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

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

We report the case of a 56-year-old black woman, complaining of intense cutaneous pruritus and generalized scaling, lymphadenopathy, a 5 kg weight loss and nocturnal sweating for two years. Laboratory tests showed leukocytosis (23030 cells/mm3) and lymphocytosis (18447 cells/mm3), peripheral blood immunophenotyping revealed 68.6% abnormal T lymphocytes (CD4+ CD26-) and negative serology for HTLV-1.

On physical examination, there was erythroderma, lymphadenopathy in cervical, supraclavicular, axillary, and inguinal chains, measuring up to 3 centimeters. Skin biopsies and histopathological examination revealed a lichenoid infiltrate of small to medium-sized lymphocytes with cerebriform nuclei and epidermotropism, positive for CD2, CD3, CD5, CD7, and CD4. Diagnosis of 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.

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, confirmed by sequencing. She was prescribed doxycycline 100 mg bid for 8 weeks. Patient resolved pruritus and improved erythema and scaling. Phototherapy and doxepin were discontinued. Patient remains almost clear on methotrexate, with abnormal lymphocytes decreasing to 48.28% of total 7690 leukocytes/mm3.

Discussion

Bartonella spp. are Gram-negative, fastidious bacilli adapted to a wide variety of reservoir mammals hosts. These bacteria are capable of infecting and surviving within erythrocytes, resulting in prolonged and recurrent infection. Clinical manifestations include angioproliferative forms such as bacillary angiomatosis and Carrion's disease, granulomatous forms like cat scratch disease, and asymptomatic forms[2].

Pappalardo *et al.* demonstrated sustained reduction in CD8 T lymphocytes, decreased antigen presentation, and reduced macrophage activity in canine model with bacteremia for *Bartonella vinsonii*[3]. Furthermore, Sorg *et al.* suggest that bacteremia by *B. henselae* may, through the STAT3 pathway, decrease the secretion of the pro-inflammatory cytokine TNF-alpha and increase the secretion of the anti-inflammatory cytokine interleukin (IL) 10 to establish its chronic infection[4]. Pons *et al.* demonstrated that 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[5].

The correlation between immunodeficiency caused by *B. henselae* infection and worsening of SS in infected patients is not well-established. Nevertheless, a shift to the T helper 2 response induced by the bacterial infection may hinder malignant cell eradication and enable lymphoma dissemination. Therefore, further research is needed to understand this relationship and determine the impact of *Bartonella spp.* 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. Pappalardo 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. https://doi.org/10.1016/s0165-2427(01) 00372-5.
4. Sorg I, Schmutz C, Lu YY, et al. 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.
5. Pons MJ, Gomes C, Aguilar R, et al. 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.