Hepatosplenic gamma-delta T-cell lymphoma in a female patient after delivery

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Abstract

Hepatosplenic γδ T-cell lymphoma (HSTCL) is a very rare peripheral T-cell lymphoma characterized by extranodal infiltration of mature malignant post-thymic T-lymphocytes into sinusoids of the liver and spleen without lymphadenopathy and significant cytopenias. The aetiology of the disease is unknown. We describe the case of a female patient in whom HSTCL developed after delivery and who was previously without disease. Flow cytometry and liver puncture are essential for diagnosing HSTCL, especially in patients with unexplained pancytopenia and hepatosplenomegaly. Since phenotypic results can easily be misinterpreted as non-malignant, the examiner should have enough experience to recognize clonal changes of T-lymphocytes. Namely, in contrast to B-lymphocytes, T-lymphocytes do not have an efficient indicator of clonality and are recognized by flow cytometry based only on aberrant expression of commonly present antigens of T-cell and NK-cell subsets. At present, there is no known cure for HSTCL with a maximum survival up to 2 years.

Introduction

Hepatosplenic γδ T-cell lymphoma (HSTCL) is a rare peripheral T-cell lymphoma with predominant occurrence in young male adults and characterized by extranodal infiltration of mature malignant post-thymic T-lymphocytes into sinusoids of the liver and spleen without lymphadenopathy and significant cytopenias.[1] Increased numbers of normal γδ T-cells can be found in patients with chronic antigen stimulation, autoimmune disease, post solid organ transplantation (kidney, liver) and splenectomy. A precise phenotype of γδ T-lymphocytes has not been described until recently.[2] Malignant neoplasms arising from γδ T-lymphocytes are very rare. Among those, the HSTCL represents <5% of peripheral T/ NK-lymphomas, and is less common than αβ peripheral T cell lymphoma.[3] Only 150 cases have been described in literature since the initial description by Farcet and Gaulard in 1990.

Case Report

A 20-year old patient was admitted to the Department of Haematology for clarification of haematomata in both hands, hepatosplenomegaly and pancytopenia. No enlarged lymph nodes were palpated. Three months ago she had a normal delivery of a healthy female baby. She had a normal pregnancy. She has never taken any contraceptives or other medication and previously she was healthy. During pregnancy her blood work was normal. Two months before admittance to our department she first noticed haematomata in extremities, and more recently she had become tired, dizzy and pale. She did not have a fever and did not lose weight. Clinical examination revealed an enlarged liver and spleen (15 cm) besides paleness and haematomata in her extremities. No enlarged lymph nodes were palpated. Blood test revealed pancytopenia (red blood cells (RBC) $3{,}5\times10^{12}$/ L, haemoglobin (Hb) 91 g/L, reticulocytes 85×10^{9}/L, white blood cells (WBC) $3{,}4\times10^{9}$/L with 7% of atypical lymphocytes, platelets 28×10^{9}/L, elevated total bilirubin (28 μmol/L) and C reactive protein (22 mg/L), low cholinesterase (CHE) 92 μkat/L and prothrombin time 0,55 E, other blood tests (aspartate transaminase (AST), alanine transaminase (ALT), urea, creatinine, lactate dehydrogenase (LDH), vitamin B_{12}, folates, electrolytes, tumour markers and immunological markers) were within normal limits. Viral and bacterial serology was performed (toxoplasmosis, cytomegalovirus, tularaemia, HIV, Wassermann test, Yersinia, human herpesvirus, Epstein-Barr virus (EBV), hepatitis) and showed the presence of antibodies to EBV (Table 1). Lung and heart x-rays were normal. Ultrasound and abdominal computed tomography (CT) showed a slightly enlarged liver with a homogeneous pattern and markedly enlarged spleen reaching into the pelvis, bulging the anterior abdominal wall, pressing onto stomach and left kidney and pushing the left liver lobe away. There were no enlarged lymph nodes (Figure 1). Because of the suspicion of a blood disease, we performed a bone marrow phenotyping, which showed a population of $CD3^+$ lymphocytes expressing CD56+, CD16 $partly^+$, $CD38^+$, CD8 low^+, $CD2^+$, $CD7^+$ but not $CD5^-$ or TdT^-. Of the additionally tested antigens, CD45RO and CD161 were positive, however the intracellular granzyme B was negative (Figure 2). This population with aberrant expression of antigen CD5 and low expression of antigen CD8 (in Figure 3 appearing red) presented 16% of leukocytes, 70% of all lymphocytes and 77% of T-lymphocytes in the bone marrow sample. The immunophenotyping results caused suspicion for the involvement of the extremely rare γδ hepatosplenic lymphoma that was later confirmed by liver puncture. The liver puncture revealed that the liver was diffusely infiltrated with lymphoma cells which were typically distributed in the sinusoids instead of in the portal tracts as seen in usual lymphomas. The nuclei of the lymphoid cells were round, ovoid, occasionally irregular with quite dense chromatin, and a small amount of pale to clear cytoplasm (Figure 3). Lymphoma cells were immunohistochemically highlighted with T-lineage markers. A bone biopsy revealed similar cells. The patient was treated with high-dose chemotherapy (CHOP) and autologous bone-marrow transplant. Signs of disease progression (pancytopenia, spleen-growth reaching into pelvis) appeared after one year with B-signs. A specific oncological treatment was not decided upon.

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Discussion

Although the aetiology of the HSTCL is still unknown, approximately 10% to 20% of affected patients have a previous history of immunocompromise, including solid organ transplant (renal, liver, heart), inflammatory bowel disease (mostly Crohn's disease), hepatitis B infection, or the patients have been treated with immunosuppressive therapy (*e.g.* due to rheumatoid arthritis, systemic lupus erythematosus). Generally it is not associated with EBV.[4,5] It can occur during pregnancy.[6] To date it was not described after delivery.[6] HSTCL was also described in animals. It has been established that during pregnancy the placenta contains more NK cells, αβ T cells and γδ T-cells, which express more cytotoxic molecules than T-cell intracellular antigen 1, granzyme B and especially perforin. It is assumed that during pregnancy the high progesterone concentration might affect the perforin expression and that maternal immunity and hormonal changes during pregnancy and presumably delivery might eventually provide a chance for decidual lymphocytes to transform and develop HSTCL.[7]

The leading sign of HSTCL is hepatosplenomegaly and cytopenia, while lymph node enlargement excludes the disease. However, other clinical features like fatigue, Coombs negative haemolytic anaemia, jaundice due to hepatic involvement and purpura due to thrombocytopenia may occur. The main sign of the disease is blood cell reduction, ranging from isolated reduction of one lineage to pancytopenia as a consequence of hypersplenism and/or suppression of bone marrow precursor cells by cytokines released by neoplastic cells. The most obvious appears to be thrombocytopenia. The blood smear is usually normal, a leukemic picture or lymphocytosis can yet be found, or, as in our case, a minor population of atypical lymphocytes. Elevated LDH or changes in liver enzymes are also possible. All the above mentioned clinical and laboratory tests are non-specific and if not recognized they can lead to misdiagnosis of virus infection (mostly EBV), immune thrombocytopenia or acute lymphoblastic leukaemia.[8]

Table 1. Patient's laboratory data.

Parameter, units	Patient	Reference values
WBC , E×10^9/L	3,4	4,0-10,0
Blood smear, %		
Segmented neutrophils	45	40-60
Banded neutrophils	3	0-3
Lymphocytes	36	20-40
Monocytes	9	2-8
RBC , E×10^{12}/L	3,5	4,2-6,3
Hb, g/L	91	120-180
MCV, fl	79	81-94
Reticulocytes, E×10^9/L	85,1	21-94
Platelets , E×10^9/L	28	140-340
Biochemistry		
AST, μkat/L	0,15	0-0,58
ALT , μkat/L	0,23	0-0,74
CHE, μkat/L	118	117-317
Total bilirubin, μmol/L	30	0 -17
Urea, mmol/L	5,3	2,8-7,5
Creatinine, mmol/L	71	44-97
Folic acid, μ mol/L	12,9	6,1-32,6
B_{12}, pmol/L	114	132-857
CRP, mg/L	4	0 -5
LDH, μkat/L	1,05	0-4,13
Prothrombin time, E	0,55	0,7-1,2
ANA, ANCA, ACA, AMA	negative	negative
CA 19-9, CA 15-3, CEA, αFP	negative	negative
Serological tests		
Toxoplasmosis, CMV, Yersinia, Human herpesvirus, EBV	EBV (IgG 1: 160, IgM 1:10, EBNA 1: 10), other negative	
Hepatitis A, B, C, HIV	negative	negative
Wasserman test	negative	negative

MCV, mean corpuscular volume; ANA, antinuclear antibody; ANCA, anti- neutrophil cytoplasmatic antibody; ACA, anti-centromere antibody; AMA, anti-mitochondrial antibody; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

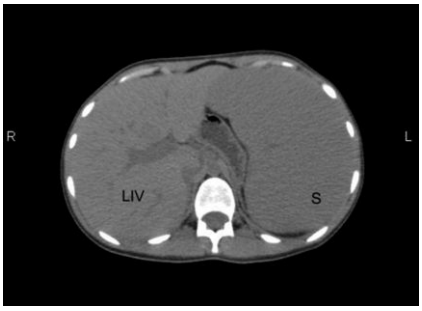

Figure 1. Computer tomography of the patient's abdomen, transverse scan. L, left; R, right; S, very enlarged spleen; LIV, enlarged liver

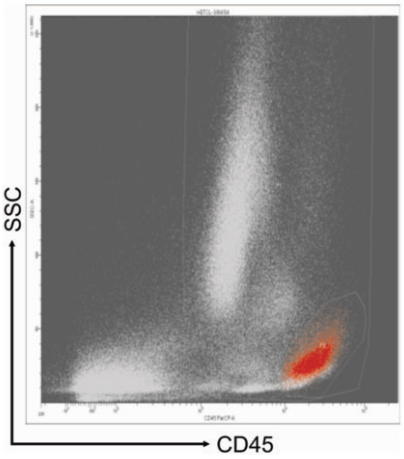

Figure 2. Flow cytometry in our patient: population of 77 % CD3$^+$ T-lymphocytes are marked red on the CD 45 - SSC diagram (phenotype CD56+, CD16 partially$^+$, CD38$^+$, CD8 low$^+$, CD2$^+$, CD7$^+$, CD5$^-$, TdT$^-$, CD45RO$^+$, CD161$^+$, intracellular granzyme B negative).

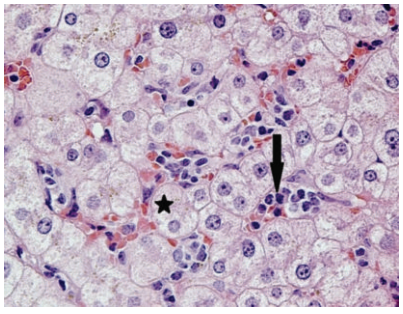

Figure 3. Liver histology of our patient shows lymphoma cells (arrow) between hepatocytes (star) (Haemotoxylin - Eosin stain, ξ400).

To diagnose HSTCL, a flow cytometric immunophenotyping of lymphocytes and liver biopsy is sufficient.[3] Flow cytometric immunophenotyping is extremely helpful in diagnosing, however both, the diagnostic and the examiner, should be experienced enough to recognize clonal changes of T-lymphocytes. Unlike B-lymphocytes, T-lymphocytes do not have an efficient indicator of clonality on the membrane, so they can be recognized by flow cytometry based only on aberrant expression of usually present antigens of the T-cell and NK-cell subsets.[9] Malignant-changed T-lymphocytes, including the rare-ones, can often be recognized, since the antigen of the T-cell subset can be completely absent or its intensity of expression has changed when compared to other normal-polyclonal T lymphocytes. HSTCL commonly has the phenotype described in our patient.[3,8] There are also exceptions to the *common phenotype*, since expression of CD5, CD7, CD8, CD16 and CD56 is variable. Antigens characteristic for B-lymphocytes (CD19, CD20, CD21, and CD22), immunoglobulins, TCR αß-chain, TdT, CD10, CD15, CD25, CD33, CD34, CD41, and CD68 are not expressed.[10] A special subcategory shows αß TCR expression as well as clinical and pathologic features that resemble those of HSTCL. Based on the flow cytometry of our patient's bone marrow aspirate we were able to establish the phenotype of cells-suspicious for HSTCL in a few hours, which was later additionally confirmed by the bone and liver biopsy. Since the bone marrow examination with regular staining does not show the cells typical for this disease (however the flow cytometry does reveal the phenotype suspicious for HSTCL), it is recommended to additionally perform immunohistochemical staining tests for T-lymphocytes, which reveal a hypercellular bone marrow with a sinusoidal infiltration of atypical, medium sized lymphoid cells with abundant light and basophilic cytoplasm and multiple granulations.[1,11] Both, liver and spleen puncture, reveal sinusal infiltration with atypical lymphocytes. The splenic white pulp is reduced or completely lost. Since the normal γδ T-lymphocytes have special homing receptors for splenic sinuses it is most likely that the HSTCL originates in the splenic red pulp.[1] A special phenomenon is erythrophagocytosis documented in areas invaded by malignant cells. Mostly in male patients cytogenetic changes can occur (isochromosome 7q, trisomy 8 or absent Y-chromosome), but this is not sufficient to define the disease.[8] Differential diagnosis should exclude other rare T-cell lymphomas/leukaemia (T-lymphoblastic lymphoma expressing TCR γδ, peripheral cytotoxic T-cell lymphomas and unusual forms of T chronic lymphocytic/promyelocytic leukaemia with CD8 phenotype); however all these entities usually express TCR αβ chains.[8]

HSTCL is an extremely aggressive disease with median survival rate of 8 months to a maximum of 2 years, with possible remission due to treatment. At the present time an effective treatment of HSTCL is lacking, as treatment modalities for other lymphoma appear to be ineffective in most patients. Moreover there is no known biomarker for the prediction of a prognosis. A wide array of therapies have been used, including steroid or alkylating treatment, purine analogs, splenectomy and high dose chemotherapy with or without allogeneic stem cell transplantation.[12,13] Prolonged disease free survival has been reported in patients who underwent allogeneic stem cell transplantation, receiving combined treatment with cytostatics and alemtuzumab, as pralatrexate and romidepsin for progressive or relapsed HSTCL.[14-17]

Conclusions

HSTCL is a rare entity of T-cell lymphoma, uncommon in female patients and not reported after delivery so far. The majority of patients presents with hepatosplenomegaly, bone marrow infiltration and cytopenia. Flow cytometry is essential in diagnosing HSTCL rapidly, and should additionally be confirmed by bone marrow examination and liver and/or spleen puncture. Since it is a rare disease the examiner should have enough experience to recognize clonal changes of T-lymphocytes. The patient's fate, however, lies in good cooperation between departments, diagnostic laboratory for flow cytometry and eventually the pathologist. Cooperation is the only way to diagnose this rare condition soon enough to help the patient.

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