Leukemic phase of hepatosplenic T cell lymphoma: a case report and review of the literature

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Introduction

Hepatosplenic T cell lymphoma (HSTL) is a rare subset of peripheral T cell lymphoma derived from cytotoxic T cells usually of gamma–delta T cell receptor type. Clinically, HSTL is characterized by hepatosplenomegaly, absence of lymphadenopathy, cytopenias, and an aggressive clinical course with a median survival of less than 1 year. The peak incidence occurs in adolescents and young adults (median 35 years) with a male predominance. A subset of HSTL arises in the setting of chronic immune suppression, most commonly chronic immunosuppression for solid organ transplantation or immunosuppressive therapy for Crohn's disease. Histologically, HSTL preferentially infiltrates the hepatic sinusoids and splenic red pulp but also may involve lymph node sinuses, bone marrow, and peripheral blood. Hepatosplenic T cell lymphoma exhibits a characteristic immunophenotype that expresses both T cell and NK cell markers. Typical cases express CD2, CD3, CD7, CD16, CD56, gamma–delta TCR and are negative for CD4, CD8, and the alpha–beta TCR. A minority of cases appear to be of alpha–beta type, which is considered to be a variant of the more common gamma–delta form of the disease. The characteristic clinical, histologic, immunophenotypic, and cytogenetic signature of this lymphoma has led to its recognition as a distinct entity in the revised European–American classification of lymphoid neoplasms in 1994 and subsequently in the WHO classification [5].

The classic initial clinical presentation of HSTL is hepatosplenomegaly, minimal or absent lymphadenopathy, and significant cytopenias. Thrombocytopenia is a constant feature and is frequently associated with anemia and/or leukopenia. A minor population of atypical lymphocytes can be identified in the peripheral blood of many patients; however, an overt leukemic presentation with leukocytosis due to large number of circulating T cell lymphoma is unusual at presentation. A number of sporadic reports of leukemic phase HSTL exist; however, the biological and clinical implications of leukemic phase have not been explored. We describe the case of a 65-year-old man with leukemic phase of HSTL. The original diagnosis was established by flow cytometric analysis of the peripheral blood. Subsequent autopsy findings confirmed the diagnosis. We review 15 previously presented cases of leukemic phase HSTL and evaluate clinicopathologic features, response to therapy, and prognosis.

Case presentation

A 65-year-old man presented to a community hospital with 3 weeks history of daily fevers. His past medical history was noteworthy for a single vessel coronary artery bypass 14 years prior to admission; and his outpatient medications included rosuvastatin, metoprolol, lisinopril, and an aspirin. The patient had no history of autoimmune disease, immunosuppressive medication, or organ transplantation. On admission, physical examination showed splenomegaly and fever of 38.8°C. Laboratory findings were remarkable for abnormal liver functions tests (AST of 351 U/L; ALT of 121 U/L; alkaline phosphatase of 350 U/L; total bilirubin of 5.5 mg/dL; and LDH of 4,329 U/L) and pancytopenia (WBC, $2.6 \times 10^9/L$; hematocrit, 26%; platelets, $78 \times 10^9/L$).

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Imaging revealed hepatosplenomegaly with no lymphadenopathy, and biopsies were performed of the liver and of the bone marrow. By report, the biopsies remained inconclusive as the liver biopsy showed zone 3 necrosis, and the bone marrow was interpreted as normal. An extensive infectious workup was negative.

He was transferred to our institution for further evaluation. In contrast to his prior pancytopenia, on the day of transfer, his CBC revealed a leukocytosis with a WBC of $18.6 \times 10^9/L$ and with persistent anemia and thrombocyto-

penia. His WBC differential showed 43% abnormal lymphocytes, 21% neutrophils, 14% bands, 21% small lymphocytes, and 1% monocytes.

Morphologic review of the peripheral blood smear (Fig. 1a, b) showed leukocytosis and a predominant population of large atypical lymphocytes with irregular nuclear contours, visible to prominent nucleoli, and variable amounts of basophilic cytoplasm with granules. In addition, the neutrophils showed toxic changes and a shift to immaturity with myelocytes and metamyelocytes. There

Fig. 1 **a, b.** Morphologic findings of the peripheral blood smear. There is a leukocytosis (WBC, $18.6 \times 10^6/L$) with absolute lymphocytosis of $10.6 \times 10^6/L$. 43% of the white blood cells are abnormal large lymphocytes showing variable amount of basophilic cytoplasm with cytoplasmic granules, irregular nuclei, and visible to prominent, often multiple nucleoli. The neutrophils show toxic changes and a shift to immaturity with myelocytes and metamyelocytes. In addition, there is a thrombocytopenia and a normochromic normocytic anemia with occasional nucleated red blood cells. **c.** Microscopic examination of the spleen, hematoxylin and eosin (H&E). The red pulp sinusoids are

filled with a population of highly pleomorphic lymphocytes, characterized by large size, high nuclear/cytoplasmic ratios and hyperchromatic nuclei. **d.** H&E-stained section of the liver shows focal macro- and microvesicular fatty change and infiltration of atypical lymphocytes in a primarily periportal pattern. Sinusoidal infiltrate is minimal. **e, f** H&E-stained section of the bone marrow shows hypercellular marrow (80%) with trilineage hematopoiesis and a sinusoidal and interstitial infiltrate of large, pleomorphic lymphocytes. Immunohistochemical staining with the T cell marker CD3 is positive and primarily highlights the sinusoidal content

was a normochromic normocytic anemia, and occasional nucleated red blood cells were present. Platelets were also decreased.

Flow cytometric analysis of the peripheral blood was performed and identified an abnormal T cell population representing 44% of the white blood cells, remarkable for uniform positivity of the gamma–delta T cell receptor (TCR) and expression of CD2, CD3, CD56, and without expression of CD5, CD4, CD8, CD7, and the alpha–beta T cell receptor (flow cytometric findings are shown in Fig. 2). Subsequently, PCR for the T cell receptor gamma region identified a clonal T cell population. Cytogenetic analysis of the peripheral blood by fluorescent in situ hybridization was negative for abnormalities of chromosomes 7 and 8. The peripheral blood findings were interpreted as peripheral blood involvement by a T cell lymphoma/leukemia, most consistent with a gamma–delta hepatosplenic T cell lymphoma.

Over the subsequent 36 h, the patient became progressively unstable with hypotension leading to acute renal failure. On hospital day 2, he developed chest pain accompanied by ST segment elevation on EKG, followed by cardiovascular arrest, and death. An autopsy was performed.

Autopsy findings

There was cardiomegaly (500 g), a single coronary bypass, severe occlusive atherosclerosis of the native left anterior

descending artery, and a large scar in the left ventricle. No acute infarct was identified. Based on the history of chest pain associated with ST segment elevation and the evidence of chronic ischemic heart disease, the cause of death was assumed to be an acute myocardial infarct, too recent to produce histologic changes. The spleen weighed 980 g and showed a homogenously red cut surface. Histologic sections showed infiltration of the splenic red pulp by lymphocytes with abnormal pleomorphic morphology and primarily distributed within the sinusoids as shown in Fig. 1c. The lymphoid cells were similar cytologically to the lymphoma cells identified in the peripheral blood. The liver weighed 2,270 g with no localized masses. Microscopic analysis showed focal macrovesicular steatosis and periportal infiltration of abnormal medium to large pleomorphic lymphocytes (see Fig. 1d). The periportal lymphocytic infiltrate focally extended into adjacent sinusoids; however, the sinusoidal involvement was minimal. There was no lymphadenopathy identified in the autopsy. However, microscopic analysis of a randomly sampled 1 cm thoracic node showed partial sinusoidal involvement by the lymphoma. The bone marrow sections from rib and vertebrae showed a hypercellular bone marrow (cellularity estimated at 80%) with trilineage hematopoiesis. Abnormal medium- to large-sized lymphocytes with irregular nuclei and a moderate cytoplasm were diffusely distributed throughout the marrow in a predominantly sinusoidal and interstitial pattern as shown in Fig. 1e. The pleomorphic lymphocytes filling the sinus-

Fig. 2 Flow cytometric analysis of the peripheral blood identifies an immunophenotypically abnormal T cell population that comprises 43% of total leukocytes (76% of lymphocytes) and shows the

following immunophenotype: CD2+, CD3+, CD45+, CD56+, uniformly positive for gamma–delta T cell receptor and negative for CD5, CD7, CD4, CD8, and alpha beta T cell receptor

oids are CD3 positive T cells (Fig. 1f). Histiocytes were not increased and hemophagocytosis was not identified. Gross examination of other major organs including brain, gastrointestinal system, kidneys, and testes was unremarkable. Microscopic examination showed presence of abnormal pleomorphic lymphocytes in the vascular spaces of all these organs; however, there was no evidence of tissue invasion or disruption of normal morphology seen in these organs. The prominence of the lymphoid cells in the vascular spaces most likely reflects the heavy involvement of the peripheral blood by lymphoma. Immunohistochemical staining was performed on sections from bone marrow, spleen, liver, and lymph node. The lymphocytic infiltrate in all these organs showed abnormal T cell immunophenotype expressing CD2, CD3, and CD7 and without expression of CD5, CD4, or CD8. The abnormal T cells were positive for expression of the cytotoxic granule-associated proteins granzyme B and TIA-1. EBER in situ hybridization for Epstein Barr virus (EBV) RNA was negative on the lymphoma cells. The immunophenotype reproduced the flow cytometric immunophenotypic findings observed in the peripheral blood with the exception that deletion of CD7 was not observed by immunohistochemistry.

Discussion

Hepatosplenic T cell lymphoma (HSTL) represents a diagnostic challenge, and the specific diagnosis is commonly delayed with a median of 60 days after presentation [2]. The classic combination of hepatosplenomegaly, fever, jaundice, and elevated liver enzymes often lead the diagnostic pursuit towards a viral infection, which is usually not confirmed [10]. Another common pitfall is misinterpretation of the isolated thrombocytopenia as idiopathic thrombocytopenic purpura [1, 3, 7]. The impact of the delay of the diagnosis on prognosis is not clear.

We report here the case of a 65-year-old Caucasian male, who initially presented with hepatosplenomegaly, no lymphadenopathy, elevated liver enzymes, fever, and pancytopenia. Despite a detailed workup, a specific diagnosis was not reached until 3 weeks after his original presentation, when he developed a leukocytosis and flow cytometric analysis identified an abnormal T cell population with an immunophenotype (CD2+, CD3+, CD45+, CD56+, negative for CD5, CD7, CD4, and CD8, uniform gamma-delta TCR positive), highly suggestive of a gamma-delta HSTL. Within 2 days of the onset of leukocytosis, the patient died. The autopsy confirmed the diagnosis of in the spleen and in sections of the bone marrow in a primarily sinusoidal distribution. The liver was involved; however, the distribution of HSTL cells was somewhat unusual in that it was predominantly periportal, with minimal exten-

sion into sinusoids. This pattern of liver infiltration, though rare, has been described in HSTL [17]. In situ hybridization was negative for EBV. The aberrant immunophenotype of the T cell lymphoma was reproduced by immunohistochemistry in sections of the bone marrow, spleen, and liver, and also demonstrated expression of two cytotoxic granule-associated proteins granzyme B and TIA-1. This pattern of cytotoxic granule-associated protein expression has been reported previously by several investigators in HSTL [3, 12, 20].

The most remarkable feature of this case is the leukemic type peripheral blood involvement by HSTL and the impact of the peripheral blood involvement on the diagnostic workup. The biological and clinical implications of the leukemic phase of HSTL are not clear. In fact, exact criteria for a “leukemic phase” of HSTL do not exist. In our interpretation, a case of HSTL was considered leukemic if it is associated with absolute lymphocytosis of $4 \times 10^6/L$ due to circulating T cell lymphoma cells. Using these criteria, we identified 15 previously published cases of leukemic HTCL in the literature. Demographic, clinicopathologic, and molecular features as well as clinical outcome of the 15 cases of HSTL with leukemic peripheral blood involvement are summarized in Table 1.

The age of patients with leukemic phase HSTL ranged from 8 to 65 years, (median of 39), with three patients in the pediatric age group (8, 9, and 17). The male to female ratio is 1:1. Just like HSTL in general, the majority of published cases were of gamma-delta TCR type (14/16) [2, 4, 6, 7, 9, 11–14, 16–19]; however, two cases of alpha-beta TCR type with leukemic phase were also described in the literature [8]. Four of the 16 described cases occurred in transplant patients, including three kidney transplant and one bone marrow transplant patient [11, 14, 17, 19]. In this series, no cases of HSTL arising in the setting of immunosuppression, for reasons other than organ transplant, were identified. The onset of leukemic phase was variable in the course of the disease. In seven patients (43%), the leukemic phase heralded a terminal event and occurred just prior to death, similar to our patient. In another 37% (6/16), the leukemic phase was already present at initial presentation and in two patients (12%) developed in mid-phase, at 3 months, and 18 months after presentation, respectively.

From the morphologic point of view of the circulating T cell lymphoma cells, two different morphologic subtypes were described. In approximately two thirds of cases, the circulating T cell lymphoma cells were large, mature-appearing, and pleomorphic, even bizarre, just like in our patient. In one third of cases, however, they appeared blast-like, with scant amount of cytoplasm, dispersed chromatin, and visible nucleoli. The two different morphologies might be important diagnostically, since they bring up different

Table 1 Demographic, clinicopathologic, and molecular features of 16 cases of HSTL with a leukemic phase

Author/year	Age/sex	Immune suppression	Onset of leukemic phase after diagnosis	WBC/Let count 10 ⁹ /L	Morphology	Flow cytometry	T cell clonality	Cytogenetics	Treatment	Survival from diagnosis
[7]	23/M	No	2 months	NA/5	Mature pleomorphic	CD2 ⁺ , CD3 ⁺ , CD7 ⁺ , γδ ⁺	Not done	48,XY,-7,-i (7q), der (6)	2 cycles of CHOP ^a	9 months
[9]	48/F	No	14 months	26/17	Blast-like	CD2 ⁺ , CD3 ⁺ , CD7 ⁺ , CD56 ⁺ , γδ ⁺	Clonal by PCR	Normal	3 cycles of L-Asp ^b	14 months
[11]	31/M	Kidney transplant	At initial presentation	144/NA	Mature pleomorphic	CD2 ⁺ , CD3 ⁺ , CD7 ⁺ , CD16 ⁺ , CD56 ⁺ , γδ ⁺	Clonal by PCR	45, XY, t (7;9) (p15q13)	Pred,Vinc, Dauno, L-Asp ^c	3 months
[18]	39/M	No	At initial presentation	6.3/4.2	Mature pleomorphic	CD2 ⁺ , CD3 ⁺ , CD5 ⁺ , CD7 ⁺ , CD56 ⁺ , γδ ⁺	Clonal by PCR	44,-X,-Y,-11,-22,+ marker	Chlorambucil COP ^d , m-BACOP ^e	Complete remission at 12 months
[16]	29/M	No	9 months	NA/NA	NA	CD2 ⁺ , CD3 ⁺ , CD8 ⁺ , γδ ⁺	Not done	46, X,-Y, i (7) (q10), +8	High dose CTP ^f	9 months
[4]	8/M	No	18 months	NA/NA	NA	CD2 ⁺ , CD3 ⁺ , CD7 ⁺ , CD45 ⁺ , Tdt ⁺	Clonal by PCR	NA	None	22 months
[12]	32/M	No	"Before death"	NA/NA	Blast-like	CD2 ⁺ , CD3 ⁺ , CD16 ⁺ , CD56 ⁺ , γδ ⁺	Clonal by PCR	46X,-Y, i (7q10), +8, del (10q)	None	Died at onset of leukemic phase
[19]	42/F	Kidney transplant	6 months	NA/NA	Mature pleomorphic	CD2 ⁺ , CD3 ⁺ , CD7 ⁺ , CD16 ⁺ , CD56 ⁺ , γδ ⁺	Clonal by PCR	i (7q10), +8	None	6 months
[17]	41/F	Bone marrow Tx	At initial presentation	80/NA	Blast-like	CD2 ⁺ , CD3 ⁺ , CD5 ⁺ , CD7 ⁺ , CD45 ⁺ , γδ ⁺	Clonal by PCR	FISH negative for i (7q), +8	PSCT ^g	24 months
[6]	39/F	No	3 months	65/48	Mature pleomorphic	CD3 ⁺ , CD7 ⁺ , CD16 ⁺ , CD56 ⁺ , γδ ⁺	Clonal by PCR	NA	COP ^d plus αIFN no response; then 2 CdA ^h	Complete remission at 21 months
[14]	50/M	Kidney transplant	At initial presentation	9.1/6.4	Blast-like	CD3 ⁺ , CD7 ⁺ , CD45 ⁺ , CD56 ⁺ , γδ ⁺	Clonal by PCR	46X,-Y, t (1;4) i (7q), +8	Dauno, Methypred, L-asap	2 weeks
[2]	NA	No	"Before death"	NA/96	Blast-like	NA	NA	NA	None	NA
[13]	17/F	No	At initial presentation	29/13	Blast-like	CD2, CD3, CD7, CD45, CD56, γδ ⁺	NA	i (7q) and +8	COG AALL0434 ⁱ FLA ^j ARAC ^k Allo HSCT ^l	Complete remission at 16 months
Kehr et al. 2010 (this article)	65/M	No	1.5 months	18.6/8	Mature pleomorphic	CD2 ⁺ , CD3 ⁺ , CD16, CD56 ⁺ , γδ ⁺	Clonal by PCR	FISH negative for i (7q), +8	None	Died at onset of leukemic phase
Alpha-beta hepatosplenic T cell lymphomas with leukemic phase										
[8]	62/F	No	At initial presentation	55/44	Mature pleomorphic	CD2 ⁺ , CD3 ⁺ , CD7 ⁺ , CD16 ⁺ , CD56 ⁺ , αβ ⁺	Clonal by PCR	47, XX, +i (7q), add (19) (q13)	CHOP ^a	2 months
[8]	9/F	No	At initial presentation	18/15	Mature pleomorphic	CD2 ⁺ , CD3 ⁺ , CD7 ⁺ , CD8 ⁺ , αβ ⁺	Clonal by PCR	46, XX, t (2;17) (q34;q21), add (1;4) (q32)	MSK-NY-II ^m	Complete remission at 58 months

^a Cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone^b L-asparaginase^c Prednisone, vincristine, daunorubicin, L-asparaginase^d Cyclophosphamide, vincristine, prednisone^e Methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisolone^f Cytidine triphosphate^g Peripheral stem cell transplantation^h 2-Chlordeoxyadenosineⁱ Vincristine, daunorubicin, prednisone, PEG-asparaginase, and intrathecal cytarabine followed by intrathecal methotrexate^j Fludarabine^k Cytarabine arabinoside^l Allogeneic hematopoietic stem cell transplant^m Asparaginase, cyclophosphamide, daunorubicin, methotrexate, prednisone, vincristine

differential diagnostic entities, such as large granular lymphocyte leukemia, diffuse large B cell lymphoma in the mature pleomorphic type versus a T acute lymphoblastic leukemia or blastic NK cell leukemia in the blast-like type. Despite the two very different morphological forms, the flow cytometric immunophenotype appeared remarkably consistent and uniform: the circulating T cells are CD2+, CD3+, show downregulation of CD5 and/or CD7, commonly positive for NK cell markers CD16+ and CD56+, are bright CD45+, and most commonly double negative for CD4 and CD8. Rare cases, as expected, show CD8 positivity (1 of 13 gamma–delta TCR type and one of the two alpha–beta TCR-type HSTL were CD8 positive). The flow cytometric immunophenotype differentiates HSTL from other differential diagnostic entities, such as a large granular lymphocyte leukemia or blastic NK cell leukemia based on positivity for CD3 and negativity for EBV respectively; from T acute lymphoblastic leukemia based on lack of immature markers Tdt, CD10, and CD34, and the gamma–delta TCR differentiates it from other peripheral T cell lymphomas such as Sezary syndrome, T prolymphocytic leukemia, adult T cell leukemia/lymphoma, or peripheral T cell lymphoma not otherwise specified. Associated cytogenetic abnormalities of leukemic HSTL were in overlap with the cytogenetic abnormalities of HSTL without leukemic phase, isochromosome 7 with or without trisomy 8 being the most commonly detected abnormalities, and there was no evidence of clonal evolution or distinct chromosomal abnormality in the leukemic phase.

The prognosis of leukemic phase HSTL was poor but not significantly different from HSTL without leukemic involvement (range 0–58 months, median 9 months). Five cases with leukemic involvement achieved clinical remission greater than 12 months with treatment. This subset of patients was younger with a mean of 27 years of age. Interestingly, in all cases that were able to reach clinical remission, the leukemic peripheral blood involvement was present early in their disease (four of them were leukemic at initial presentation and one entered leukemic phase at 3 months after diagnosis). This suggests that the early peripheral blood involvement may have an impact on prognosis by providing an opportunity for quick noninvasive diagnosis by the means of peripheral blood flow cytometry.

Although leukemic peripheral blood involvement is rare in HSTL, a low level of circulating T cell lymphomas might be more common. Cooke et al. reviewed 19 cases of gamma–delta HTCL and found that 15 had some degree of peripheral blood involvement, though absolute lymphocytosis was rare [3]. Weidmann et al. describe the presence of lymphoma cells in peripheral blood in 16 of 32 patients (50%) [17]. Vega et al. reported eight patients with HSTL, and although none of them had absolute lymphocytosis,

five of them had evidence of low-level peripheral blood involvement [15]. Similarly, in a series of 21 patients with HSTL, Belhadj et al. observed ten cases with peripheral blood involvement, including one patient with leukemic phase, and seven additional subjects with low level of circulating T cell lymphoma [2]. Considering the remarkable stability of flow cytometric immunophenotype, even low-level circulating lymphoma cells may provide an opportunity for a fast noninvasive and very specific diagnosis, if peripheral blood flow cytometry is attempted.

In summary, leukemic phase of HSTL is rare; however, low level of circulating T cell lymphoma are commonly present in the peripheral blood, with a reported frequency between 40–80% of cases. The highly characteristic immunophenotype enables a quick, noninvasive diagnosis of HSTL; yet, flow cytometry of peripheral blood has not been acknowledged as a primary tool in the diagnostic algorithm of HSTL, especially in cases where leukocytosis is not present. We conclude that low-level peripheral blood involvement is an important feature of HSTL, despite the usual presentation with pancytopenia. Morphologic review of the peripheral blood smear and flow cytometric analysis of the peripheral blood should be incorporated into the early diagnostic workup and might facilitate an earlier diagnosis for patients whose differential diagnosis includes HSTL.

Conflict of interest The authors declare that they have no conflict of interest.

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