A case of HIV-associated diffuse infiltrative lymphocytosis syndrome simulating primary Sjögren Syndrome and BALT Lymphoma

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ACTA REUMATOL PORT. 2015;40:68-71

ABSTRACT

Diffuse infiltrative lymphocytic syndrome (DILS) is a clinical identity that can be part of the spectrum of Human Immunodeficiency Virus (HIV) infection. It is characterized by sicca symptoms, parotid and lachrymal enlargement and extra-articular manifestations.

We report the case of a 60-years-old woman with clinical sicca syndrome in association with leukopenia, positive anti-nuclear antibody (ANA) and polyclonal hypergammaglobulinemia. During the follow-up the patient developed a mucosa-associated lymphoid tissue pulmonary neoplasm. Furthermore, the clinical diagnosis work-up revealed human immunodeficiency virus (HIV) positive serology.

In this particular case report, we must underline the clinical presentation of a sicca syndrome as a manifestation of the HIV infection, bearing in mind that, frequently, the differential diagnosis from other diseases, namely the Sjögren's syndrome, is a real challenge.

Keywords: Sjögren's syndrome; HIV; DILS

INTRODUCTION

The Sjögren's syndrome (SS) is estimated to be the second most common rheumatologic disorder affecting 0,1-4% of the population1. However sicca symptoms are much more common than SS[2].

A broad range of factors, such as inflammation, drugs, infection, radiation and autonomic nervous system dysfunction, can affect the lachrymal and salivary function3. One of the infectious agents that can manifest itself through a sicca syndrome is the human immunodeficiency virus (HIV). The involvement of the exocrine glands, when there is an infection by this agent, is well documented. However, the incidence of this clinical condition has been decreasing since the introduction of the highly active anti-retroviral therapy (HAART).

We report a case of a patient with keratoconjuntivitis sicca and oral dryness with a final diagnosis of HIV associated diffuse infiltrative lymphocytic syndrome (DILS). Firstly we emphasize the initial clinical and laboratorial features presented by this patient that mimic SS with absence of parotid or lacrimal gland engorgement characteristic of DILS and secondly the rare appearance of a mucosa associated lymphoid tissue pulmonary neoplasm (BALT) lymphoma in the context of an HIV infection, that can also be present later in the course of SS.

CASE REPORT

A 60-years-old female patient was referred to rheumatology outpatient clinic due to xerophthalmia, xerostomia, recurrent oral aphthosis, tooth decay, episodes of red eye, odynophagia, dysphagia, with frequent choking, and dyspareunia.

The physical examination revealed multiple malar telangiectasias, a left submandibular lymphadenopathy, painless and mobile, nonspecific jugal lesions, multiple dental caries and the lack of some dental pieces. The patient did not suffer from arthralgias/arthritis or peripheral oedema. The cardiopulmonary auscultation

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and the examination of the abdomen were normal and he was hemodynamically stable. Moreover, performing the Schirmer's test, we registered 25mm in the left eye and 30mm in the right eye (under treatment with artificial tears). The analytical evaluation showed lymphopenia (1100G/L), normal C3 and decreased C4 serum proteins. The erythrocyte sedimentation rate (ESR) was 35mm in the first hour and the C-reactive protein (CRP) was negative. The electrophoretic protein profile showed polyclonal IgG and IgM gammopathy.

The urinalysis reveled leukocyturia (2+) and erythrocyturia (1+). Urine culture was negative. Rheumatoid factor was negative and the anti-nuclear antibodies (ANA) were positive (1/320), with a dense and fine granular pattern.

During the follow-up, the patient presented a persistent cough, with hemoptoic expectoration. Thorax-X ray showed opacity at the middle level of the left hemithorax. Other complementary studies, such as the electrophoretic protein profile, showed an IgG kappa monoclonal gammopathy. The patient performed a thoracic computed tomography scan (CTS) that revealed changes in the permeability of the lingula and left lower lobe, compatible with a neoformation. A biopsy was performed and the result was consistent with the diagnosis of a bronchial-associated lymphoid tissue (BALT) lymphoma (CD20+ and CD3+).

Additionally, in the clinical evaluation, serologic analyses were performed, with a final diagnosis of HIV infection. Therefore, the patient started an anti-viral therapy (HAART).

The minor salivary gland biopsy, performed after the establishment of the anti-retroviral therapy, showed a lymphoplasmacytic infiltration, with the prevalence of CD3+ and with no apparent predominance of CD4+ or CD8+.

Following the initiation of the HAART therapeutics, there was an improvement of the oral aphthosis, chronic coughing, xerostomia and xerophthalmia. Moreover, there was an analytical improvement, with the normalization of the lymphocyte values (1880G/L) and normalization of the C4 serum protein values. The BALT lymphoma also regressed.

DISCUSSION

The clinical manifestations of the HIV infection are diverse and can mimic a large number of nosological entities, consisting in one of the conditions in which the diagnosis is more challenging, due to its form of presentation. Its clinical spectrum can range from an acute retroviral syndrome to an extended asymptomatic state or an advanced disease.

Since the advent of HIV infection, in the 80's, this condition has been associated with a broad range of rheumatic manifestations. HIV infected individuals have, in fact, an increased risk of developing musculoskeletal disease[3,4].

DILS syndrome was first described in 1989, by Itescu, as a discrete clinical entity[5]. This finding was proven in the advent of the knowledge of HIV infection, by the scientific community, and of the emergence of the first drug to control the disease, the zidovudine (AZT). At the time, HIV infection was a shortly fatal disease and the first signs and symptoms, for the characterization of DILS, arise from the objective observation of patients[6].

Sometimes, the differential diagnosis between DILS and the SS is difficult, for the two clinical entities have common manifestations and the patients present a subtle condition. However, there are clinical, laboratory and histological features that differentiate the two

TABLE I. COMPARISON BETWEEN SJOGREN SYNDROME AND DILS

	Sjögren syndrome	DILS
Sicca symptoms	Present – moderate parotid enlargement	Present – moderate to severe parotid enlargement
Extra-glandular manifestations	Mainly pulmonary, gastrointestinal, renal and neurologic	Frequent - mainly musculoskeletal, pulmonary, gastrointestinal and neurologic
Infiltration phenotype	CD4 lymphocyts	CD8 lymphocyts
Auto-antibodies	Present	Absent
HLA association	HLA DR3	HLA DRB1

Adapted from Basu D et al 2006 [6]

pathologies, which should be explored to achieve the proper diagnosis (Table I).

Firstly, in our case we emphasize the initial clinical presentation. Our patient had complains of dry mouth, dry eyes and left submandibular lymphadenopathy without parotid and or lacrimal glands enlargement.

The clinical aspects of DILS are well characterized. They include bilateral parotid and lacrimal glands engorgement, with symptoms of xerostomia and xerophthalmia[7], that mimic the most common form of presentation of Sjögren's syndrome. In patients with DILS, we should underline the disproportionately larger engorgement especially if they are not being treated with HAART[6,8]. However, our patient did not have parotid or lacrimal gland enlargement, thus widening the possible diagnosis. Furthermore, data from the first assessments in patients with this disease suggested that these patients, more than a sicca condition, also had several extra-glandular manifestations, such as pneumonia, lymphocytic hepatitis, renal tubular acidosis, paralysis of the seventh cranial nerve and lymphoma, emerging several years after sera-conversion and is thought to result from an immune host response to HIV infection. Some reports state that the group of patients with HIV/DILS shows a lower prevalence of opportunistic infections and slower progression to death[8-11], suggesting an excessive response of the host to the infection[5,8]. In our case the patient had lymphadenopathy that has a prevalence of 7%[2] in SS and in 14-19% in patients with DILS[6], thus favouring the diagnosis of the later.

Another extra-glandular manifestation that can complicate the SS and rise in association with HIV and DILS is lymphoma.

The prevalence of non-Hodgkin lymphoma, in patients with SS, is 4.3%, with an average age of diagnosis of 58 years and occurring 7.5 years after the SS diagnosis. The majority are MALT lymphomas of extra-nodal marginal location[12-14]. Regardless of its occurrence, the literature is not clear when concerning to the characterization of DILS and the progression to lymphomatous transformation. In the context of HIV virus type 1 infection, MALT lymphomas are usually rare[15]. Commonly, the associated conditions are B lymphomas of high or intermediate grade[16]. The development of indolent lymphomas (MALT) was associated with higher average counts of CD4+, with greater bone marrow involvement and greater average of survival[17]. In the current clinical case, a BALT lymphoma was diagnosed in the patient. Although rare in the context of HIV infection, the regression after the therapeutics with HAART is in favour of the infection.

TABLE II. PROPOSED DIAGNOSIS CRITERIA FOR DILS

1. HIV seropositivity
2. Bilateral salivary gland enlargement or xerostomia that has persisted for more than 6 months
3. Either histologically confirmed lymphocytic infiltration CD 8+ of the lacrimal or salivary glands, in the absence of granulomatous or neoplastic enlargement

Adapted from Rashmi M Mangati et al 2008 [19]

In the laboratorial analysis investigation we found positivity to ANA, but anti-Ro/SSA and anti-La/SSB antibodies, as well as rheumatoid factor were negative. This could also add the differential diagnosis between the two entities, since the frequency of anti-Ro/SSA and anti-La/SSB antibodies, as well as rheumatoid factor, is scarce in DILS syndrome but not in Sjögren syndrome[6].

The salivary gland biopsy shows infiltrating CD4+ lymphocytes, in the SS, while in DILS the infiltrating lymphocytes are CD8+[6,8,18]. This characteristic was the hallmark for the final diagnosis, in the period before the highly active anti-retroviral therapy (HAART). Nowadays, because almost all patients are treated with this therapy, so the biopsy can appear normal[19] as revealed in the biopsy that we perform in our patient. In such cases the 67Ga scintigraphy procedure can be useful for the differential diagnosis[20], although it was not performed in this case. Moreover, in HAART treated patients, considering that one of the drugs used are protease inhibitors, parotid lipomatosis may arise the scintigram is also useful for its diagnosis[20,21].

Another difference is the association with the HLA locus. Genetic studies revealed susceptibility to the HLA DRB1, more frequently to HLA DRB1*1102, and DRB1*1301 in patients with DILS. On the other hand, the Sjögrens syndrome is strongly associated with the presence of HLA-DR3[22].

Nevertheless, we assumed a diagnosis of DILS (Table II – proposed diagnostic criteria for DILS), due to the presence of sicca syndrome, lymphadenopathy, absence of anti-Ro/SSa, anti-La/SSb, rheumatoid factor and an excellent response to anti-retroviral therapy: recovery from the xerostomia, xerophthalmia and oral aphthosis, regression of the BALT lymphoma and nor-

malization of laboratory parameters. Note that, by itself, the HIV infection is an exclusion criterion of the diagnosis of SS[23].

The therapeutic basis of this syndrome is mainly the anti-retroviral drugs (that were applied in our case report), which may be associated with a low-dose of corticosteroids[8]. This strategy may be effective in the treatment of the parotid involvement, of the sicca condition and of the neuropathy. Higher doses (60 mg/day of prednisone) are required when there is an involvement of major organs that endanger patient's life such as in interstitial pneumonitis[24].

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