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Assessing smoldering adult T-cell leukemia/lymphoma: a case report

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Abstract

Adult T-cell leukemia/lymphoma (ATLL) is a rare, extremely aggressive malignancy with four different clinical variants, all of which are associated with human T cell lymphotropic virus type 1. Antiretrovirals have been recognized as an effective therapy after study in clinical trials around the world. However, oncologists traditionally wait for asymptomatic patients with ATLL to reach a more severe stage of disease before treatment is initiated. We describe a patient with Fitzpatrick Skin Type V who presented with asymptomatic dyschromia of her neck, breast, and jaw. Her clinical, laboratory, and histological findings were consistent with smoldering type-ATLL. We teamed up with her oncologist to successfully treat her cutaneous symptoms with interferon-alpha/zidovudine. This report demonstrates efficacy with the employment of antiretroviral therapy immediately following a diagnosis of smoldering type ATLL.

Keywords: adult T-cell leukemia/lymphoma, antiretrovirals, ATLL, cutaneous manifestations, HTLV1, human T cell lymphotropic virus type 1, leukemia, lymphoma, smoldering

Introduction

Smoldering adult T-cell leukemia/lymphoma (ATLL), the subtype of ATLL confined to the skin, poses a challenge to diagnose and treat owing to asymptomatic onset, varied clinical manifestations, and indolent course of illness [1]. It is associated with human T cell lymphotropic virus type 1 (HTLV1) and carries a prognosis of 4.1 years median survival time [2]. HTLV1 is present throughout the world and highly endemic in Japan, sub-Saharan African, South America, the Caribbean, Australo-Melanesia, and some areas of the Middle East [3]. Although serological testing and bone marrow biopsy can assess for systemic ATLL, a skin biopsy is necessary to diagnose smoldering ATLL. Chemotherapeutic options exist for systemic subtypes; however, few treatment options are available for smoldering ATLL. Watchful waiting is among the standard of care treatment options. However, clinical trials with immunomodulators have shifted care to early intervention at time of diagnosis [4-6].

Case Synopsis

A 63-year-old woman with Fitzpatrick skin type V presented with asymptomatic dyschromia of the neck for eight months duration. On examination, the patient displayed erythematous plaques with mild induration and areas of dyschromia with mixed hyper- and hypopigmented patches on the right neck extending to the bilateral breasts in a serpiginous pattern (**Figure 1**).

No lichenification, excoriations, or scaling were noted; she also exhibited neither lymphadenopathy nor splenomegaly. Review of systems was negative and the patient denied pain or pruritus. Medical history was significant for diabetes, hypertension, and hyperlipidemia. The differential diagnosis included mycosis fungoides, contact dermatitis, nummular eczema, cutaneous lupus erythematosus, and sarcoidosis.

Punch biopsies of the right jawline and left breast exhibited infiltrates of patchy lichenoid

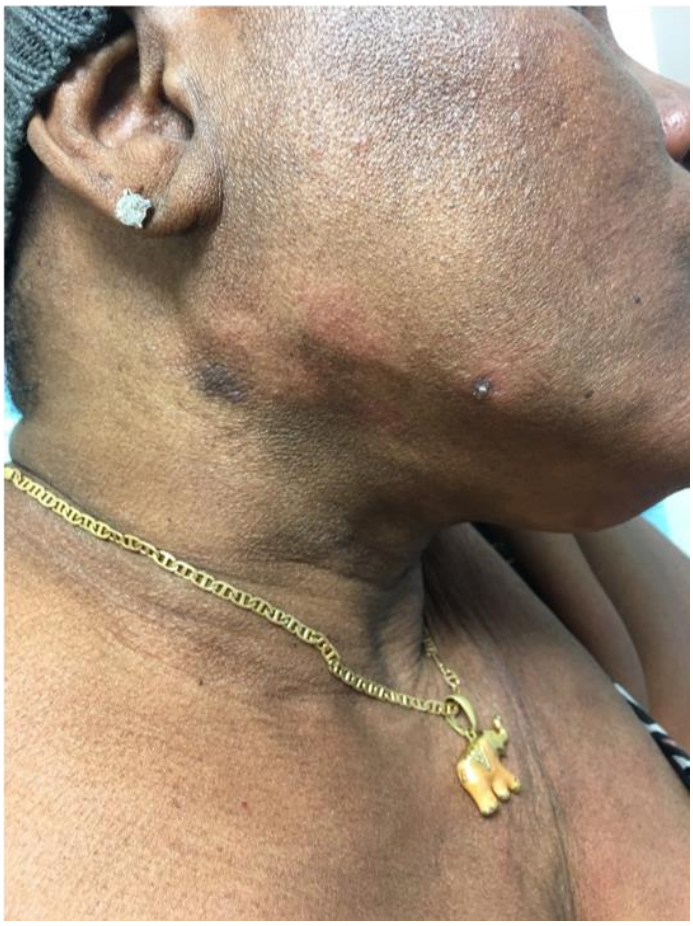

Figure 1. *Baseline examination of the patient displaying indurated, erythematous plaques with dyschromia on the right jawline.*

mononuclear cells filling the papillary dermis with exocytosis of atypical mononuclear cells arranged as nests throughout all levels of the epidermis (**Figure 2**). Cluster of differentiation 25 (CD25) antibody stain revealed numerous atypical CD25+ cells in the epidermis (**Figure 3**).

Laboratory testing including complete blood count, comprehensive metabolic panel, including lactate dehydrogenase (LDH) and calcium levels, thyroid hormone panel, and antinuclear antibodies were within normal limits. Human immunodeficiency virus (HIV) testing was negative. The patient tested positive for HTLV1 on initial and repeat testing. These findings are consistent with the diagnosis of ATLL with a positive prognostic outcome due to lack of systemic findings and a normal blood calcium level. Further extensive workup including peripheral blood smear indicated atypical white blood cells with cleaved nuclei in a slight "flowery" appearance. Red blood cell smear was normal. Upon referral to the hematology/oncology department, a bone marrow biopsy and flow cytometry indicated no evidence for abnormal myeloid maturation or increased blast populations and therefore no evidence for a lymphoproliferative disorder.

The patient received a final diagnosis of smoldering adult T-cell leukemia/lymphoma. The oncologist who initially worked up the patient opted to not pursue treatment per current oncology guidelines until she reached a higher cancer staging that would require chemotherapy. This option carried a prognosis of 3-5 years without treatment [7]. Upon researching recent clinical trials and treatment options, we referred the patient to a second oncologist. She received interferon-alpha and zidovudine antiretroviral therapy along with topical triamcinolone. The patient exhibited clearance of her cutaneous symptoms within the first three months of treatment. She continued to follow-up with her new oncologist.

Case Discussion

There are four clinical variants of ATLL: smoldering, acute, chronic, and lymphomatous, according to criteria proposed by Shimoyama in 1991 that have since been adopted by the National Comprehensive Cancer Care Network (NCCN), [6,8]. All four are associated with vertically transmitted chronic infection with HTLV1. Despite infection with HTLV1, the risk of developing ATLL is 2-4% regardless of the subtype [9]. Of that percentage, less than 10% are smoldering ATLL, also referred to as primary presenting cutaneous ATLL. Due to varying cutaneous manifestations and asymptomatic nature, diagnosis can be delayed, prolonging initiation of appropriate treatment. Hypercalcemia and increased LDH secondary to tumor lysis syndrome are considered poor prognostic factors and should be considered during treatment regimen implementation [10].

In Japan, watchful waiting is employed in chronic and smoldering (indolent) subtypes until the disease has become aggressive and symptomatic, at which point the disease is no longer indolent and

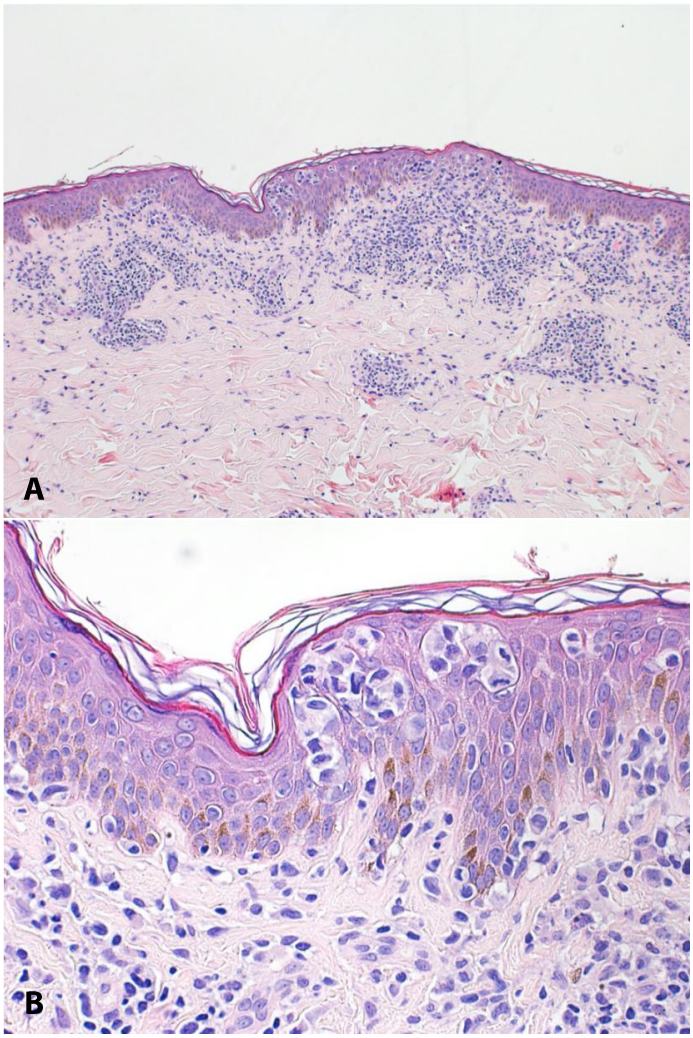

Figure 2. ***A)*** *Patchy lichenoid mononuclear cell infiltration of the superficial dermis. H&E, 40×.* ***B)*** *Magification of atypical mononuclear cells arranged as nests in the epidermis. H&E, 100×.*

antiretroviral regimens such as interferon alpha/zidovudine (IFNα/AZT) are administered [11]. The smoldering type responds to antiretroviral therapy based on a multiple site retrospective meta-analysis on smoldering/chronic ATLL, indicating a 100% median 5-year survival rate (N=17) with IFNα/AZT, compared to 42% median survival with chemotherapy-initiated therapy (N=6), [12]. Based on this evidence, treatment of smoldering ATLL is encouraged. However, it is unclear if IFNα/AZT therapy is curative or if it is a lifelong treatment regimen. In light of the promising results of the meta-analysis, a prospective study comparing the employment of watchful waiting versus immediate treatment with IFNα/AZT in the indolent subtype of ATLL is currently underway, through the Japan

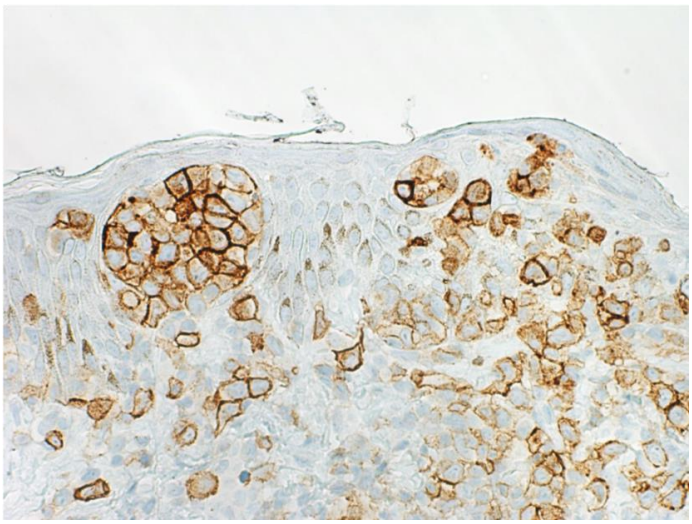

Figure 3. *Immunochemical stain showing atypical mononuclear cells in the epidermis expressing CD25, a T cell marker, 400×.*

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Immunomodulators, monoclonal antibodies, and allogeneic stem cell transplants provide optimistic treatment outcomes in individuals with aggressive or relapsing presentation and are usually not indicated in limited cutaneous manifestations of pathology. Lenalidomide, an immunomodulator with tumoricidal and antiangiogenic properties, has been evaluated in a phase II study in patients with recurrent relapsed ATLL and resulted in an overall response rate of 3.8 months [13]. The monoclonal antibody mogamulizumab targets cysteine-cysteine chemokine receptor 4 (CCR4), a protein overexpressed on ATLL cells, and induces cell cytotoxicity. This has proven successful in phase II clinical trials in Japan studying relapsed ATLL of all subtypes [14]. Allogeneic bone marrow transplants have also been successfully utilized but are reserved for aggressive forms of ATLL including the acute and lymphomatous subtypes [15]. Arsenic trioxide has demonstrated efficacy when in conjunction with IFNα in the refractory relapsed subtypes, as well as in newly diagnosed chronic ATLL [16-18].

Conclusion

This case report highlights the difficulty in diagnosing smoldering ATLL along with the

challenges involved to effectively treat this condition. It is often difficult to recognize cutaneous ATLL without systemic findings and it can be challenging to treat as it requires a multidisciplinary method of management. The antiretroviral approach demonstrated efficacy in this patient with smoldering type ATLL and provides optimistic outcomes when used in combination with other modalities in more aggressive forms of ATLL.

Potential conflicts of interest

The authors declare no conflicts of interests.

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