

Case Report

HTLV-1 Lymphomas, the Skin and its Histiogenesis

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Abstract

Human T-cell leukemia/lymphoma virus type 1 (HTLV-1) associated lymphomas, namely adult T-cell leukemia/lymphoma (ATLL), are endemic in the Caribbean. Generalized lymphadenopathy, hepatosplenomegaly, maculopapular rash and hypercalcemia are some of the distinguishing clinical features of this lymphoma. Historically much attention was given to the development of adult T-cell lymphoma (ATL) within lymph nodes with secondary involvement of the skin.

It has become apparent that the histiogenesis of ATL may originate within the skin (Primary ATL of the skin) with a protracted indolent course, which eventually involves lymph nodes and other organs.

Three cases of primary ATL of the skin are presented in support of this theory.

Keywords

ATL; Histiogenesis; Primary ATL of the Skin; HTLV-1

Introduction

The HTLV-1 virus is endemic in the Caribbean, Southwestern Japan, Central and South America and certain regions of Africa [1-5].

The virus is transmitted via blood transfusion, breast milk and sexual contact [6]. Like HIV infection, HTLV-1 is associated with immune suppression and carriers of HTLV-1 may be infested with Norwegian scabies [7] and *Strongyloides stercoralis* [8].

HTLV-1 is also associated with childhood infective dermatitis [9] the inflammatory condition HAM/TSP [10] and ATL or HTLV-1 lymphomas.

ATL/ HTLV-1 associated adult T-cell lymphomas is an aggressive type of leukemia/Lymphoma which has classically presented with generalized lymphadenopathy, hepatosplenomegaly, a maculopapular rash, peripheral blood leukocytosis, elevated levels of Lactate dehydrogenase and bilirubin, and intractable hypercalcaemia. [2,11,12].

It has been postulated that in HTLV-1 induced oncogenesis, viral proteins such as Tax and HBZ promote the proliferation of HTLV-1 infected cells and induce ATL in about 2-6% of carriers after a long latent period [13-15].

ATL is generally resistant to chemotherapy and carries a dismal prognosis particularly for the acute and lymphoma subtypes [16,17].

The histiogenesis of ATL is unclear and like morphologically similar non-HTLV1 non-Hodgkin's lymphomas, may originate from lymph nodes, which may secondarily involve other organs like the heart and the skin.

However there is a body of evidence, which shows the skin as the primary site of ATL evolution [18-20]. This latter form of ATL is primary cutaneous ATL. The three cases described from Trinidad W.I serve to support the histiogenesis of ATL from the skin.

Case Reports

Case 1

The history is that of a 58-year-old African female who developed a pruritic rash on her face and upper trunk since 2005. A clinical diagnosis was made on her presentation to the Dermatology clinic as acne conglobata, with a differential of granulomatous rosacea. She was treated with topical ointments and oral antibiotics with some good effect.

A skin biopsy then showed keratotic plugging and a dermal non-specific perivascular chronic inflammatory cell infiltrate. She migrated to another island and was lost to follow up for nine years. She reappeared in 2015 with pruritic papules involving her face (Figure 1) and upper trunk and a swelling in her scalp. Biopsy of the skin lesion from her back revealed a T-cell lymphoma. This was manifested as a band like lymphocytic infiltrate within the dermis amongst dermal blood vessels (Figure 2). This infiltrate was also seen in a mild patchy fashion in the deeper layers of the skin, and expressed CD3 positivity, CD5 positivity and CD45 positivity. Occasional cells expressed CD20 positivity.



Figure 1: Shows papules on the face of the 58-year-old female in case 1.

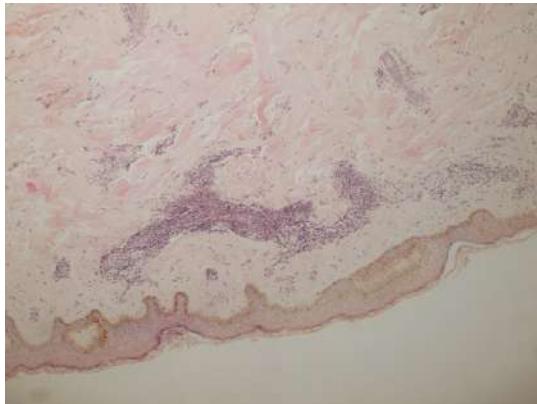


Figure 2: The biopsy of the papule shows band like infiltrate of lymphocytes in the dermis of the 58 year old female.

The bone marrow biopsy showed no infiltrate of lymphoma cells. She was tested for HTLV-1 and was positive. She was HIV negative. Whole body CT scan showed a 4cm

lymph node in the right infraclavicular region. No other organ showed involvement on CT scan.

Her Hb was 12.3 g/dL, HCT 38.1 uL, MCH 27.2 pg, MCV 84.8 fL, MCHC 32.4 g/dL, platelets 211 ($10^3/\mu\text{L}$), WBC 8.6 ($10^3/\mu\text{L}$), Neutrophils 31%. Lymphocytes 47% Eosinophil 2%. There were no atypical lymphocytes seen.

Her C-reactive protein (CRP) was positive, Rheumatoid Factor (RF) was positive and also her Antinuclear Antibody (ANA) was positive. Serum Calcium 10.3 mg/dL, LDH 169 U/L.

She was started on CHOP chemotherapy regimen with a repeat cycle every 21 days. She has been responding favorably to therapy. One of her daughters is also HTLV-1 positive but is free of HTLV-1 disease.

Case 2

This is a 52-year-old African female who presented with non-pruritic discoid plaques on both forearms since October 2014.

She was afebrile, and had no lymphadenopathy. She suffered no weight loss. Biopsy of the plaque showed a cutaneous T-cell lymphoma (Figures 3 and 4), which was CD3 and CD7 positive, and CD20 negative. She was HTLV-1 positive. She was HIV negative.

Skeletal survey revealed an absence of lytic lesions, and whole CT scan revealed a nodule of the left lobe of the thyroid gland, fibroid uterus, and an absence of internal lymphadenopathy.

Her bone marrow was hypercellular with lymphocytes bearing CD3 positivity (>20%), CD20 expression (<20%), and CD138 expression (>20%).

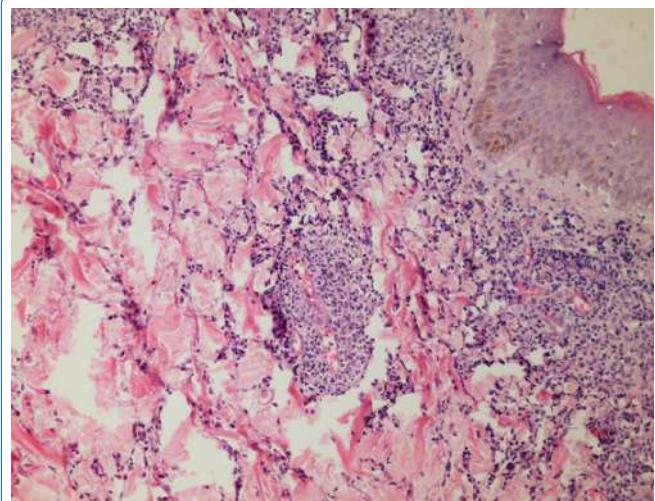


Figure 3: Shows the ATL cell infiltrate with the dermis and deeper layer of the skin in the 52-year-old female.

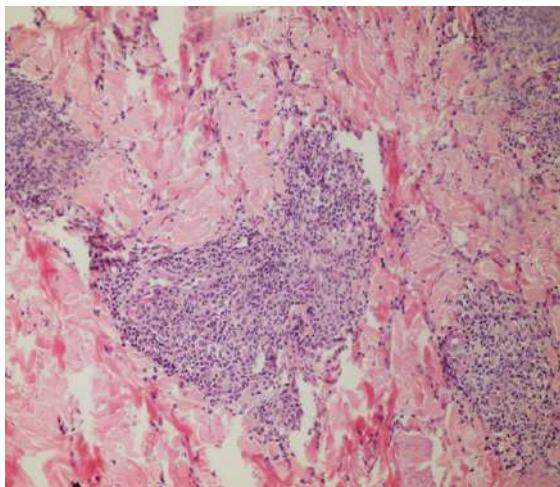


Figure 4: Shows a higher magnification of the biopsy from case 2. Note the perivascular infiltrate.

Her Hb was 8.5 g/dL, HCT 30.1 uL, MCV 62 fL, MCH 17.5 pg, MCHC 283 g/dL, Platelets 269 (10³/uL), LDH 158 U/L, Calcium 9.2 mg/dL, Total Protein 8.7 g/dL Albumin 4.2 g/dL, Globulin 4.5 g/dL TSH 1.52 mIU/L, IgG 2250 mg/dL, IgA 333 mg/dL, IgM 68 mg/dL-polyclonal gammopathy.

She was started on Zidovudine and Interferon therapy. In 2016 her plaques transformed into nodules (Figure 5).



Figure 5: Shows the nodules on the upper limb of the 52-year-old female.

Case 3

This is a 26-year-old African female who presented in 2015 with a history of having a hypo-pigmented rash for the past 6 months. These hypo-pigmented discoid patches had a generalized body distribution involving trunk face and limbs. They then were gradually transformed from hypo pigmented to a pigmented scaly macular rash. (Figures 6 and 7) Clinically diagnoses of Psoriasis, Dermatitis, and Mycosis Fungoides were made and she was treated with topical steroids.

In July 2015 a biopsy of the lesion from her back showed a cutaneous T-cell lymphoma, with CD3, CD5 and CD45

positivity. CD20 was negative. She was HTLV-1 positive. Her RF was positive, ANA positive, HIV negative.

Whole body CT scan showed no abnormality. Bone marrow biopsy showed no infiltration with lymphoma cells. Her Hb was 12.3 g/dL. WBC 5.3 (10³/uL) lymphocytes 42%, platelets 317(10³/uL), LDH 261 U/L, Calcium 8.0 mg/dL. IgG 1572 mg/dL, IgA 273 mg/dL, and IgM 178 mg-dL-polyclonal gammopathy.

She has been started on Zidovudine and interferon.



Figure 6: Shows the hypo-pigmented spots on the upper limb of the 26-year-old female.



Figure 7: Shows the hyper-pigmented macular rash on upper limb off the 26-year-old female.

Discussion

HTLV-1 lymphoma often presented with generalized lymphadenopathy and or a leukemic spill, hepatosplenomegaly, hypercalcaemia and a maculopapular rash. In the earlier years of its observance, little attention was given to the skin lesion in ATL [21,22] and it was considered to be a secondary accompaniment and stigmata of ATL. This presentation of ATL was seen most often in the 1980's and represented advanced or late presentation of the disease [2].

The three cases presented above are primary cutaneous HTLV-1 associated adult T-cell lymphomas [23,24]. Case 1 has

a 10-year progression of the disease, which started as papules, which now clinically demonstrates supra-clavicular nodal involvement and hypercalcemia. Case 2 started off as plaques but now has advanced to tumor nodules. Case 3 most likely bears the true histiogenesis of ATL lymphomas which begins with early macular lesions which transform into plaques and may then transform into tumor nodules with progressive involvement of other organs. These three cases resemble the smoldering type of ATL reported by Bittencourt et al. [19] and Lyra-Da-Silva et al. [20] in Brazil. Barring the HTLV-1 positivity, these cases clinically resemble mycoses fungoides by their indolent course evolving from patches to plaques and eventually tumor nodules, although epidermotrophism was not a feature of their histology. They may very well represent the histiogenesis of ATL.

The early presentation of ATL may very well be ill defined skin manifestations in HTLV-1 carriers, since the skin manifestation may have a protracted insidious course and may resemble other common dermatomes such as acne, rosacea, etc., before the advanced manifestation of ATL is seen. La Grenade et al. [9] in Kingston Jamaica described the clinical pathological and immunological features of Human T-Lymphocytic virus type 1 associated infective dermatitis in children. What in fact this group of workers was describing was the early manifestation of cutaneous ATL for these children were all HTLV-1 positive, and had dermatopathic lymphadenitis with palpable lymph nodes and T-cell activation with elevated CD4 and CD8. This group of workers earlier in 1991 described a case of infective dermatitis, which evolved into ATL after 17 years [25]. There have been similar reports of childhood infective dermatitis evolving into HAM/TSP and ATL in Brazil [26,27]. Goncalves et al [28] stated that HTLV-1 associated infective dermatitis might be an indolent HTLV-1 associated lymphoma [28]. These bodies of evidence support the notion that the skin is the primary site of ATL evolution. Yves et al. [29] reporting from Martinique on the characteristics of Adult T-Cell Leukemia/Lymphoma patients with long survival concur with the hypothesis that the skin tissue could be a primary, precocious and privileged location for ATL cell, and that infiltration of other tissues would therefore be secondary, delayed, and metastatic in nature.

The early presentation of ATL may very well be ill-defined skin lesions in HTLV-1 carriers, since the skin manifestations may have a protracted insidious course and may resemble other common dermatoses such as acne, rosacea, eczemas [27] or infective dermatitis [28].

Because of the fact that HTLV-1 positive carriers can have insidious skin manifestation of ATL, it should be mandatory that all HTLV-1 positive carriers be examined carefully for early skin manifestations of the disease. These early skin lesions should be biopsied and biomarker studies be performed to verify their pathogenesis, and treatment with Zidovudine and Interferon [30,31] commenced to halt the progression of the disease to its advanced stage. Education in the prevention

of the transmission of the HTLV-1 virus should be part of the public health drive to eradicate ATL in endemic regions [32].

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