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We report a well documented case of LGL leukemia with unusual biological features. A 46-year old woman was sent to our Hematology Department for study of a stable, isolated chronic severe neutropenia (neutrophils 0.145x10^9/L, lymphocytes 2.904x10^9/L) of 5 years of duration. Morphologic evaluation of the peripheral blood and bone marrow aspiration smears showed the presence of 40% and 13% LGLs, respectively. The LGs in peripheral blood showed expression of CD2, CD7, CD94, CD11c and CD16 and negativity for surface and cytoplasmic CD3, CD56, CD57, TCRαβ, TCRγδ, CD5, CD34 and TdT. Conventional cytogenetics performed on peripheral blood stimulated with PHA showed a normal karyotype. The molecular analysis by polymerase chain reaction and Southern blot revealed rearrangement of the TCRγ and β genes. To our knowledge, this is the second case reported of TCR gene rearrangement in a patient with CD3$^-$ LGL leukemia. Among seven patients with CD3$^-$ LGL leukemia analyzed for rearrangement of the TCR genes, Hara *et al.*[6] found one patient with TCR-δ gene rearrangement. Their findings indicate that CD3- LGLs include not only cells belonging to the NK-cell lineage but also precursor cells committed to the T-cell lineage. In the human thymus there are progenitors cells with the capacity to develop into T, NK, and dendritic cells.[7] It has been recently shown that the TCR genes of early thymocyte subpopulations rearrange in an ordered way during human T-cell differentiation; TCRδ rearrange first followed by TCRγ and TCRβ.[8] The rearrangement of the TCR-β gene initiates in T-thymic progenitors.

Taken together, an attractive hypothesis to explain the CD3$^-$ phenotype and the TCRγ and β genes rearrangement in our case would be that the LGL clone may have arisen in a T-thymic progenitor. Since rearrangement of the TCRβ gene strongly suggests T-cell commitment,[8] the cells of this patient may have been arrested at a differentiation stage earlier than the stage of TCRα gene rearrangement and would have differentiated to CD3$^+$ T-cells bearing the gδ or αβ heterodimer. This concept may be supported by the absence on the cell surface in this patient of CD5, TCRγδ, TCRαβ and CD56, which are antigens with lineage-specific and maturation dependent expression, and the positivity for HLA-DR and CD7, antigens that may be associated with immaturity. Overall, our case would support the theory that some cases of CD3$^-$ LGL leukemia may represent immature proliferations originating in T-thymic progenitors rather than true peripheral NK neoplasias. Molecular characterization of TCR gene rearrangement status in a greater number of cases of CD3$^-$ LGL leukemia would be of great interest to increase our knowledge of this rare pathology.

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Key words

Large granular lymphocyte leukemia, CD3, T-cell receptor gene rearrangement.

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Successful treatment of angioimmunoblastic lymphadenopathy with dysproteinemia-type T-cell lymphoma by combined methotrexate and prednisone

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD)-type T-cell lymphoma has a very poor prognosis in most patients. Here we report a complete clinical response in a patient treated with low-dose oral methotrexate (10 mg/m^2 weekly) in combination with prednisone (15 mg/day) in whom conventional chemotherapy was not effective. This regimen was not associated with

major side effects. Our findings suggest that methotrexate may have beneficial effects in AILD-type T-cell lymphoma. Pilot clinical trials are needed to verify its efficacy in this setting.

Sir,

AILD-type T-cell lymphoma is a rare variant of peripheral T-cell lymphoma and is included in the REAL classification under the term of angioimmunoblastic T-cell lymphoma. AILD-type T-cell lymphoma has a very poor prognosis in most patients.[1] There are no randomized clinical trials evaluating the effectiveness of different therapeutic modalities. Here we report a complete clinical response in a patient treated with oral low-dose methotrexate in combination with prednisone in whom conventional chemotherapy was not effective.

A 67-year old male presented in February 1999 with fever, skin rash, and pruritus, which are unresponsive to antibiotics and low-dose prednisone. Physical examination was unremarkable except for bilateral enlargement of inguinal and cervical lymph nodes. Laboratory findings were as follows: leukocytes $3.7x10^9$/L, lymphocytes $0.8x10^3$/L, hemoglobin 9.9 g/dL, hematocrit 15.2%, platelets $10.5x10^9$/L, lactate dehydrogenase level 617 U/L (normal value < 350), ESR 100 mm, hypergammaglobulinemia (15.7 g/L). In addition, autoimmune phenomena such as a strongly positive direct antiglobulin test (DAT) with anti-IgG, monomeric IgM and C3d serum, smooth muscle antibodies, and antinuclear antibodies were observed. Tests for viral (HIV, EBV, CMV), bacterial and toxoplasmosis infection were negative. A right cervical node was excised. A histologic diagnosis of AILD-type T-cell lymphoma was made. Staging procedures revealed the involvement of cervical, para-aortic, para-iliac, and inguinal lymph nodes. Bone marrow examination showed multinodular involvement. Initial corticosteroid treatment was followed by chemotherapy. The patient was treated for 8 weeks (between February and April 1999) with P-VABEC[2] because VACPE, a similar regimen, is an effective approach in the management of AILD-type T-cell lymphoma[3] and because a standard therapy has not yet been established. A partial response was documented, which persisted until July 1999 when progression with involvement of the bone marrow and cervical, axillary, para-tracheal, mediastinal, para-aortic, para-iliac, and inguinal lymph nodes occurred. At that time the patient received cyclosporin A (CsA). CsA is considered to be able to control the T-cell disorder, and in a few cases it has been used and given encouraging results.[4] Our patient was asymptomatic for 4 weeks before developing, in a few days, enlarged, tumoral axillary lymph node, from which a diagnosis of AILD-type T-cell lymphoma was again made by histologic examination. Thoracic and abdominal CT scan showed multinodal involvement and enlargement of the spleen. At that time treatment options, including the use of methotrexate or new purine analogs, were discussed. Selected series have reported some improvements with the use of new purine analogs.[5,6] The decision to treat the patient by low-dose methotrexate was made because it is an effective treatment for some patients with LGL leukemia.[7] Methotrexate was administered orally as low-dose 15 mg (10 mg/m^2) once weekly. The patient did not receive other treatment with the exception of prednisone (15 mg/day tapered down to 5 mg/day). This regimen was not associated with major side effects. On day +100 bone marrow biopsy, thoracic and abdominal CT scan, full blood counts, chemistry and autoimmunity were normal. In March 2000 the patient is alive and well with a Karnofsky score of 100% and in the absence of any sign of relapse. Based on these encouraging results, and in the absence of standard treatment, we believe that methotrexate-based treatment may provide an active front-line therapy for this disorder.

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Key words

AILD-type T-cell lymphoma, treatment , methotrexate.

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