MedCrave
Step into the World of Research

Journal of Human Virology & Retrovirology

Erythema Nodosum Caused by *Mycobacterium tuberculosis* in HTLV-1 Infected Patients

Abstract

HTLV-1 infection seems to increase the susceptibility to tuberculosis (TB), however in that HTLV-1 and TB co infected patients, skin lesions due to *Mycobacterium tuberculosis* have rarely been described. Erythema nodosum is a skin disorder clinically associated a subcutaneous nodules induced by various pathogens, drugs and other miscellaneous conditions. Here, were described two cases of HTLV-1 patients with recurrent Erythema nodosum associated with *M. tuberculosis*. One of the patients did not present any TB pulmonary symptoms or X-ray abnormalities. Skin culture, sputum and acid fast bacilli staining for mycobacterium were all negatives. The tuberculin skin test was strongly positives and the infection with *M. tuberculosis* was detected by qPCR at skin lesions. Both patients were treated for TB and the Erythema nodosum clinically ameliorated. In conclusion, these data reveals that Erythema nodosum in HTLV infected patients might be a clinical manifestation associated to cutaneous tuberculosis.

Keywords: HTLV-1; Tuberculosis; Erythema nodosum

Case Report

Volume 5 Issue 7 - 2017

Hayana Ramos Lima[1], Camila Ribeiro[2], Fernanda Saloum de Neves-Manta[3], Suellen Justo Maria Moreira[3], Milton Osório de Moraes[3], Sérgio Arruda[1]*, Edgar M Carvalho[1,2] and Maria de Lourdes Santana Bastos[2]

[1]Laboratory of Public Health (LASP), Gonçalo Moniz Research Institute, Brazil
[2]Immunology Service, Professor Edgard Santos University Hospital, Federal University of Bahia, Brazil
[3]Laboratory of Leprosy-Oswaldo Cruz Foundation (FIOCRUZ), Brazil

***Corresponding author:** Sérgio Arruda, Gonçalo Moniz Research Institute, Oswaldo Cruz Foundation (FIOCRUZ), R.Waldemar Falcão, n. 121. 40296-710, Salvador, BA, Brazil, Tel: +55 71 31762232; Email: sa@bahia.fiocruz.br

Received: March 24, 2017 | **Published:** November 08, 2017

Abbreviations: HTLV: Human T Lymphotropic Virus; TB: Tuberculosis; TST: Tuberculin Skin Test; HAM/TSP: HTLV-1 Associated Myelopathy or Tropical Spastic Paraparesis; ATL: Adult T-Cell Leukemia; HIV: Human Immunodeficiency Virus; Aghbs: Hepatitis B Surface Antigen; VDRL: Venereal Disease Research; Laboratory; ANA: Antinuclear Antibodies; INH: Ionized; PCR: Polymerase Chain Reaction; TNF: Tumor Necrosis Factor; IFN: Interferon; IL: Interleukin

Introduction

HTLV-1 infection has a worldwide distribution but the majority of patients infected by the virus are in Africa, Central and South American and in the Southern of Japan [1]. The HTLV-1 associated myelopathy or tropical spastic paraparesis (HAM/TSP) and Adult T-cell leukemia (ATL) are the main diseases related to the virus but they occur in less than 5% of infected subjects [2]. However, nowadays it is known that a large number of diseases and syndromes such as sicca syndrome, uveitis, HTLV-1 associated Arthropathy, chronic periodontitis, overactive bladder and erectile dysfunction have been related to HTLV-1 [3-5]. Moreover, HTLV-1 increases the susceptibility and modifies the clinical presentation of other infectious diseases such as helminths infections [6,7] tuberculosis [8] and fungal infections [9,10]. In countries where both tuberculosis and HTLV-1 are endemics, the association between these two diseases is highly relevant, as HTLV-1 increases in 2-4 fold the risk for tuberculosis [8,11]. It is not clear if HTLV-1 influences the severity of tuberculosis or the appearance of extra pulmonary tuberculosis, but there are more death among tuberculosis patients co-infected with HTLV-1 [12] and extra pulmonary tuberculosis have been reported in a few HTLV-1 infected subjects [13]. Erythema nodosum is characterized by nodular erythematosus lesions predominantly in the lower limbs.

The histopathological picture is a lobular panicullitis with lymphocyte inflammatory infiltrates around vessels, and areas of necrosis with granuloma infiltrates may also be documented [14]. The manifestation was initially described by Bazin in the XIX century and later it was associated to past history of tuberculosis [15] but there are other infectious and inflammatory causes of Erythema nodosum [16]. Skin manifestations are very common in HTLV-1 and while 79% of 191 patients may present xerosis, acquired ictuses and seborrhea dermatitis [17], more than 30% of 171 HTLV-1 infected subjects had superficial mycosis Dantas [10]. However, in these both large series of cases Erythema nodosum was not described [10,17]. In patients with HAM/TSP, Erythema nodosum was documented in 1 out 60 patients but there was neither histopathologic study, previous history of tuberculosis or information about the tuberculin skin test [18].

Here we report two cases of HTLV-1 infected ladies who developed a chronic picture of Erythema nodosum with documentation of DNA for *M. tuberculosis* in the nodule biopsied. In both of them there was no evidence of past or active pulmonary tuberculosis. Due to the association between tuberculosis and HTLV-1, the documentation of Erythema nodosum associated with *Mycobacterium tuberculosis* infection in patients with HTLV-1 point out for the necessity to look for extra pulmonary tuberculosis in HTLV-1 infected patients and to perform effective therapy anti-tuberculosis in these patients.

Case Presentation

Case 1

A59 years-old woman, diagnosed with HTLV-1 for 14 years, showed recurrent and painful erythematosus subcutaneous nodules for the last 9 years (Figure 1). Her medical history included a chronic infection with HCV, urinary disorders and neurogenic bladder; she was also scored as OSAME-0 for neurological test, since HTLV-1 diagnosis. The serological tests for HIV, AgHBs, VDRL, Chagas and ANA were all negatives. The first episode of Erythema nodosum was detected at lower limb, 5 years after HTLV-1 diagnosis and some months after the treatment with interferon against HCV. At this moment the patient was also submitted to a hysterectomy. The nodule disappears during a hypo chromic macules but new erythematosus nodules at face and buttocks one year later. At this time she was treated with prednisone and once more there was a remission of the nodules.

Two years after the first episode of Erythema nodosum, the patient reported pneumonia and the chest X-ray demonstrated a small calcified lymph node at pretracheal space, compatible with previous tuberculosis. The sputum baciloscopy was negative but the tuberculin skin test (TST) was strongly positive (18mm). Five years from the first episode of Erythema nodosum, new skin lesion were detected; those lesions were biopsied and histological diagnosed as paniculitis with inflammation and micro abscess, granulomas with caseous necrosis without vacuities (Figure 2). The Groccot and Faraco-Fite staining for fungi and Mycobacterial detection were both negative. She was treated for 6 months with isoniazid (INH; 100mg/daily). New skins lesions were again detected after 5 months after INH treatment.

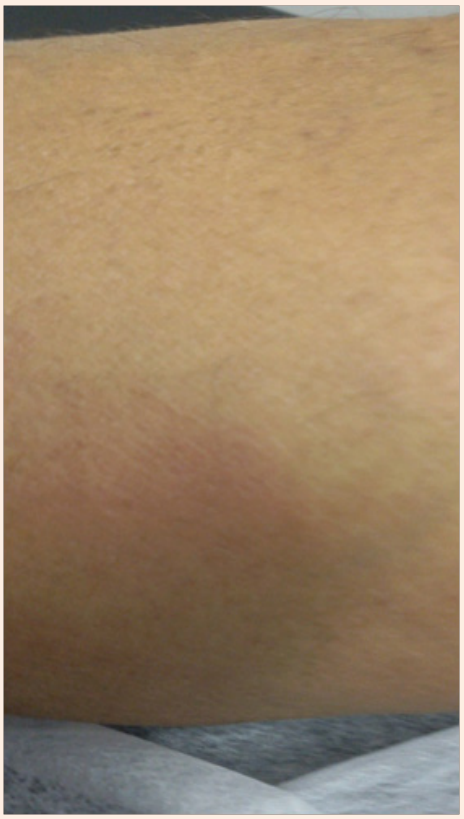

Figure 1: Skin Erythematosus macule.

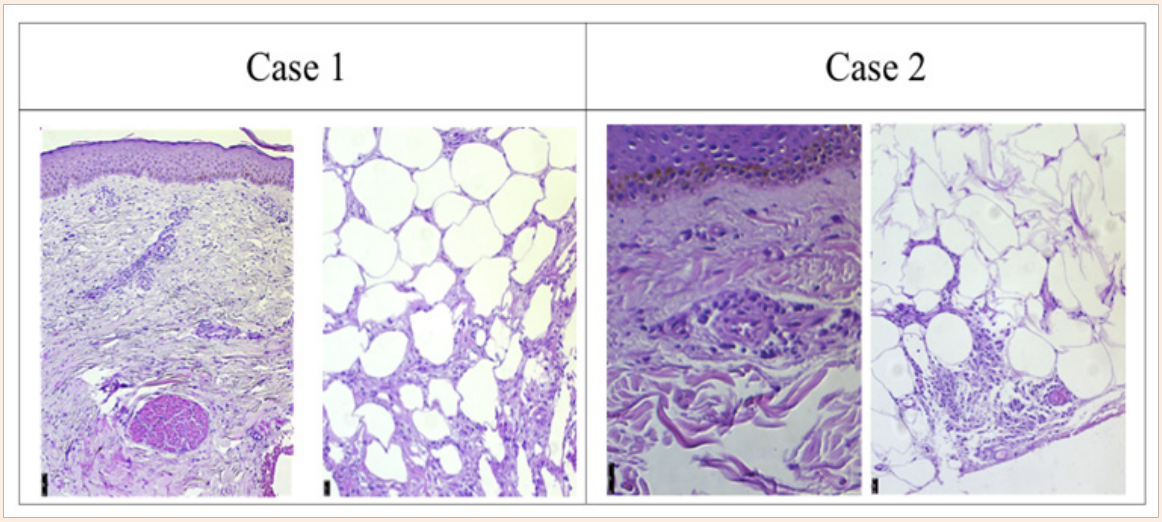

Figure 2: Histopathology analyses of skin lesions. The analysis reveals a chronic dermatitis in the superficial dermis and in subcutaneous associated a fibrous septal formation, diagnosed as paniculitis. Neutrophils forming abscess were observed in one biopsy. Caseous necrosis and vacuities were not detected in case 1. Fungi and mycobacterium staining were negative in both four biopsies.

Case 2

A68 years-old woman, diagnosed with HTLV-1 for 11 years, showed recurrent erythematosus subcutaneous nodules for the last years (Figure 3). Her medical history included xerostomia, chronic urinary infection and her neurological test was scored as OSAME-1. The serological tests for HIV, AgHBs, HCV, VDRL, Chagas and ANA were all negatives. She also presented a macule at shoulder that was previously histological described as amyloidosis and unspecific dermatitis. After 3 years of the HTLV-

1 diagnosis, she had multiples Erythema nodosum. The skin lesions were biopsied and a paniculitis was observed, without any caseous necrosis. In addition, Mycobacterial cultures and staining to acid fast bacilli in the skin lesions were both negatives. Despite of the absence of pulmonary symptoms, it was performed the treatment with ionized 300mg/daily for 4 months. She remained asymptomatic for the next 3 years, when new skin lesions were detected. At this time, TST was performed and it was strongly positive (21mm).

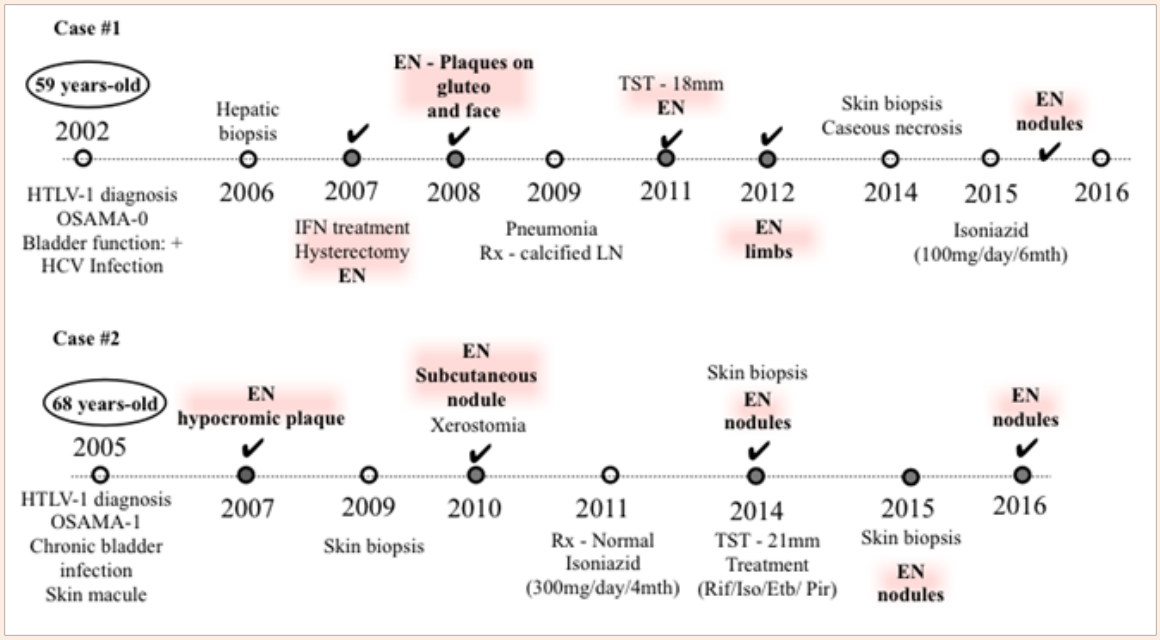

Figure 3: Timeline of HTLV-1 and EN clinical evolution. EN- Erythema nodosum.

No any pulmonary symptoms or abnormality at chest X-ray were detected and the patient was submitted to treatment with rifampicin, pyrazinamide and ethambutol for 6 months. Skin lesions remained for 11 months after the beginning of the antibacterial treatment and five months after the end of treatment the lesions changed to hypo chromic macules. In order to confirm the for *Mycobacterium tuberculosis* infection, PCR were conducted from skin samples at paraffined blocks. Sections were obtained from formalin-fixed paraffin-embedded skin lesions according to previously described [19]. The DNA extraction was performed with the DN easy Blood and Tissue Kit (Quiagen, Inc., Valencia, CA), according to manufacturer's recommendations. DNA quantification was performed by Real-Time PCR and the 16S rDNA and IS6110 were targeted. Briefly, reaction mixtures were prepared in triplicate for each target and exposed to 50ºC for 2 min, 95ºC for 10 min and 40 cycles of denaturing for 15s at 95ºC and annealing/extension at 60ºC for 60s using TaqMan (Appplied Biosystems) probe labeled with 6-carboxyfluorescein for *Mycobacterium leprae* 16S gene (5'- CAT CCT GCA CCG CA - 3') and primer set (sense 5'- GCA TGT CTT GTG GTG GAA AGC-3' and anti-sense 5' - CAC CCC ACC AAG CTG AT -3') or *Mycobacterium tuberculosis* IS6110 probe (5'- TCG GAA GCT CCT ATG AC -3') and primer set (sense 5'-GATCGTCTCGGCTAGTGCATT-3' and anti-sense 5'-CCGAGGCAGGCATCCA-3). The fluorescence accumulation data were captured by StepOne Sequence Detection System software (Life Technologies) and the ΔRn values were extracted to estimate the cycle threshold (Ct), which was compared to the standard curves, constructed using *M. leprae* and *M. tuberculosis* DNA. The qPCR results were classified as positive or negative.

A result was considered positive if the detected amplification resulted in a Ct value that was lower than at the 38th cycle for at least one amplified target gene. For both cases, the qPCR was positive for *M. tuberculosis* and negative for *M. leprae*. Skin samples of both patients were negative for others mycobacterium, except one of the skin samples from case #1, biopsied at 2014, whose bacteria specie determination was performed trough gene sequencing and it was indicated the presence of *Mycobacteria kansasii* (96%), a non tuberculous mycobacterium which has also been associated with pulmonary infections.

Discussion

The Erythema nodosum is an inflammatory condition associated with a variety of causes including tuberculosis, streptococcus infections, hepatitis C virus, inflammatory diseases, sarcoidosis, leprosy and drugs [14,16]. However, the etiologic agent of Erythema nodosum is rarely documented. The HTLV-1 infection induces an exaggerated inflammatory response with production of pro-inflammatory cytokines [20,21]. More recently tuberculosis has been reported more frequent in HTLV-1 than in seronegative controls [22]. Herein, we describe two patients infected with HTLV-1 with Erythema nodosum caused by *M. tuberculosis*.

The association between tuberculosis and HTLV-1 infection has been reported for over 10 years, but the mechanisms for the increased susceptibility of HTLV-1 infected subjects to develop tuberculosis is not known, and most of these patients present pulmonary tuberculosis [8,11,23]. Erythema nodosum are not frequently reported in HTLV-1 [10,17]. The histopathologic analysis of the nodular lesion showed a panicullitis typical of Erythema nodosum and in one case neutrophilia inflammatory infiltrate and granulomas with caseous necrosis were detected. Similar to other cases previously reported of Erythema nodosum in patients with tuberculosis, fast acid bacillus were not detected [24,25] and the culture for *M. tuberculosis* was negative in both patients.

The patients also denied previous history of tuberculosis and chest X rays were normal. However, in both cases the TST was strongly positive. There are discordant results about the use of TST to detect *M. tuberculosis* infection in subjects infected with HTLV-1. In studies performed in elderly Japanese, the sensitivity of the TST was lower among HTLV-1 infected subjects than in controls [26]. However, in three different studies performed in Brazil the TST was positive in a large percentage of HTLV-1 infected subjects without or with history of tuberculosis, indicating that there is no impairment in the delayed type hypersensitivity response to Mycobacterial antigens in HTLV-1 infected subjects [11,23].

Erythema nodosum is an inflammatory reaction and in leprosy patients with Erythema nodosum the pathogenesis of the disease has been associated with TNF production [27]. Actually thalidomide and pentoxyfilline, drugs known to decrease TNF production, attenuate clinical manifestations of Erythema nodosum in patients with lepromatosus leprae [28,29]. The HTLV-1 infects a variety of immune cells as TCD4, TCD8, B cells, macrophages and dendritic cells [30]. As the Tax gene of the virus transactivates human genes in infected cells, HTLV-1 is associated with high production of pro-inflammatory cytokines such as TNF, IFN-γ, IL-1 and IL-6 [31]. The production of these inflammatory cytokine is higher in patients with HAM/TSP than in HTLV-1 carriers (Santos 2006, Santos 2012) but HTLV-1 carriers may also produce high levels of these molecules [32]. However, in the reviewed literature we only found a report of one case of Erythema nodosum in HTLV-1 infected subjects [33]. In this specific case the patient had HAM/TSP and the cause of the erythema nodosum was not determined.

The treatment of Erythema nodosum without a defined cause is usually performed with corticosteroids, but although remission usually occurs, there is a relapse weeks or months after the use of the anti-inflammatory drug [15]. Based on the detection of a caseous necrosis in one of our cases the patient was treated with ionized without clinical response. Later therapy with anti-tuberculosis drugs induced a remission of the manifestation in both cases. These reported cases indicate that in addition to pulmonary tuberculosis HTLV-1 infected patients may present Erythema nodosum as a manifestation of the *M. tuberculosis* infection. Moreover due to the association between tuberculosis and HTLV-1 and because HTLV-1 infection induce a potent inflammatory reaction, Erythema nodosum should be looked for in patients infected with HTLV-1 and *M. tuberculosis* infection should be considered as the cause of Erythema nodosum in these patients.

Acknowledgment

We thank Hospital Especializado Octávio Mangabeira, IBIT (Instituto Brasileiro de Pesquisa em Tuberculose and Centro de Referência em Tuberculose Hélio Fraga- Fiocruz, Rio de Janeiro for M. tuberculosis cultures.

Conflict of Interest

None.

References

1. Gessain A, Cassar O (2012) Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 3: 388.
2. Gonçalves DU, Proietti FA, Ribas JG, Araújo MG, Pinheiro SR, et al. (2010) Epidemiology, treatment, and prevention of Human T-Cell Leukemia Virus Type 1-associated diseases. Clin Microbiol Rev 23(3): 577-589.
3. Caskey MF, Morgan DJ, Porto AF, Giozza SP, Muniz AL, et al. (2007) Clinical Manifestations Associated with HTLV Type I Infection: A Cross-Sectional Study. AIDS Res Hum Retroviruses 23(3): 365-371.
4. Castro NM, Rodrigues W Jr, Freitas DM, Muniz A, Oliveira P, et al. (2007) Urinary symptoms associated with human T-cell lymphotropic virus type I infection: evidence of urinary manifestations in large group of HTLV-I carriers. Urology 69(5): 813-818.
5. Garlet GP, Giozza SP, Silveira EM, Claudino M, Santos SB, et al (2010) Association of human T lymphotropic virus 1 amplification of periodontitis severity with altered cytokine expression in response to a standard periodontopathogen infection. Clin Infect Dis 50(3): e11-88.
6. Neva FA, Filho JO, Gam AA, Thompson R, Freitas V, et al. (1998) Interferon-gamma and interleukin-4 responses in relation to serum IgE levels in persons infected with human T lymphotropic virus type I and Strongyloides stercoralis. J Infect Dis 178(6): 1856-1859.
7. Porto AF, Santos SB, Alcântara L, Guerreiro JB, Passos J, et al. (2004) HTLV-1 modifies the clinical and immunological response to schistosomiasis. Clin Exp Immunol 137(2): 424-429.
8. Marinho J, Galvão-Castro B, Rodrigues LC, Barreto ML (2005) Increased risk of tuberculosis with human T-lymphotropic virus-1 infection: a case-control study. J Acquir Immune Defic Syndr 40(5): 625-628.
9. Gonçalves DU, Guedes AC, Proietti AB, Martins ML, Proietti FA, et al. (2003) Dermatologic lesions in asymptomatic blood donors seropositive for human T cell lymphotropic virus type-1. Am J Trop Med Hyg 68(5): 562-555.
10. Dantas L, Netto E, Glesby MJ, Carvalho EM, Machado P (2014) Dermatological manifestations of individuals infected with human T cell lymphotropic virus type I (HTLV-I). Int J Dermatol 53(9): 1098-102.
11. de Lourdes Bastos M, Osterbauer B, Mesquita DL, Carrera CA, Albuquerque MJ, Silva, L, et al. (2009) Prevalence of human T-cell lymphotropic virus type 1 infection in hospitalized patients with tuberculosis. Int J Tuberc Lung Dis 13(12): 1519-1523.
12. Pedral-Sampaio DB, Martins Netto E, Pedrosa C, Brites C, Duarte M, et al. (1997) Co-infection of tuberculosis and HIV/HTLV retroviruses. Frequency and prognosis among patients admitted in a Brazilian hospital. Braz J Infect Dis 1(1):31-35.
13. Menna-Barreto M, Machado DC (2006) Tuberculous meningoencephalomyelitis and coinfection with HTLV-I + HTLV-II: case report. Arq Neuro-Psiquiatr 64(1): 125-127.

14. Segura S, Pujol RM, Trindade F, Requena L (2008) Vasculitis in erythema induratum of Bazin: a histopathologic study of 101 biopsy specimens from 86 patients. J Am Acad Dermatol 59(5): 839-851.

15. Mascaró JM Jr, Baselga E (2008) Erythema induratum of bazin. Dermatol Clin 26(4): 439-445.

16. Requena L, Yus ES (2008) Erythema nodosum. Dermatol Clin 26(4): 425-438.

17. Okajima R, Oliveira ACP, Smid J, Casseb J, Sanches JA Jr (2013) High Prevalence of Skin Disorders among HTLV-1 Infected Individuals Independent of Clinical Status. PLoS Negl Trop Dis 7(11): e2546.

18. Koufakis T, Gabranis I (2014) Erythema nodosum leads to the diagnosis of pulmonary tuberculosis. Pan Afr Med J 18: 291.

19. Martinez AN, Britto CF, Nery JA, Sampaio EP, Jardim MR, et al. (2006) Evaluation of real-time and conventional QPCR targeting complex 85 genes for detection of Mycobacterium leprae DNA in skin biopsy samples from patients diagnosed with leprosy. J Clin Microbiol 44(9): 3154-3159.

20. Santos SB, Porto AF, Muniz AL, Luna T, Nascimento MC, et al. (2006) Modulation of T cell responses in HTLV-1 carriers and in patients with myelopathy associated with HTLV-1. Neuroimmunomodulation 13(3): 145-151.

21. Santos SB, Oliveira P, Luna T, Souza A, Nascimento M, et al. (2012) Immunological and viral features in patients with overactive bladder associated with human T-cell lymphotropic virus type 1 infection. J Med Virol 84(11): 1809-1817.

22. Grassi MF, Dos Santos NP, Lírio M, Kritski AL, Chagas Almeida M da C, et al. (2016) Tuberculosis incidence in a cohort of individuals infected with human T-lymphotropic virus type 1 (HTLV-1) in Salvador, Brazil. BMC Infect Dis 16: 491.

23. Bastos M de L, Santos SB, Souza A, Finkmoore B, Bispo O, et al. (2012) Influence of HTLV-1 on the clinical, microbiologic and immunologic presentation of tuberculosis. BMC Infect Dis 12: 199.

24. Sharma S, Sehgal VN, Bhattacharya SN, Mahajan G, Gupta R (2015) Clinicopathologic spectrum of cutaneous tuberculosis: a retrospective analysis of 165 Indians. Am J Dermatopathol 37(6): 444-450.

25. Chen S, Chen J, Chen L, Zhang Q, Luo X, et al. (2013) Mycobacterium tuberculosis infection is associated with the development of erythema nodosum and nodular vasculitis. PLoS One 8(5): e62653.

26. Murai K, Tachibana N, Shioiri S, Shishime E, Okayama A, et al. (1990) Suppression of delayed-type hypersensitivity to PPD and PHA in elderly HTLV-I carriers. J Acquir Immune Defic Syndr 3(10): 1006-1009.

27. Lockwood DNJ, Suneetha L, Sagili KD, Chaduvula MV, Mohammed I, et al. (2011) Cytokine and Protein Markers of Leprosy Reactions in Skin and Nerves: Baseline Results for the North Indian INFIR Cohort. PLoS Negl Trop Dis 5(12): e1327.

28. De Carsalade GY, Achirafi A, Flageul B (2003) Pentoxifylline in the treatment of erythema nodosum leprosum. J Dermatol 30(1): 64-88.

29. Sales AM, de Matos HJ, Nery JA, Duppre NC, Sampaio EP et al. (2007) Double-blind trial of the efficacy of pentoxifylline vs thalidomide for the treatment of type II reaction in leprosy. Braz J Med Biol Res 40(2): 243-248.

30. Dutartre H, Clavière M, Journo C, Mahieux R (2016) Cell-Free versus Cell-to-Cell Infection by Human Immunodeficiency Virus Type 1 and Human T-Lymphotropic Virus Type 1: Exploring the Link among Viral Source, Viral Trafficking, and Viral Replication. J Virol 90(17): 7607-7617.

31. Peloponese JM Jr, Yeung ML, Jeang KT (2006) Modulation of nuclear factor-κB by human T cell leukemia virus type 1 tax protein: Implications for oncogenesis and inflammation. Immunol Res 34(1): 1-12.

32. Carvalho EM, Bacellar O, Porto AF, Braga S, Galvão-Castro B, et al. (2001) Cytokine profile and immunomodulation in asymptomatic human T-lymphotropic virus type 1-infected blood donors. J Acquir Immune Defic Syndr 27(1): 1-6.

33. Kaneko Y, Tatsuno K, Fujiyama T, Ito T, Tokura Y (2015) Recurrent Facial Erythema with Cytotoxic T Cell Infiltration as a Possible Reactive Eruption in a Human T-Cell Lymphotropic Virus Type 1 Carrier. Case Rep Dermatol 7(2): 95-99.

Citation: Lima HR, Ribeiro C, Neves-Manta FS, Moreira SJM, Moraes MO et al. (2017) Erythema Nodosum Caused by *Mycobacterium tuberculosis* in HTLV-1 Infected Patients. J Hum Virol Retrovirol 5(5): 00181. DOI: 10.15406/jhvrv.2017.05.00181