Malays J Pathol 2026; 48(1): 133 – 137

CASE REPORT

Hepatosplenic T-cell Lymphoma Masquerading as Idiopathic Cytopenia

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Abstract

Introduction: Hepatosplenic T-cell lymphoma (HSTL) is a highly aggressive form of mature T-cell lymphoma, characterised by abnormal proliferation of cytotoxic T cells in the spleen, liver, and bone marrow. It accounts for <1.0% of all non-Hodgkin lymphomas. *Case report*: We present a case of HSTL in a 32-year-old male who came with pancytopenia, abdominal distension, constitutional symptoms, and splenomegaly. Initial bone marrow examination was misdiagnosed as Myelodysplastic Syndrome (MDS) or Myelodysplastic Syndrome/Myeloproliferative Neoplasm (MDS/MPN). A repeated bone marrow examination showed CD3-positive neoplastic lymphoid cells in the bone marrow intrasinusoidally and immunophenotyping revealed predominance of gamma-delta (γδ) T-cells. *Conclusion*: This case highlights the importance of including HSTL in the differential diagnosis when a patient exhibits splenomegaly and pancytopenia even though background dyspoiesis is prominent. This will enable an early diagnosis of this aggressive cancer.

Keywords: gamma-delta, intrasinusoidal, hepatosplenic T-cell lymphoma, HSTL

INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTL) is a rare type of non-Hodgkin Lymphoma, derived from γδ cytotoxic T-cells. They usually occur in a young adult and can present with hepatosplenomegaly. Lymphadenopathies are usually absent. Histologically, they are characterised by extranodal involvement with typical sinusoidal patterns. Background dyspoiesis is commonly seen. These findings could mask the subtle infiltration especially in the early stages which might cause a delayed diagnosis. Dysplasia does not seem to correlate with the prognosis of the disease. High dose chemotherapy and eventually haematopoietic cell transplantation is the treatment option currently. We herein describe a case of HSTL that was initially misdiagnosed and only on second bone marrow examination, the diagnosis was established.

CASE REPORT

A 32-year-old male presented with abdominal distension, loss of appetite, and night sweats. He did not have any previous medical history. On examination, he had a huge splenomegaly, no hepatomegaly and no lymphadenopathies. A computed tomography of the thorax, abdomen and peritoneum (CT-TAP) revealed a huge spleen crossing midline and encroaching the pelvic cavity. A baseline positron emission tomography (PET) scan showed an enlarged liver with massive splenomegaly (29 cm) with no abnormal enlarged lymph nodes. Full blood count (FBC) showed pancytopenia with haemoglobin of 85 g/L, white blood cells of 1.0×10^9/L, neutrophils of 0.32×10^9/L, lymphocytes of 0.55×10^9/L, and platelets of 48×10^9/L. Full blood picture (FBP) did not reveal any blasts/abnormal lymphoid cells. A bone marrow procedure (BMAT) was

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undertaken in another centre. It was initially diagnosed as Myelodysplastic Syndrome (MDS) or Myelodysplatic Syndrome/Myeloproliferative Neoplasm (MDS/MPN) need to be considered due to the background trilineage dysplasia seen. No lymphocytosis was noted in the bone marrow aspirate. The patient was then referred to our centre for continuation of care. Upon referral, he remained with pancytopenia with haemoglobin of 86 g/L, white blood cells of 0.8×10^9/L, neutrophils of 0.2×10^9/L, lymphocytes of 0.5×10^9/L, and platelets of 40×10^9/L. Lactate dehydrogenase (LDH) was within normal range. Viral screenings were non-reactive. No evidence of any chronic immunosuppression or underlying immune dysregulation was identified. Blood culture and sensitivity showed no growth. A repeated BMAT was done (approximately 3 months from the previous/first BMAT). Bone marrow aspirate showed hypercellularity with the presence of 15.0% abnormal lymphoid cells (Figure 1). Immunophenotyping analysis revealed 9.0% abnormal T-cells with gamma-delta (γδ) restriction with dim CD8 (Figure 3). Trephine biopsy showed evidence of abnormal lymphoid cells with prominent intrasinusoidal involvement (Figure 2). The abnormal lymphoid cells were positive for CD3, TIA1, CD56 and high Ki-67 proliferative index with negative CD1a, CD4, CD5, CD10, TdT, CD30, CD34, and EBER-ish. CD8 was negative in trephine biopsy.

He was then started on cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy which was complicated with neutropenic sepsis and profound cytopenia requiring transfusion support in each cycle. Following the third cycle, he developed splenic abscesses and sub-diaphragmatic collection treated with intravenous (IV) ceftazidime for 4 weeks. A CT scan taken in the interim showed a reduction in spleen size to 22 cm, with persistent splenic lesions.

He underwent splenectomy and a histopathological examination of the spleen showed scattered T-cells with abnormal phenotype (CD3 positive and CD5 negative), suggestive of residual disease. Post splenectomy, his pancytopenia resolved, and his chemotherapy treatment was switched to cyclophosphamide, vincristine, adriamycin, doxorubicin, methotrexate and cytarabine as per the hyper-CVAD protocol and scheduled for allogeneic stem cell transplant (ASCT) following completion of chemotherapy.

DISCUSSION

HSTL is an uncommon, extranodal T-cell lymphoma that affects the spleen, liver, and bone marrow. They account for 1.4%-2.0% of peripheral T-cell lymphoma cases.[1] It usually affects young adults and has a poor prognosis.

They often present with constitutional symptoms, hepatosplenomegaly, and peripheral cytopenias, findings that may overlap with various myeloid and lymphoid neoplasms. Leukemic and blastic evolution have also been documented in more advanced cases.[2]

Point to note in this case was the patient was initially misdiagnosed with a MDS or MDS/MPN based on persistent cytopenias, splenomegaly, and a hypercellular bone marrow with dysplatic features. Dyspoietic changes in the bone marrow are increasingly recognized

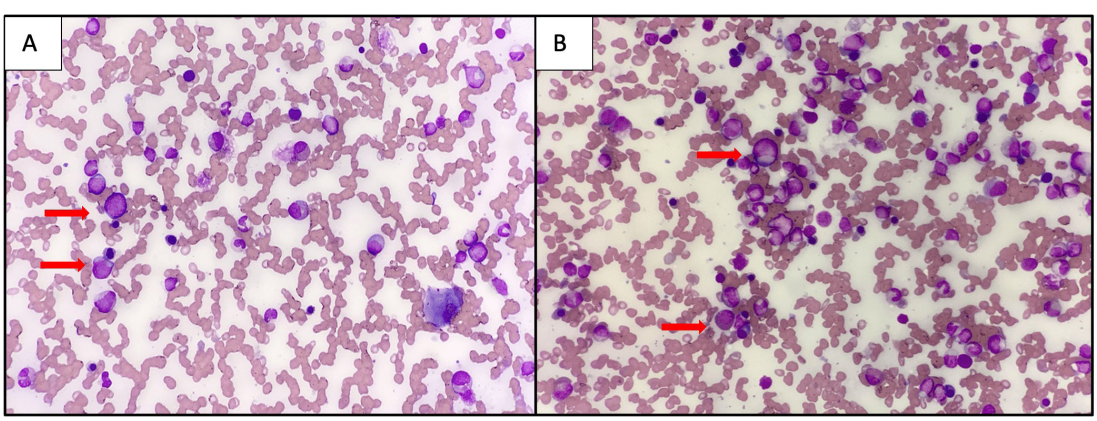

Figure 1. Bone marrow aspirate (×400) A&B) abnormal lymphoid cells (red arrow) which are medium in size, with round nuclei, pale cytoplasm and inconspicuous nucleoli. Occasional cells show prominent nucleoli.

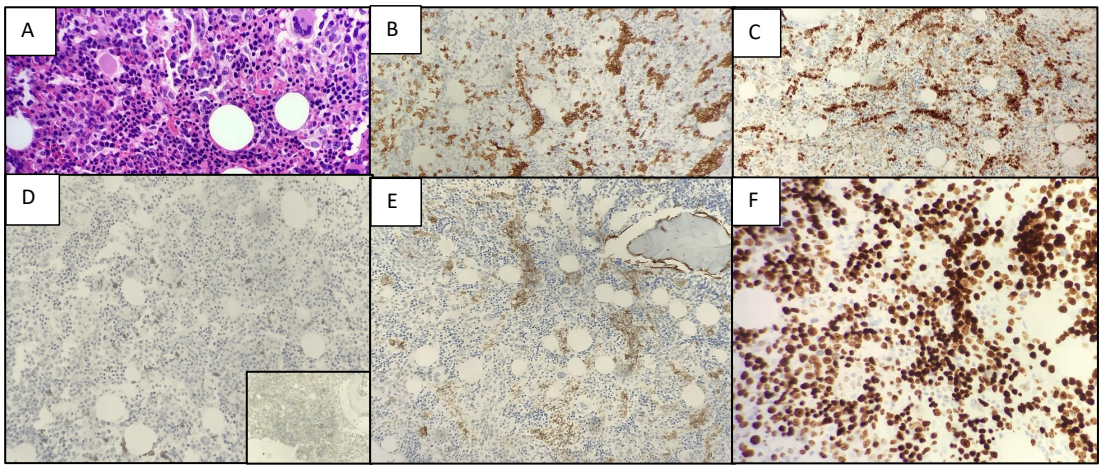

Figure 2. Trephine biopsy A) presence of abnormal lymphoid (×400), B) CD3 positive (intrasinusoidal pattern) (×400), C) TIA1 positive (×400), D) CD8 negative (×200) and inset show CD4 negative (×200), E) CD56 positive (×400), F) high Ki-67 (×400).

in HSTL, often leading to diagnostic confusion with MDS or MDS/MPN. In a series of 25 patients with HSTL, Yabe *et al*. observed that 80.0% exhibited dyspoetic features in one or more haematopoietic lineages.[3] These morphologic abnormalities, when accompanied by cytopenias and splenomegaly, can mimic other myeloid neoplasms, particularly in early disease when lymphoid infiltrates are sparse or predominantly sinusoidal. Importantly, the study concluded that these dysplastic changes are reactive or secondary to the marrow infiltration rather than indicative of a true clonal myeloid disorder.[3] This highlights a common diagnostic pitfall, as the marrow findings in HSTL can be subtle and non-specific in early stages. Given the rarity of HSTL, clinicians/pathologists may not immediately suspect it, leading to misinterpretation and misdiagnosis.

The γδ T-cells are primarily located in

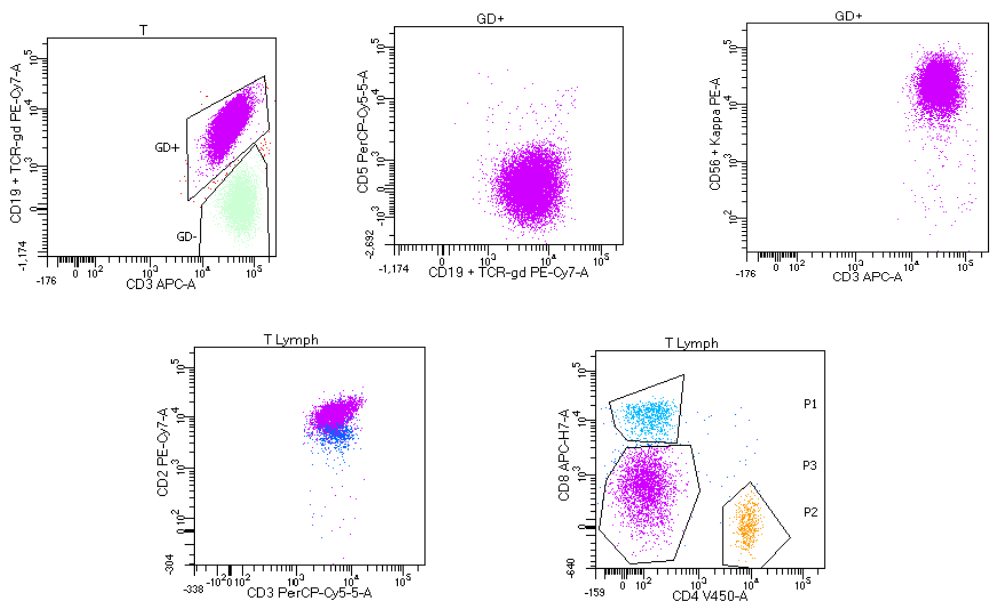

Figure 3. Immunophenotyping shows the presence of 9% abnormal lymphoid cells (purple population) which are positive for CD3, CD56, CD2, dim CD8, and exhibit gamma delta restriction. They are negative for CD19, CD5, and CD4. Normal T-cells which are CD8 and CD4 positive are represented by light blue and orange populations, respectively.

mucosal areas, gastrointestinal system, lymphoid and cutaneous tissues, and the splenic red pulp, but they comprise less than 5.0% of circulating lymphocytes in healthy adults with spleen being the most prevalent area.[2] In the bone marrow, double-negative (CD4−/CD8−) thymic precursors give rise to γδ T-cells. They can act as early-effectors in immunological responses since they are cytotoxic and a part of the innate immune system.[2]

HSTL is identified histopathologically by medium-sized lymphoid cells invading the splenic red pulp and bone marrow sinusoids.[1] A modest amount of pale cytoplasm, absence of granules, mature chromatin pattern, inconspicuous nucleoli, and uneven nuclear outlines are other described characteristics.[2] T-cell large granular lymphocytic leukaemia (T-LGL), which is distinguished by lymphocytes containing azurophilic granules (fine or coarse), can be distinguished from HSTL using these morphologic characteristics.[4] Nowadays, a bone marrow sample is typically sufficient to provide a diagnosis, splenectomy is rarely necessary.[1] Lymphocytosis and leukemic presentations can usually be the first clue towards the diagnosis of lymphoma, however, in HSTL they are rare, occurring in only 1% to 2% of cases even though bone marrow involvement is common.[2] In our case, there was no lymphocytosis even in the bone marrow aspirate. Immunophenotyping plays an essential role in establishing the diagnosis. Gamma-delta T-cell subtype of HSTL is the commonest and has a male predominance. Trephine biopsy often reveals prominent sinusoidal involvement. The malignant cells are usually double-negative (CD4− and CD8−) in immunohistochemistry, albeit occasionally CD8 expression may be seen. They are negative for CD5, CD1a, terminal deoxynucleotidyl transferase, and CD10, and positive for CD3, CD2, and CD7.[1,5] The γδ T-cell receptor (TCR) is expressed in the majority of cases. While CD57 is typically negative, CD56 is seen in 70.0% of cases.[1,5] Markers associated with cytotoxic granules, such as TIA-1 and granzyme M, are usually positive, whereas perforin and granzyme B are negative, indicating a non-activated cytotoxic phenotype. It is said that mild to moderate dyspoiesis of hematopoietic cells may be present which could cause further diagnostic confusion.[1]

In HSTL, the TCR β (TCRB) and λ (TCRG) genes are typically rearranged.[2] Approximately 75.0% of cases are positive for TCR γδ , 20.0% are positive for TCRab and 5% are of silent/null type (lack T-cell receptors).[1] Notably, the majority of γδ HSTLs have rearranged β-chains that are not productive and similarly γ-chains are usually present in αβ-restricted cases. Therefore, molecular clonality studies to determine the specific T-cell subtype may be difficult to ascertain.[2] Cytogenetic hallmark for HSTL is isochromosome (7q), though it is not universally present.[1]

Among the T-cell neoplasms, CD4−/CD8− γδ T-cell large granular lymphocytic leukaemia (T-LGL) shares significant overlap with HSTL. However, T-LGL typically affects older individuals and has a more indolent clinical course. Presence of large granular lymphocytes and the absence of isochromosome (7q) in T-LGL can aid in differentiating it from HSTL.[6] In our patient, we did not detect any large granular lymphocytes and surprisingly, he had a normal cytogenetic study. A study showed that findings of marked splenomegaly, sinusoidal involvement in the bone marrow, and a lack of lymphocytes with azurophilic granules were significantly more common in HSTL cases than T-LGL.[4] While T-LGL may also affect the bone marrow's sinusoids, the sinusoidal involvement of T-LGL is distinguished by a single, short linear layer of cytotoxic T cells, as opposed to the sinusoidal expansion seen in HSTL.[6]

T- acute lymphoblastic leukaemia (T-ALL), primary cutaneous γδ T-cell lymphoma, intestinal T-cell lymphomas, and EBV+ T-cell lymphoma are additional T-cell neoplasms to take into account in the differential diagnosis. However, because of their more unique clinical and immunophenotypic characteristics, these conditions can generally be distinguished from HSTL. For instance, the presence of blasts morphology and immaturity markers such as CD34 and TdT would be in favour of T-acute lymphoblastic leukaemia.[1] In contrast, primary cutaneous γδ T-cell lymphoma usually presents with skin manifestation, with extracutanous involvement being uncommon.[1] Intestinal T-cell lymphomas presentation usually involve the small intestine and colon, with no prominent intrasinusoidal infiltration seen as in HSTL.[1] An EBV positivity is needed to diagnose EBV positive T-cell lymphoma.[1]

Our patient has massive splenomegaly with pancytopenia, no lymphadenopathies, no large granular lymphocytes in the peripheral blood film with γδ restriction in immunophenotyping. On top of that, trephine biopsy showed prominent

intrasinusoidal involvement with CD3 and CD56 positivity with CD4 and CD8 negativity as well as EBV negativity. We, then, concluded that the diagnosis is most likely HSTL.

HSTL responds poorly to traditional chemotherapy and has an aggressive clinical course.[7] Haematopoietic stem cell transplant (HSCT) remains the only curative option. In the absence of transplant, the patient will have a poor outcome with 5-year survival of <10.0%, emphasizing the need for early and accurate diagnosis.[8] Delayed recognition may lead to inappropriate treatment strategies which may worsen the prognosis. Novel therapeutic approaches such as targeted therapy of EZH2 (enhancer of zeste homolog 2) are currently under investigation.[9]

CONCLUSION

This case underscores the importance of considering HSTL in young patients with cytopenias and organomegalies. A high index of suspicion, combined with a thorough immunophenotypic and molecular workup, is essential to avoid diagnostic pitfalls. Given its aggressive nature, prompt recognition and referral for HSCT are critical to improve patient outcomes.

Acknowledgements: We would like to thank the Director General of Health Malaysia for his permission to publish this article.

Informed Consent Statement: Informed consent was obtained from the patient in the study.

Authors' contributions: Conceptualization: HP Raghvan, SY Wee, CCK Liam; formal analysis: HP Raghvan, SY Wee, N Mohd Shakri, I Subbiah, N Khalid; writing: HP Raghvan, SY Wee, CSL Ho, N Mohd Shakri; review and editing: CCK Liam, I Subbiah, E Jamian, N Khalid; supervision: CSL Ho, CCK Liam, I Subbiah, E Jamian, N Khalid; funding acquisition: N/A; final approval of the manuscript: All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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