

CASE REPORT

Hepatosplenic T cell lymphoma with no expression of cytotoxic molecules

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Hepatosplenic T cell lymphoma is defined as an extranodal and systemic neoplasm derived from cytotoxic T cells. This report describes a postmortem case of T cell lymphoma that showed histological features of hepatosplenic T cell lymphoma but did not express cytotoxic molecules. The patient was a 57 year old man who presented with severe icterus and hepatosplenomegaly, followed by an aggressive clinical course. The liver and spleen were enlarged, weighing 2000 g and 360 g, respectively. Histologically, the liver, spleen, and bone marrow were entirely affected by lymphoma, comprising pleomorphic small and large cells, which displayed sinusoidal infiltration in the liver, diffuse infiltration in the splenic cord, and interstitial/diffuse infiltration with fibrosis in the bone marrow. Lymphoma cells showed positivity for CD3 ϵ , CD8, and CD45RO and clonal rearrangement of the TCR γ gene by the polymerase chain reaction on paraffin wax embedded sections. However, they were negative for TIA-1 and granzyme B, in addition to β F1, CD4, and CD56. Few neoplastic cells were stained for Epstein-Barr virus encoded mRNA 1. These findings indicate that this case might represent a variant of hepatosplenic T cell lymphoma despite the absence of cytotoxic molecules.

Hepatosplenic T cell lymphoma (HSTCL) is a distinctive clinicopathological entity that should be distinguished from other T/natural killer cell (NK) lymphomas.^{1–3} The lymphoma occurs at a young age and is characterised by hepatosplenomegaly, anaemia, thrombocytopenia, no swelling of superficial lymph nodes, and an aggressive clinical course. Histologically, the lymphoma shows sinusoidal/sinusoidal infiltration to the liver, spleen, and bone marrow. Lymphoma cells are usually intermediate in size, with round to oval nuclei and clear cytoplasm, and are either $\alpha\beta$ T or $\gamma\delta$ T cell in origin.³ Regardless of the cell of origin, HSTCL constitutively expresses T cell intracellular antigen (TIA-1), which is a cytolytic granule associated protein, and is expressed in 49–64% of resting CD8+ T cells.^{3–6} However, Khan *et al* recently reported two cases of CD8+, TIA-1– hepatosplenic $\gamma\delta$ T cell lymphoma that developed in renal transplantation patients, which suggests the presence of HSTCL without the characteristic cytotoxic cells.⁷

“Hepatosplenic T cell lymphoma constitutively expresses TIA-1, which is a cytolytic granule associated protein, and is expressed in 49–64% of resting CD8+ T cells”

In our study, we examined a postmortem case of T cell lymphoma that had the clinical and histological features of HSTCL but did not express TIA-1.

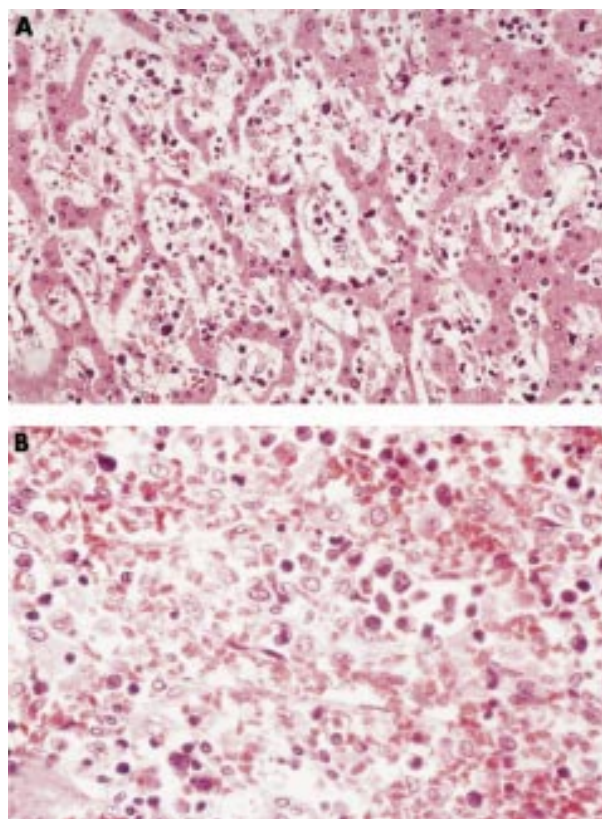


Figure 1 Histological appearance of our present case. Haematoxylin and eosin staining. (A) Liver: the neoplastic cells diffusely infiltrate the sinusoids; original magnification, $\times 70$. (B) Spleen: the neoplastic cells infiltrate the red pulp cord; sinusoidal infiltration is not evident; original magnification, $\times 140$.

CASE HISTORY

A 57 year old man was admitted to our hospital because of icterus. His consciousness was unclear. On physical examination, hepatosplenomegaly and floppy tremor were diagnosed. No superficial lymph node was palpable. Laboratory findings were as follows: serum bilirubin, 108 mg/litre; alkaline phosphatase, 195 IU/litre; γ -guanosine 5c-triphosphate, 25 IU/litre; lactate dehydrogenase (LDH), 472 IU/litre; LDH1, 151 IU/litre; LDH2, 185 IU/litre; LDH3, 120 IU/litre; LDH4, 50 IU/litre; LDH5, 16.7 IU/litre; alanine aminotransferase (ALT), 21 IU/

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EBV, Epstein-Barr virus encoded mRNA 1; EBV, Epstein-Barr virus; HB, hepatitis B; HPTL, hepatosplenic T cell lymphoma; LDH, lactate dehydrogenase; NK, natural killer; TIA-1, T cell intracellular antigen

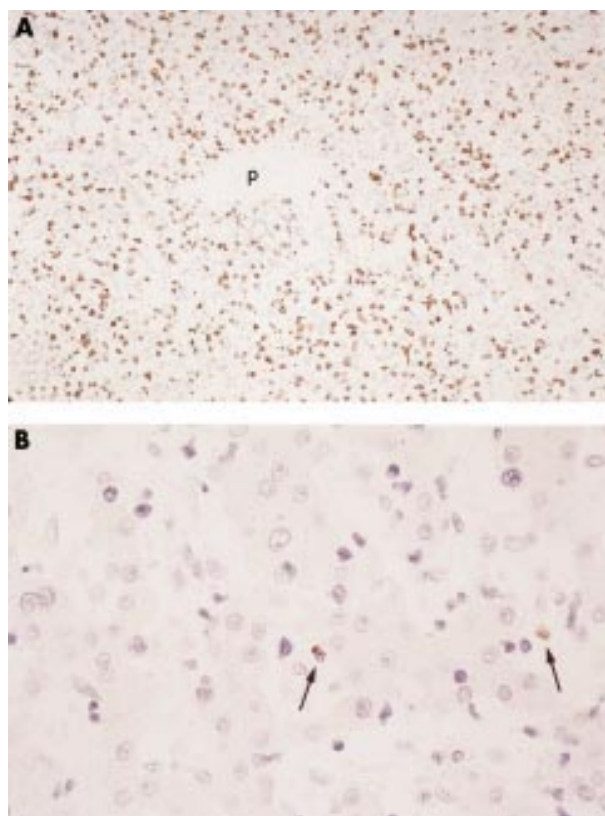


Figure 2 Phenotypical characteristics of neoplastic cells. Immunoperoxidase staining. (A) Strong staining for CD3 ϵ ; P, portal vein; original magnification, $\times 35$. (B) No expression of TIA-1 in lymphoma cells; non-neoplastic small lymphocytes (arrows) are intrinsic positive controls; original magnification, $\times 140$.

litre; aspartate aminotransferase (AST), 51 IU/litre; total protein, 54 g/litre; serum ammonia, 2360 μ g/litre; red blood cells, 332×10^6 cells/ μ l (332×10^{10} /litre); haemoglobin, 110 g/litre; white blood cells, 5×10^3 cells/ μ l (5×10^9 /litre); platelets, 6.5×10^6 cells/ μ l (65×10^9 /litre); hepatitis B (HB) virus surface antigen, negative; and HB virus surface antibody, positive. Serum antibodies against HB virus core antigen, HB virus envelope antigen, hepatitis C virus, human T cell leukaemia virus I, and human immunodeficiency virus were not measured. Abdominal computed tomography revealed a slightly low density area in the right lobe and in the spleen. However, because no mass lesion was identified by ultrasound sonography, liver cirrhosis was diagnosed. His serum bilirubin value increased to 348 mg/litre at day 14 and he died of hepatic coma at day 15. Finally, he was suspected of hepatocellular carcinoma.

POSTMORTEM FINDINGS

The liver weighed 2000 g. Macroscopically, no mass was identified. There was no evidence of cirrhosis. Histologically, the liver was entirely affected by atypical lymphoid cells that proliferated mainly in the sinusoid (fig 1A). The sinusoids were greatly expanded, hepatic cords were atrophic, and sinusoidal fibrosis was accompanied by an infiltration of lymphoma cells. The lymphoma cells showed pleomorphic nuclei with prominent nucleoli and moderate cytoplasm. In the portal area, lymphoma cells were sparse. Bile stasis was evident in the hepatocytes. No necrotic lesion was seen. The spleen weighed 360 g. Lymphoma cells were diffusely infiltrated in the splenic cord of the red pulp (fig 1B). The white pulp was atrophic. A few lymphoma cells were seen in the sinusoid. In the bone marrow of the vertebral bone, lymphoma cells displayed interstitial or diffuse infiltration with fibrosis. Myeloid and

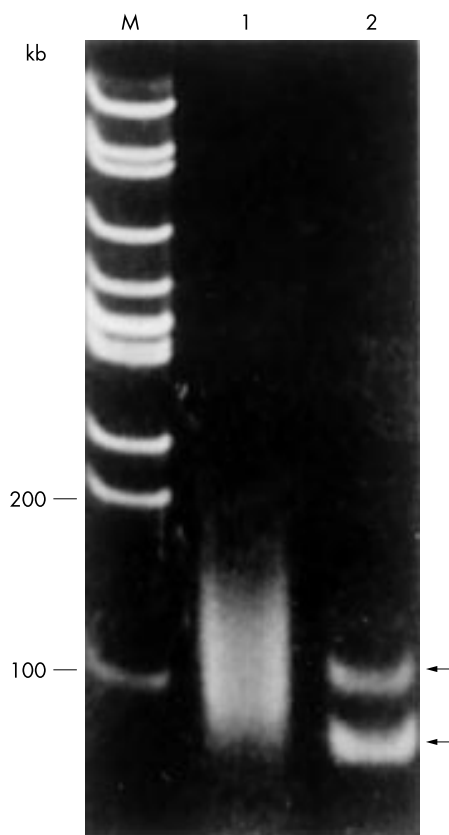


Figure 3 Polymerase chain reaction for TCR γ chain gene amplified genomic DNA extracted from paraffin wax embedded sections. M, molecular size marker; 1, negative control (blood lymphocytes); P, positive control (intestinal T cell lymphoma); 2, liver of our present case. Note two rearranged bands.

erythroid precursor cells were seen in clusters but megakaryocytes were hardly seen. Sinuses were dilatated but no lymphoma cell cluster was observed.

Paraffin wax embedded sections were immunostained by an avidin-biotin horseradish peroxidase complex method. Pretreatment for unmasking of antigens was carried out either by digestion with 0.05% preheated pronase E (type XXIV; Sigma Chemical Co, St Louis, Missouri, USA) in phosphate buffered saline for 20 minutes at 25°C (for β F1 and CD3 ϵ), by microwaving in citrate buffer (10 mmol/litre, pH 6.3) twice for five minutes each at 600 W (granzyme B, TIA-1, CD20, CD30, CD8, CD56, and p53), or by autoclaving at 1 bar for 20 minutes, followed by cooling down for 40 minutes (for CD4). The lymphoma cells expressed CD3 ϵ , CD8, CD43 and CD45RO. The CD3 ϵ staining highlighted sinusoidal infiltration of the liver (fig 2A). TIA-1 (fig 2B), granzyme B, β F1, CD4, CD20, CD30, CD56, CD57, S100, and p53 were not expressed.

Epstein-Barr virus (EBV) encoded mRNA 1 (EBER-1) in situ hybridisation was performed on the paraffin wax embedded sections using a fluorescein isothionate labelled EBER-1 30 base oligonucleotide probe under RNase free conditions. The EBER-1 signal was detected on a few lymphoid cells (2%) in the liver sections (not shown).

A polymerase chain reaction study of paraffin wax embedded sections of the liver was performed to detect TCR γ gene rearrangement. DNA was amplified with the following primers: V γ 1, 5'-TCTGG[G/A]GTCTATTACTGTGC-3'; V γ 2, 5'-CTC ACACTCC/CTACTTC-3'; V γ 3, 5'-GAAAGGAATCTGGCATTCCG-3'; J γ 1-2, 5'-CAAGTGTGTTCCACTGCC-3'; J γ 1-2, 5'-GTT ACTATGAGC[T/C]TAGTC-3'; and J γ , 5'-TGTAATGATAAG CTTTGTCC-3'. This clearly showed two distinct bands, which suggests clonal rearrangement of two alleles of the TCR γ gene (fig 3).

A small number of the lymphoma cells had also infiltrated the kidneys, pancreas, heart, tonsil, stomach, ileum, urinary bladder, prostate, salivary gland, and lymph nodes, including peripancreas, mesentery, and paraaortic lymph nodes.

DISCUSSION

In our study, we examined a postmortem case of T cell lymphoma with clonal rearrangement of the TCR γ gene and the immunophenotype: β F1 $^{-}$, CD3 ϵ $^{+}$, CD4 $^{-}$, CD5 $^{-}$, CD8 $^{+}$, CD20 $^{-}$, CD43 $^{+}$, CD45RO $^{+}$, CD56 $^{-}$, and CD57 $^{-}$. The patient initially presented with hepatic failure and the clinical course was aggressive. Histologically, the liver, spleen, and bone marrow were entirely affected by lymphoma, comprising pleomorphic small and large cells, which displayed sinusoidal infiltration in the liver, diffuse infiltration in the splenic cord, and interstitial/diffuse infiltration with fibrosis in the bone marrow. These clinicopathological features suggest that this case could be classified as a hepatosplenic $\gamma\delta$ T cell lymphoma.¹⁻³ However, this case is unusual compared with previous HSTCL cases for the following reasons. First, the patient was older than is typical of patients with HSTCL. Second, the neoplastic cells in our patient were larger and more pleomorphic. HSTCLs are usually composed of monomorphic intermediate sized cells, although a heterogeneous cell composition has been described in some cases.⁶ Third, sinusoidal involvement of the liver was easily recognised, but sinus involvement of the bone marrow and spleen was not evident. Finally, lymphoma cells were negative for the cytotoxic molecule, TIA-1, whereas the neoplastic cells of HSTCL are usually positive for CD56 and TIA-1.^{2,5} However, because three cases of TIA-1 negative HPTCL have been reported,⁷ TIA-1 expression does not appear to be an essential criterion for a diagnosis of HSTCL.

It has been shown that liver involvement by peripheral T cell lymphoma frequently results in severe hepatic damage.⁸ The clinical diagnosis of some types of T cell lymphoma, including HSTCL, is sometimes extremely difficult and these cases are frequently misdiagnosed as hepatobiliary disease. We reported three postmortem cases of TIA-1 positive T/NK cell lymphoma mimicking fulminant hepatitis.⁹ In those cases, the neoplastic cells infiltrated mainly the portal area and apoptosis of periportal hepatocytes was frequently seen, which might explain the abnormally high values of ALS and AST. Bone marrow examination and measurement of LDH isozymes appear to be valuable for making the differential diagnosis. In our present case, neoplastic cells showed sinusoidal infiltration that led to the atrophic degeneration of hepatic cords. The laboratory findings (extremely high serum bilirubin concentration and slightly raised serum ALS and AST values) were indicative of intrahepatic cholestasis rather than parenchymal damage. This might be relevant to the finding that the lymphoma cells did not express cytotoxic molecules, in contrast to the usual type of HPTCL. It is suggested that hepatic damage by lymphoma cell infiltration depends on not only the localisation of the lymphoma cell infiltration—that is, portal or sinusoidal—but also the cytotoxic characteristics, such as the presence of cytotoxic granules containing various types of cytotoxic molecules.^{9,10}

“TIA-1 expression does not appear to be an essential criterion for a diagnosis of hepatosplenic T cell lymphoma”

The pathogenesis of our present case remains unknown. With regard to EBV, Oshima *et al* described three Japanese cases of EBV $^{-}$ and TIA-1 $^{+}$ hepatosplenic $\gamma\delta$ T cell lymphoma.¹¹ In contrast to their findings, EBV infection was found in only 2% of lymphoid cells in the liver of our patient, which suggested that EBV harbouring cells were non-neoplastic infiltrating lymphocytes.

Take home messages

- This report described a case of CD8 $^{+}$ T cell lymphoma, which clinically and histologically resembled hepatosplenic T cell lymphoma (HPTL) but did not express cytotoxic molecules
- This case represents a variation of HPTL and provides further evidence that the expression of cytotoxic molecules is not an essential criterion for a diagnosis of HSTCL
- Further studies should help to identify any clinicopathological differences between HSTCL with and without cytotoxic molecules

In conclusion, we described a case of CD8 $^{+}$ T cell lymphoma, which clinically and histologically resembled HPTL but did not express cytotoxic molecules. This case represents a variation of HPTL. Further studies may clarify the clinicopathological differences between HSTCL with cytotoxic molecules and that without cytotoxic molecules.

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