Cytotoxic hepatosplenic $\gamma\delta$ T-cell lymphoma following acute myeloid leukemia bearing two distinct $\gamma$ chains of the T-cell receptor. Biological and clinical features

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ABSTRACT

Background and Objectives. Hepatosplenic $\gamma\delta$ T-cell lymphoma is a rare entity of peripheral T-cell lymphomas. We characterized in detail the first case of hepatosplenic $\gamma\delta$ T-cell lymphoma following acute myeloid leukemia.

Design and Methods. Hepatosplenic $\gamma\delta$ T-cell lymphoma was diagnosed in a woman who had been in complete remission (CR) of acute myeloid leukemia (AML) for two years. Improvement but no objective response of the disease was observed after various types of chemotherapy. CR was achieved after related donor stem cell transplantation. Thirteen months later relapse of hepatosplenic $\gamma\delta$ T-cell lymphoma was diagnosed. While being prepared for a second transplantation the patient developed meningeal lymphoma. In the majority of the cases the disease affects young male adults. Any of the patients present with systemic symptoms and pancytopenia.

Results. Lymphoma cells expressed the $\gamma\delta$ T-cell receptor (TCR), CD2, CD3, CD5, CD7, CD38, CD45, CD161 (NKR-P1), TIA and Ki67. Further analysis revealed expression of $V_\gamma$1 and two distinct TCR $\gamma$ chains, $V_\gamma$3 and $V_\gamma$9, by the malignant cell clone. The clonality of the T-cells was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) followed by sequencing of TCR $V_\gamma$3, $V_\gamma$9 and $V_\delta$I functional regions. Clone-specific PCR was negative at diagnosis of AML and was positive at all times during follow-up of the hepatosplenic $\gamma\delta$ T-cell lymphoma. The lymphoma cells mediated strong natural killer-like cytotoxic activity, possibly explained by expression of CD161 and a lack of killer inhibitory receptor.

Interpretation and Conclusions. Several so far undescribed features were observed in this case of hepatosplenic $\gamma\delta$ T-cell lymphoma, such as T-cell lymphoma following AML, expression of two distinct T-cell receptor $\gamma$-chains, and an unexpected cytotoxic phenotype.

Hepatosplenic $\gamma\delta$ T-cell lymphoma was reported as a distinct lymphoma entity in 1990 and recognized as such in 1994 by the REAL classification because of several characteristic clinicopathologic features. Since the initial description by Farcet et al., approximately 45 cases have been published in detail. The disease has a rather aggressive clinical course. The clinical appearance is usually characterized by hepatosplenomegaly with a sinusoidal infiltration of the liver and a sinusoidal infiltration of the spleen, but no or little lymphadenopathy. In the majority of the cases the disease affects young male adults. Many of the patients present with systemic symptoms and pancytopenia.

A number of cases of hepatosplenic $\gamma\delta$ T-cell lymphoma have been reported following organ transplantation, and 1 case after treatment of Hodgkin’s disease. The malignant cells usually appear as small to medium size lymphocytes with agranular, pale blue, somewhat abundant cytoplasm, however, blast-like transformation has been observed, mostly in association with a terminal event. Immunologically, most of the cases have been characterized to express CD2, CD3, CD7, $\gamma\delta$ T-cell receptor (TCR), $\delta$I, and the cytotoxic granule associated protein (TIA-1) and in part CD5D, CD8, CD56 and CD11c. The predominant chromosomal aberration is an isochromosome 7q often in combination with trisomy 8. In humans, $\gamma\delta$ T-lymphocytes represent 1-10% of peripheral blood T-cells. The TCR $\gamma$ locus comprises only 6 expressed variable gene segments, i.e. $V_\gamma$2/3/4/5/6 belonging to the highly homologous $V_\delta$I family, and $V_\gamma$9 of the single member family $V_\gamma$I. Eight expressed $V_\delta$ genes were described of which several can be used to construct functional TCR $\alpha$ chains. Because hepatosplenic $\gamma\delta$ T-cell lymphoma is a rarely diagnosed lymphoma entity, the purpose of our study was to characterize the clinical and biological features of this case, which may add information to previous reports.
Case Report

The 41-year old patient was admitted to our hospital in December 1994. She presented in the 21st week of pregnancy with severe anemia and thrombocytopenia, weakness and fatigue. Acute myeloid leukemia FAB M2 with a normal karyotype (46, XX) was diagnosed by cytology, cytochemistry, histology and immunophenotype (CD34+CD13+DR+). The patient decided not to interrupt her pregnancy. Two induction chemotherapies were needed to achieve complete remission (CR). Cesarean section was performed during the 27th week of pregnancy. The child is alive, but has a history of recurrent pneumonia. Consolidation therapy using intermediate-high dose cytarabine and amscarine with peripheral stem cell apheresis followed by late consolidation with high dose cytarabine and daunorubicin was administered. In June 1997, the patient presented with marked lymphocytosis with partly enlarged cytoplasm at a routine check up. Because she had suffered from a strong viral infection immediately before, lymphocytosis was interpreted as reactive following the infection. However, in August, the patient had a leukocytosis of 80×10⁹/L, anemia (hemoglobin 9.9 g/dL) and thrombocytopenia (32×10⁹/L). Lactate dehydrogenase (LDH) concentration was 873 U/L, aspartate transerase (AST) 29 U/L, and alanine transerase (ALT) 34 U/L; all other routine parameters were normal. Epstein Barr virus (EBV), cytomegalovirus and human immunodeficiency virus titers were negative. Blood and bone marrow smears demonstrated the presence of blast cells within a population of small and medium sized lymphoid cells. Because of the patient’s history and the evident presence of blast cells, relapse of AML was assumed. During pancytopenia following treatment with intermediate-high dose cytarabine/etoposide, a population of 4-6×10⁹/L predominately small lymphocytes persisted. Immunophenotyping these lymphocytes showed that they expressed the γδ-T-cell receptor (Table 1). Because of the immunophenotype in combination with moderate hepatosplenomegaly (longitudinal diameter 16 cm), anemia, thrombocytopenia and elevated LDH, at that point hepatosplenic γδ-T-cell lymphoma was diagnosed, even though a fine-needle liver biopsy demonstrated that portal infiltration was more pronounced than sinusal infiltration. Because of the diagnosis of a T-cell lymphoma, a bone marrow biopsy was performed. Due to chemotherapy the marrow was hypocellular, but was diffusely infiltrated by CD3 positive T-cells. After further chemotherapy consisting of fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF), and idarubicin (FLAG-Ida), the number of lymphocytes decreased to 0.5×10⁹/L with the proportion of γδ-T cells being 12% (Table 1). The patient received related donor peripheral stem cell transplantation after conditioning with total body irradiation (TBI) (12.5 Gy) and 600 mg thiotepa, without major complications. Thirteen months after transplantation the patient relapsed from γδ T-cell lymphoma with marked lymphocytosis (40×10⁹/L), anemia, thrombocytopenia, and elevated LDH and aminotransferases, and mild systemic symptoms. While a donor related non-

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The percentage (%) of positive mononuclear cells are shown. A: at diagnosis of hepatosplenetic γδ-T-cell lymphoma; B: after FLAG-Ida; C: before related donor stem cell transplantation; D: after transplantation; E: in relapse. PB = peripheral blood; BM = bone marrow; empty spaces = not done. For comparison see the Case report section.
myeloablatve transplant in combination with radioimmunotherapy was prepared, the patient presented with right-sided Bell’s pulsy. Cranial computed tomography was unremarkable. A cytospin of the cerebrospinal fluid revealed close to 100% small to medium sized agranular lymphoid cells, 15% of them with a blast like appearance and irregular nuclei. By flow cytometry, these cells were found to express the γδ T-cell receptor (data not shown). The diagnosis of meningeosis lymphomatosa was, therefore, established. The patient died shortly thereafter, 2 years after diagnosis of hepatosplenic γδ T-cell lymphoma. A post mortem autopsy was refused by the husband.

Design and Methods

Immunophenotyping

Surface expression of the following antigens on the patient’s lymphocytes was analyzed by flow cytometry (FACScalibur, Becton-Dickinson, Heidelberg, Germany) using the FITC- or PE-labeled monoclonal antibodies: HLA-DR, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD13, CD16, CD19, CD20, CD25, CD33, CD34, CD38, CD45, CD56, CD57, CD161, TCRβ-1, TCRγδ-1, purchased from Becton Dickinson, δ-TCS1 (T-cell Diagnostics, Cambridge, MA, USA), 23D12 (Vγ2/3/4),15 7A5 (Vγ9),16 Tu27 (IL-2 receptor β chain, Endogen, St Woburn, MA, USA), NKβ1 (killer inhibitory receptor, Pharmingen, Düsseldorf, Germany) FasL (Alexis, San Diego, CA, USA). Flow cytometric analysis of cytoplasmic proteins was performed after permeabilization of the cells using a Fix and Perm kit (An der Grub Bio Research, Kaumberg, Austria) according to the manufacturer’s instruction and staining the cells with TIA, perforin (Pharminogen, Düsseldorf, Germany), Ki67 (Dianova, Hamburg, Germany), or TdT (Coulter Immunotech, Krefeld, Germany).

Polymerase chain reaction (PCR)

RT-PCR amplification of Vδ1, Vγ3, and Vγ9 junctional sequences was performed as described elsewhere.17 Clonality of γδ TCR rearrangements was determined by using the following junction-specific oligonucleotides: 5'-GCTACTTCTGAT-TCCCTC-3' (sense, specific for the Vγ9 junction); 5'-TTCTTATGCCATAGGTGC-3' (antisense, specific for the Vγ9 junction).

Cloning and sequencing of PCR products

PCR products were loaded onto 1% agarose gels, isolated with Qiagen (Hilden, Germany) and ligated into pCR2.1 TOPO (Invitrogen, De Schelp, The Netherlands). Competent E. coli (XL2-Blue, Stratagene, Heidelberg, Germany) were transformed with the ligation mixture. Recombinant plasmids were isolated with QIAwell 8 Plus Plasmid Kit (Qiagen). They were sequenced on 373 and 377 DNA Sequencers (Applied Biosystems, Darmstadt, Germany) by using the Dye Terminator Cycle Sequencing Kit with Ampli Taq, FS (Applied Biosystems).

Immunofluorescent cytotoxicity assay using PKH67 target labeling

Cytotoxic activity of the patient’s γδ T-cells was analyzed against autologous blast cells from the time of the initial diagnosis of AML and against cultured Daudi (Burkitt’s lymphoma), K562 (CMML blast crisis) and KG-1 (AML) cell lines. The target cells were labeled with PKH67 dye according to the instructions provided by the manufacturer (Sigma, Desenhoefen, Germany). The patient’s γδ T-cells were used as effector cells without and after incubation with 500 IU/mL interleukin-2 (IL-2) for 3 days. Effector and target cells were incubated in complete RPMI 1640 media at effector:target ratios of 20:1, 10:1, 5:1, and 1:1 for 3 hours. Subsequently, the cells were pelleted and resuspended in 300 µl propidium iodide (PI) (Sigma) at a concentration of 10 µg/mL. Percentages of lysed target cells were analyzed by flow cytometry using a FACScan and the following equation:

\[
\text{Lysis} \% = \frac{E - S}{100 - S} \times 100
\]

where:

- E = percentage of PI positive cells in the effector-target cell co-culture;
- S = spontaneous percentage of PI positive cells.

Results

At diagnosis of hepatosplenic γδ T-cell lymphoma a lymphoid population of mature lymphocytes with a somewhat abundant pale blue cytoplasm predominated in the peripheral blood smear. The bone marrow smear demonstrated hypocellular normal hematopoiesis and the above mentioned lymphoid population (not shown). Retrospectively, the blast cells noted when AML relapse was suspected were probably blast-like transformed γδ-lymphoma cells. Unfortunately, no material was preserved for further analysis. At the time when hepatosplenic γδ T-cell lymphoma was diagnosed, approximately 90% of peripheral and bone marrow mononuclear cells expressed the γδ T-cell receptor (Table 1). The cells co-expressed CD2, CD3, CD5, CD7, CD38, CD45, CD161 (NK-R-P1), TIA, Ki67, and in part CD11c, CD13, and Tu27 (Table 1). B-cell markers, CD4, CD8, CD10, CD25, CD33, CD34, HLA-DR, perforin, NKB1 (KIR), TdT, and the αβ T-cell receptor were negative (Table 1). Expression of CD16, CD56, CD57 and Fas ligand was...
low (Table 1). Virtually the same expression pattern was found in relapse of the disease. Only expression of TIA had decreased to 29% (Table 1). Expression of TIA, granzyme B and perforin was additionally analyzed by immunohistochemistry of a bone marrow biopsy. According to the results obtained by FACS, the cells did express TIA but not perforin. Granzyme B was likewise not detectable (data not shown). Further flow cytometric characterization of the γδ T-cell receptor using Vγ- and Vδ-specific monoclonal antibodies revealed that almost all peripheral blood mononuclear cells were 23D12+ (recognizing Vγ2/3/4) and 7A5+ (recognizing Vδ1) (Table 1, Figure 1). At the same time the lymphoma cells were Vδ1+Vγ2/3/4+ and Vδ1+Vγ2/3/4+. Amplification of the Vγ1 family junctional region followed by cloning and sequencing revealed the presence of a single in-frame Vγ3 junctional sequence (Figure 2). Additionally, single Vδ1 and Vγ9 junctional sequences were detected (Figure 2). These results demonstrated clonality of the cells and proved expression of two distinct TCR-γδ chains: 10 out of 10 TCR-δ-chain cDNA clones showed an identical in-frame sequence with a Vδ1-Dδ2-Jδ1 rearrangement including N-region diversity (Figure 2). Regarding the TCR-γ chain, in 18 out of 18 sequenced Vγ3 cDNA clones we found the same in-frame junctional region. Similarly, all of the Vγ9 cDNA clones (23/23) harbored the same junctional in-frame sequence displaying N-region diversity (Figure 2). From these nucleotide sequences, clone-specific primers annealing to the junctional regions were designed to monitor, by reverse transcriptase-PCR, the presence of the clonal γδ-cell population at diagnosis of AML, at the time of stem cell apheresis and during follow-up of the hepatosplenic γδ T-cell lymphoma. In bone marrow from diagnosis of AML and in the leukapheresis product after the first consolidation therapy neither specific Vγ9 nor Vδ1 rearrangements were detected (Figure 3). Specific PCR products for TCR Vγ1 and TCR Vδ9 were detected at the time when relapse of AML was assumed, at diagnosis of hepatosplenic γδ T-cell lymphoma, after two different chemotherapy regimens and in relapse of the disease (Figure 3). Three attempts were made to perform cytogenetic analysis from frozen cells from diagnosis of the disease and from relapse. Unfortunately the cells did not grow in culture. Fluorescent in situ hybridization (FISH) analysis was performed and excluded the presence of isochromosome 7 and trisomy 8 (data not shown). Cytotoxic activity of the patient’s γδ T-cell lymphoma cells was tested against autologous AML blasts or 3 cell lines. The cells did not mediate lysis of autologous AML cells and the KG1 (myeloid) cell line (Figure 4). Of the natural-killer cell sensitive cell line K562 (myeloid), more than 70% of the cells were killed by the γδ T-cells at effector:target ratios of 20:1 and 10:1 (Figure 4). Some cytotoxic activity was also detected against the Daudi (Burkitt’s lymphoma) cell line (Figure 4). Incubation of the lymphoma cells with interleukin-2 for 3 days did not result in any difference regarding cytotoxicity as compared to the γδ T-cells not incubated with IL-2 (data not shown).

Discussion

Peripheral T-cell lymphomas account for approximately 10-15% of all non-Hodgkin’s lymphomas. A rare entity of these is hepatosplenic γδ T-cell lymphoma, a disease with a number of common clinicopathologic features, such as hepatosplenomegaly with a typical infiltration pattern, presentation with systemic symptoms, pancytopenia, predominant occurrence in
young men, and the frequent presence of isochromosome 7q often in combination with trisomy 8. Our patient represents the first case with secondary hepatosplenic \( \gamma \delta \) T-cell lymphoma following AML. Secondary disease accounts for approximately 20% of all cases of hepatosplenic \( \gamma \delta \) T-cell lymphoma, however, the majority of those have been documented after organ transplantation. In a recent review on 45 cases, 6 patients were described to have a history of renal transplantation and 1 patient a history of heart transplantation. One patient had previously had Hodgkin’s disease. There was

\[
\begin{array}{cccccc}
V\delta 1 & N & D\delta 2 & N & J\delta 1 & n & IF \\
\hline
TGTGCTCTTGGGAC & TCCCTGGCA & CCTTCCTAC & TGGATCCCTC & AGACCGATAAATTCATC & 10/10 & + \\
TGTGCCACCTGGGAC & TGT & GAATTATATAAGAAA & ATTATAAGAAA & 18/18 & + & 3 \\
TGTGCCCTTCTGGGAC & TGCACTCATGGC & GAATTATATAAGAAA & ATAAGAAA & 23/23 & + & 9 \\
\end{array}
\]

Figure 2. Junctional sequences of \( V\gamma 3, V\gamma 9, \) and \( V\delta 1 \gamma \delta \)-TCR rearrangements. The 3' ends of \( V\gamma 3, V\gamma 9, \) and \( V\delta 1 \) beginning at the highly conserved cysteine (TGT) are shown. N: non-germline encoded nucleotides; D: diversity segment; J: joining segment; n: number of identical cDNA clones/total number of sequenced clones; IF+: in-frame sequence. Germline sequences are underlined.

Cytotoxicity of \( \gamma \delta \) T-cell lymphoma cells

Figure 4. Cytotoxic activity of \( \gamma \delta \) T-cell lymphoma cells. Autologous AML blasts and the cell lines K562, Daudi, and KG-1 were used as target cells.
been a recent report of an additional case after renal transplantation in a patient who experienced EBV infection, most likely as a late event following transformation of the γδ T-cells. At presentation with marked leukocytosis, thrombocytopenia and anemia, relapse of AML was assumed because of the history of AML, the unfavorable prognostic factor of not having achieved CR after induction therapy and the presence of blast cells even though the majority of the cells were small lymphocytes. Retrospectively, clone-specific PCR demonstrated the presence of the lymphoma. Thus the blast cells must be interpreted as blast-like transformed γδ T-cells, as described in other cases. In accordance with most of the reported cases with hepatosplenic γδ T-cell lymphoma the present patient shared features such as hepatosplenomegaly, bone marrow hypocellularity with anemia and thrombocytopenia, increased LDH serum level, mild systemic symptoms, lack of lymphadenopathy, and presence of Vδ1. Clinical features, which have not been described before in hepatosplenic γδ T-cell lymphoma were marked lymphocytosis at presentation, secondary disease after AML, and meningeosis lymphomatosa (see the Case report section). Pronounced or exclusively portal infiltration of the liver has been described only in a few patients. In view of the marked leukemic spread at presentation, hepatosplenomegaly and the aggressive clinical course, the present case resembles the aggressive variant of T-LGL (large granular lymphocyte) leukemia described by Gentile et al. However these cases have been described with extensive lymphadenopathy. Furthermore, the T-LGL cells expressed CD56 and the αβ T-cell receptor. The clinical course of the patient is just another example of this very aggressive type of peripheral T-cell lymphoma. Even though a wide variety of therapies have been tried, the median survival of the cases reported so far is less than one year. A few patients in CR after bone marrow transplantation have been described; the observation time was, however, short. Thus, a curative treatment of hepatosplenic γδ T-cell lymphoma has not been established.

A phenotype which has been accepted to be common in hepatosplenic γδ T-cell lymphoma is CD2+CD3+CD4 CD5 CD7 CD8 CD38 CD45 TCRγδ TdT-. NK-related antigens CD16 and CD56 are frequently expressed. There are exceptions to this phenotype since expression of at least CD5, CD7, CD8, CD16 and CD56 is variable. Therefore, expression of the T-cell associated marker CD5 and the low frequency of NK-cell markers CD16 and CD56 may, as in our patient, occur. In analogy with the vast majority of the cases analysis of the γδ TCR V regions revealed expression of Vδ1. Surprisingly, however, the tumor cells were reactive with both monoclonal antibodies, 23D12 (Vγ2/3/4) and 7A5 (Vγ9). This finding of surface expression of two distinct Vγ chains was confirmed by PCR using a panel of Vγ specific oligonucleotides and subsequent cloning and sequencing of the PCR products. The data indicate that allelic exclusion did not take place in this malignant clone. The phenomenon of not undergoing allelic exclusion of normal, mature T-cells has been observed for all TCR chains, although its frequency is low in normal γδ T-cells. In malignant γδ T-cells expression of two distinct γ chains has been described only once and never yet recognized in hepatosplenic γδ T-cell lymphoma. CDR3-region specific primers were designed to monitor presence of the disease at different times during follow-up. At diagnosis of AML and in a sample of leukapheresed cells after treatment of AML, specific TCRγδ transcripts were not detectable. Because of the possibility of primary splenic disease this does not exclude the presence of hepatosplenic γδ T-cell lymphoma, but the sensitivity of the method indicates that the lymphoma occurred secondary to AML. Strong signals for Vδ1 and Vγ9 appeared at all times after diagnosis of hepatosplenic γδ T-cell lymphoma. Despite several approaches, we were unable to karyotype the lymphoma cells of our patient. Isochromosome 7 or trisomy 8, shown to be present in approximately 50% of the cases, was not detected by FISH. However, this does not exclude hepatosplenic γδ T-cell lymphoma, because other chromosomal aberrations and even normal karyotypes occur.

Regarding the cytotoxic phenotype in hepatosplenic γδ T-cell lymphoma, expression of TIA but neither perforin nor granzyme B in 10 cases has been described by Boulland et al. These authors concluded that this lymphoma entity represents a tumor consisting of more immature, non-activated γδ T-cells. However, because of the paucity of functional studies, there are few experimental data to confirm this hypothesis. Furthermore, perforin and granzyme B immunopositivity has been reported in hepatosplenic γδ T-cell lymphoma by others. Functional data have been obtained in two previous studies. Falcao et al. demonstrated NK-like cytotoxicity. Salhany et al. observed quite unusual features in one of their cases: cytotoxicity was mediated by the lymphoma cells after prestimulation with CD3 and CD16 antibodies, suggesting TCR-mediated- or antibody-dependent cellular cytotoxicity. In our case, despite a lack of perforin expression, NK-like cytotoxicity...
was clearly demonstrated by strong lysis of K562 cells implicating mature NK-cell function by the γδ T-cells. Autologous AML blasts were not lysed, even after incubation with IL-2. This may be related to low expression of CD25 or to strong resistance to lymphokine-activated killer-cell cytotoxocity by AML blasts in some cases (own observation, not shown). Whether this observation has an in vivo relevance remains unclear. Because of the low frequency of expression of CD16 and CD56 in the present case, NK-like cytotoxicity of the lymphoma cells may be somewhat surprising, but is supported by expression of CD161 (NK-R-P1, an NK-cell activating receptor) and absence of NKB1 (KIR, killer inhibitory receptor), neither of which has been previously studied in hepatosplenic γδ T-cell lymphoma cells. These receptors belong to receptor families (CD161: lectin-like receptors; NKB1: immunoglobulin-like receptors) that control different activating and inhibiting pathways and whose balance determines the behavior of cytotoxic lymphocytes. Killer inhibitory receptors are activated by HLA-class I molecules. The potentially activating capacity by NKR-P1 in the absence of this inhibitory pathway may explain the strong NK-like activity in our particular case. The reason for the lack of perforin and granzyme B expression remains unclear. Possibly the cytotoxicity by the malignant γδ T-cells was mediated through TIA or some other cytotoxic mechanism. One may speculate that these cells, despite an immature cytotoxic phenotype, may exhibit cytotoxic activity or that they represent functionally mature cytotoxic cells with defective granzyme B or perforin expression. In conclusion, despite an atypical infiltration pattern of the liver and absence of typical cytogenetic features, extranodal lymphoma with hepatosplenomegaly, TCR γδ expression and characteristic routine laboratory parameters in our patient indicated the presence of hepatosplenic γδ T-cell lymphoma. Previous acute myeloid leukemia, the expression of two TCR γ-γ chains by the malignant clone and the unusual cytotoxic phenotype are so far undescribed features of this disease.

Contributions and Acknowledgments

EW evaluated the clinical case, coordinated the experimental work, took care of the immunophenotyping and wrote the paper. TH did all the work involving the γδ T-cell receptor. Both authors agreed that their contributions to the work were equal. SK was responsible for patient care and took part in immunophenotyping. DK performed the cytotoxicity assays. SH carried out the FISH. SK did the histopathology work. DK, DH and PSM supervised the study and critically reviewed the drafts of the manuscript for important intellectual content. All contributors approved the final version of the manuscript and agreed to the order of the authors.

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Disclosures

Conflict of interest: none.

Redundant publications: the patient described in detail in this paper was included in a recently published review by EW on 45 cases with hepatosplenic T-cell lymphomas (ref. #3). In that review it was stated that our patient had a history of AML and that her lymphoma cells were cytotoxic. However, besides mention of liver histology and immunohistochemistry, detailed individual data and discussion of the present case were not presented.

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Potential implications for clinical practice

- Hepatosplenic γδ T-cell lymphoma may occur following acute myeloid leukemia. Meningo/lymphomatosa may develop as a complication of this disease.

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