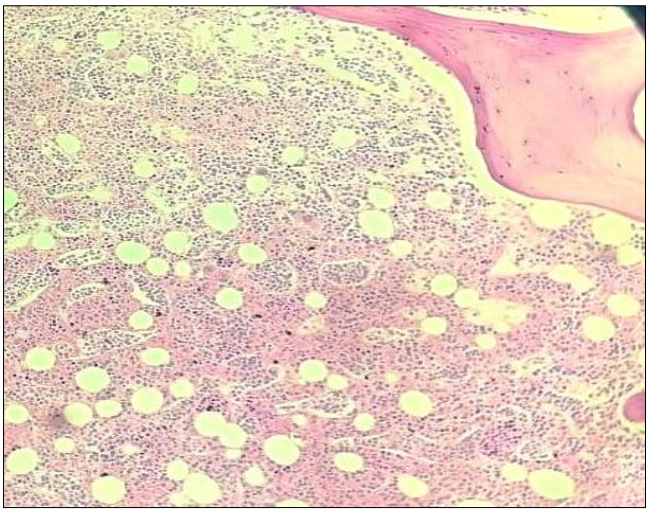

Fig. 3: Bone marrow biopsy revealing sinusoidal infiltration by atypical lymphoid cells

The sinusoidal proliferation of lymphocytes highlighted on immunohistochemistry by expression of CD3, CD7 & CD2. They are negative for CD5, CD4 & CD8 (dual negative).

TCR gamma is not expressed. TCR alpha beta could not be adequately assessed.

CD34 & CD117 do not highlight increased blast.

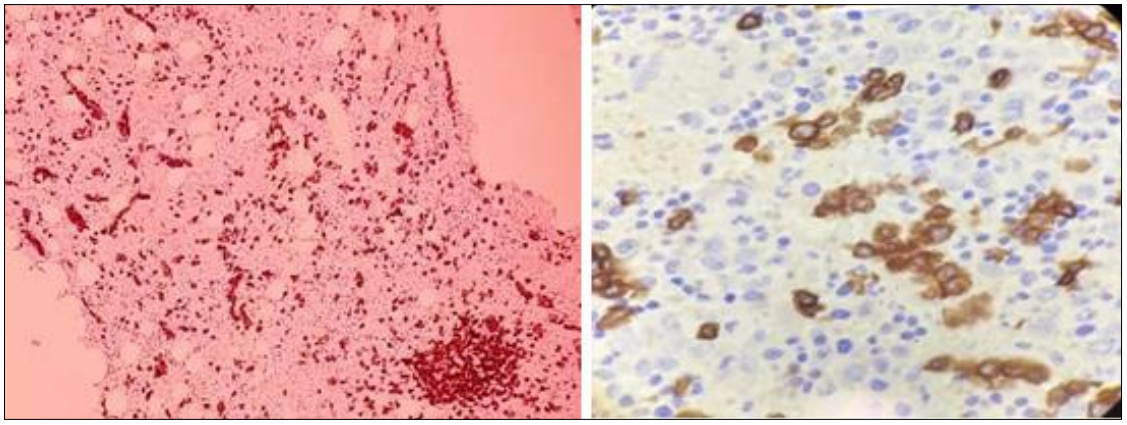

Fig. 4.1: Bone marrow biopsy revealing sinusoidal infiltration by atypical lymphoid cells

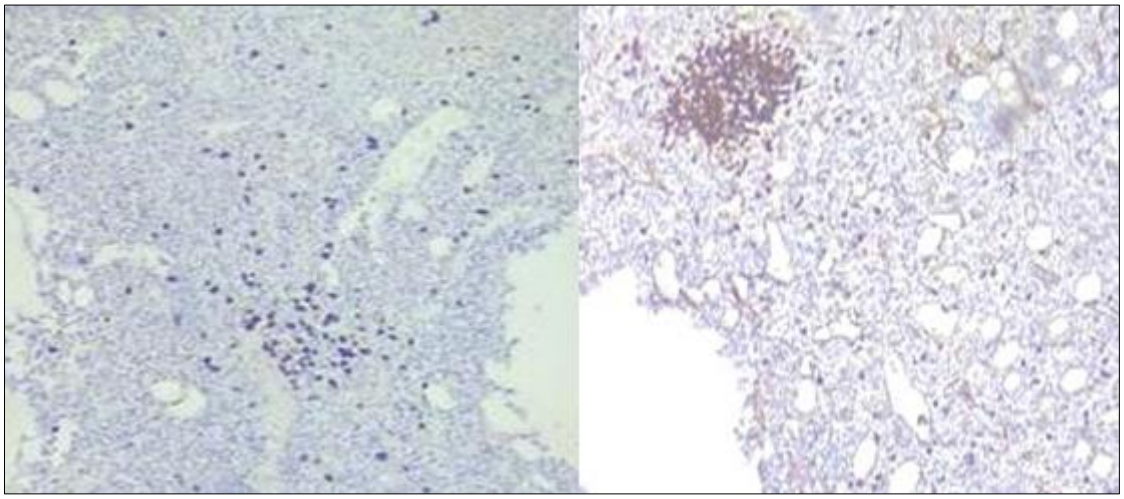

Fig. 4.2: Bone marrow biopsy showing infiltration by atypical lymphoid cells, which are negative for CD4& CD8 on IHC along with a reactive lymphoid follicle

In view of loss of CD5, CD4 CD8 and massive Splenomegaly, a diagnosis suspicious of hepatosplenic 'T' cell lymphoma was given also suggested to obtain a biopsy from the spleen for exact categorization.

All these findings thus corroborated and confirmed the diagnosis of HSTCL, Hepatosplenic T cell lymphoma involving the liver, spleen and bone marrow. Further ancillary tests such as cytogenetics/molecular analysis could not be done.

IV. DISCUSSION

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive form of T-cell lymphoma, primarily affecting adolescents and young adult males, with a median age of onset between 29 and 38 years [2]. The male-to-female ratio is approximately 9:1 [9]. According to a retrospective study of 1,314 cases of T-cell lymphoma worldwide, HSTCL accounts for only 1.4% of cases. Although the exact pathogenesis of HSTCL is poorly understood, persistent antigenic stimulation is thought to play a role. The disease occurs more frequently in immunocompromised patients, particularly those on long-term immunosuppressive therapy [7,10].

Patients with HSTCL typically present with symptoms such as fever, fatigue, weight loss, and abdominal discomfort due to hepatosplenomegaly. Jaundice may also occur if the liver is involved. Lymphadenopathy is uncommon, reported in less than 25% of patients [11]. Physical and radiographic examinations commonly reveal hepatomegaly and splenomegaly, often massive, with bone marrow involvement nearly always present. Patients usually exhibit thrombocytopenia, along with leukopenia and anaemia [4].

In this case, the female patient lacked a history of immunosuppression, which is unusual given that most cases in the literature involve males. Despite being asymptomatic initially, the patient's pancytopenia was initially attributed to secondary bone marrow suppression, and a diagnosis of paroxysmal nocturnal haemoglobinuria (PNH) was ruled out due to elevated bilirubin and anaemia.

HSTCL can present with different patterns of bone marrow involvement, including sinusoidal, interstitial, or mixed sinusoidal and interstitial. The neoplastic cells in HSTCL vary in size, ranging from small to medium to large, and may resemble blasts with irregular nuclear membranes and small but conspicuous nucleoli. In our case, medium-sized blast-like cells were identified infiltrating the marrow, raising the possibility of lymphoma infiltration [8].

Diagnosis of HSTCL relies on a combination of clinical findings, morphologic analysis of liver, spleen, or bone marrow biopsy, peripheral blood smear, immunophenotyping, and cytogenetic or molecular studies [7]. The characteristic immunophenotype of HSTCL cells—CD3+, usually TCRγδ+, TCRαβ-, CD56+/-, CD4-, CD8-/+, CD5-, and TIA1+—is crucial for diagnosis [1]. In resource-limited settings where T-cell receptor markers may not be available, delineation of the T-cell receptor type is not mandatory. Flow cytometry is preferred over immunohistochemistry (IHC) for distinguishing HSTCL from other aggressive T-cell neoplasms, as it allows for the detection of surface and cytoplasmic CD3 and surface TCR [9].

The differential diagnosis includes T-cell acute lymphoblastic leukaemia/lymphoma (T-ALL), which typically expresses TdT, CD34, and CD10, and T-cell large granular lymphocyte leukaemia (T-LGL), which involves older individuals and has a more indolent clinical course. Unlike HSTCL, T-LGL is characterized by moderately sized spleen, no increase in serum LDH, large granular lymphocyte morphology, and absence of the i(7q) chromosomal abnormality [10].

HSTCL's sinusoidal infiltrate can be subtle on bone marrow biopsy, sometimes obscured by reactive hematopoietic cells, which may lead to a misdiagnosis of myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm (MDS/MPN) [11]. Therefore, a high index of suspicion and the use of immunohistochemistry are crucial for accurate diagnosis, especially in the presence of hepatosplenomegaly, cytopenia, and absence of lymphadenopathy.

HSTCL is known for its rapid and progressive course, and due to its rarity, there is no established standard therapy. Common treatment regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and Hyper CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate and cytarabine), often followed by stem cell transplantation. Although some patients initially respond to chemotherapy, relapse is common, and the overall prognosis remains extremely poor, with a median survival of less than two years [11].

V. CONCLUSION

The diagnosis of Hepatosplenic T-cell Lymphoma (HSTCL) can be particularly challenging due to its ability to mimic infectious etiologies or other malignant disorders, which often leads to significant delays in diagnosis and treatment. The rarity of HSTCL and the absence of nodal involvement in most cases further complicate the diagnostic process. Clinicians should suspect HSTCL when presented with classical clinical features such as bi/pancytopenia, organomegaly (particularly hepatosplenomegaly), and the lack of significant lymphadenopathy, alongside the presence of abnormal lymphoid cells (but not blasts) in the blood.

Historically, splenectomy was a common diagnostic procedure for HSTCL. However, in current practice, liver and/or bone marrow biopsy, supplemented by flow cytometry, are typically used to make the diagnosis. The study underscores the importance of

considering HSTCL in cases of cytopenia accompanied by atypical lymphoid cells in the bone marrow, massive hepatosplenomegaly, and the absence of significant lymphadenopathy, particularly in young males and females. The often-misleading morphology seen during diagnosis, coupled with the typical immunophenotype and sinusoidal bone marrow involvement, can provide important clues for an accurate diagnosis.

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