CASE REPORT

Hepatosplenic T-cell lymphoma: a rare cause of hepatosplenomegaly

Ana Cristina Lladó,¹ Ana Luisa Tomé,² Maria Henrique,² Pedro Farinha³

¹Department of Internal Medicine, Hospital Santo António dos Capuchos, Lisbon, Portugal

²Department of Hematology, Hospital Santo António dos Capuchos, Lisbon, Portugal

³Department of Pathology, Hospital de São José, Lisbon, Portugal

Correspondence to
Dr Ana Cristina Lladó, ana.llado@sapo.pt

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SUMMARY

We report a case of a man presenting with an unexplained fever, pancytopenia and hepatosplenomegaly without lymphadenopathy. Bone marrow flow cytometry strongly suggested hepatosplenic $\gamma\delta$ T-cell lymphoma and infiltration of bone marrow samples by pathological T-lymphocytes confirmed the diagnosis. Despite chemotherapy the patient died 1 year after diagnosis. This is a rare disease that should be considered in the differential diagnosis of hepatosplenomegaly especially when it presents with B-symptoms and no lymph node enlargement. There is no standard therapy and the prognosis is poor.

BACKGROUND

Hepatosplenic $\gamma\delta$ T-cell lymphoma is a very rare condition that represents less than 1% of non-Hodgkin lymphomas.¹ Its exact incidence is unknown, fewer than 100 cases have been reported in the literature² and it is often related to some grade of immunosuppression. By sharing our experience we aim to call other physicians' attention to the importance of a high grade of suspicion as clinical course, prognosis and therapeutic options (as inclusion on clinical trials) differ from other lymphomas and demand a histological confirmation. It is also interesting to denote that sequential bone marrow biopsies and reviews were needed as well as the correlation between its immunophenotyping and clinical course during the process of 'chasing' an accurate diagnosis.

CASE PRESENTATION

A middle-aged man presented with a 4-week history of fever, drenching night sweats, generalised malaise, fatigue, non-selective anorexia and non-quantified weight loss. Physical examination showed enlarged liver and spleen, without peripheral lymphadenopathy.

INVESTIGATIONS

Laboratory investigations showed pancytopenia (haemoglobin 6.1 g/dL, white cell count $2.86 \times 10^3/\mu\text{L}$, platelets $47 \times 10^3/\mu\text{L}$) with Coombs negative haemolysis and very high lactic dehydrogenase (LDH) levels (2537 U/L). Vitamin B₁₂ and folate levels, coagulation tests and triglyceride levels were normal. Ferritin was slightly above the upper normal limit. Peripheral blood smear revealed erythroid and platelet anisocytosis. Serology tests for HIV, hepatitis and Epstein-Barr virus, cytomegalovirus, toxoplasmosis and parvovirus B₁₉

were negative as well as bacterial cultural examinations.

CT of the chest, abdomen and pelvis showed massive splenomegaly (30 cm) and homogeneous hepatomegaly (25 cm); there were no enlarged lymph nodes. A cavernous malformation of portal vein was also found (figure 1).

Because of the suspicion of a blood disease, a bone marrow aspiration and biopsy were performed, showing a hypercellular marrow with no other pathological signs (figure 2). Considering that we still had no diagnosis and the suspicion of a blood disease persisted, a second bone marrow sample was collected and immunophenotyping showed a population of large abnormal T lymphocytes representing 83% of the T cells (figures 3–5). These cells expressed strong CD45, T-cell receptor (TCR) $\gamma\delta+$, CD3 low⁺, CD7, CD16, but CD4[–], CD5[–], CD56 and TCR $\alpha\beta$ –. These results in this clinical context strongly suggested hepatosplenic $\gamma\delta$ T-cell lymphoma. The bone marrow biopsy showed a bland infiltration by T lymphoproliferative disease with an intrasinusoid pattern supporting the diagnosis. Chromosomal analysis was not conclusive. Haemophagocytic features were not observed during the course of the disease.

In presence of a high clinical suspicion or even after the diagnosis is achieved it is important to proceed to a directed reassessment of histological slides. Sometimes, like in our case, reviewing the

Figure 1 C T of the abdomen—massive splenomegaly (30 cm) and homogeneous hepatomegaly (25 cm); there are no enlarged lymph nodes.

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Figure 2 Bone marrow aspiration-hypercellular marrow.

first biopsy, bone marrow sample already showed subtle atypical lymphocytes infiltration ([figure 6](#)).

DIFFERENTIAL DIAGNOSIS

Before a patient presenting with massive hepatosplenomegaly, B symptoms and cytopenias the diagnosis of lymphoproliferative disease was strongly considered namely aggressive B or T-cell/natural killer-cell lymphomas, as well as splenic marginal zone lymphoma, hairy cell leukaemia and acute lymphoblastic leukaemia. The differential diagnosis was also made

with myeloproliferative syndromes such as myelofibrosis, infectious diseases such as leishmania and haemophagocytic syndrome.

TREATMENT

The patient was treated with chemotherapy (CHOP-6 cycles) with a transient response. After disease progression, a second-line regimen was started with autologous bone marrow transplant intent.

Figure 3 Second bone marrow aspiration—a progressive sinusoidal infiltration by monotonous, medium-sized lymphoid cells with round or slightly irregular nuclei, loosely condensed chromatin and a moderate amount of pale cytoplasm. Nucleoli are small and distinct. Mitotic activity is generally low.

Figure 4 Immunohistochemistry: usually tumour expresses CD2, surface CD3, CD7 and CD16. B-cell surface markers (eg, CD20) are not present.

Figure 5 Immunohistochemistry, $\times 40$ magnification.

OUTCOME AND FOLLOW-UP

Signs and symptoms of disease progression (pancytopenia, hepatosplenomegaly, B symptoms) reappeared 1 month after the start of the first-line regimen. Despite the second-line treatment, the disease control was not achieved and the patient died 1 year after the diagnosis.

DISCUSSION

Hepatosplenic $\gamma\delta$ T-cell lymphoma is a very rare T-cell lymphoma that is seen mainly in young men (median age 35 years).³

Despite unknown aetiology, approximately 10–20% affected patients have a previous history of chronic immune suppression, such as solid organ transplantation, lymphoproliferative disorder, inflammatory bowel disease, hepatitis B infection or immunosuppressive therapy.^{2 4–6}

The clinical presentation is peculiar and characterised by extranodal infiltration of malignant post-thymic T lymphocytes into the sinusoids of the liver, spleen and bone marrow without lymphadenopathy. The sinusoidal infiltration can lead to an important hepatosplenomegaly. Significant cytopenias are less common, aside from thrombocytopenia which may be severe. Upto 80% of cases present with B symptoms namely fever, night sweats and weight loss.^{7–9}

The blood smear changes are inconspicuous so that diagnosis is generally based on biopsy specimens of bone marrow, liver and/or spleen. The morphology of infiltrating atypical lymphoid cells on the histological examination is similar whether they involve the spleen, liver or bone marrow^{3 10 11} showing an intrasinusoidal infiltration which can sometimes be subtle (see figure 1—first biopsy). As this is a rare diagnosis, a high grade of suspicion is extremely important.

Flow cytometry and immunophenotyping of biopsy specimens is an essential tool for diagnosis. The tumour usually expresses CD2, surface CD3, CD7 and CD16. In most cases CD4, CD5 and CD8 are not expressed. B-cell surface markers (eg, CD20) are not present. CD56 expression is variable. Most cases of hepatosplenic T-cell lymphoma express the $\gamma\delta$ T-cell receptor but rare cases can express the $\alpha\beta$ receptor. Cytotoxic granule-associated proteins TIA1 or granzyme M are present but perforin and granzyme B are absent, features consistent with a non-activated cytotoxic T-cell phenotype.^{3 9 12 13}

Cytogenetic changes occur with isochromosome 7q being present in most cases.^{1 3 14} Other mechanisms of 7q amplification as well as trisomy 8^{1 15 16} and loss of Y chromosome¹ have been reported but they are not enough or necessary to define the disease.

Differential diagnosis should exclude other rare T-cell leukaemia/lymphoma (eg, T-lymphoblastic lymphoma expressing TCR $\gamma\delta$ or peripheral cytotoxic T-cell lymphomas). Another rare condition usually presenting with hepatosplenomegaly, fever and peripheral blood cytopenias is the haemophagocytic syndrome, often associated in adults with T-cell lymphomas. This syndrome may actually mimic hepatosplenic T-cell lymphoma as the clinical presentation may be similar. Features such as hypertriglyceridaemia, high ferritin levels, immunophenotyping and evidence of haemophagocytosis help in distinguishing these entities.¹⁷

The clinical course is highly aggressive, with a certain fatal outcome and a median overall survival barely exceeding 1 year.^{3 18} At the present time an effective treatment of hepatosplenic $\gamma\delta$ T-cell lymphoma is lacking, as treatment modalities for other lymphoma appear to be ineffective in most patients. Autologous or allogeneic transplantation should be considered as well as patient recruitment to clinical trials. Although data to support these aggressive strategies are limited, the outcome is poor with chemotherapy alone.^{2 3}

Figure 6 Chronological comparison.

Learning points

- ▶ Hepatosplenic $\gamma\delta$ T-cell lymphoma is a very rare entity with a peculiar clinical presentation.
- ▶ Although rare, this diagnosis should be considered in a patient presenting with fever and unexplained hepatosplenomegaly without lymph node enlargement, even in a patient with no chronic immune suppression.
- ▶ The diagnosis is based on biopsy specimens of bone marrow, liver and/or spleen and flow cytometry analysis.
- ▶ No standard therapy exists. The chemotherapy regimen is largely based on the extrapolation of studies in other aggressive lymphomas.
- ▶ Despite treatment the outcome is poor. Median overall survival is around 1 year.

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