

Sjögren's Disease and Asymptomatic Anti-Ro/Ss-A Antibodies with Neonatal Lupus Associated with Human T-lymphotropic Virus Infection

Luísa Rodrigues Cordeiro MD¹, Marjorie Vieira Batista MD PhD², and Jozélio Freire de Carvalho MD PhD³

¹Department of Medicine, Escola Bahiana de Medicina, Salvador-BA, Brazil

²Department of Infectious Diseases, A.C. Camargo Cancer Center, São Paulo, Brazil

³Department of Internal Medicine and Diagnostic Support, Medical School, Federal University of Bahia, Salvador, Bahia, Brazil

KEY WORDS: autoimmune diseases, deltaretrovirus, human T-cell leukemia virus, human T-lymphotropic virus (HTLV-I), Sjögren's disease

IMAJ 2026; 28: 672–674

Human T-cell leukemia virus (HTLV) was first described in 1980 as a retrovirus known by its ability to infect CD4 T cells or macrophages, leading to a chronic infection that may develop into adult T-cell leukemia/lymphoma (ATLL) and chronic progressive myelopathy known as HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [1]. Viral transmission occurs from unprotected sexual intercourse, vertical transmission, and contact with a contaminated blood sample. There is evidence of an association between HTLV-1 infection and rheumatic diseases [2,3].

HTLV-1 infection has been associated with several rheumatic and autoimmune manifestations, including rheumatoid arthritis and Sjögren's disease, although a direct causal relationship remains uncertain [2,3]. These data suggest that severe viral infection presentations may lead to the development or exacerbation of previous ophthalmologic pathologies. In a systematic epidemiological

review, Schierhout and colleagues [2] showed that HTLV-1 infection was associated with a higher risk to develop rheumatoid arthritis and Sjögren's disease than all other rheumatological conditions.

In this article we report on two uncommon cases of a mother and a daughter infected with HTLV who subsequently developed autoimmune conditions.

PATIENT DESCRIPTION

CASE 1

A 41-year-old previously healthy female attended a consultation with a previous neonatal lupus gestation history in November 2016. The fetus had bradycardia and ascites followed by premature delivery at 24 weeks, progressing to fetal death. At that time, the patient denied arthralgia, arthritis, xerostomia, xerophthalmia, xeroderma, and parotiditis. Physical examination was unremarkable.

Laboratory tests revealed normal blood cell count, thyroid-stimulating hormone (TSH) of 0.94 mU/ml (normal range [nr] 0.3–4.0 mU/ml), free thyroxine 1.16 (nr 0.74–1.72 ng/dl), erythrocyte sedimentation rate of 8 mm/1st hour, and C-reactive protein 1.17 mg/L (nr < 5 mg/L). A positive

antinuclear antibody with a titer of 1:1280 and fine speckled pattern was detected, and an anti-Ro/SS-A > 280 U/ml (nr < 7 U/ml), and anti-La/SS-B 137 U/ml (nr < 7 U/ml) were also observed. Anti-dsDNA, anti-U1RNP, anti-Sm, anti-CCP, rheumatoid factor anti-Scl70, anticardiolipin, lupus anticoagulant, anti-thyroglobulin, anti-thyroid peroxidase, IgA and IgG anti-endomysium, anti-deaminated gliadin, anti-tissue transglutaminase, IgG and IgM anticardiolipin, and anti-beta2 glycoprotein I antibodies were all negative. Complements levels (CH100 of 217, C1q of 22, C3 of 97, and C4 of 17) were within the normal range. Thrombophilia tests were all negative and included factor V Leiden, mutant prothrombin, homocysteine, protein C and S, and anti-thrombin III. IgG for HTLV I and II was positive with a titer of 141.1 (nr < 1) and confirmed twice on different occasions. Polymerase chain reaction (PCR) for HTLV was negative.

The patient denied she had a blood transfusion. Serology for hepatitis B and C, HIV 1 and 2, Chagas disease, and syphilis were negative. IgG for Epstein-Barr, human cytomegalovirus, toxoplasmosis, and rubella was positive with negative IgM. Salivary gland scintigraphy showed reduced uptake and excretion on parotid and

submandibular glands. Schirmer test was 15 mm/5min in both eyes, and Rose Bengal showed a mild positivity on bulbar conjunctive in the two eyes.

Hydroxychloroquine 400 mg/day and omega-3, 2 g/day were initiated. A neurological and hematological evaluation was performed. Leukemia and neurological features linked to HTLV were excluded. After one year, the patient became pregnant. Obstetrical follow-up and serial fetal echocardiography were initiated with a normal fetus delivered at 39 weeks. No drugs except hydroxychloroquine and omega-3 were kept during pregnancy. The child's health parameters were normal. Electrocardiogram and echocardiography were unaltered, and no skin lesions were noted. Currently, the patient remains asymptomatic with positive antinuclear antibody, anti-Ro/SS-A, and anti-La/SS-B as well as positive IgG for HTLV.

CASE 2

A 67-year-old female with a past medical history of systemic hypertension, Hashimoto's thyroiditis, chronic headache, gastritis, and sleep apnea came to our private clinic due to mild dyspnea on efforts, sporadic dry cough, and fatigue started 3 months before. She was taking losartan 50 mg/day. She denied a history of smoking or tuberculosis. She also had a long-term history of mild xerostomia and xerophthalmia. Her physical examination showed 12 tender points, crepitation on her knees, and obesity. Laboratory tests revealed normal cell blood count, vitamin D of 21.9 ng/ml (nr > 30 ng/dl), TSH of 2.9 mU/ml, free thyroxine of 0.78 ng/dl, and anti-thyroglobulin 618 IU/ml (nr < 115 IU/ml).

A thorax x-ray was normal. Echocardiography showed mild diastolic

dysfunction and 24-hour ambulatory blood pressure monitoring was normal. Thyroid ultrasound revealed multiple nodules and simple cysts compatible with thyroiditis. A vitamin D 50,000 Iu/week supplementation and *Rhodiola rosea* 400 mg/day was prescribed.

After one month, she returned asymptomatic, with no dyspnea or dry cough. New laboratory data demonstrated vitamin D of 44.5 ng/ml. A positive IgG for HTLV 1 and 2 with a titer of 210 (nr < 1.0) was observed and confirmed twice on different occasions. PCR for HTLV was negative. She denied having a blood transfusion. Positive anti-Ro/SS-A (titer of 52 U/ml; nr < 7 U/ml) antibody was detected. Antinuclear antibodies, anti-dsDNA, anti-U1RNP, anti-Sm, anti-CCP, rheumatoid factor anti-Scl70, anticardiolipin, lupus anticoagulant, anti-thyroid peroxidase, IgA and IgG anti-endomysium, anti-deaminated gliadin, anti-tissue transglutaminase, IgG and IgM anticardiolipin, and anti-beta2 glycoprotein I, were all negative. Complement levels (C3 of 113 and C4 of 18) were within the normal range.

Salivary gland scintigraphy showed reduced uptake and excretion on submandibular glands. The salivary flow was reduced to < 0.1 ml. A Schirmer test was 8 mm in the right eye and 6 mm in the left eye, and Rose Bengal showed alterations compatible with sicca syndrome in both eyes with a score > 5. She denied a minor salivary gland biopsy.

A diagnosis of Sjögren's disease was determined. Hydroxychloroquine 400 mg/day, eye lubricants, and vitamin D3 were started. A neurological and hematological evaluation was performed. Leukemia and neurological features linked to HTLV were excluded. After 4

months, the patient was asymptomatic and denied xerostomia or xerophthalmia under lubricants and hydroxychloroquine.

COMMENT

Our article adds to the literature two new cases of patients with asymptomatic HTLV who developed autoimmune disorders. One of the cases was a previously asymptomatic patient with positive anti-Ro/SS-A that progressed to neonatal lupus and fetal death. The other case evolved to a diagnosis of Sjögren's disease.

Our cases add more material to an old discussion. Is HTLV-1 virus linked to the pathogenesis of autoimmune diseases or do autoimmune diseases develop faster and more aggressively in the presence of this viral infection?

HTLV-1 infection has been associated with several rheumatic and autoimmune manifestations, including rheumatoid arthritis and Sjögren's disease, although a direct causal relationship remains uncertain [2,3].

Even though immunological in vitro trials have shown considerable evidence that the unregulated production of cytokines and immune system mediators is biologically plausible to cause a higher incidence of autoimmune diseases in HTLV1 patients, there is not enough clinical evidence to support this theory. According to Schierhout and colleagues [2], there were approximately 14 diseases with significant associations or substantially elevated risk with HTLV-1 from single studies, including fibromyalgia, in a recent meta-analysis of rheumatoid arthritis, arthritis, and dermatophytosis. However, low-quality evidence and difficulties in ascertaining the time of acquisition and duration of infec-

tion and the diversity of factors that might moderate the immunological response to the virus were not considered in these studies, posing a critical limitation confirming the causality between the virus and autoimmunity [2].

Another variable to be considered is the higher epidemiological prevalence of autoimmunity and HTLV in women of childbearing age, an essential bias to these epidemiological studies. Genetically inherited factors to autoimmunity should also be considered in patients with a medical or familial history of previous autoimmunity.

Concerning the positivity for HTLV between mother and daughter, a possible explanation might be due to maternal-fetal transmission.

Viral infections could be associated with the activation of innate immunity and followed by an acquired immune response. The activation of innate immunity, led by interferon-gamma (IFN- γ), produced a virus infection. The induction of major histocompatibility complex is followed by antigen-specific autoreactive T cells. This hypothesis is supported by a series of 14 epidemiological and case-report studies in which HTLV-1-related genes and proteins were found in sera or salivary glands of patients diagnosed with Sjögren's disease [4].

Following the same rationale behind cytokine production by viruses and autoimmunity, various epidemiological studies did not find a

meaningful correlation between the manifestations in patients diagnosed with HTLV1 infection. Conversely, epidemiological evidence has not consistently demonstrated an association between HTLV-1 infection and systemic autoimmune diseases. Bailer and co-authors [5] analyzed 115 patients with connective tissue autoimmune diseases and other rheumatological disorders and failed to establish an association between HTLV-I/II infection and SLE, RA, or other rheumatological disorders.

Regarding neonatal SLE associated with HTLV-1 infection, we found no evidence or case reports in the scientific literature. To the best of our knowledge, our descriptions are the first cases to be reported.

Although more data from robust perspective studies (including a Sjögren's disease activity index) are needed to conclude the real link between autoimmunity and HTLV-1 infection, recent studies have shown an important correlation among these diseases. Higher incidence of rheumatoid arthritis and Sjögren's disease in patients with aggressive HTLV progression gives the scientific community an essential red flag toward the careful investigation of viral infection in rheumatological patients or rheumatological serum markers in chronic viral infected patients.

CONCLUSIONS

We described two patients with asymptomatic HTLV who developed autoimmune disorders linked to

anti-Ro/SS-A antibodies. These patients presented with signs showing an association between asymptomatic HTLV and autoimmune diseases. Most cases that have been reported exhibit severe cases of HTLV infection such as ATLL and TSP/HAM. Unfortunately, we did not perform a Western blot to determine the specific subtype of HTLV. Screening for infectious diseases in patients diagnosed with Sjögren's disease should be mandatory.

Correspondence

Dr. J.F. de Carvalho

Dept. of Internal Medicine and Diagnostic Support, Medical School, Federal University of Bahia, Salvador, Bahia 41810-080, Brazil

Phone: (55-71) 9187-1169

Email: jotafo@gmail.com

References

1. Futsch N, Mahieux R, Dutartre H. HTLV-1, the other pathogenic yet neglected human retrovirus: from transmission to therapeutic treatment. *Viruses* 2018; 10 (1): 1-25.
2. Schierhout G, McGregor S, Gessain A, Einsiedel L, Martinello M, Kaldor J. Association between HTLV-1 infection and adverse health outcomes: a systematic review and meta-analysis of epidemiological studies. *Lancet Infect Dis* 2020; 20 (1): 133-43.
3. Umekita K, Okayama A. HTLV-1 Infection and rheumatic diseases. *Front Microbiol* 2020; 11: 1-7.
4. Nakamura H, Shimizu T, Kawakami A. Role of viral infections in the pathogenesis of Sjögren's syndrome: different characteristics of Epstein-Barr Virus and HTLV-1. *J Clin Med* 2020; 9 (5): 1459.
5. Bailer RT, Lazo A, Harisdangkul V, et al. Lack of evidence for human T cell lymphotropic virus type I or II infection in patients with systemic lupus erythematosus or rheumatoid arthritis. *J Rheumatol* 1994; 21 (12): 2217-24.

Neither great poverty nor great riches will hear reason.

Henry Fielding (1707–1754), English writer and judge known for the use of humor and satire in his works

The art of life is to know how to enjoy a little and to endure much.

William Hazlitt (1778–1830), English essayist, drama and literary critic, painter, social commentator, and philosopher