Hepatosplenic T cell lymphoma (HSTCL) is a distinctive clinicopathological entity that should be distinguished from other T/natural killer cell (NK) lymphomas. 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/sinusal 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 αβ or γδ T cell in origin. 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. However, Khan et al recently reported two cases of CD8+, TIA-1− hepatosplenic γδ T cell lymphoma that developed in renal transplantation patients, which suggests the presence of HSTCL without the characteristic cytotoxic cells.

“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.
Finally, he was suspected of hepatocellular carcinoma. 348 mg/litre at day 14 and he died of hepatic coma at day 15. Cirrhosis was diagnosed. His serum bilirubin value increased to 360 g. Lymphoma cells were diffusely infiltrated in the splenic cords of the red pulp (fig 1B). The white pulp was atrophic. A lymphoma cell cluster was observed. In the bone marrow of the vertebral bone, lymphoma cells displayed interstitial or diffuse infiltration with fibrosis. Myeloid and erythroid precursor cells were seen in clusters but megakaryocytes were hardly seen. Sinuses were dilated 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 XXV; Sigma Chemical Co, St Louis, Missouri, USA) in phosphate buffered saline for 20 minutes at 25°C (for βF1 and CD3ε), or by autoclaving at 1 bar for 20 minutes, followed by cooling down for 40 minutes (for CD4). The lymphoma cells expressed CD3ε, CD8, CD43 and CD45RO. The CD3ε staining highlighted sinusoidal infiltration of the liver (fig 2A). TIA-1 (fig 2B), granzyme B, CD20, CD30, CD56, 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 TCRγ gene rearrangement. DNA was amplified with the following primers: Vγ1, 5′-TCTGG[G/A]GTCTATACTGTCG-3′; Vγ2, 5′-CTC AACTCC/TCACTTC-3′; Vγ3, 5′-GAAAGGAATCTGGCATC CG-3′; Jγ1–2, 5′-CAAGTGTTGTTCCACTGCC-3′; Jγ1–2, 5′-GTT ACTATGAGC[T/C]TAATC-3′; and Jpγ, 5′-TGTAATGATAAG TGGCCAG-3′. This clearly showed two distinct bands, which suggest clonal rearrangement of two alleles of the TCRγ 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 periappendic, mesentry, and paraaortic lymph nodes.

**DISCUSSION**

In our study, we examined a postmortem case of T cell lymphoma with clonal rearrangement of the TCRγ gene and the immunophenotype: BF−, CD3e+, CD4−, CD5−, CD8+, CD20−, CD43+, CD45R0+, 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 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 γδ T cell lymphoma. 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. Third, sinusoidal involvement of the liver was easily recognised, but sinusal 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. However, because three cases of TIA-1 negative HPTCL have been reported, 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. 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. In those cases, the neoplastic cells infiltrated mainly the portal area and apoptosis of pericanal 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 HPTL. 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.

"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 γδ T cell lymphoma. 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.

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Hepatosplenic T cell lymphoma with no expression of cytotoxic molecules

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