

## Fulminant Acute Liver and Heart Failure from Hepatosplenic T-Cell Lymphoma

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### ABSTRACT

Hepatosplenic T-cell lymphoma is a rare extranodal lymphoma, involving primarily the spleen and liver of young male adults. Diffuse lymphoma cell infiltration can cause moderate liver impairment, yet acute liver or even multiorgan failure is an infrequent initial manifestation. We report on a case of a 71-year-old woman, who presented with acute liver failure, anemia, lymphopenia and thrombocytopenia. Previous medication with clindamycin for diarrhea was suggestive for drug-induced liver failure. However, due to elevated lactate dehydrogenase (LDH), fever, hypoproteinemia, elevated sCD25 and lack of other hepatic disorders including any infectious disease, lymphoma was suspected. On CT scan lymphadenopathy was excluded. Thus, due to hepatosplenomegaly, hepatosplenic T-cell lymphoma was assumed. While histopathological analysis was still pending, the patient's condition rapidly deteriorated. Cardiorespiratory failure necessitated mechanical ventilation on day 5 after admission. The patient died some hours later in catecholamine-refractory cardiac shock. On autopsy, widespread systemic disease with infiltration of heart, liver, spleen, and bone marrow became apparent with intravascular manifestation in the kidneys and lungs. Infiltration of the myocardium had resulted in acute cardiac failure. As a characteristic

of hepatosplenic T-cell lymphoma, molecular pathology and cytogenetic analysis revealed a monoclonal  $\gamma\delta$  T-cell receptor and an immunofluorescence staining compatible with isochromosome 7q in 20% and trisomy of chromosome 8 in 35% of tumor cells.

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**Key words:** Acute liver failure; Acute heart failure; Hepatosplenic T-cell lymphoma

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### INTRODUCTION

Acute liver failure is a life threatening condition, defined as the presence of encephalopathy and coagulopathy (INR >1.5) in patients without preexisting liver disease<sup>[1]</sup>. Neoplastic liver infiltration represents an infrequent cause of acute liver failure. Hepatosplenic T-cell lymphoma is a rare variant of peripheral T-cell lymphomas, which primarily affects liver and spleen and typically presents in young male adults. Although liver function at initial presentation is only moderately affected by infiltrating tumor cells in most cases, acute hepatic failure has been anecdotically reported in hepatosplenic T-cell lymphoma<sup>[2,3]</sup>. We report on a 71-year-old patient with fatal acute hepatic, renal and cardiac failure due to diffuse infiltration by a  $\gamma\delta$  hepatosplenic T-cell lymphoma.

### CASE REPORT

In December 2012, a 71-year-old woman was referred to our intensive care unit from a primary care hospital where she had been admitted to for acute hepatic failure.

At the end of November, having spent one week on Fuerteventura (Canary Islands), the patient developed fever (39.0°C), fatigue and diarrhea for which she was treated with clindamycin and probiotics (*Lactobacillus acidophilus*). Having returned to Germany, fatigue and fever persisted. She consulted her general practitioner and was admitted to a primary care hospital for acute hepatic failure with

jaundice (total bilirubin 6.4 mg/dL, direct bilirubin 5.3 mg/dL), coagulopathy (INR>6.3) and encephalopathy grade 2-3. Alcohol intake, drug abuse, sexual risk behavior, insect bites, and close contact to animals were denied. Except for low doses of ibuprofen and acetylsalicylic acid she denied any regular medication or allergies. Medical history was otherwise empty. Laboratory results before referral are shown in table 1. Malaria, HIV and acute viral hepatitis (HAV, HBV, HCV, HEV) were excluded. Ammoniac level and cranial computed tomography (CCT) were normal. On ultrasound she showed hepatomegaly (33×24 cm), splenomegaly (17×8 cm), minimal ascites and minimal bilateral pleural effusions. Cardiac and gynecological examinations were normal. Imbalanced electrolytes were compensated. She received fresh frozen plasma transfusion, N-acetylcysteine, lactulose, amantadine sulfate, and ceftriaxon for suspected pneumonia and was transferred to our hospital.

After admission to our intensive care unit for suspected clindamycin-induced hepatic failure, coagulopathy, renal failure, transaminases and encephalopathy had significantly improved. The time course of her laboratory values is listed in table 1. Further serological and microbiological diagnostics did not reveal any evidence of viral, bacterial or parasitic disease. Laboratory results were not suggestive for autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis or Wilson's disease. Mechanical cholestasis was excluded. Laboratory patterns indicated a rather toxic cholestatic liver damage with only moderately elevated transaminases, as has been described for clindamycin<sup>[4]</sup>. Peripheral blood count showed normocytic anemia and thrombocytopenia with absolute lymphopenia (0.1/nL, normal range 1.0-4.8), suggestive for drug-induced bone marrow toxicity.

**Table 1** Time course of laboratory results.

Parameter	Normal range	Before referral	Day 1	Day 2	Day 3	Day 4	Day 5
Sodium	135-145 mmol/L	111	119	119	120	126	133
Potassium	3.5-4.8 mmol/L	5.7	4.2	4.2	4.4	4.5	4.0
GOT/AST	<35 U/L	207	169	147	153	156	275
GPT/ALT	<35 U/L	109	81	71	69	64	62
Bilirubin (total)	<1 mg/dL	6.4	4.6	3.9	3.5	3.4	3.3
Alkaline Phosphatase	55-105 U/L	587	385	345	369	366	339
$\gamma$ -Glutamyl transferase	<40 U/L	671	497	446	482	491	440
Lactate dehydrogenase	<248 U/L	1857	1138	1112	1266	1459	2847
GFR	>80 mL/min	44.9	89.2	88.7	87.4	79.2	56.1
Lactate	0.9-1.6 mmol/L	7.04	7.04	6.59		11.1	19.8
Leucocytes	4-10/nL	13.4	8.1	6.3	8.7	8.0	14.8
Thrombocytes	150-440/nL	34	35	29	34	31	19
Haemoglobin	12-15 g/dL	11.5	8.8	7.9	7.8	7.6	7.5
pH (arterial)	7.37-7.45	7.41	7.35	7.40	7.32	7.41	7.12
Base excess	-2 till +3 mmol/L	-6.3	-6.7	-6.1	-15.4	-8.1	-20.2
C reactive protein	<5 mg/L	9.0	10.6	12.6	13.1	17.4	18.9
INR	<1.2	>6.3	1.23	1.27	1.31	1.43	1.85

However, due to highly elevated LDH with near normal haptoglobin and negative Coombs test (Table 1), persistent fever, hypoproteinemia and elevated sCD25 (27197 U/mL, normal range <900) intestinal lymphoma was suspected. CT scan showed bilateral pleural effusion, hepatosplenomegaly and minimal ascites but no lymphadenopathy (Figure 1).

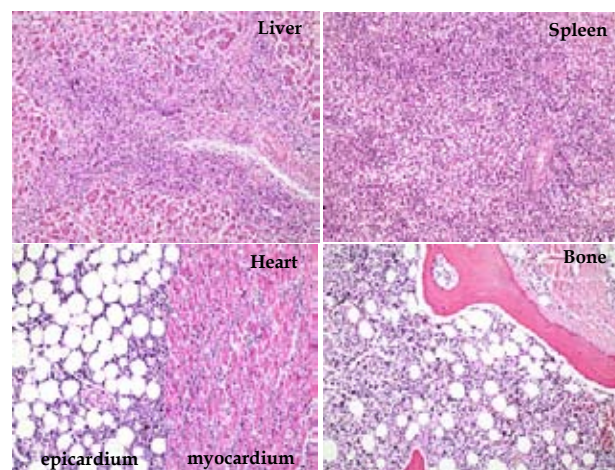
Elevated serum lactate (7.04 mmol/L, normal range 0.9-1.6) was attributed to acute liver failure since intestinal ischemia could be excluded on CT scan. Thus, as a differential diagnosis, hepatosplenic T-cell lymphoma was considered. Bone marrow aspirate on day 3 after admission was sicca. Therefore, bone marrow biopsy was performed at the very same session. Percutaneous liver biopsy was discussed, but postponed because of severe coagulopathy and thrombocytopenia. On the morning of day 5 after admission, while the histopathological results from the bone marrow biopsy were still

pending, the clinical condition of the patient deteriorated rapidly with development of severe lactate acidosis, renal insufficiency, steep LDH increase and worsening of coagulopathy. Despite mechanical ventilation, fluid resuscitation and buffering the patient developed rapid circulatory failure which was refractory to high doses of catecholamines. Acute diagnostics of ascites, heart, lung or abdomen did not reveal any septic focus, thrombosis, pericardial effusion or intestinal perforation. The patient died 5 hours after intubation from acute cardiovascular failure.



**Figure 1** CT scan of the abdomen demonstrated hepatosplenomegaly without lymphadenopathy.

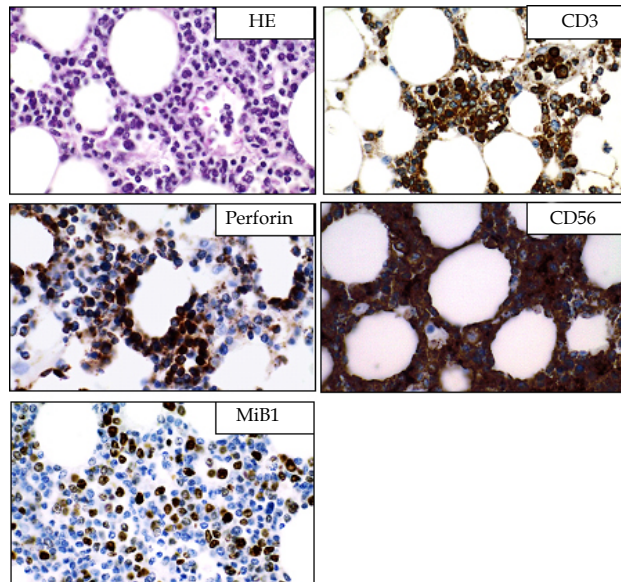
On autopsy, widespread systemic disease with infiltration of heart, liver, spleen, and bone marrow became apparent. Liver tissue showed extended necrosis. Liver (1800 g) and spleen (670 g) were enlarged and demonstrated diffuse and sinusoidal infiltration by medium-sized pleomorphic cells, which was also evident for heart, bone marrow (Figure 2), lungs, and kidney (not shown). Interestingly, lung and kidney tissues demonstrated an intravascular infiltration pattern. The spleen showed infarcted subcapsular areas caused by vascular tumor emboli.



**Figure 2** Histopathology. HE-staining (×100) of liver, spleen, heart, and bone marrow demonstrated diffuse infiltration by tumor cell which induced single cell necrosis of the liver in infiltrated areas and necrosis of the spleen due to intravascular tumor cell emboli.

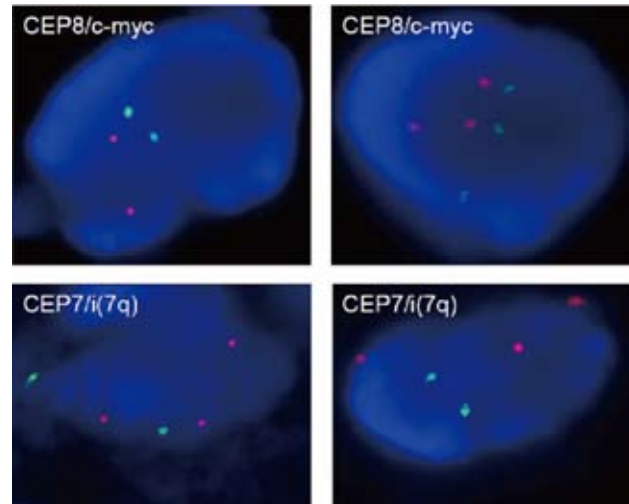
Infiltrating lymphocytes of the heart were positive for CD3, CD56 and perforin (Figure 3), but negative for MPO, lysozyme, CD5, CD20, CD30, CD34, CD99, and TdT. Detection of monoclonal  $\gamma\delta$  T-cell receptor (Figure 4) confirmed the diagnosis of hepatosplenic T cell lymphoma.

Molecular cytogenetic analysis of infiltrating tumor cells of the heart revealed trisomy 8 in approximately 20% of tumor cells (Figure 5A, B) as has been described for hepatosplenic T-cell lymphoma. In 35% of tumor cells with a normal copy number of chromosome

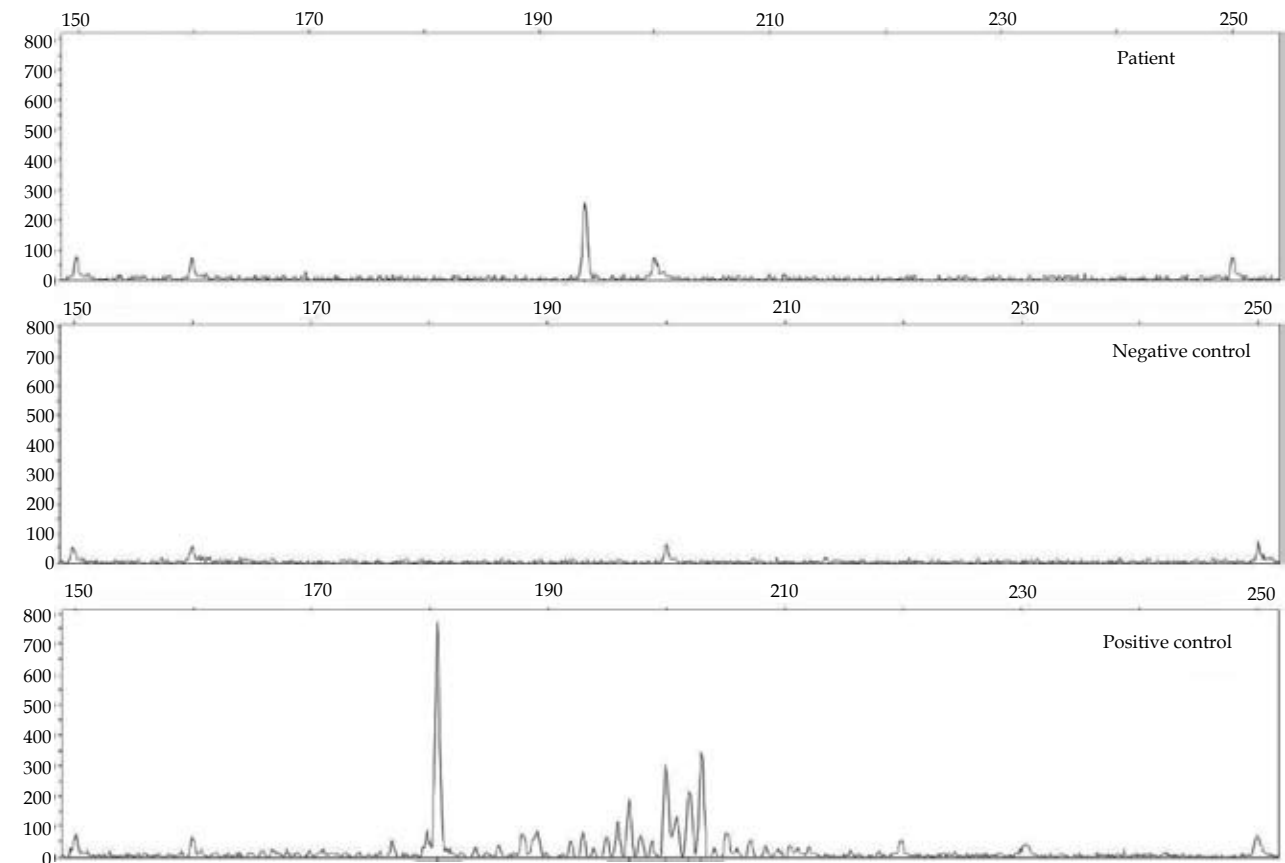


**Figure 3** Immunohistochemistry ( $\times 400$ ) demonstrates positivity of heart infiltrating tumor cells for CD3, perforin and CD56 with a proliferation index (MiB1) of approximately 40%.

7, three fluorescent signals per nucleus were obtained with a subtelomeric probe for chromosome 7q (Figure 5C, D). This signal pattern is compatible with the presence of isochromosome 7q in a subset of tumor cells as described before for this tumor entity<sup>[5]</sup>. Our patient died due to acute congestive heart failure, caused by diffuse neoplastic myocardial infiltration with a proliferation fraction (MiB1) of up to 40% (Figure 3).



**Figure 5** Molecular cytogenetic analysis of infiltrating tumor cells of the myocardium (paraffin-embedded material). FISH using CEP8/LSI C-MYC (spectrum green/orange) demonstrated normal copy number of chromosome 8 in some neoplastic T-cells (A), but trisomy 8 in 20% of tumor cells (B). Simultaneous FISH analysis with the probe mixture CEP7/i(7q) (spectrum green/orange) revealed normal signal pattern (diploidy of chromosome 7) in some tumor cells (C), but three signals for the subtelomere region of chromosome 7q (D) in 35% of tumor cells, compatible with presence of isochromosome 7q.



**Figure 4** Monoclonal  $\gamma\delta$  T-cell receptor was demonstrated by PCR: T-cell receptor  $\gamma$  chain gene rearrangement analysis was performed on formalin-fixed, paraffin-embedded autopsy material from the heart using polymerase chain reaction followed by gel scan analysis.

## DISCUSSION

Hepatosplenic T-cell lymphoma was established as a distinct entity in 1994 and accounts for only 5% of all hepatic lymphomas<sup>[6,7]</sup>. Unlike in our patient, hepatosplenic T-cell lymphoma mainly affects young men at a median age of 36 years<sup>[8]</sup>. Retrospectively, all common, yet unspecific features of hepatosplenic T-cell lymphoma (hepatosplenomegaly, anemia, thrombocytopenia, leucopenia, elevated LDH, bone marrow involvement, lack of lymphadenopathy, jaundice, B-symptoms) had been present in our patient. Tumor cells are characterized by the phenotype CD2+ CD3+ CD5- CD7+ CD56+ and often lack CD4 or CD8 expression, although expression of CD5, CD7, CD8, CD16 and CD56 is variable.  $\gamma\delta$  T-cell receptor rearrangement is a hallmark of hepatosplenic T-cell lymphoma, although  $\gamma\delta$  variants have also been described<sup>[9]</sup>. In our case, PCR demonstrated monoclonal  $\gamma\delta$  T-cell receptor rearrangement (Figure 4). Some primary hepatic NHL have been associated with other pathological conditions like primary biliary cirrhosis, chronic hepatitis C, HIV, history of inflammatory bowel disease, immunosuppressive therapy, organ transplantation, and lupus erythematosus<sup>[8,10-12]</sup>, none of which applied to our patient. The simultaneous occurrence of isochromosome 7q and trisomy 8 has been described as a characteristic cytogenetic aberration of hepatosplenic T-cell lymphoma<sup>[5]</sup>. Using fluorescence in-situ hybridization (FISH) of infiltrating tumor cells of the heart, we could detect a signal pattern compatible with trisomy 8 in 20% and isochromosome 7q in 35% of tumor cells (Figure 5).

In contrast to frequently reported mild elevation of liver enzymes and obstructive jaundice by periportal adenopathy<sup>[13]</sup>, fulminant liver failure with severe lactate acidosis is a rarely reported complication of peripheral T-cell lymphomas with an average survival of 10.7 days from diagnosis<sup>[14]</sup>. Due to the fulminant course, as in our case, the correct diagnosis in cases of acute hepatic failure is often only made at autopsy<sup>[2]</sup>. The previous medication with antibiotics like clindamycin, suggesting drug-induced liver failure, was diagnostically misleading in this context. However, after a short clinical improvement, pulmonary and myo- and epicardial infiltration by aggressive tumor cells first led to severe lactate acidosis (lactate 19.8 mmol/L at maximum), respiratory failure and eventually catecholamine refractory circulatory failure with fatal outcome only 5 days after admission.

Clindamycin can induce cholestatic hepatitis as previously reported<sup>[15]</sup>. Drug induced hepatitis presents with lobular and portal tract inflammation, liver cell steatosis, cholestasis and infiltrating T-cells<sup>[16]</sup>. However, in our patient, clindamycin-induced hepatic injury could be ruled out, since liver tissue was infiltrated by monomorphic neoplastic T-cells resulting in single and grouped liver cell necrosis. In contrast to tumor cell infiltrated areas, liver tissue which were not affected by neoplastic infiltrates appeared normal, lacking all characteristics of clindamycin-induced liver damage. Furthermore, eosinophilic granulocytes which often accompany drug-induced hepatitis were lacking.

To our knowledge, our case represents the first report on simultaneous liver, spleen, bone marrow, kidney, pulmonary and cardiac infiltration at first presentation of hepatosplenic T-cell lymphoma leading to acute and fatal organ failure.

Although chemotherapy can induce remission, prognosis of hepatosplenic T-cell lymphoma is still dismal due to frequent and early tumor relapse. Long term survival was only achieved in cases with consolidating stem cell transplantation<sup>[8,17,18]</sup>. Nevertheless, the fulminant progress in our patient leading to catecholamine-refractory

circulatory failure only 5 days after admission excluded any anti-neoplastic treatment options.

## CONCLUSION

We report on a case of hepatosplenic T-cell lymphoma which is uncommon regarding age, sex and clinical course with fulminant multiorgan failure. With our report we would like to increase the awareness of this rare, but life threatening disease.

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