Case Report: An Uncommon Clinical Case of Fatal Adult T-Cell Leukemia/Lymphoma Associated with HTLV-1 and Suspected due to Cutaneous Lesions and Epidemiologic Data

Isabelle Carvalho de Assis,* João Gabriel Rodrigues Alberti, and Paulo Ricardo Criado

Department of Dermatology, Faculdade de Medicina do ABC, São Paulo, Brazil

Abstract. Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell neoplasm caused by the human T-cell leukemia virus type 1 (HTLV-1). It is characterized by a short survival time and lack of response to chemotherapy. We report a case of a 56-year-old woman, from the Brazilian northeast state of Bahia, who presented with a 2-month history of infiltrated papular and nodular skin lesions, especially on her forehead and also on her lower and upper limbs. Laboratory tests revealed positive serology for HTLV-1. Histopathological findings and the immunohistochemical profile confirmed the diagnosis of adult T-cell lymphoma/leukemia. A month after the diagnosis, the patient presented acute fatigue and pronounced paleness of the skin, dying of septic shock after her first chemotherapy cycle. The aim of this case report was to emphasize the importance of maintaining high clinical suspicion for ATLL, considering the epidemiological profile of the disease, especially for patients whose only early symptoms are cutaneous lesions.

INTRODUCTION

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell neoplasm, CD4⁺, and CD25⁺, caused by human T-cell leukemia virus type 1 (HTLV-1).^{1,2} The city of Salvador, capital of Bahia, the biggest northeast state in Brazil, has been identified as the epicenter of HTLV-1 infection in this country.³ The aim of this case report was to emphasize the importance of maintaining high clinical suspicion for ATLL, considering the epidemiology of this disease, to provide early treatment for ATLL cases, especially for patients whose only early symptoms are cutaneous lesions.

CASE REPORT

A 56-year-old woman from the Brazilian state of Bahia, who had lived for the last 20 years in the city of Diadema (São Paulo metropolitan region), was admitted to the emergency unit reporting progressive development of cutaneous lesions over the prior 2 months. On performing dermatological examination, we observed erythematous and infiltrated papular and nodular skin lesions, located on her upper (Figure 1A) and lower limbs, and forehead (Figure 1B). She did not present fever, weight loss, fatigue, or paresthesia. Physical examination did not reveal hepatosplenomegaly or lymph node enlargements, but laboratory tests showed leukocytosis and elevated alkaline phosphatase, gamma-glutamyl transferase, and lactic dehydrogenase. Ultrasonographic examination ruled out biliary obstructions, and laboratory tests revealed positive serology for HTLV-1. Four days later, cutaneous biopsies of two lesions on her right upper limb were performed; they showed a superficial and deep dermis with dense infiltration of medium and small lymphoid cells, diffusely distributed with cleaved nuclei, but not compromising the epidermis (Figure 2). The immunohistochemical profile was compatible with ATLL (Ki-67 positive in more than 90% of lymphocytes; CD2, CD3, CD4, CD5, and CD30 positive in most lymphocytes) (Figure 3). Within a month, the patient reported acute fatigue,

presenting weakness in the scapular and pelvic girdles and intense skin paleness. She was referred to a specialized oncology service, where she received CHOP chemotherapy (cyclophosphamide 100 mg combined with doxorubicin 70 mg, vincristine 2 mg, and 100 mg of prednisone) as first-line chemotherapy. Antiviral therapy was not prescribed.

FIGURE 1. (A) Infiltrated papules and nodules on the dorsum of the hand. (B) Infiltrated papules and nodules on the forehead. This figure appears in color at www.ajtmh.org.

* Address correspondence to Isabelle Carvalho de Assis, Department of Dermatology, Faculdade de Medicina do ABC, Rua Alves Guimarães, 434, apto 111, Pinheiros, São Paulo 05410-000, Brazil. E-mail: isa_assis@hotmail.com

FIGURE 2. Superficial and deep dermis with dense infiltration of medium and small lymphoid cells, diffusely distributed and with cleaved nuclei, without compromising the epidermis. This figure appears in color at www.ajtmh.org.

According to the patient's medical record, she presented clinical deterioration during hospitalization, and comfort measures were established as a priority. She died of respiratory failure 11 days after hospital admission. Her death certificate stated septic shock due to pneumonia; however, blood cultures were not available, and an autopsy was not performed.

DISCUSSION

Approximately 10–20 million people are infected by HTLV-1 around the world, but only 5–10% develop the disease. The main manifestations of this viral infection are ATLL, as reported with our patient; however, other conditions may be present, such as tropical spastic paraparesis/HTLV-1-associated myelopathy, human T-cell lymphotropic virus type 1-associated infective dermatitis, and HTLV-1-associated uveitis.⁴ Adult T-cell leukemia/lymphoma is a peripheral T-cell neoplasm that occurs exclusively in adults, and the distribution of this disease depends on the geographical coverage of HTLV-1.^{1,2,5} Our patient had been born and lived for 36 years in the state of Bahia, where HTLV-1 infection is endemic, with an overall rate of 14.4 per 100,000 inhabitants.⁶ The aforementioned state's capital city, Salvador, has the highest number of HTLV-1-infected individuals in Brazil, with an overall prevalence of 1.8%.³ Adult T-cell leukemia/lymphoma has been clinically classified as acute, lymphomatous, chronic,

FIGURE 3. Immunohistochemical study. (A) CD2 positive in most lymphocytes. (B) CD30 positive in more than 50% of lymphocytes. (C) Ki-67 positive in more than 90% of lymphocytes. This figure appears in color at www.ajtmh.org.

and smoldering types.⁷ The skin is affected in approximately half of all cases, and cutaneous lesions can be the first manifestation of the disease, as described in the patient analyzed in this study.⁸ The skin lesions of ATLL are polymorphous and manifest themselves as erythroderma, plaques, papules, nodules, and tumors. At times, such lesions appear remarkably similar to multibacillary leprosy, which may lead to misdiagnosis during clinical examinations.

There is a correlation between the dermatological lesions and their clinical types: nodules and tumors are present in the aggressive clinical forms (acute, lymphomatous, and primary cutaneous tumors).⁹ A high suspicion of lymphoma related to HTLV-1 is mandatory on clinical examination if such lesions are detected in patients inhabiting or coming from regions where the virus is more prevalent. In such cases, one must pay close attention to the disease's epidemiology and request laboratory tests to confirm the diagnosis of ATLL: a biopsy and serology for HTLV-1 are, therefore, essential. Aggressive ATLL is reported to have a poor prognosis mainly because of multidrug-resistant malignant cells, large tumor burdens with multi-organ failure, hypercalcemia, and infectious complications.¹⁰ As previously observed by Bittencourt et al.,¹¹ patients with acute clinical types were found to have a median survival time (MST) of about 4 months, which tends to be even lower in patients with skin lesions.

There is no optimal standard treatment regimen for ATLL; therefore, it is recommended to include the patient in prospective clinical trials.^{10,12} In Brazil, a therapeutic protocol for

ATLL is still needed, but generally, ATLL is treated with chemotherapy and/or antivirals.¹³ It was demonstrated that ATLL patients did not respond to antivirals and chemotherapy simultaneously, and in its acute form, they showed higher MST when they received only chemotherapy with the CHOP (cyclophosphamide combined with doxorubicin, vincristine, and prednisone) regimen. Unfortunately, the most aggressive forms of ATLL (acute, lymphomatous, unfavorable chronic, and primary cutaneous tumoral subtype) had lower MST, regardless of the therapeutic approaches used, resulting in a poor prognosis, as reported in the aforementioned patient.¹³

Hence, physicians must be alert to infiltrative skin lesions, especially in patients from Brazil's northeast region, considering not only the endemic levels of HTLV-1 in this area of the country but also its inherent transmission characteristics, which occur mainly through blood transfusions and vertical transmission.³

Received May 6, 2020. Accepted for publication June 29, 2020.

Published online August 10, 2020.

Authors' addresses: Isabelle Carvalho de Assis, Paulo Ricardo Criado, and João Gabriel Rodrigues Alberti, Department of Dermatology, Faculdade de Medicina do ABC, São Paulo, Brazil, E-mails: isa_assis@hotmail.com, prcriado@uol.com.br, and joao.alberti@hotmail.com.

REFERENCES

1. Bittencourt Achiléa L, Farré L, 2008. Leucemia/linfoma de células T do adulto. *An Bras Dermatol* 83: 351–359.
2. Barrionuevo-Cornejo C, Dueñas-Hancco D, 2019. Neoplastic hematological diseases associated with HTLV-1 infection. *Semin Diagn Pathol* 37: 98–103.
3. Dourado I, Alcantara LCJ, Barreto ML, da Gloria Teixeira M, Galvão-Castro B, 2003. HTLV-I in the general population of Salvador, Brazil. *J Acquir Immune Defic Syndr* 34: 527–531.
4. McGill NK, Vyas J, Shimauchi T, Tokura Y, Piquet V, 2012. HTLV-1-associated infective dermatitis: updates on the pathogenesis. *Exp Dermatol* 21: 815–821.
5. Gessain A, Cassar O, 2012. Epidemiological aspects and world distribution of HTLV-1 infection. *Front Microbiol* 3: 388.
6. Pereira FM, de Almeida MDCC, Santos FLN, Carreiro RP, Regis-Silva CG, Galvão-Castro B, Grassi MFR, 2019. Evidence of new endemic clusters of human T-cell leukemia virus (HTLV) infection in Bahia, Brazil. *Front Microbiol* 10: 1002.
7. Shimoyama M, 1991. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984–1987). *Br J Haematol* 79: 428–437.
8. Casavilca-Zambrano S, 2019. Cutaneous manifestations of adult T-cell leukemia/lymphoma. *Semin Diagn Pathol* 37: 81–89.
9. Bittencourt AL, Barbosa HS, Vieira MDG, Farré L, 2009. Adult T-cell leukemia/lymphoma (ATL) presenting in the skin: clinical, histological and immunohistochemical features of 52 cases. *Acta Oncol* 48: 598–604.
10. Tsukasaki K et al., 2009. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. *J Clin Oncol* 27: 453–459.
11. Bittencourt AL, da Graças Vieira M, Brites CR, Farre L, Barbosa HS, 2007. Adult T-cell leukemia/lymphoma in Bahia, Brazil: analysis of prognostic factors in a group of 70 patients. *Am J Clin Pathol* 128: 875–882.
12. Malpica L, Pimentel A, Reis IM, Gotuzzo E, Lekakis L, Komanduri K, Harrington T, Barber GN, Ramos JC, 2018. Epidemiology, clinical features, and outcome of HTLV-1-related ATLL in an area of prevalence in the United States. *Blood Adv* 2: 607–620.
13. Oliveira PD, Gomes Í, Souza VH, Pires EC, Arruda GB, Bittencourt A, 2017. Adult T-cell leukemia/lymphoma treatment in Bahia, Brazil. *Rev Bras Hematol Hemoter* 39: 13–19.