VOLUME 25 · NUMBER 17 · JUNE 10 2007

JOURNAL OF CLINICAL ONCOLOGY

DIAGNOSIS IN ONCOLOGY

## Adult T-Cell Leukemia/Lymphoma With a Mixed $CD4^+$ and $CD8^+$ Phenotype and Indolent Course

A 9-year-old boy was first examined in January 1991 and reported a history of skin lesions since the age of 7. The patient had multiple small erythematous papules on the outer rims of his ears (Fig 1A) and infiltrated plaques on his upper limbs. Hemogram was within normal limits. Computed tomography scans of the chest and abdomen were normal. A skin biopsy revealed an intense, diffuse infiltration of small, irregular lymphocytes in the dermis and subcutaneous tissue. Some scattered blast cells also were observed. Histology was conclusive for unspecified T-cell peripheral lymphoma. As Bahia State in Brazil is endemic for human T-lymphotropic virus type I (HTLV-I),[1] serology for HTLV-I and HIV was investigated. The patient and both parents were HTLV-I seropositive (enzyme-linked immunosorbent assay and Western blot analysis) and HIV negative. Thus, clinical, histological, and laboratory findings were considered compatible with the smoldering type of adult T-cell leukemia/lymphoma (ATL), an aggressive tumor associated with the HTLV-I, generally reported in adults. No treatment was prescribed, and the child was followed up periodically.

From 1991 to 2001, he presented occasional lymphocytosis varying from 4,000 to 7,000 lymphocytes/$\mu$L and up to 4% atypical lymphocytes in the peripheral blood. Bone marrow aspiration and biopsy performed in April 1997 revealed no abnormalities. Physical examination, blood levels of calcium and lactate dehydrogenase (LDH), chest x-ray, and computed tomography scans of the abdomen and chest were found to be normal at all the follow-up evaluations, except in January 2001 when a slight increase in lactate dehydrogenase was observed. On that occasion, new skin lesions had appeared on the patient's flank and knees, and the already existing lesions had increased in size and become confluent (Fig 1B). Therefore, the patient was treated with electron-beam irradiation, resulting in complete regression of all skin lesions except those on the ear, which did not regress completely. A myelogram performed at the same time revealed a normocellular bone marrow, but detected 4% atypical lymphocytes. Skin biopsies performed in 1995, 1998, and 2001 revealed an intense, diffuse, and deep infiltration of atypical lymphocytes (small and medium) in the dermis and subcutaneous tissue. Multinucleated giant cells and frequent macrophages were found in all biopsies (Fig 1C). At the last follow-up in April 2006, all tests were normal and no lymphocytosis was found; however, 8% atypical lymphocytes were detected. The skin lesions were restricted to the ears. To confirm ATL diagnostic, clonal integration of HTLV-I and T-cell receptor gene rearrangement was investigated in DNA extracted from peripheral-blood mononuclear cells (PBMCs). Monoclonal integration of HTLV-I was detected by long, inverse polymerase chain reaction[2] as shown in Figure 2A (line P), and the presence of HTLV-I proviral and genomic host DNA sequences was confirmed by sequencing. Analysis of T-cell receptor gene rearrangement[3] revealed a discrete size polymerase chain reaction product indicating a monoclonal population in PBMC (P), in contrast to the wide range in size observed in DNA extracted from PBMC of a representative healthy control (H) individual (Fig 2B, line C, positive control).

Although the patient presented mild, intermittent lymphocytosis, this case was considered smoldering subtype because of the clinical aspects. Survival in the smoldering subtype is quite variable, with some patients living for many years and others developing dissemination of the disease in less than a year.[4] Smoldering subtypes with skin lesions as the principal manifestation, as observed in this patient, were associated to a mean survival time of 16 months.[5] Unexpectedly, this case presented an indolent course during 15 years of follow-up. All skin biopsies revealed an intense, diffuse, and deep infiltration of atypical lymphocytes (small and medium) in the dermis and subcutaneous tissue. ATL cases presenting deeply infiltrating skin lesions were

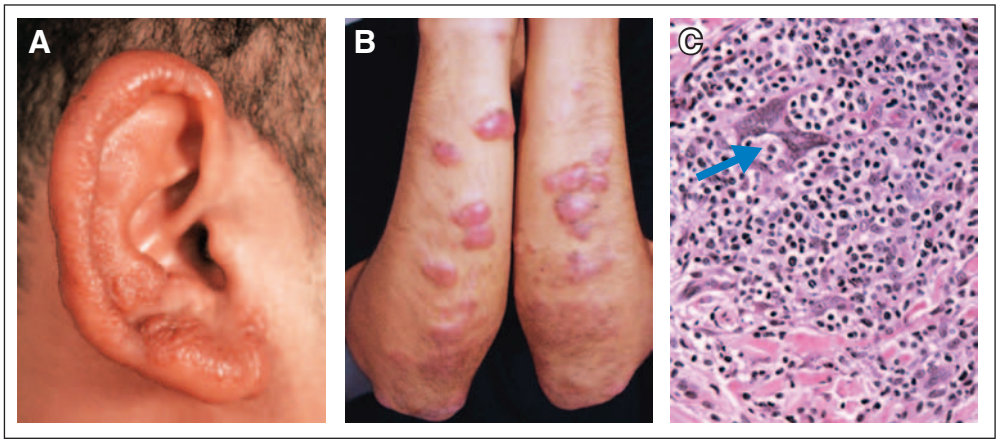


**Fig 1.**

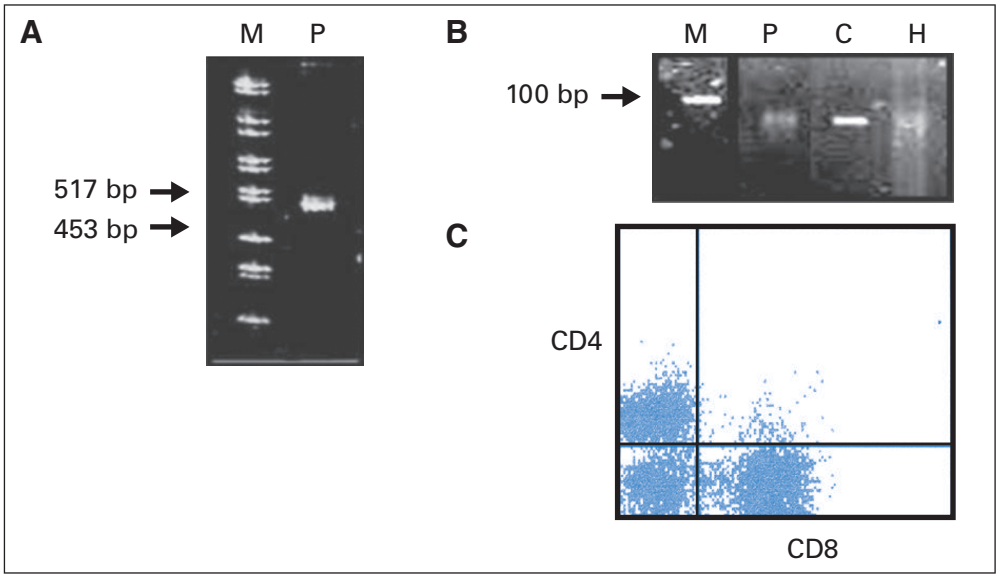


Fig 2.

associated to a mean survival time of 14 months.[5] In this case, survival was prolonged. The malignant cells in ATL usually have a $CD4^+/CD8^-$ phenotype.[6] Interestingly, in all biopsies performed approximately 50% of atypical lymphocytes were positive for CD4, and surprisingly, approximately 50% were positive for CD8. $CD8^+$ cells presented a malignant phenotype and were negative for granzyme B and perforin. The atypical lymphocytes also were positive for CD45RO, CD3, OPD4, CD5, and CD25, and they were negative for CD7, CD56, CD57, CD30, and CD20. Around 10% were positive for TIA-1. All antibodies were from Dako (Glostrup, Denmark), except CD4, which was purchased from Novocastra (Newcastle, United Kingdom). This rare mixed $CD4^+$ and $CD8^+$ single phenotype also was observed in peripheral blood lymphocyte subpopulations (B, T, CD4, and CD8 cells) by flow cytometry (Fig 2C) at two time points (May 2003 and February 2005) and showed remarkably stable levels over a period of almost 2 years. The percentage of B ($CD19^+$, 6.8% to 10.1%) and T cells ($CD3^+$, 78.5% to 84.0%) was similar to both normal and ATL controls. Unexpectedly, $CD8^+$ levels were much higher (46.5% to 49.1%; $P < .0001$) than those of normal controls and other ATL patients (17.6% $\pm$ 2.3%), whereas $CD4^+$ cells were within the normal range (36.3% to 38.0%), but significantly lower than in other ATL patients (61.2 $\pm$ 4.2%, $P < .0001$), resulting in an inverted CD4:CD8 ratio (0.77 to 0.78). We have not found a previous description of a mixed $CD4^+$ and $CD8^+$ single positive ATL phenotype. The malignant cells in ATL usually have a $CD4^+/CD8^-$ phenotype. Only few $CD4^+$and $CD8^+$ double positive cases have been reported, and all of them were associated with an aggressive clinical course.[7,8] We documented the mixed $CD4^+$ and $CD8^+$ single positive phenotype by both immunohistochemistry (in skin biopsy) and flow cytometry (in PBMC). As monoclonality was demonstrated for both the integration site and the T-cell antigen receptor gamma chain, it suggested that both $CD4^+$ and $CD8^+$ atypical malignant cells may derive of the same cellular clone. The absence of cytotoxic effector molecules, granzyme B, and perforin in situ indicate CD8 positivity as an aberrant noncytotoxic phenotype.[9] This monoclonal mixed $CD4^+$ and $CD8^+$ phenotype is unique in its remarkable stability over several years. Inflammatory multinucleated giant cells and frequent macrophages were found in all biopsies performed (Fig 1C), though special staining techniques (Ziehl-Nielsen, Grocott, and Periodic Acid Schiff) failed to detect any microorganisms. The association of ATL with granulomatous reaction has rarely been reported.[10-12] The presence of granulomas may indicate a protective response of the host.[11] Very few cases of ATL have been reported in children and adolescents,[12-15] and even fewer in which monoclonal integration of HTLV-I has been demonstrated,[13] as in the present case, confirming the relationship between the lymphoma and the virus. The child most probably acquired HTLV-1 infection by vertical transmission, as he has no history of blood transfusions. Considering that he was breastfed for only 2 months, and it is generally accepted that transmission occurs more commonly after prolonged breastfeeding,[16] the early manifestation of ATL could be related to a precocious intrauterine infection. The present case increases awareness that in endemic areas HTLV-I infection should also be investigated in children and adolescents with T-cell leukemia/lymphoma, regardless of the CD4/CD8 phenotype and breastfed period. Viral integration and analysis of T-cell antigen receptor rearrangement could be useful in pediatric ATL diagnostic mainly in the smoldering cases with skin lesions as principal manifestation.

*Achiléa L. Bittencourt, Helenemarie S. Barbosa, and Cristiane Requião*
Departments of Pathology and Internal Medicine, Hospital Universitário Prof Edgard Santos, Federal University of Bahia, Brazil

*Aline Clara da Silva*
Laboratory of Immunoregulation and Microbiology, CPqGM–FIOCRUZ, Bahia, Brazil

*Anne-Mieke Vandamme*
Clinical and Epidemiological Virology, Rega Institute, Leuven, Belgium

*Johan Van Weyenbergh and Lourdes Farré*
Laboratory of Immunoregulation and Microbiology, CPqGM–FIOCRUZ, Bahia, Brazil

## ACKNOWLEDGMENT

This work was supported by Conselho Nacional de Pesquisa and Fundação de Amparo à Pesquisa do Estado da Bahia

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## REFERENCES

**1.** Dourado I, Alcantara LCJ, Barreto ML, et al: HTLV-I in the general population of Salvador, Brazil: A city with African ethnic and sociodemographic characteristics. J Acquir Immune Defic Syndr 34:527-531, 2003

**2.** Etoh K, Tamiya S, Yamaguchi K, et al: Persistent clonal proliferation of human T-lymphotropic virus type I-infected cells in vivo. Cancer Res 57:4862-4867, 1997

**3.** Diss TC, Watts M, Pan LX, et al: The polymerase chain reaction in the demonstration of monoclonality in T cell lymphomas. J Clin Pathol 48:1045-1050, 1995

**4.** Shimoyama M: Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma: A report from the Lymphoma Study Group (1984-87). Br J Haematol 79:428-437, 1991

**5.** Setoyama M, Katahira Y, Kanzaki T: Clinicopathologic analysis of 124 cases of adult T cell leucemia/lymphoma with cutaneous manifestations: The smouldering type with skin manifestations has a poorer prognosis than previously thought. J Dermatol 26:785-790, 1999

**6.** Kikuchi M, Jaffe ES, Ralfkiaer E: Adult T-cell leucemia/lymphoma, in Jaffe ES, Harris N, Stein H, et al (eds): WHO Classification of Tumors: Pathology and Genetics: Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France, International Agency for Research on Cancer, 2001, pp 200-203

**7.** Kamihira S, Sohda H, Atogami S, et al: Phenotypic diversity and prognosis of adult T-cell leukemia. Leukemia Res 16:435-441, 1992

**8.** Ciminale V, Hatziyanni M, Felber BK, et al: Unusual CD4+CD8+ phenotype in a Greek patient diagnosed with adult T-cell leukemia positive for human T-cell leukemia virus type I (HTLV-I). Leukemia Res 24:353-358, 2000

**9.** Ohshima K, Haraoka S, Suzumiya J, et al: Absence of cytotoxic molecules in CD8- and/or CD56-positive adult T-cell leukaemia/lymphoma. Virchows Arch 435:101-104, 1999

**10.** DiCaudo DJ, Perniciaro C, Worrell JT, et al: Clinical and histologic spectrum of human T-cell lymphotropic virus type I-associated lymphoma involving the skin. J Am Acad Dermatol 34:69-76, 1996

**11.** Setoyama M, Katahira Y, Kanzaki T, et al: Adult T-cell leukemia/lymphoma associated with noninfectious epithelioid granuloma in the skin: A clinicopathologic study. Am J Dermatopathol 19:591-595, 1997

**12.** Lewis JM, Vasef MA, Seabury Stone M: HTLV-I-associated granulomatous T-cell lymphoma in a child. J Am Acad Dermatol 44:525-529, 2001

**13.** Pombo de Oliveira MS, Dobbin JA, Loureiro P, et al: Genetic mutation and early onset of T cell leukemia in pediatric patients infected at birth with HTLV-I. Leukemia Res 26:155-161, 2002

**14.** Valle ACF, Galhardo MCG, Leite ACC, et al: Adult T-cell leukaemia/lymphoma associated with HTLV-I infection in a Brazilian adolescent: Case report. Rev Inst Med Trop S ão Paulo 43:283-286, 2001

**15.** Mahé A, Meertens L, Ly F, et al: Human T-cell leukaemia/lymphoma virus type 1-associated infective dermatitis in Africa: A report of five cases from Senegal. Br J Dermatol 150:958-965, 2004

**16.** Hino S, Katamine S, Miyata H, et al: Primary prevention of HTLV-I in Japan. J Acquir Immune Defic Syndr Hum Retrovirol 13:S199-203, 1996 (suppl 1)

DOI: 10.1200/JCO.2007.11.3043

# Persistent Positron Emission Tomography–Positive Liver Lesions After Successful Chemotherapy in Mediastinal Seminoma

A 27-year-old Filipino man with no known past medical history presented with a 2-week history of progressive symmetric facial and neck swelling. On physical examination, the neck and anterior chest wall veins were engorged and distended. The examination was otherwise unremarkable, including a lack of lymphadenopathy in the cervical, axillary, or inguinal regions. Computed tomography (CT) of the chest showed a large mediastinal mass (10 × 6.5 × 8 cm) that had almost completely compressed the superior vena cava (Fig 1A). Additionally, several enlarged mediastinal lymph nodes were identified. A transthoracic biopsy of the mediastinal mass was performed, and the histology and immunostains were consistent with seminoma. Testicular ultrasound did not reveal a gonadal mass. Alpha fetal protein and beta-human chorionic gonadotropin levels were within normal limits. Lactate dehydrogenase was slightly elevated at 266 IU/L (0 to 200 U/L). A diagnosis of extragonadal seminoma presenting as superior vena cava syndrome was made. Interestingly, an abdominal CT showed three ill-defined hypodensities in the liver, with the largest measuring 1.5 cm in diameter. These lesions (Fig 1C; arrows), in addition to the mediastinal mass and one right hilar node, all demonstrated intense 2-[$^{18}$F]fluorodeoxyglucose ([$^{18}$F]FDG) uptake (Figs 1A and 1C). The patient underwent standard chemotherapy with three cycles of bleomycin, etoposide, and cisplatin, and one cycle of etoposide and cisplatin. He had a dramatic clinical response to the chemotherapy, with complete resolution of symptoms and physical examination findings. After completing four cycles of chemotherapy, whole-body positron emission tomography (PET)/CT showed almost complete resolution of the mediastinal mass, with insignificant standard uptake value levels. However, the previously described liver lesions and the one right hilar node (Fig 1B, arrow) did not change in size or number and continued to show intense [$^{18}$F]FDG uptake. Six weeks later, a repeat PET/CT remained unchanged.

Germ cell tumors account for approximately 1% of all malignancies, but are the most common tumors in men between the ages of 15 to 35 years.[1] Small subsets of these tumors (2% to 5%) are of extragonadal origin.[2] Liver has been a rarely described site for metastatic extragonadal seminoma. In the largest case series of patients with extragonadal germ cell tumors, liver metastasis was only described in one of 51 patients.[3] Residual masses found in patients with bulky seminoma after chemotherapy are commonly reported in approximately 56% to 78%[4]; however only a small fraction of these lesions were found to actually harbor viable tumor cells. There is a disagreement on whether the size of residual masses after chemotherapy predicts for the presence of active disease. Although not proven, there is postulation that the size of the residual mass may be a predictor for residual disease as a large residual mass may have a higher potential to contain tumor cells. One study[5] determined that there was a higher likelihood of finding viable tumor tissue within residual lesions that were 3 cm or larger, whereas another study[6] did not see such a correlation. Based on the experience from Memorial Sloan-Kettering Cancer Center (New York, NY), patients with residual masses of 3 cm or larger are recommended to undergo surgical excision of the lesion.[5] In contrast, the experience of the Indiana University group (Indianapolis, IN) suggests that an initial period of observation is a plausible option, regardless of the size of the residual mass, and further therapy is reserved for patients with progressive disease.[6] PET imaging has been assessed for its validity in predicting persistent disease in patients with residual mass after apparent successful chemotherapy for testicular cancer. The largest prospective study showed that this imaging modality was highly sensitive and specific in predicting residual disease, particularly in patients with residual mass larger than 3 cm. From the 56 scans performed in 51 patients, the sensitivity, specificity,