Recently, we showed that CIK cells can be directed to leukemia and lymphoma cells via reverse antibody-dependent cellular cytotoxicity.[1] There was an increase in sensitivity to CIK-mediated lysis of various lymphoma and leukemia cell lines by preincubation of the targets with a monoclonal antibody against CD3. This increase could be partially blocked by preincubation with anti-CD16 (Fc receptor III) and anti-CD32 (Fc receptor II) antibodies. These data suggest that the increase in cytotoxic activity is due to Fc receptor-mediated antibody binding. Cytotoxic activity could be further increased by addition of an anti-CD28 antibody to anti-CD3. In accordance, we show here that the addition of an anti-CD3 antibody leads to an increase in cytotoxic activity of CIK cells against CLL cells. CIK cells are effective against allogeneic leukemia cells.[2] However, there was only a minor effect against autologous leukemia cells. We speculate that the reason for this resistance lies in the lack of co-stimulatory signals on the cell surface of CLL cells. Further studies will concentrate on activating CIK cells on autologous CLL cells.

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***Key words***

*NK cells, T cells, CIK cells, CLL.K*

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## Non-ALC peripheral T-cell lymphomas in children: report on two cases and a review of the literature

**Peripheral T-cells lymphomas (PTCLs) in children are usually good prognosis Ki1+ ALCL; other PTCLs have the same poor prognosis as in adults.[1,2] We report the cases of two children with PTCL, whose disease had an aggressive clinical course. There are only scanty reports dealing with optimal therapy for this rare disease. Considering the bad prognosis shared by adults and children, a common study is recommended.**

### *Case reports*

The two clinical histories are summarized in Table 1 and the methods used for histopathologic and molecular biology studies are illustrated in Table 2.

At light microscopy (3rd biopsy, case #1, 3rd and 4th biopsies, case #2) both cases showed effacement of lymph node architecture with increased vascularity and branching endothelial venules. The neoplastic cells were small-medium sized with polymorphic nuclei, small nucleoli and scanty, pale gray cytoplasm. There were some large, basophilic blast cells and a moderate number of mitotic figures. The neoplastic cells were obscured by epithelioid histiocytes, polyclonal plasma cells, eosinophils and hyperplastic clusters of follicular dendritic cells (Figure 1) and a polymorphous cellular infiltrate of plasmacells, eosinophils, histiocytes and numerous immunoblasts. The T-cell origin of the NHL was derived from the pattern of immunoreactivity (CD $3^+$, $CD4^+$, $CD7^+$, $CD8^-$, $CD19^-$, $CD20^-$, $CD22^-$, $CD30^-$, $CD79a^-$, $TdT^-$). The initial biopsy of case #1 was viewed by RG: the lymphoid tissue was composed of a mixed population with immunoblasts scattered among small lymphocytes; small areas of necrosis were present without multinucleate giant cells. In the second biopsy of case #1, the nodal architecture was severe-

**Table 1. Case reports.**

CASE #1.
October '85. 8-year old boy with cervical and mediastinal lymph node enlargement.
Cervical biopsy→tubercular infection.
January '86. Widespread enlarged peripheral lymph nodes, hepatosplenomegaly, poor nutritional and performance status. Biochemistry: neutrophilia, hypergammaglobulinemia, high ESR and cupremia. HbsAg positive, high EBV and CMV IgG titers and inverted T4/T8 ratio .
Spinal node biopsy→lymphoid hyperplasia secondary to EBV infection.
Acyclovir medication, than MOPP/ABVD as immunosuppressive schedule.
March '88. After transient objective improvement, further peripheral and visceral lymph node enlargement, hepatosplenomegaly and fever.
Inguinal lymph node biopsy→angioimmunoblastic PTCL[1] or angioimmunoblastic T-cell lymphoma.[2]
Chemotherapy for high-grade pediatric NHL with good partial remission.
Allogenic bone-marrow transplantation refused by parents. The boy died 14 months later due to progressive disease.

CASE #2.
July '91. 16-month old baby-girl with widespread enlarged peripheral lymph nodes and hepatosplenomegaly. Weight and height below the third percentile. Biochemistry: normochromic anemia, hypergammaglobulinemia, high alkaline-phosphatase levels. EBV-VCA positive; HTLV1, HIV, and HbsAg negative.
inguinal lymph node biopsy→reactive lymphoadenitis.
February '93. Progressive enlargement of peripheral and retroperitoneal lymph nodes.
Left groin lymph nodal biopsy→Langerhans'cell histiocytosis.
Vincristine and cyclophosphamide for one year with complete remission.
September '94. Disease relapse. Adriamycin and vinblastine for six months.
October '95. Third relapse.
Spinal lymph node biopsy→angioimmunoblastic PTCL. Polychemotherapy followed by allogeneic bone marrow-transplantation with complete remission.
One week after transplantation. Supraclavicular lymph nodal enlargement.
Biopsy→angioimmunoblastic PTCL relapse.
Weekly vindesine and oral retinoic acid for one year with continuous complete remission.

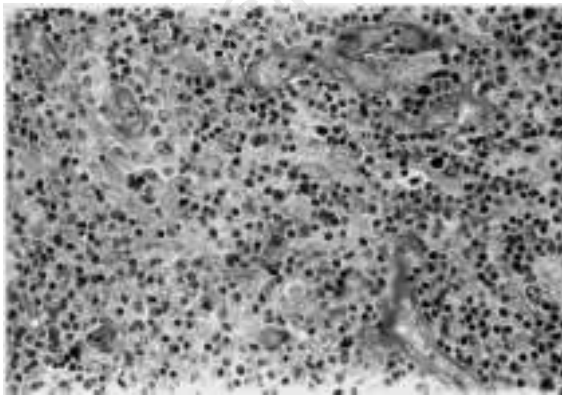

**Figure 1. Case #1. Angioimmunoblastic NHL: the T-cells, with irregular nuclei and scanty cytoplasm are interspersed with numerous follicular dendritic cells; there are numerous venules with thickened walls. Giemsa staining 250 X.**

**Table 2. Pathology and molecular biology methods.**

***Pathology***
H & E and Giemsa on paraffin embedded biopsies
Immunohistochemistry (ABC peroxidase methods):
MoAb anti-kappa and anti-lambda immunoglobulin light chains (Dako, Denmark)
MoAb anti T: CD3 (Dako)
MoAb anti B: CD20 (L26 Dako), CD 79a (HM57 Dako)
MoAb anti TDT (Seralab, Great Britain)
MoAb CD30 (Ber $H^2$, Dako)
Immunohistochemistry from cryopreserved tissue blocks
MoAb for CD3 (Leu4, Becton Dickinson, USA)
MoAb for CD4 (Leu3a, Becton Dickinson)
MoAb for CD7 (Leu9, Becton Dickinson)
MoAb for CD8 (Leu2, Becton Dickinson)
MoAb for CD19 (Leu12, Becton Dickinson)
MoAb for CD20 (Leu16, Becton Dickinson)
MoAb for CD22 (4KB 128 Dako)

***Molecular biology***
- Primers targeting the U2 region of the virus (B95/8) encoding for EBNA-2 protein expressed in latently infected and growth-transformed cells
- 20 µL aliquot of amplification product separated by agarose gel electrophoresis and stained with ethidium bromide from each sample
- EBNA-2 primers pair used to perform PCR to detect the possible presence of EBV in 3 specimens of each case

ly distorted: reactive follicles were separated by expansion of the paracortical region, with scattered immunoblasts. The sinuses contained several immunoblasts; there were many focal areas of intraparenchymal necrosis. The previous two biopsies of case #2 were also reviewed: there was a large amount of remnants of follicular germinal centers with expansion of the paracortical area and rare foci of scattered interfollicular immunoblasts. With the support of immunocytochemical stains, small foci of atypical lymphoid cells of T-lineage in the paracortical area, with abundant clear cytoplasm, distinct cytoplasmic membranes, vesicular nuclei and prominent eosinophilic nucleoli were detected. None of the samples showed amplification of viral DNA, while the EBV DNA band obtained from the positive control was intense. EBV *in situ* staining was not performed. Cytogenetics studies were not available.

Non-Ki 1+ PTCLs are extremely rare in children and have a dismal prognosis.[3,4] Both our patients had angioimmunoblastic PTCL, usually characterized by an aggressive evolution but sometimes underlying a chronic history of undulating lymph node enlargement, skin rash, fever and weight loss with an inflammatory background and "B"-symptoms; this can account for delayed diagnosis or misdiagnoses of tuberculosis, Langerhans' cell histiocytosis or chronic EBV mononucleosis. Other PTCLs progress more rapidly, being fatal.[5] Hitherto, there have been only a few reports on pediatric angioimmunoblastic PTCLs, concerning patients aged 5 months-14 years.[6-8] Leake reported two children with PTCL surviving 10 and 24 months.[8] Lin[3]

reported 5 cases of PTCL, all with a long-lasting history of granulomatosis, hepatosplenomegaly, HBsAg and EBV-VCA positivity. The only surviving patient had received an allogeneic bone-marrow transplantation. Our two children had been infected by EBV with a chronic high titer of IgG against EBV-VCA, consistent with a life-long infection.[9] EBV may infect T-cells creating reactive lymphoid proliferations without contributing to the neoplastic process; however EBV or other viral infections (i.e. Cytomegalovirus, hepatitis B), or immune defects suppressing NK activity – such as altered T4/T8 ratio – may lead to neoplastic transformation in particular hosts, and this could be the case with our patients. All available lymph node samples were therefore submitted to EBV-DNA detection without finding amplification of the viral genome. The presence of EBV-DNA is a feature of angioimmunoblastic PTCL found in Eastern Countries, being less common in Europe.[3,10] As to optimal treatment, we agree with the Taiwan group:[3] marrow transplantation can cure this disease. The role of retinoic acid cannot be assessed by anecdotal experiences, even though malignant cell differentiation and apoptosis might depend on retinoic acid administration.[10] No national or international co-operative group is currently dealing with poor-prognosis PTCL: a common study is therefore needed, perhaps including both adults and children.

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## Low-dose thalidomide in the treatment of refractory myeloma

**In this report we present five cases of refractory multiple myeloma successfully treated with low doses of thalidomide.**

Sir,

Barlogie's group recently reported the results of a phase 2 study with thalidomide, as a single agent, in the treatment of refractory myeloma.[1] In this study the rate of response was 32%, as shown by a reduction of at least 25% of the M-component. The study considered a gradual increase in the dose of thalidomide up to a maximum daily dose of 800 mg. The toxicity linked to the treatment was not negligible. Furthermore, in the last six months several preliminary reports have shown the efficacy of low dose thalidomide in the treatment of resistant myeloma.[2-8] We present our experience on a small group of patients with refractory myeloma treated with low dose thalidomide. The study included five patients (4 males, 1 female; median age 67 years, range 58-76). All patients had received two or more different regimens of conventional therapy. No patient had been submitted to high dose chemotherapy with autologous hematopoietic stem cell transplantation. At the start of thalidomide therapy all patients had progressive disease. The patients started with 200 mg/day of thalidomide as a single therapeutic agent after providing written consent. The dose has not been increased during the whole period of the treatment. In our patients the side effects were mild or moderate (grade 1 or 2 according