T-cell lymphomas represent a problematic diagnostic group, most cases arising from αβ T-cells. Malignant γδ T-cell lymphoproliferations are uncommon and need more precise clinical and biological characterization. We describe here clinical, immunophenotypic and molecular analyses of a particular case of CD4+ γδ T-cell leukemia/lymphoma. A 74-year old white man was hospitalized with a twenty-day history of generalized pruritus, profuse jaundice and nocturnal fever (38°C). Physical examination showed an enlarged liver and spleen (9 cm and 4 cm b.c.m., respectively) without lymph node enlargement. The hemogram revealed hemoglobin 12.2 g/dL, platelet count 72 x 10^9/L and leukocyte count 79.3 x 10^9 cells/L with 87% lymphocytes. Liver function revealed bilirubin levels of 10.46 mg % and LDH 1370 U. Serological tests for HCV, CMV and HTLV-1 were negative. Bone marrow (BM) biopsy showed diffuse interstitial infiltration of CD45RO+ and CD3+ cells (Figure 1.). Peripheral involvement was confirmed by CD99 negativity (DAKO). BM and peripheral blood (PB) smears showed medium sized cells with moderately condensed chromatin, nucleoli and absence of detectable cytoplasmic granules. Abundant mitotic cells were observed in PB smears (Figure 2.). Initial treatment was based on chlorambucil (Leukeran®) and prednisone with no response. Thereafter a COP scheme was instituted. The patient deteriorated progressively with an increase in leukocyte count up to 120 x 10^9 cells/L in the third week and died after 20 days of hospitalization. Hemophagocytic features and disseminated intravascular coagulation were not observed during the course of the disease. His family did not authorize post-mortem analyses.

Flow cytometry using monoclonal antibodies against a panel of B and T-cells (Becton Dickinson) showed a homogeneous T-cell population with expression of CD7 (99.7%), CD2 (97.63%), CD5 (99.7%), CD3 (99.49), CD4 (55.5%) and the γδ T-cell receptor (TCR) (55.5%). αβ-TCR, CD1a, CD8 and B-cell antigen expression were negative. EBV and HHV-8 genomes were not detected by PCR in tumor cells. TCRγ and TCRδ clonalities were assessed by PCR with primers for the most used Vγ, Vδ and Jγ and D segments, followed by heteroduplex analysis.2,3 The presence of a complete Vδ1(DD)Jδ1 clonal rearrangement (Figure 3A) and VγI-Jγ1.3/2.3 and Vγ9-Jγ1.3/2.3 clonal rearrangements (Figure 3B.), was determined. γδ T-cells comprise about 4% of T lymphocytes. In peripheral blood of healthy adults, 70-90% express a Vδ2/Vγ9 TCR, while 10-30%, express Vδ1 with any Vγ.4 The latter is the predominant resident population in normal spleen and liver. γδ T-cell lymphomas include a group of aggressive diseases whose differential diagnosis is complex.5,6 Besides hepatosplenic γδ T-cell lymphomas (HSTL) which display a quite distinct morphologic, immunologic and clinical picture,6 γδ T-cell lymphomas can arise at different extranodal non-hepatosplenic locations (skin or mucosae)7 and shows substantial morphological heterogeneity. In general terms, it could be considered that HSTL arise from Vδ1+ γδ cells while non-hepatosplenic lymphomas arise from Vδ2+ γδ cells. Immunomolecular characteristics of the reported case indicated a Vδ1 γδ T-cell population expressing CD4+ as a target for leukemic transformation. It may represent a HSTL with early leukemic spread or an aggressive variant of γδ large granular leukemia as described by Gentile et al.8 Lack of spleen/liver microscopic examination prevented detection of only intrasinusoidal/sinusal infiltra- tion, typical of HSTL. BM interstitial infiltration is not
described a case of which may have had as suggested by the findings that T-cell lymphoma/leukemia. 

Third, there was an important leukocytosis pointing to a role of the latency associated dot protein in replacing the immune deficit in the elderly. This agrees with the suggestion that impaired immune function may have a pathogenic role in T-cell malignancy, with a very acute onset and a pan-T-CD4+ immunophenotype. The scarcity of similar cases makes delineation of a clinical-pathological entity difficult. Instead, it would be important to consider the functional redundancy of the immune system in the origin of different and perhaps equivalent ab and γδ neoplasias. Inclusion of γδ lymphoproliferations in diagnostic schemes is also very important because without complete immunophenotyping and molecular confirmation of monoclonality, the histopathologic findings can be difficult to interpret.

uncommon, and leukemic transformation is a frequent final manifestation of HSTL. However, the observed cell morphology, the expression of CD5 (very infrequent) and of CD4 antigens (never described in this entity), are against this possibility. Some of the morphologic and immunophenotypic features observed in the leukemia herein described resemble T-cell prolymphocytic leukemia (T-PLL), for instance the expression of a complete pan-T profile, including CD4 marker in 55% of cells. Sugimoto et al. described a case of γδ T-PLL in a 30-year-old man, but that leukemia showed a CD4-, CD8-phenotype. The present case has several unusual aspects. First, its course was fulminant; there are few cases described with that outcome despite aggressiveness being characteristic of γδ T-cell lymphoproliferations. Second, these diseases are more frequent in young patients, with few cases occurring over fifty years.

To our knowledge, this is the oldest reported patient having a γδ T-cell lymphoma leukemia. Vδ1 T cell populations might be at risk of leukemic transformation in elderly patients as a result of processes of immunosenescence as suggested by the findings that the Vδ2/Vδ1 ratio is inverted in old subjects and that Vδ1 T cells are more activated pointing to a role of the latter in replacing the immune deficit in the elderly. This agrees with the suggestion that impaired immune function may have a pathogenic role in γδ T-cell malignancies such as HSTL. Third, there was an important leukocytosis at the expense of CD4+ T cells with normal hemoglobin levels and non-severe thrombocytopenia. ab and γδ T-cells are characterised by the expression of a similar subset of pan T cell markers. Most γδ T cells -and also most γδ T cell lymphomas- have a CD4-CD8-immunophenotype. The rare CD4+ γδ T cell clones produce large amounts of cytokines which may have had a differential effect on the haematological profile of the disease here reported. Here we describe the oldest known patient with a γδ T-cell malignancy, with a very acute onset and a pan-T-CD4+ immunophenotype.

References


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Key Words: γδ T-cell leukemia/lymphoma, immunophenotype, γδ TCR.

