

# Skin-first nodulotumoral adult T-cell lymphoma mimicking cutaneous T-cell lymphoma



Leah Cohen, BA,<sup>a</sup> Pei-Ling Chen, MD, PhD,<sup>b,c</sup> Ling Zhang, MD,<sup>c</sup> Lubomir Sokol, MD, PhD,<sup>d</sup> and Lucia Seminario-Vidal, MD, PhD<sup>b,c</sup>  
Miami and Tampa, Florida

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## INTRODUCTION

Adult T-cell leukemia-lymphoma (ATLL) is a peripheral T-cell neoplasm caused by human T-cell lymphotropic virus-1 (HTLV-1) that may resemble other lymphomas clinically and histopathologically. Approximately half of patients with ATLL present with heterogeneous cutaneous findings at some point in their disease course, which are delineated by skin-first, skin-second, and skin-uninvolved courses.<sup>1,2</sup> With skin-first presentation, more than 80% of ATLL patients in the United States have a diagnosis of cutaneous T-cell lymphoma (CTCL).<sup>1</sup> The rarity of ATLL in the United States, coupled with its clinicopathologic mimicry of other primary CTCLs, such as mycosis fungoides (MF) and systemic T-cell lymphomas involving the skin, causes a diagnostic challenge. Delays in diagnosis of ATLL can negatively affect patient survival, necessitating greater awareness of this disease in the United States.<sup>1</sup>

## CASE REPORT

We report the case of a 67-year-old Haitian man who presented with a 10-month history of nodular lesions of his lower legs, which were initially pruritic but became progressively painful. He denied any fevers, chills, or unintentional weight loss. His medical history was significant for hypertension and chronic active hepatitis B infection. On physical examination, vital signs were stable. Skin

### Abbreviations used:

|         |                                   |
|---------|-----------------------------------|
| ATLL:   | adult T-cell leukemia-lymphoma    |
| CTCL:   | cutaneous T-cell lymphoma         |
| HTLV-1: | human T-cell lymphotropic virus-1 |
| MF:     | mycosis fungoides                 |
| PCR:    | polymerase chain reaction         |



**Fig 1.** The largest cutaneous lesion was an approximately 30- × 10-cm ulcerated tumor with fibrinous exudate on the right shin.

From Florida International University, Herbert Wertheim College of Medicine, Miami<sup>a</sup>; the Departments of Cutaneous Oncology,<sup>b</sup> Pathology,<sup>c</sup> and Malignant Hematology,<sup>d</sup> Moffitt Cancer Center; and the Department of Dermatology and Cutaneous Surgery, University of South Florida.<sup>e</sup>

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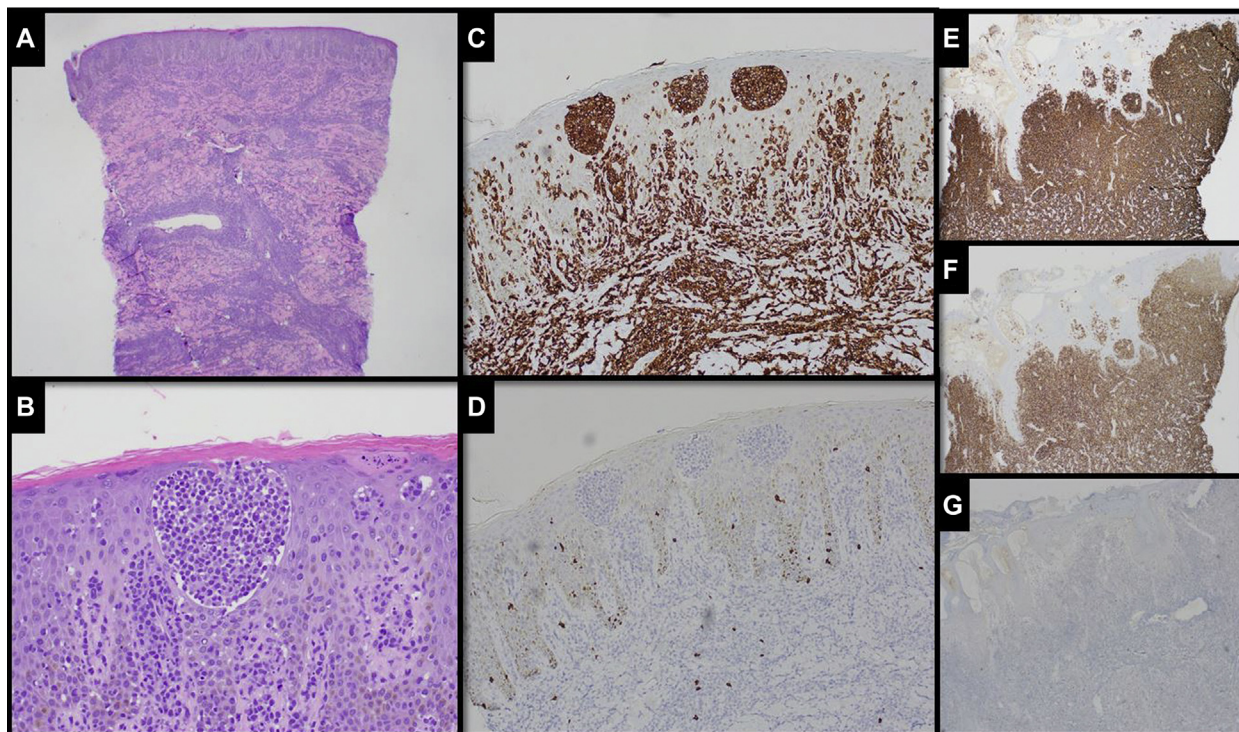
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Correspondence to: Lucia Seminario-Vidal, MD, PhD, 13330 USF Laurel Drive, 6th Floor, Tampa, FL 33612. E-mail: [luciasem@health.usf.edu](mailto:luciasem@health.usf.edu).

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**Fig 2.** Biopsy results of the 5 lesions. **A**, Hematoxylin-eosin stain; original magnification:  $\times 2$ . **B**, Hematoxylin-eosin stain; original magnification:  $\times 10$ . **C**, CD3. **D**, CD8. **E**, CD4. **F**, CD5. **G**, CD7.

examination found numerous indurated hyperpigmented and erythematous patches, subcutaneous nodules, and tumors scattered on the trunk and extremities, covering approximately 21% of body surface area (Fig 1). Lymphatic examination found bilateral inguinal lymphadenopathy. Mucosal examination was negative for lesions.

Initial biopsies 4 months prior found skin with pseudoepitheliomatous hyperplasia and an atypical lymphoid infiltrate, predominately CD3<sup>+</sup>, CD4<sup>+</sup>, and CD30<sup>-</sup>, suggesting MF. Peripheral blood flow cytometry found no abnormal T-cell population, and computed tomography scan was negative. Treatment was not initiated at that time. Four months later, he was seen at our institution for a second opinion. Biopsies of 5 lesions found a pan-dermal atypical lymphoid infiltrate with epidermotropism and prominent Pautrier-like microabscesses (Fig 2, A and B). The atypical infiltrate comprised sheets of medium-to-large cells with vesicular chromatin, ovoid/irregular nuclear contours, and nucleoli (>30%). Immunohistochemical studies found a predominance of CD3<sup>+</sup> T cells with CD4/CD8 ratio of >10:1 (Fig 2, C-E). The atypical cells expressed CD5 and CD25, with loss of CD7 (Fig 2, F and G). CD30 immunostaining highlighted scattered cells in dermis. CD20 highlighted rare B

cells. HTLV-1 serology was positive. Peripheral blood smear showed medium-to-large atypical lymphoid cells with flower-shaped nuclei and basophilic cytoplasm. Flow cytometry of peripheral blood identified atypical T cells (140 cells/ $\mu$ L), positive for CD4, CD25, CCR4, and PD-1, with loss of CD7 and CD26, consistent with ATLL. Identical monoclonal T-cell receptor  $\gamma$  and  $\beta$  gene rearrangements were identified by polymerase chain reaction (PCR) in blood and skin specimens. The patient's complete blood count was within normal limits except for hemoglobin concentration of 9.5 g/dL. Lactate dehydrogenase was elevated at 470 U/L (normal range, 135-225 U/L), and calcium corrected was 13.4 mg/dL (normal range, 8.6-10.2 mg/dL). Computed tomography scan found borderline bilateral inguinal and femoral lymphadenopathy. The patient was hospitalized for hypercalcemia, given entecavir for his hepatitis, and radiation with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy for his ATLL. Four months later he was admitted to the hospital for sepsis and had central nervous system involvement. He did not respond to high-dose methotrexate followed by intrathecal cytarabine, and his family opted for hospice care.

## DISCUSSION

We describe a case of skin-first nodulotumoral ATLL with a presentation suggestive of MF. Both ATLL and MF are malignancies of mature CD4<sup>+</sup> T cells with overlapping clinicopathologic features.<sup>3</sup> Although 50% of ATLL patients have cutaneous involvement at some point in their disease, only one third will present with it.<sup>1,2</sup> Cutaneous manifestations are heterogeneous, and when disease presents skin first, most of diagnoses are erroneous.<sup>1,4</sup> A patient's country of origin and consideration of areas in which HTLV-1 is endemic, such as Japan, the Caribbean, South America, and West Africa, are important.<sup>5</sup> A negative HTLV-1 serology test can rule out ATLL, but when positive, ATLL should be considered. Factors favoring the diagnosis of ATLL over MF include initial presentation with lymph node involvement, hepatosplenomegaly, hypercalcemia, leukemic manifestations, and an aggressive course.<sup>3</sup> In contrast to MF, ATLL is fatal in most patients.

A study of patients with ATLL in the United States found that the most commonly affected extranodal site, excluding the peripheral blood and bone marrow, was the skin in 28% of subjects.<sup>6</sup> Another US series found that 82% (14 of 17) of skin-first ATLL patients received a non-ATLL diagnosis leading to a median delay in diagnosis of 3.7 months, with the median overall survival of patients with skin involvement of 10.1 months.<sup>1</sup> Therefore, the diagnosis of ATLL in the United States should be considered in patients with suspicious skin lesions with the following features: (1) prior residence in an HTLV-1 endemic region; (2) clinicopathologic features of MF/Sézary syndrome, including prominent Pautrier-like microabscesses with large cell morphology; (3) nodulotumoral skin lesions appearing early in the disease course of suspected CTCL; and (4) CTCL not consistent with another well-recognized lymphoma.<sup>1</sup>

Histologically, the differential diagnoses of ATLL includes Sézary syndrome/MF with large cell transformation, peripheral T-cell lymphoma not otherwise specified (a diagnosis made after exclusion of other T-cell lymphomas within specific World Health Organization classifications) and T-prolymphocytic leukemia involving the skin. Generally, ATLL cells express mature T-cell markers CD2, CD5, CD25 (strong and uniform), with a CD4/CD8 ratio > 10:1 and loss of CD7.<sup>3</sup> Expression of CCR4 and PD-1 is typically strong in ATLL.<sup>4</sup>

Current National Comprehensive Cancer Network guidelines for T-cell lymphomas recommend HTLV-1 screening in at risk populations, such as immigrants from endemic areas. Diagnosis of ATLL requires histopathology and immunophenotyping of tumors, peripheral blood cytology, or morphology and immunophenotyping of peripheral blood and HTLV-1 serology. If enzyme-linked immunosorbent assay is positive, a confirmatory western blot is indicated. If the western blot is indeterminate, then HTLV-1 PCR is recommended.<sup>7</sup> Demonstration of monoclonal insertion of HTLV-1 DNA into genomic DNA of tumor cells leads to a definitive diagnosis; however, PCR is not routinely available in non-endemic areas.

The frequency of erroneous diagnosis necessitates greater awareness of ATLL for physicians, specifically in regions in which migration from endemic areas is common. We recommend the use of histologic clues in patients without blood involvement to identify potential ATLL cases such as prominent Pautrier-like microabscesses of large atypical cells, large cells with a high CD4/CD8 ratio >10:1, and strong CD25 expression. These clues should trigger testing for HTLV-1 serology. The case described here with skin-first nodulotumoral ATLL demonstrates the importance of distinguishing between ATLL and MF to improve patient outcomes.

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