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Primary cutaneous smoldering adult T-cell leukemia/lymphoma

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Abstract

HTLV-1 is a virus that is endemic in southwestern Japan and the Caribbean and has been implicated in the development of ATLL. ATLL, which is an uncommon malignant condition of peripheral T-lymphocytes, is characterized by four clinical subtypes, which include acute, lymphomatous, chronic, and smoldering types, that are based on LDH levels, calcium levels, and extent of organ involvement. We present a 52-year-old woman with pruritic patches with scale on the buttocks and with tender, hyperpigmented macules and papules of two-years duration. Histopathologic examination was suggestive of mycosis fungoides, laboratory results showed HTLV-I and II, and the patient was diagnosed with primary cutaneous ATLL. We review the literature on HTLV-1 and ATLL and specifically the prognosis of cutaneous ATLL. The literature suggests that a diagnosis of ATLL should be considered among patients of Caribbean origin or other endemic areas with skin lesions that suggest a cutaneous T-cell lymphoma, with clinicopathologic features of mycosis fungoides. Differentiation between ATLL and cutaneous T-cell lymphoma is imperative as they have different prognoses and treatment approaches.



Figure 1. On the lower legs were multiple, scattered, hyperpigmented macules and papules, with one hyperpigmented nodule with central crusting.

Case Presentation

PATIENT: 52-year-old-woman

DURATION: Two years

DISTRIBUTION: Hips, buttocks, and lower extremities

HISTORY: A 52-year-old woman originally from Barbados with a history of systemic lupus erythematosus (SLE) presented to the Skin and

Cancer Unit for the evaluation of pruritic patches on the buttocks and tender papules on the legs of two years' duration. Two years prior to presentation, the patient was diagnosed with SLE when she presented with fevers, fatigue, myalgias, and uveitis, and she was started on hydroxychloroquine. Around that time, she also developed a pruritic eruption on her lower legs, to which she applied topical glucocorticoids without improvement. Over time, the lesions became painful. One year prior to presentation, she developed new, pruritic



Figure 2. On the right hip and buttocks were well-demarcated, erythematous, atrophic patches with scale.

patches on the buttocks, to which she applied topical glucocorticoids with some improvement. At the time of presentation, she reported occasional fatigue, weakness, and myalgias that were limited to the shoulders and neck. She denied fevers, chills, weight loss, and night sweats.

PHYSICAL EXAMINATION: On the lower legs were multiple, scattered, hyperpigmented macules and papules, with one hyperpigmented nodule with central crusting (**Figure 1**). On the right hip and buttocks were well-demarcated, erythematous, atrophic patches with scale (**Figure 2**).

LABORATORY DATA: A complete blood count showed an elevated white-cell count of 11.9 K/uL and hemoglobin of 11.6 g/dL. A comprehensive metabolic panel showed an alkaline phosphatase of 297 U/L. Lactate dehydrogenase was normal. Flow cytometry of peripheral blood was negative for immunophenotypic evidence of non-Hodgkin's lymphoma or acute leukemia as well as for T-cell receptor gamma chain gene monoclonal rearrangement. Right lateral hip paraffin shavings were positive for T-cell receptor gamma chain monoclonal gene rearrangement. HTLV-I/II ELISA and Western blot was positive for HTLV-I and HTLV-II antibodies.

HISTOPATHOLOGY: There is a patchy, band-like and perivascular, lymphocytic infiltrate with exocytosis of lymphocytes into the epidermis where there is a relative lack of spongiosis (**Figure 3**). Intraepidermal

lymphocytes are mildly atypical with enlarged, hyperchromatic nuclei. Perinuclear halos are noted.

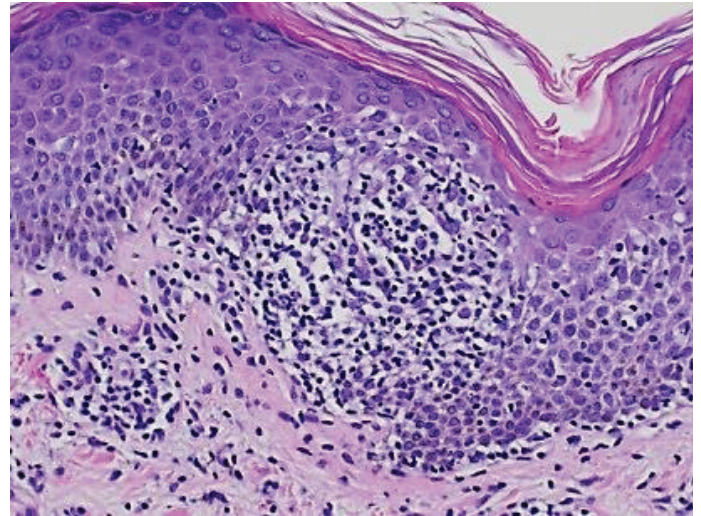


Figure 3. On histopathology, there was a patchy, band-like and perivascular, lymphocytic infiltrate with exocytosis of lymphocytes into the epidermis where there is a relative lack of spongiosis.

DIAGNOSIS: Primary cutaneous smoldering adult T-cell leukemia/lymphoma

Discussion

Human T-lymphotropic virus type-1 (HTLV-1) is an enveloped, double-stranded RNA virus that belongs to the family of Retroviridae. It has been implicated in the development of adult T-cell leukemia/lymphoma (ATLL), which is an uncommon malignant condition of peripheral T-lymphocytes as well as of several inflammatory disorders, such as tropical spastic paraparesis (TSP)/HTLV-1-associated myelopathy (HAM), infective dermatitis, and HTLV-associated uveitis [1,2]. The disparate development of malignant or inflammatory diseases is related to differences in the immune response to HTLV-1 in infected individuals, which are partially dependent on HLA haplotypes. A low viral load results in a weak immune response and persistence of the virus, which induces a clonal cellular expansion with ATLL development. Conversely, a vigorous immune response is induced by high viral protein expression and development of HAM/TSP [3].

An estimated five to 20 million individuals are infected with HTLV-1 worldwide, and infection

is considered endemic in southwestern Japan, the Caribbean, intertropical Africa, the Middle East, South America, and Papua New Guinea. The majority of those infected remain asymptomatic, and the lifetime risk of development of ATLL in HTLV-1 carriers is 3 to 5%, with a latency period of 20 to 30 years after infection [4]. The three major HTLV-1 transmission routes are mother-to-child (via breastfeeding), sexual intercourse, and blood transfusions. Transmission via transfusion, however, has been virtually eliminated by donor blood screening. Individuals infected with HTLV-1 after adolescence are considered to be at low-risk of developing ATLL. Therefore, mother-to-child transmission is important route of transmission for HTLV-1 infection that is associated with ATLL [5]. Reported risk factors for ATLL development among HTLV-1 carriers include HTLV infection in early life, increasing age, male gender, family history of ATLL, past history of infectious dermatitis, smoking, HTLV-1 proviral load, and several HLA subtypes [1,6]. Although the United States incidence of ATLL is low, with 0.05 male and 0.03 female per 100,000 cases diagnosed annually, its incidence is rising, especially in those areas with large Caribbean migrant populations [7].

The clinical course of ATLL is characterized by four clinical subtypes, which include acute, lymphomatous, chronic (unfavorable and favorable subtypes), and smoldering types, which are based on LDH levels, calcium values, and the extent of organ involvement [8]. Acute, lymphomatous, and unfavorable chronic types are considered to be aggressive while favorable chronic and smoldering types are indolent. Clinical features are diverse and include generalized lymphadenopathy, skin lesions, hepatosplenomegaly, leukocytosis with increased abnormal lymphocytes that show cerebriform or flower-like nuclei or with increased neutrophils, hypercalcemia, lytic bone lesions, and opportunistic infections due to *Pneumocystis jirovecii*, candida, cytomegalovirus, and *Strongyloides stercoralis* [4]. The most common form is acute ATLL, which is observed in about 65% of patients and is characterized by systemic symptoms, organomegaly, and a leukemic picture. Smoldering ATLL is the least common form, which occurs in 5 to 10% of patients and is usually

asymptomatic but may manifest with skin lesions and/or lung infiltrates. Unlike the chronic form, the white-cell count is normal, and fewer than 5% of peripheral CD4+ cells are involved, with proviral DNA integrated monoclonally [3,5]. Specific skin lesions that are caused by infiltration of the skin by malignant cells have been described in 43 to 72% of patients with ATLL [9]. Cutaneous lesion morphology at diagnosis includes nodulotumoral, multipapular, plaques, patches, and erythroderma [7]. The presence of cutaneous lesions in smoldering-type ATLL confers a worse prognosis. However, primary cutaneous ATLL has a prolonged survival as compared to secondary cutaneous ATLL although the presence of tumors is associated with a reduced survival time [10,11]. In a recent retrospective study of patients with ATLL, who presented with primary cutaneous involvement, the majority of the patients were of Caribbean origin, had overall prolonged survival compared to those with secondary cutaneous involvement, and often were misdiagnosed initially on initial skin biopsy [7]. Histopathologic features may show dermal lymphoid infiltrates, epidermotropism with Pautrier's microabscesses, with a pattern that is indistinguishable from that of mycosis fungoides and Sézary syndrome [5].

The diagnosis of ATLL generally is based upon a combination of typical clinical features, morphologic and immunophenotypic changes of the neoplastic cells, and confirmation of HTLV-I infection, which is established with serologic tests to detect antibodies to the virus, most commonly via enzyme-linked immunosorbent assay (ELISA) [3]. The prognosis of ATLL is poor, with a median survival of less than one year for the acute and lymphomatous forms but a projected four-year survival of 26.9% and 62%, respectively, for the chronic and smoldering forms [8]. Treatment of ATLL includes observation for the development of indolent disease, intensive chemotherapeutic regimens that are followed by allogeneic hematopoietic stem-cell transplantation for aggressive forms, and a combination of interferon- α and zidovudine for ATLL with leukemic manifestations [12]. Skin lesions should be treated with skin-directed treatments, such as topical glucocorticoids; with phototherapy, and radiation; or with systemic therapy, such as glucocorticoids,

oral retinoids, or single agent chemotherapy [13]. There are currently ongoing phase III clinical trials with the anti-chemokine receptor 4 (anti-CCR4) monoclonal antibody mogamulizumab, which may prolong survival.

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