Posted on 10 Mar 2023 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.167845637.71143654/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Hepatosplenic T cell lymphoma: A Rare and Aggressive Disease

Yea Bing Tham[1], Asral Wirda Ahmad Asnawi[1], Ngee Siang Lau[1], Alina Fauzi[1], Sharifah Shahnaz Syed Abdul Kadir[1], Pek Kuen Liew[1], and Sen Mui Tan[1]

[1]Hospital Ampang

March 10, 2023

Abstract

Hepatosplenic T-cell lymphoma mimics various infectious diseases, immunological conditions, and other malignancies. Because there is no lymph node involvement, it causes difficulty in diagnosing lymphoma and significant delays in the initiation of treatment. This type of lymphoma should be considered in the presence of hepatosplenomegaly and cytopenia.

Hepatosplenic T cell lymphoma: A Rare and Aggressive Disease Mimicker

Abstract

Hepatosplenic T-cell lymphoma mimics various infectious diseases, immunological conditions, and other malignancies. Because there is no lymph node involvement, it causes difficulty in diagnosing lymphoma and significant delays in the initiation of treatment. This type of lymphoma should be considered in the presence of hepatosplenomegaly and cytopenia. Management of this rare lymphoma is challenging due to its presentation and aggressiveness in terms of its refractory nature to conventional chemotherapy. There is lack of international guidelines for its treatment. In most of the cases, treatment is often guided by case series.

Keywords

Lymphoma, T-cell, cytopenia, hepatomegaly, splenomegaly

Introduction

Lymphomas are a group of heterogeneous malignancies that involve any tissue that houses lymphoid cells, especially the lymph nodes. However, Hepatosplenic T-cell lymphoma (HSTCL) can present without lymph node or extranodal involvement. It is an aggressive subtype of extranodal lymphoma with characteristic hepatosplenic presentation without lymphadenopathy [1]. It was first described using the term erythrophagocytic T-γ-lymphoma in 1981 by Kadin et al., who reported two adults presenting with hepatosplenomegaly and minimal lymphadenopathy [2]. The term hepatosplenic T-cell lymphoma was subsequently used in 1990 to describe two patients with malignant lymphoma with hepatosplenic disease and by sinusal/sinusoidal pattern and the gamma delta phenotype of malignant cells [3]. HSTCL results from the proliferation of cytotoxic T cells of the gamma delta T-cell receptor type [1]. It is comprised of medium-sized lymphoid cells that exhibit marked sinusoidal infiltration of spleen, liver, and bone marrow [4, 5]. T-cell lymphomas are uncommon compared to its B-cell counterpart with HSTCL making up 1-2% of all peripheral T-cell lymphomas [6]. Diagnosing HSTL can be challenging, especially when the associated signs and symptoms are nonspecific and easily mimics various other conditions, mostly infectious etiologies and other malignant disorders. Given the rarity of this disease and the absence of significant nodal involvement, delay in reaching a diagnosis and initiation of treatment is substantial and a common problem for hematologists. In most cases, the diagnosis

Posted on 10 Mar 2023 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.167845637.71143654/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

is made by liver, spleen, and/or bone marrow biopsy. The disease course is progressively rapid and standard therapy is yet to be established. Here, we present a series of six patients diagnosed with Hepatosplenic T-cell lymphoma over a 10-year period, describing the collective presentation, diagnosis, management, and outcome.

Case history

Patient 1

A 14-year-old girl who 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, but 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). Her 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 the diagnosis of HSTCL (Table 3). Therefore, chemotherapy was initiated (Table 4). However, she developed neutropenic sepsis and was transferred to the intensive care unit. She 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 complaining of being unwell and a distended abdomen for 2 weeks. The patient was initially treated for sepsis. Upon referral to a hematologist, she was extremely pale with hepatomegaly (18 cm) and massive splenomegaly (30 cm) (Table 1). A complete blood count showed severe pancytopenia (Table 2). She finally agreed to undergo 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 chemotherapy and subsequently developed neutropenic sepsis with *Pseudomonas aeruginosa* and*Staphylococcus aerus* bacteremia and succumbed.

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 over a 1 month period. The patient was initially treated for megaloblastic anemia secondary to vitamin B12 deficiency. It had been nearly one month after his initial presentation, he was referred to a hematologist. Upon examination, there was hepatomegaly (18 cm), splenomegaly (18 cm) (Table 1), and a full blood count showed pancytopenia. He was counseled for a bone marrow examination where a diagnosis of HSTCL was made (Table 2). Chemotherapy was initiated, but the regimen had to be changed halfway through the course because of unsatisfactory clearance of malignant cells upon reassessment. 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 one month. The patient was treated for infection. He was the only patient who presented with jaundice; therefore, he was initially diagnosed with chronic liver disease. Abdominal computed tomography (CT) showed no evidence of biliary obstruction. Viral screening results were negative. Upon referral to a hematologist, his symptoms worsened. His liver and spleen were enlarged, measuring 22 and 16 cm, respectively (Table 1). His blood count also revealed pancytopenia with severe neutropenia (Table 2). Bone marrow examination was performed, and the patient was diagnosed with HSTCL. Chemotherapy was initiated and the patient was followed up until disease remission was achieved. However, the patient declined further workup for allogeneic hematopoietic stem cell transplantation (allo-HSCT). His disease relapsed 6 months after the completion of chemotherapy. He

Posted on 10 Mar 2023 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.167845637.71143654/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

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 chest pain. She had a history of chronic hypertension and dyslipidemia, both of which were controlled with medication 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 cm and 25 cm, respectively (Table 1). A full blood count revealed severe pancytopenia with absolute neutropenia (Table 2). The first bone marrow biopsy did not reveal the cause of the pancytopenia. Thus, splenic biopsy was performed. Splenic biopsy was extensively examined with immunophenotyping and immunohistochemistry markers, which revealed HSTCL (Table 3). She completed six cycles of chemotherapy and achieved disease remission. The patient underwent matched unrelated donor allo-HSCT. Her donor CMV (cytomegalovirus) status was negative and her CMV status was positive. She was administered myeloablative conditioning using total body irradiation (10 Gy) and etoposide. Cyclosporin/mycophenolate mofotil/antithymocyte globulin was administered as graft-versus-host disease prophylaxis. Three months post-AlloSCT, she experienced CMV reactivation with CMV meningoencephalitis and Candida pneumonia and died 130 days post-AlloSCT 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 showed negative results. Upon examination, hepatosplenomegaly measuring 19 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, and a diagnosis of T-cell Large Granular Lymphocyte Leukemia 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 was noted (Table 2). A second bone marrow examination was performed, and extensive immunophenotyping revealed HSTCL (Table 3). Chemotherapy was initiated, and she is currently undergoing follow-up and assessment. The patient was planned to undergo an allogeneic stem cell transplantation if remission with chemotherapy was achieved.

Table 1: Clinical Characteristicsof Patients with Hepatosplenic T Cell Lymphoma

Presentation	**Case 1**	**Case 2**	**Case 3**
Age (Years)	14	40	56
Gender	Female	Female	Male
Duration of Symptoms	1 week	2 weeks	1 month
Fever	Yes	Yes	Yes
Night Sweats	No	No	Yes
Fatigue	Yes	Yes	Yes
Loss of appetite/weight	Yes	Yes	Yes
Abdominal Pain	Yes	Yes	No
Mucosal Bleeding	No	No	No
Physical Examination	**Physical Examination**	**Physical Examination**	**Physical Examinati**
Pallor	Yes	Yes	Yes
Jaundice	No	No	No
Petechiae	No	No	No
Ecchymoses	No	No	No

Posted on 10 Mar 2023 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.167845637.71143654/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Presentation	**Case 1**	**Case 2**	**Case 3**
Lymphadenopathy	Yes, shorty cervical lymph nodes	Yes, shorty paraaortic lymph nodes	No
Hepatomegaly	25cm	22cm	18cm
Splenomegaly	24cm	30cm	18cm

Table 2: Investigations of Patients with Hepatosplenic T Cell Lymphoma

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	1478	473	355	1059	359	2529
TB	1.71 – 20.5	26 12 13	38 20 18	48 25 23	90 28 62	27 16 10	21 ND ND
Indirect	3.4-12.0						
Direct	<5.1						
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)

Table 3: The Immunophenotypic Features of Patients with Hepatosplenic T Cell Lymphoma

Immunophenotypic analysis	**Case1**	**Case2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
CD2	+	+	+	+	+	+
CD3	+	+	+	+	+	+
CD4	-	-	ND	-	-	-
CD5	-	-	+	ND	-	ND
CD7	+	+	+	+	+	+
CD8	+	-	+	-	-	-
CD30	-	-	-	ND	ND	ND
CD34	-	-	-	-	ND	-
CD56	-	-	+	ND	-	+
TdT	-	-	ND	ND	ND	-
Gamma delta T cell receptor	ND	+	ND	ND	+	+
Alpha beta T cell receptor	ND	ND	ND	+	-	-

Posted on 10 Mar 2023 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.167845637.71143654/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Immunophenotypic analysis	Case1	Case2	Case 3	Case 4	Case 5	Case 6
TIA1	+	w+	+	+	+	-
Granzyme B	-	-	+	+	-	-

W, weak; ND, not done

Table 4: Summary of treatment, outcome, and overall survival of patients with HSTCL

Management and outcome	Case 1	Case 2
Chemotherapy regime	GMALL induction	MACOP-B
Response to chemotherapy	Unable to assess	Unable to assess
Outcome	passed away due to neutropenic sepsis after GMALL induction	Passed away due to neutr
Overall Survival	6 weeks	3 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)

Discussion

The median age of the patients at diagnosis was 38 years (range:14-65). HSTCL has been reported to have a male predominance; however, most of our patients were female. The clinical presentation described in the literature include hepatosplenomegaly, systemic or constitutional symptoms, cytopenias (marked thrombocytopenia, anemia or leukopenia), and bone marrow involvement by lymphomatous cells which was similarly seen in our patients [6-9]. Patients usually present with. Median age at diagnosis is around 35 years where a peak incidence occurs in adolescents and young adults and reportedly male predominance [1, 6]. A number of patients may have a history of immunosuppression, either through treatment for other hematological malignancy, inflammatory conditions such as in patients with inflammatory bowel disease, or after solid organ transplants [10]. Diagnosing HSTCL is challenging because of its rarity and absence of lymphadenopathy, as demonstrated in Patient 6. The patient was initially misdiagnosed with T-cell Large Granular Lymphocyte Leukemia. Retrospectively, her clinical presentation did not fit into the diagnosis of T-cell Large Granular Lymphocyte Leukemia(T-LGLL). First, the age group did not fit T-LGLL. She was 24 years old. T-LGLL is rare in individuals aged less than 25 years, and most cases of T-LGLL occur in individuals aged–45-75 years old. Another feature is that T-LGLL is usually indolent in nature, but the disease progresses rapidly.

Obtaining a histopathological confirmation of this disease is challenging. Patients with HSTCL often present 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

Posted on 10 Mar 2023 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.167845637.71143654/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

lymphocytes with medium-sized nuclei containing loosely condensed chromatin with small inconspicuous nucleoli and a rim with pale cytoplasm. Diagnosis, however, depends on the immunophenotypic characterization of neoplastic T-cells using extensive immunohistochemical markers. Neoplastic cells were also identified using multicolor flow cytometry analysis. The immunophenotype of malignant cells is typically CD2+, CD3+, γδTCR+, CD4 -, CD5 -, CD8 -, and CD56± [11]. The main immunophenotypic features of our cohort of patients were consistent with those of patients from previous studies. In all cases, neoplastic lymphocytes were positive for the 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 two cases). The majority of the cases tested positive for TIA-1 and negative for Granzyme B, which was consistent with a non-activated cytotoxic T-cell phenotype. As the 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 the common genetic abnormalities associated with HSTCL. Isochromosome 7q [i(7q)] has been reported in most cases, whereas trisomy 8 may also be present in some cases [10]. In our patients whom cytogenetic studies were performed, i(7q) was detected. The role of i(7q) in this disease is not well understood. However, the genetic alteration in patient 1 was 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 recurrent genetic alterations that are actionable. These include JAK/STAT pathways, phosphatidylinositol 3-kinase (PI3K) signaling pathways, and epigenetic alterations such as *SETD2, INO80, TET3 and SMARCA2* [12, 13]. Recurrent somatic mutations have also been identified, such as PIK3CD and missense mutations in STAT5B and STAT3, which are not unique to HSTCL [14, 15]. Many targeted therapies that are available require further evaluation in clinical trials.

A variety of 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) [16, 17]. Hematopoietic stem cell transplantation is potentially curative [18]. Regardless of the treatment modality the median overall survival (OS) was reportedly 6-28.3 months, [6]. Most patients received chemotherapy alone, and only 1 patient received chemotherapy followed by allogeneic stem cell transplantation. Two of our patients deteriorated after 1st cycle of chemotherapy and died of neutropenic sepsis. This showed that hepatosplenic T-cell lymphoma 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 five 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 achieved remission. This showed that high dose cytarabine may be needed as the backbone of intensive chemotherapy to achieve remission for this disease. However, one patient who achieved remission after chemotherapy experienced early relapse within 6 months. This showed that intensive chemotherapy alone did not result in sustained remission in this aggressive lymphoma. Consolidation with hematopoietic stem cell transplantation after remission appears to be a better option for managing this disease. Consolidation with allogeneic stem cell transplantation tends to yield better results than autologous stem cell transplantation in this disease. A systematic review of 44 patients who were subjected to allogeneic stem cell transplantation demonstrated that the estimated 3-year OS for transplants was 56%. However, the non-relapse mortality rate of allogeneic tranplantation was as high as 68% [12, 18]. One of the patients in our cohort underwent matched unrelated donor allogeneic stem cell transplantation; however, it died due to infectious complications post allogeneic stem cell transplantation. The median overall survival of our patients was 5 (range 1.5-22) months. This was comparable with most reported case series with median survival duration of less than one year despite using multiagent chemotherapy [19].

In conclusion, HSTCL is an aggressive subtype of peripheral T-cell lymphoma with poor outcomes. Diagnosis of the disease requires clinicians to have a degree of suspicion. To date, no standard treatment has been established for this condition. Investigations include unifying morphological, immunophenotyping, cytogenetic and molecular findings. In our cohort, induction chemotherapy strategy using high-dose

cytarabine-based chemotherapy followed by consolidation with hematopoietic stem cell transplantation appears to be a promising treatment option for this rare and aggressive disease.

Acknowledgements

The authors thank the Director General of the Ministry of Health Malaysia for allowing publication of this case series.

Funding

No funding was required for the write-up of this case series.

Authorship (Credit format)

Yea Bing Tham: Writing-original draft preparation (lead). Asral Wirda Ahmad Asnawi: writing – original draft preparation (Supporting Information). Ngee Siang Lau: Writing – reviewing and editing (equal). Alina Fauzi: Writing, reviewing, and editing (equal). Sharifah Shahnaz Syed Abd Kadir: Investigation (equal). Pek Kuen, Liew: Investigation (equal). Sen Mui Tan: supervision.

Conflict of interest

The authors have no conflicts of interest to disclose.

Reference

[1] S. H. Swerdlow, E. Campo, S. A. Pileri, N. L. Harris, H. Stein, R. Siebert, R. Advani, M. Ghielmini, G. A. Salles, A. D. Zelenetz, and E. S. Jaffe, "The 2016 revision of the World Health Organization classification of lymphoid neoplasms," *Blood,* vol. 127, no. 20, pp. 2375-90, May 19, 2016.

[2] M. E. Kadin, M. Kamoun, and J. Lamberg, "Erythrophagocytic Tγ lymphoma: A clinicopathologic entity resembling malignant histiocytosis," *New England Journal of Medicine,* vol. 304, no. 11, pp. 648-653, 1981.

[3] J.-P. Farcet, P. Gaulard, J.-P. Marolleau, J.-P. Le Couedic, T. Henni, M.-F. Gourdin, M. Divine, C. Haioun, S. Zafrani, and M. Goossens, "Hepatosplenic T-cell lymphoma: sinusal/sinusoidal localization of malignant cells expressing the T-cell receptor gamma delta," 1990.

[4] L. Gowda, and F. Foss, "Hepatosplenic T-cell lymphomas," *T-Cell and NK-Cell Lymphomas* , pp. 185-193: Springer, 2019.

[5] S. Jauhari, and M. McKinney, "Hepatosplenic T-cell lymphoma," *Novel Therapeutics for Rare Lymphomas* , pp. 209-220: Springer, 2020.

[6] F. M. Foss, S. M. Horwitz, M. Civallero, M. Bellei, L. Marcheselli, W. S. Kim, M. E. Cabrera, I. Dlouhy, A. Nagler, and R. H. Advani, "Incidence and outcomes of rare T cell lymphomas from the T Cell Project: hepatosplenic, enteropathy associated and peripheral gamma delta T cell lymphomas," *American journal of hematology,* vol. 95, no. 2, pp. 151-155, 2020.

[7] M. G. Ochenrider, D. J. Patterson, and D. M. Aboulafia, "Hepatosplenic T-cell lymphoma in a young man with Crohn's disease: case report and literature review," *Clinical Lymphoma Myeloma and Leukemia,* vol. 10, no. 2, pp. 144-148, 2010.

[8] A. Nosari, P. L. Oreste, A. Biondi, M. C. Costantini, L. Santoleri, L. Intropido, G. Muti, E. Pungolino, L. Gargantini, and E. Morra, "Hepato-splenic γδ T-cell lymphoma: A rare entity mimicking the hemophagocytic syndrome," *American journal of hematology,* vol. 60, no. 1, pp. 61-65, 1999.

[9] M. Yabe, L. J. Medeiros, G. Tang, S. A. Wang, S. Ahmed, Y. Nieto, S. Hu, G. Bhagat, Y. Oki, and K. P. Patel, "Prognostic factors of hepatosplenic T-cell lymphoma," *The American journal of surgical pathology,* vol. 40, no. 5, pp. 676-688, 2016.

[10] E. Weidmann, "Hepatosplenic T cell lymphoma. A review on 45 cases since the first report describing the disease as a distinct lymphoma entity in 1990," *Leukemia,* vol. 14, no. 6, pp. 991-997, 2000.

Posted on 10 Mar 2023 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.167845637.71143654/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Posted on 10 Mar 2023 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.167845637.71143654/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

[11] E. Ahmad, D. W. Kingma, E. S. Jaffe, J. A. Schrager, J. Janik, W. Wilson, and M. Stetler-Stevenson, "Flow cytometric immunophenotypic profiles of mature gamma delta T-cell malignancies involving peripheral blood and bone marrow," *Cytometry Part B: Clinical Cytometry: The Journal of the International Society for Analytical Cytology,* vol. 67, no. 1, pp. 6-12, 2005.

[12] B. Pro, P. Allen, and A. Behdad, "Hepatosplenic T-cell lymphoma: a rare but challenging entity," *Blood,* vol. 136, no. 18, pp. 2018-2026, 2020.

[13] J. S. Van Arnam, M. S. Lim, and K. S. Elenitoba-Johnson, "Novel insights into the pathogenesis of T-cell lymphomas," *Blood, The Journal of the American Society of Hematology,* vol. 131, no. 21, pp. 2320-2330, 2018.

[14] A. Nicolae, L. Xi, S. Pittaluga, Z. Abdullaev, S. Pack, J. Chen, T. Waldmann, E. Jaffe, and M. Raffeld, "Frequent STAT5B mutations in γδ hepatosplenic T-cell lymphomas," *Leukemia,* vol. 28, no. 11, pp. 2244-2248, 2014.

[15] C. Kücük, B. Jiang, X. Hu, W. Zhang, J. K. Chan, W. Xiao, N. Lack, C. Alkan, J. C. Williams, and K. N. Avery, "Activating mutations of STAT5B and STAT3 in lymphomas derived from γδ-T or NK cells," *Nature communications,* vol. 6, no. 1, pp. 6025, 2015.

[16] M. H. Voss, M. A. Lunning, J. C. Maragulia, E. B. Papadopoulos, J. Goldberg, A. D. Zelenetz, and S. M. Horwitz, "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," *Clinical Lymphoma Myeloma and Leukemia,* vol. 13, no. 1, pp. 8-14, 2013.

[17] T. Konuma, J. Ooi, S. Takahashi, A. Tomonari, N. Tsukada, T. Kobayashi, A. Sato, A. Tojo, and S. Asano, "Allogeneic stem cell transplantation for hepatosplenic gammadelta T-cell lymphoma," *Leukemia & lymphoma,* vol. 48, no. 3, pp. 630-632, 2007.

[18] A. Rashidi, and A. Cashen, "Outcomes of allogeneic stem cell transplantation in hepatosplenic T-cell lymphoma," *Blood cancer journal,* vol. 5, no. 6, pp. e318-e318, 2015.

[19] C. Cooke, L. Krenacs, M. Stetler-Stevenson, T. Greiner, M. Raffeld, D. Kingma, L. Abruzzo, C. Frantz, M. Kaviani, and E. Jaffe, "Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic gamma delta T-cell origin," *Blood,* vol. 88, no. 11, pp. 4265-4274, 1996.

Hosted file

`Title page _HSTCL_FINAL.docx` available at https://authorea.com/users/594615/articles/628976-hepatosplenic-t-cell-lymphoma-a-rare-and-aggressive-disease