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Case Report

Case Series of Hepatosplenic T-Cell Lymphoma: A Rare and Aggressive Disease

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Abstract
Hepatosplenic T-cell lymphoma is a rare form of T-cell lymphoma that predominantly emerges from neoplastic proliferation of cytotoxic T cells of γ/δ T-cell receptor-expressing lymphocytes. Isochromosome 7q and trisomy 8 are the most prevalent chromosomal abnormalities associated with hepatosplenic T-cell lymphoma, and most patients have mutations in genes related to chromatin remodeling or the JAK/STAT system. Hepatosplenic T-cell lymphoma can mimic various infectious diseases, immunological conditions, and other malignancies. Patients usually present with nonspecific constitutional symptoms and spleen and liver enlargement, with variable degrees of cytopenia. The rarity of this disease, coupled with the lack of lymph node involvement that is usually seen in lymphomas, causes significant difficulty in diagnosis, which inevitably delays the initiation of treatment. Managing this lymphoma is arduous because of its late presentation and aggressive nature, frequently resulting in rapid progression in its clinical course and refractoriness to conventional chemotherapy. There is a lack of international guidelines for its treatment, and in most cases, treatment is guided by case series. Here, we highlight the clinicopathological features and management of hepatosplenic T-cell lymphoma over a 10-year span in a single hematology referral center and review the literature.

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Introduction

Lymphomas are a group of heterogeneous malignancies that involve any tissue that houses lymphoid cells, especially the lymph nodes. Hepatosplenic T-cell lymphoma (HSTCL) is an aggressive subtype of lymphoma with a characteristic hepatosplenic presentation and without lymphadenopathy [1, 2]. It was first described in two adults presenting with hepatosplenomegaly and minimal lymphadenopathy. This malignant lymphoma was recognized as a hepatosplenic disease displaying sinusal/sinusoidal pattern, and the gamma delta phenotype of malignant cells [3]. HSTCL results from the proliferation of γ/δ T-cell receptor-type cytotoxic T cells. It usually comprises medium-sized lymphoid cells that exhibit marked sinusoidal infiltration of the spleen, liver, and bone marrow [4]. T-cell lymphomas are uncommon compared to their B-cell counterparts with HSTCL making up 1–2% of all peripheral T-cell lymphomas [2]. Diagnosing HSTCL can be challenging, especially when the associated signs and symptoms are nonspecific and easily mimic various other conditions, mostly infectious etiologies, and other malignant disorders. Given the rarity of this disease and the absence of significant nodal involvement, delays in reaching diagnosis and initiation of treatment are substantial and common problems for hematologists. In most cases, the diagnosis is made by liver, spleen, and/or bone marrow biopsies. The disease course is progressively rapid, and a standard therapy has yet to be established. Here, we present a series of 6 patients diagnosed with HSTCL over a 10-year period, describing the collective presentation, diagnosis, management, and outcomes. The CARE Checklist has been completed by the authors for this case report and attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531924).

Case History

Patient 1

A 14-year-old girl was previously well-presented to a general practitioner after being unwell with mainly constitutional symptoms for 1 week. The patient was treated for occult sepsis; however, her condition did not improve with antibiotics. Upon referral to the hematologist, her symptoms persisted, and was now showing pallor, hepatomegaly of 25 cm, and massive splenomegaly crossing the midline, measuring 24 cm (Table 1). The initial blood count revealed severe pancytopenia (Table 2). Her parents were counseled, and permission was obtained for bone marrow examination. Extensive immunohistochemistry and immunophenotyping confirmed a diagnosis of HSTCL (Table 3). Therefore, chemotherapy was initiated (Table 4) with GMALL induction (vincristine, daunorubicin, dexamethasone, L-asparaginase, and intrathecal methotrexate) with intrathecal methotrexate as central nervous system (CNS) prophylaxis. However, she developed neutropenic sepsis and was transferred to the intensive care unit. The patient died 6 weeks after diagnosis.

Patient 2

A 40-year-old woman with underlying diabetes mellitus and hypertension for 5 years presented to a general physician with complaints of being unwell and a distended abdomen for 2 weeks. The patient was initially treated for sepsis. Upon referral to a hematologist, the patient was extremely pale with hepatomegaly (18 cm) and massive splenomegaly (30 cm) (Table 1). A complete blood count revealed severe pancytopenia (Table 2). She finally agreed to undergo a bone marrow examination, and a diagnosis of HSTCL was made after extensive immunophenotyping of the marrow by flow cytometry and immunohistochemistry examination of the biopsy sample (Table 3). She had received only one cycle of MACOP-B

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Table 1. Clinical characteristics of patients with HSTCL

Presentation	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, years	14	40	56	37	65	24
Gender	Female	Female	Male	Male	Female	Female
Duration of symptoms	1 week	2 weeks	1 month	1 month	3 months	3 months
Fever	Yes	Yes	Yes	Yes	No	Yes
Night sweats	No	No	Yes	Yes	No	Yes
Fatigue	Yes	Yes	Yes	Yes	Yes	Yes
Loss of appetite/ weight	Yes	Yes	Yes	Yes	No	Yes
Abdominal pain	Yes	Yes	No	No	No	Yes
Mucosal bleeding	No	No	No	No	No	No
Physical examination						
Pallor	Yes	Yes	Yes	Yes	Yes	Yes
Jaundice	No	No	No	Yes	No	No
Petechiae	No	No	No	No	No	No
Ecchymoses	No	No	No	No	No	No
Lymphadenopathy	Yes, shotty cervical lymph nodes	Yes, shotty paraaortic lymph nodes	No	Yes, shotty cervical lymph nodes	Yes, shotty cervical lymph nodes	No
Hepatomegaly	25 cm	22 cm	18 cm	20 cm	12 cm	19 cm
Splenomegaly	24 cm	30 cm	18 cm	18 cm	24 cm	18 cm

(methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, and bleomycin) with methotrexate as CNS prophylaxis. Subsequently, she developed neutropenic sepsis with *Pseudomonas aeruginosa* and *Staphylococcus aureus* bacteremia and died.

Patient 3

A 56-year-old man, a retired executive in a bank with underlying hypertension for 10 years, presented to a general physician complaining of feeling unwell with constitutional symptoms on and off for over a month. The patient was initially treated for megaloblastic anemia secondary to a vitamin B12 deficiency. It had been nearly 1 month after his initial presentation when he was referred to a hematologist. Upon examination, hepatomegaly (18 cm), splenomegaly (18 cm) (Table 1), and full blood count showed pancytopenia (Table 2). Bone marrow examination was performed, in which a diagnosis of HSTCL was made. Chemotherapy was initiated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), but the regimen had to be changed halfway after 2 cycles because of unsatisfactory clearance of malignant cells upon reassessment. He was then given 3 cycles of CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) (Table 4). However, the disease was refractory to chemotherapy and had persistent pancytopenia. The patient was not keen on any active management and died due to disease progression.

Patient 4

A 37-year-old businessman presented with constitutional symptoms for 1 month. The patient was treated for infection. The patient was the only patient who presented with jaundice; therefore, he was initially diagnosed with chronic liver disease. Abdominal

Table 2. Investigations of patients with HSTCL

Investigations	Ref range	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
WBC	3.8–10.8	3.6	1	4	0.7	1.76	79
Hb	11.6–15.1	6	7.3	7	6.8	7	8
PLT	150–440	23	17	14	47	74	49
LDH	105–333	1,478	473	355	1,059	359	2,529
TB	1.71–20.5	26	38	48	90	27	21
Indirect	3.4–12.0	12	20	25	28	16	ND
Direct	<5.1	13	18	23	62	10	ND
ALT	4–36	8	10	<7	23	18	109
PT	11–15.4	31	14	17	ND	ND	ND
APTT	30.8–43.7	50	51	58	ND	ND	ND
Bone marrow biopsy		Yes	Yes	Yes	Yes	Yes	Yes
EBV IgG		ND	ND	Negative	Positive	Positive	ND
Cytogenetics		T	ND	ND	ND	ND	T

Ref, reference range; WBC, white blood cell ($x10^9$/L); Hb, hemoglobin (g/dL); PLT, platelet ($x10^9$/L); LDH, lactate dehydrogenase (U/L); TB, total bilirubin (μmol/L); ALT, alanine transaminase (U/L); PT, prothrombin time (seconds); APTT, activated partial thromboplastin time (s); T, tested; ND, not done.

Cytogenetics result:

Patient 1: loss of chromosome X, i(7q), tetrasomy 8, trisomy 21.

Patient 6: i(7q).

computed tomography showed no evidence of biliary obstruction. The viral screening results were negative. Upon referral to a hematologist, the patient's symptoms worsened. His liver and spleen were enlarged, measuring 22 and 16 cm, respectively (Table 1). His blood count revealed pancytopenia with severe neutropenia. Bone marrow examination was performed, and the patient was diagnosed with HSTCL (Table 2). Chemotherapy was initiated with 1 cycle of CHOP and 3 cycles of hyperCVAD-A (cyclophosphamide, vincristine, doxorubicin, dexamethasone with intrathecal methotrexate, and cytarabine) alternating with 2 cycles of hyperCVAD-B (methotrexate, cytarabine, methylprednisolone with intrathecal methotrexate, and cytarabine) (Table 4). Methotrexate and cytarabine were given intravenously and intrathecally as CNS prophylaxis. However, the patient declined further workup for allogeneic hematopoietic stem cell transplantation (alloHSCT). The patient's disease relapsed 6 months after the completion of chemotherapy. He was not keen on any active management and subsequently stopped attending follow-up sessions with a hematologist.

Patient 5

A 65-year-old woman presented to a general practitioner with reduced effort tolerance for 3 months. The patient did not complain of any chest pain. She had a history of chronic hypertension and dyslipidemia, both of which were controlled with medications and regular follow-up. She had also been diagnosed with meningioma 9 years ago, had received radiotherapy, and was in remission. Once it was clear that her initial symptoms were not due to a cardiovascular event, she was referred to a hematologist because of pancytopenia, while working up for reduced effort tolerance. Upon examination, she was severely anemic, with a massively enlarged liver and spleen measuring 22 and 25 cm, respectively (Table 1). A complete blood count revealed severe pancytopenia with absolute neutropenia. The first bone marrow biopsy did not reveal the cause of pancytopenia (Table 2). Thus, splenic biopsy was

Table 3. The immunophenotypic features of patients with HSTCL

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
CD2	+	+	+	+	+	+
CD3	+	+	+	+	+	+
Gamma delta T-cell receptor	+	+	ND	ND	+	+
Alpha beta T-cell receptor	–	–	+	+	–	–
CD4	–	–	–	–	–	–
CD5	–	–	+	+	–	Dim
CD7	+	+	+	+	+	+
CD8	+	–	+	–	–	–
CD30	–	–	–	ND	ND	ND
CD34	–	–	–	–	ND	–
CD56	–	Weak	+	ND	–	+
TdT	–	–	ND	ND	–	–
TIA–1	+	Weak	+	+	+	–
Granzyme B	–	–	+	+	–	–

ND, not done.

performed. Splenic biopsy was extensively examined using immunophenotyping and immunohistochemistry markers, which revealed HSTCL (Table 3). She completed 2 cycles of ICE (ifosfamide, carboplatin, etoposide) and 4 cycles of DHAP (cisplatin, cytarabine, and dexamethasone) with cytarabine as CNS prophylaxis (Table 4). She achieved disease remission after 6 cycles of chemotherapy. The patient underwent matched unrelated donor alloHSCT. Her donor cytomegalovirus (CMV) status was negative and her CMV status was positive. She was administered myeloablative conditioning with total body irradiation (10 Gy) and etoposide. Cyclosporin/mycophenolate mofetil/antithymocyte globulin was administered as prophylaxis for graft-versus-host disease. Three months post-alloHSCT, she experienced CMV reactivation with CMV meningoencephalitis and Candida pneumonia, and died 130 days post-alloHSCT due to infectious complications.

Patient 6

A 24-year-old woman, a previously healthy undergraduate, presented with anemic and constitutional symptoms for 1 month to a general practitioner. Extensive workup for infections and autoimmune diseases was performed, and all patients showed negative results. Upon examination, hepatosplenomegaly measuring 19 cm and 18 cm was observed (Table 1). No other mass was detected. Her initial blood count showed severe anemia, but her platelet count was normal with a slightly elevated white blood cell count (Table 2). Bone marrow aspirate and trephine biopsy were performed, a diagnosis of T-cell large granular lymphocyte leukemia (T-LGLL) was made, and weekly oral methotrexate was prescribed. However, her condition deteriorated further with persistent fever and enlarged hepatosplenomegaly. She was then referred to our center, where bicytopenia with persistent anemia, thrombocytopenia, and lymphocytosis were noted (Table 2). A second bone marrow examination was performed and extensive immunophenotyping revealed HSTCL (Table 3). Chemotherapy was initiated with 1 cycle of CHOP, followed by 1 cycle of HyperCVAD-A with intrathecal methotrexate, and cytarabine as CNS prophylaxis. She was further given 4 cycles of CHOEP.

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Table 4. Summary of treatment, outcome, and OS of patients with HSTCL

Management and outcome	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Chemotherapy regime	GMALL induction	MACOP-B	2 cycles of CHOP + 3 cycles of CHOEP	1 cycle of CHOP + 3 cycles of hyperCVAD-A alternate with 2 cycles of hyperCVAD-B	2 cycles of ICE + 4 cycles of DHAP	1 cycle of CHOP + 1 cycle of hyperCVAD-A + 4 cycles of CHOEP + 1 cycle of ICE + 3 cycles of GD
Response to chemotherapy	Unable to assess	Unable to assess	Refractory	Remission	Remission	Refractory
Outcome	Passed away due to neutropenic sepsis after GMALL induction	Passed away due to neutropenic sepsis after 1 cycle MACOP-B	Passed away due to disease progression	Relapsed after 6 months	Underwent MUD alloHSCT, passed away on day+130 post-alloSCT due to infectious complications	Passed away due to septic shock
OS	6 weeks	3 months	5 months	1 year 10 months	11 months	12 months

Patient 1: GMALL induction (vincristine, daunorubicin, dexamethasone, L-asparaginase, and intrathecal methotrexate).

Patient 2: MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, and bleomycin).

Patient 3: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone).

Patient 4: CHOP and three cycles of hyperCVAD-A (cyclophosphamide, vincristine, doxorubicin, dexamethasone with intrathecal methotrexate, and cytarabine) alternating with two cycles of hyperCVAD-B (methotrexate, cytarabine, methylprednisolone with intrathecal methotrexate, and cytarabine).

Patient 5: ICE (ifosfamide, carboplatin, etoposide) and DHAP (cisplatin, cytarabine, and dexamethasone).

Patient 6: CHOP, one cycle of hyperCVAD-A, four cycles of CHOEP, one cycle of ICE, and three cycles of GD (gemcitabine and dexamethasone).

However, her disease was refractory to prior chemotherapy, thus she was salvaged with 1 cycle of ICE and 3 cycles of GD (gemcitabine and dexamethasone) (Table 4). Her disease remained refractory and she succumbed due to septic shock with *Acinetobacter* bacteremia.

Discussion

The median age of the patients at diagnosis was 38 years (range: 14–65). A peak incidence occurs in adolescents and young adults, whereas the reported median age at diagnosis is approximately 35 years with male predominance [1, 2]. However, most of our patients were female. The clinical presentation described in the literature includes hepatosplenomegaly, systemic or constitutional symptoms, cytopenia (marked thrombocytopenia, anemia, or leukopenia), and bone marrow involvement by lymphomatous cells, which was also observed in our patients (Table 1) [2, 5]. Patients typically present with pancytopenia and hepatosplenomegaly. Several

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patients may have a history of immunosuppression, either through treatment for other hematological malignancies or inflammatory conditions such as inflammatory bowel disease or solid organ transplants [6]. Diagnosing HSTCL is challenging because of its rarity and the absence of lymphadenopathy, as demonstrated in patient 6. The patient was initially misdiagnosed with another type of lymphoma, T-LGLL. Clinically, T-LGLL is rare in individuals younger than 25 years of age, and most cases occur in individuals aged 45–75 years old. T-LGLL also usually follows an indolent clinical course. It was challenging to differentiate the diagnosis of HSTCL and T-LGLL because both present with cytopenias without lymphadenopathy and overlapping immunophenotypic features. A comparison between cases of HSTCL and T-LGLL made by Mariko et al. [7] showed that features of massive splenomegaly, bone marrow sinusoidal expansion by lymphoma cells, and lymphocytes devoid of azurophilic granules were significantly more common in HSTCL patients than in □δ T-LGL patients. Histologically, predominant intrasinusoidal infiltration of the red pulp and atrophy or loss of the white pulp are typically observed in HSTCL [8]. T-LGLL lymphocytes have cytoplasmic azurophilic granules and a characteristic immunophenotype (CD2+, CD3+, CD8+, CD57+). The immunophenotype of HSTCL is distinctive in contrast to T-LGLL, where the malignant cells of HSTCL have a nonactivated cytotoxic phenotype (TIA-1+, granzyme B−). A literature review by Yabe et al. [9] showed that up to 41% of HSTCL cases are granzyme B-positive. The presence of isochromosome 7q (i(7q)) by FISH and/or trisomy 8 karyotyping was also significantly correlated with the diagnosis of HSTCL at 69% and 53%, respectively [8].

Obtaining a histopathological confirmation of this disease is challenging. Patients with HSTCL are often quite ill, and their condition limits the ability to obtain sufficient tissue sampling in the form of liver, spleen, or bone marrow trephine biopsies to correctly subtype and classify this lymphoma. Typical findings of tissue biopsies would show lymphoid cells demonstrating marked sinusoidal infiltration. The cells were homogenous lymphocytes with medium-sized nuclei containing loosely condensed chromatin with small inconspicuous nucleoli and a rim with pale cytoplasm. However, diagnosis depends on the immunophenotypic characterization of neoplastic T cells using extensive immunohistochemical markers. Neoplastic cells were also identified using multicolor flow cytometry. The immunophenotype of malignant cells is typically CD3+, CD4−, CD5−, CD8−, CD56+, CD57−, TIA-1+, granzyme B−, CD2+, CD3+ with coexpression of γδTCR+ and CD56± [10, 11]. The main immunophenotypic features of our cohort of patients were consistent with those reported in previous studies. In all cases, neoplastic lymphocytes were positive for pan-T-cell markers CD2, CD3, and CD7. Neoplastic T cells did not express CD4, a T-helper cell marker (all cases), or CD8, a T-cytotoxic-cell marker (except in 2 cases). Most cases tested positive for TIA-1 and negative for granzyme B, which was consistent with a nonactivated cytotoxic T-cell phenotype. As neoplastic cells result from the proliferation of cytotoxic T cells of the gamma delta T-cell receptor type, γδTCR was positive in half of the cases.

Cytogenetic or molecular analyses were not performed routinely in all patients to identify common genetic abnormalities associated with HSTCL. i(7q) has been reported in most cases, whereas trisomy 8 may be present in some cases [6]. In our patients, for whom cytogenetic studies were performed, i(7q) was detected. The role of i(7q) in this disease is not yet well understood. However, the genetic alterations in patient 1 were more complex, as the patient also exhibited loss of chromosome X, tetrasomy 8, and trisomy 21. In recent years, researchers have used next-generation sequencing to identify actionable recurrent genetic alterations. These include the JAK/STAT pathways, phosphatidylinositol 3-kinase (PI3K) signaling pathways, and epigenetic alterations such as *SETD2*, *INO80*, *TET3*, *and SMARCA2* [9, 12]. Recurrent somatic mutations have also been identified, such as *PIK3CD* and missense mutations in *STAT5B* and *STAT3*, which are not unique to HSTCL [13, 14]. However, many targeted therapies require further evaluation in clinical trials.

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Various chemotherapeutic regimens have been used, including standard CHOP, CHOP-like regimens, purine analogs, monoclonal antibodies (e.g., alemtuzumab), platinum-based regimens, ICE, and IVAC (ifosfamide, etoposide, and high-dose cytarabine) [15, 16]. Hematopoietic stem cell transplantation is potentially curative [17]. Regardless of the treatment modality, the median overall survival (OS) is reportedly 6–28.3 months [2]. Most patients received chemotherapy alone, and only 1 patient received chemotherapy followed by alloHSCT. Two patients deteriorated after 1st cycle of chemotherapy and died of neutropenic sepsis. This shows that HSTCL is very aggressive, and most patients with this disease are too fragile to receive intensive chemotherapy. To date, there is no standard recommendation for chemotherapy for this rare and aggressive lymphoma. In our cohort, patients who received CHOP regimens were refractory and survived for only 5 months. Our patients who received more intensive regimens, such as HyperCVAD alternating with methotrexate and high-dose cytarabine, and ICE with DHAP, tended to perform better and achieve remission. This showed that high-dose cytarabine may be needed as the backbone of intensive chemotherapy to achieve remission of this disease. However, 1 patient who achieved remission after chemotherapy experienced early relapse within 6 months. This showed that intensive chemotherapy alone did not result in sustained remission of this aggressive lymphoma. Consolidation with hematopoietic stem cell transplantation after remission appears to be a better option to manage this disease. Consolidation with alloHSCT tends to yield better results than autologous stem cell transplantation for this disease. A systematic review of 44 patients who underwent alloHSCT demonstrated that the estimated 3-year OS for transplantation was 56%. However, the non-relapse mortality rate of allogeneic transplantation is as high as 68% [9, 17]. One of the patients in our cohort underwent matched unrelated donor allogeneic stem cell transplantation; however, she died of infectious complications after transplantation. The median OS of our patients was 5 (range 1.5–22) months. This was comparable to most reported case series with a median survival duration of less than 1 year despite multiagent chemotherapy.

Conclusion

HSTCL is an aggressive subtype of peripheral T-cell lymphoma with poor outcomes. The diagnosis of the disease requires clinicians to have a certain degree of suspicion. Investigations included unifying morphological, immunophenotyping, cytogenetic, and molecular findings. To date, no standard treatment for this condition has been established. In our cohort, an induction chemotherapy strategy using high-dose cytarabine-based chemotherapy, followed by hematopoietic stem cell transplantation, appears to be a promising treatment option for this rare and aggressive disease.

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Statement of Ethics

Ethical approval was not required for this study, in accordance with the local and national guidelines. Written informed consent was obtained from the patients for publication of their medical case and any accompanying images. Written informed consent was

obtained from the patient 6 for publication of this case report series. Written informed consent was also obtained from the parent/legal guardian of patients 1, 2, 3, 4 and 5 who passed away at the time of publication.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Dr. Yea Bing Tham cared for the patient and drafted the manuscript. Dr. Asral Wirda Ahmad Asnawi drafted the original manuscript and provided supporting information. Dr. Ngee Siang Lau cared for the patient and reviewed and edited the manuscript accordingly. Dr. Alina Fauzi reviewed and edited the manuscript. Dr. Sharifah Shahnaz Syed Abd Kadir compiled the investigation. Dr. Pek Kuen Liew compiled the investigation. Dr. Sen Mui Tan provided overall supervision, and all authors approved the version of the manuscript to be published.

Data Availability Statement

All data generated or analyzed are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding authors.

References

1 Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90. [published Online First: 20160315].
2 Foss FM, Horwitz SM, Civallero M, Bellei M, Marcheselli L, Kim WS, et al. Incidence and outcomes of rare T cell lymphomas from the T Cell Project: hepatosplenic, enteropathy associated and peripheral gamma delta T cell lymphomas. Am J Hematol. 2020;95(2):151–5.
3 Farcet J-P, Gaulard P, Marolleau J-P. Hepatosplenic T-cell lymphoma: sinusal/sinusoidal localization of malignant cells expressing the T-cell receptor gamma delta; 1990.
4 Jauhari S, McKinney M. Hepatosplenic T-cell lymphoma. Novel therapeutics for rare lymphomas. Springer; 2020. p. 209–20.
5 Yabe M, Medeiros LJ, Tang G, Wang SA, Ahmed S, Nieto Y, et al. Prognostic factors of hepatosplenic T-cell lymphoma: clinicopathologic study of 28 cases. Am J Surg Pathol. 2016;40(5):676–88.
6 Weidmann E. Hepatosplenic T cell lymphoma. A review on 45 cases since the first report describing the disease as a distinct lymphoma entity in 1990. Leukemia. 2000;14(6):991–7.
7 Yabe M, Medeiros LJ, Wang SA, Tang G, Bueso-Ramos CE, Jorgensen JL, et al. Distinguishing between hepatosplenic T-cell lymphoma and γδ T-cell large granular lymphocytic leukemia: a clinicopathologic, immunophenotypic, and molecular analysis. Am J Surg Pathol. 2017;41(1):82–93.
8 Gorodetskiy V, Probatova N, Sidorova Y, Kupryshina N, Obukhova T, Vasilyev V, et al. The non-leukemic T cell large granular lymphocytic leukemia variant with marked splenomegaly and neutropenia in the setting of rheumatoid arthritis - felty syndrome and hepatosplenic T cell lymphoma mask. Am J Blood Res. 2021;11(3):227–37. [published Online First: 20210615].

9 Pro B, Allen P, Behdad A. Hepatosplenic T-cell lymphoma: a rare but challenging entity. Blood. 2020;136(18):2018–26.
10 Ahmad E, Kingma DW, Jaffe ES, Schrager JA, Janik J, Wilson W, et al. Flow cytometric immunophenotypic profiles of mature gamma delta T-cell malignancies involving peripheral blood and bone marrow. Cytometry B Clin Cytom. 2005;67(1):6–12.
11 Yabe M, Miranda RN, Medeiros LJ. Hepatosplenic T-cell Lymphoma: a review of clinicopathologic features, pathogenesis, and prognostic factors. Hum Pathol. 2018;74:5–16.
12 Van Arnam JS, Lim MS, Elenitoba-Johnson KS. Novel insights into the pathogenesis of T-cell lymphomas. J Am Soc Hematol. 2018;131(21):2320–30.
13 Nicolae A, Xi L, Pittaluga S, Abdullaev Z, Pack SD, Chen J, et al. Frequent STAT5B mutations in γδ hepatosplenic T-cell lymphomas. Leukemia. 2014;28(11):2244–8.
14 Kücük C, Jiang B, Hu X, Zhang W, Chan JKC, Xiao W, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from γδ-T or NK cells. Nat Commun. 2015;6(1):6025.
15 Voss MH, Lunning MA, Maragulia JC, Papadopoulos EB, Goldberg J, Zelenetz AD, et al. Intensive induction chemotherapy followed by early high-dose therapy and hematopoietic stem cell transplantation results in improved outcome for patients with hepatosplenic T-cell lymphoma: a single institution experience. Clin Lymphoma Myeloma Leuk. 2013;13(1):8–14.
16 Konuma T, Ooi J, Takahashi S, Tomonari A, Tsukada N, Kobayashi T, et al. Allogeneic stem cell transplantation for hepatosplenic gammadelta T-cell lymphoma. Leuk Lymphoma. 2007;48(3):630–2.
17 Rashidi A, Cashen A. Outcomes of allogeneic stem cell transplantation in hepatosplenic T-cell lymphoma. Blood Cancer J. 2015;5(6):e318–8.