Treatment of *Bartonella henselae* infection as a modifying factor of the immune response in Sezary syndrome.

Secamill EN; Adabo IG; Massuda Serrano JY, Stelini RF; Drummond MR; Velho PENF

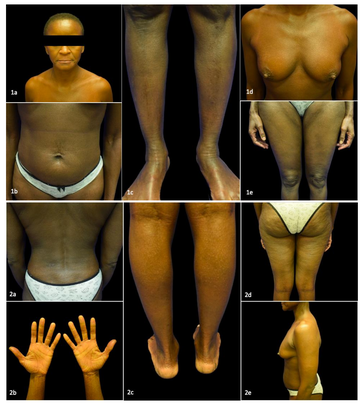
CONTACT: elisans42@gmail.com

FOCUS AREA: Challenging Cases of Cutaneous Lymphomas **Abstract Number #173**

Introduction

Sezary syndrome (SS) corresponds to the leukemic variant of cutaneous T-cell lymphoma (CTCL). It accounts for 2% of CTCL cases and has an estimated 5-year survival rate of 36%. SS is characterized by erythroderma, peripheral lymphadenopathy, and neoplastic T cells with cerebriform nuclei that are clonally related in the skin, lymph nodes, and peripheral blood[1]. There is a gap in knowledge regarding the factors that may influence the host immune response to these neoplastic cells.

Case Report



Figures 1 and 2: erythema, desquamation and infiltration affecting 90% of the body surface area

We report a case of a 56-year-old woman who complained of intense cutaneous pruritus associated with skin desquamation, lymph node enlargement, night sweats, and weight loss of 5 kg for two years. She was previously healthy and reported owning a pet dog. Physical examination revealed erythroderma and lymphadenopathy in the cervical, supraclavicular, axillary, and inguinal chains, with lymph nodes measuring up to 3 centimeters (figures 1 and 2).

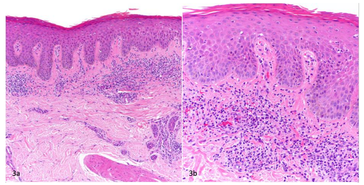


Figure 3 A and B: Hematoxylin-eosin stain: hyperkeratosis, regular acanthosis, some epidermotropic lymphocytes and subepidermal lymphoid infiltration.

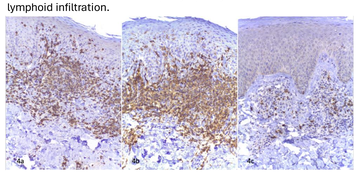


Figure 4 A, B and C: These lymphocytes show expression of CD3 (4A) and CD4 (4B) and they are negative for CD8 (4C).

Skin biopsies were performed, and histopathological examination revealed a lichenoid infiltrate of small to medium-sized lymphocytes with cerebriform nuclei and epidermotropism (figure 3). These cells exhibited expression of CD2, CD3, CD5, CD7, and CD4 (figure 4). Laboratory tests showed leukocytosis (23,030 cells/mm3) and lymphocytosis (18,447 cells/mm3), peripheral blood immunophenotyping revealed 68.6% abnormal T lymphocytes (CD4+ CD26-) and negative serology for HTLV-1 and HIV. Diagnosis of Sèzary syndrome (SS) was established. Patient was treated with weekly intramuscular methotrexate (25 mg), NB-UVB phototherapy, and daily doxepin (50 mg) for pruritus control, resulting in partial reduction of cutaneous infiltration, and partial improvement of the leukocytosis (14,710 cells/mm3) and lymphocytosis (11,290 cells/mm3) after 18 months of treatment. As part of a research protocol, patient underwent *Bartonella* sp. detection in blood and skin samples using polymerase chain reaction (PCR). *Bartonella henselae* DNA was detected by species-specific PCR targeting the *gltA* gene in both samples. She was prescribed doxycycline 100 mg bid for 8 weeks. Patient resolved pruritus and showed a 90% improvement of the remaining erythema and scaling. Phototherapy and doxepin were discontinued, and methotrexate was reduced to 15 mg weekly. Patient remains almost clear on methotrexate after one year of antibiotic treatment; blood count showed 7690 leukocytes/mm^3, 3972 lymphocytes/mm^3 with abnormal lymphocytes (CD4+ CD26-) decreasing to 48.28% of total leukocytes.

Case Report

Figure 5: Remission of erythema and infiltration, with minimal desquamation in the thighs.

Discussion

Bartonella sp. have developed mechanisms to evade the immune response, allowing chronic infections to establish. These mechanisms include avoiding recognition by the immune system and modulating the host's immune response[3]. *B. quintana*´s lipopolysaccharide component of the outer membrane acts as an antagonist of Toll-like receptor 4, inhibiting the expression of cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF) α[3]. *B. quintana* can also induce dendritic cells and mononuclear cells to secrete IL-10[3]. In patients with chronic bacteremia by *B. bacilliformis*, there is reduction in cytokines associated with the T helper 1 response, such as hepatocyte growth factor, IL-12, IL-6, and IFN-gamma-inducible protein 10[4]. In a canine model with bacteremia caused by *Bartonella vinsonii berkhoffii*, there was a sustained reduction in CD8 T lymphocytes, decreased antigen presentation, and reduced macrophage activity[5]. In cats, *B. henselae* infection results in a reduction in the number of CD4+ cells[6]. *B. henselae* can, through the STAT3 pathway, decrease the secretion of the pro-inflammatory cytokine TNF- α and increase the secretion of the anti-inflammatory cytokine IL-10[7]. This pathway is known to be hyperactivated in advanced CTCL as well. Lindahl *et al*. conducted research investigating the effect of staphylococcal enterotoxin on malignant and non-malignant T cells ex vivo. They found that this toxin can promote STAT3 activation, IL-2 receptor expression, and proliferation of primary malignant T cells. Additionally, they treated 8 patients with advanced CTCL with intravenous cephalosporin and metronidazole for ten days, and combined amoxicillin and clavulanate for 14 days. They observed a decreased expression of mRNA of STAT3 and IL-2 α receptor in skin lesions in all patients after treatment[8]. We could not find any research of this kind regarding *B. henselae*. Our patient experienced an improvement greater than we expected after the antibiotic treatment. The correlation between immunomodulation caused by *B. henselae* infection and worsening of SS in infected patients is not well-established. A shift to the T helper 2 response induced by the bacterial infection may hinder malignant cell eradication and enable lymphoma dissemination, and antibiotic therapy targeting these bacteria may revert this effect. Therefore, further research is needed to understand this relationship and determine the impact of *Bartonella* sp. infection on SS.

References: 1. Sanches JA, Cury-Martins J, Abreu RM, Miyashiro D, Pereira J. Mycosis fungoides and Sézary syndrome: focus on the current treatment scenario. An Bras Dermatol. 2021;96:458–71. 2. Lins KA, Drummond MR, Velho PENF. Cutaneous manifestations of bartonellosis. An Bras Dermatol. 2019 Sep-Oct;94(5):594-602. 3. Jin X, Gou Y, Xin Y, Li J, Sun J, Li T and Feng J. Advancements in understanding the molecular and immune mechanisms of Bartonella pathogenicity. Front. Microbiol. 2023;14:1196700. doi: 10.3389/fmicb.2023.1196700. 4. Pons MJ, Gomes C, Aguilar R, Barrios D, Aguilar-Luis MA, Ruiz J, Dobaño C, Valle-Mendoza J, Mancuilli G. Immunosuppressive and angiogenic cytokine profile associated with Bartonella bacilliformis infection in post-outbreak and endemic areas of Carrion's disease in Peru. PLoS Neglected Trop Dis 2017;11(6): e0005684. 5. Peppalardo BL, Brown TT, Tompkins M, Breitschwerdt EB. Immunopathology of Bartonella vinsonii (berkhoffii) in experimentally infected dogs. Vet Immunol Immunopathol 2001;83(3–4):125–47. 6. Kabeya H, Umehara T, Okanishi H, Tasaki I, Kamiya M, Misawa A, Mikami T, Maruyama S. Experimental infection of cats with Bartonella henselae resulted in rapid clearance associated with T helper 1 immune responses. Microbes Infect. 2009;11, 716–720. 7. Sarg I, Schmutz C, Lu YY, Fromm K, Siewert L K, Bogli A, Strack K, Harms A, Dehio C. A Bartonella effector acts as signaling hub for intrinsic STAT3 activation to trigger anti-inflammatory responses. Cell Host Microbe 2020;27(3):476–85.e7. 8. Lindahl LM, Willerslev-Olsen A, Gjerdrum LMR, et al. Antibiotics inhibit tumor and disease activity in cutaneous T-cell lymphoma. Blood. 2019; 134(13): 1072-1083.