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Sicca Syndrome and HTLV-I–Associated Myelopathy/Tropical Spastic Paraparesis

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Purpose: The objective of this study is to describe the clinical and immunological aspects observed in patients with both human T-cell lymphotropic virus type I–associated myelopathy/tropical spastic paraparesis and ocular dryness.

Methods: In 15 such patients, clinical and biological examinations completed with a biopsy of secondary salivary glands were performed to assess the etiology of the ocular dryness.

Results: Histological study of the biopsy specimens indicated that 80% of the patients had grade 3 or grade 4 lesions, according to the Chisholm scale. Polyclonal hypergammaglobulinemia was found in 60% of patients and lymphocytic alveolitis in 80%. Three patients had past medical history of chronic uveitis.

Conclusions: All findings in these patients were compatible with Sjögren's syndrome; however, no immunological disorders characteristic of the syndrome were found. Tests for antinuclear antibodies and rheumatoid factor proved negative in all cases. **Jpn J Ophthalmol 1999;43:509–512**

Key Words: Dry keratoconjunctivitis; HTLV-I–associated myelopathy/tropical spastic paraparesis; Sjögren's syndrome.

Introduction

The human T-cell lymphotropic virus type I (HTLV-I), the first identified human oncogenic retrovirus, was isolated in the United States in 1980. The HTLV-I virus is the etiological agent of two distinct diseases: a leukemia called adult T-cell leukemia/lymphoma (ATL) characterized by a malignant proliferation of T lymphocytes and a chronic myelopathy called HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP). The association between Sjögren's syndrome and HAM/TSP has already been reported,[1–4] but, as we noted in a previous report of 93 cases, not all patients with HAM/TSP present with ocular dryness.[5] The objective of this study is to describe the clinical and immunological aspects observed in patients with both HAM/TSP and ocular dryness.

Materials and Methods

This study was carried out on 15 patients in the Departments of Ophthalmology and Neurology of the Centre Hospitalier Universitaire de Fort de France. These patients, 2 men and 13 women, were all of black origin. The mean age was 57.6 years (ranging from 42 to 70 years). The serum antibodies directed against the HTLV-I virus had been assessed by two methods: ELISA (Sanofi Diagnostic Pasteur, Paris, France) and Western blot (Ortho Laboratories, Roissy, France). They were seronegative to HIV-I according to the ELISA method. They were

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all diagnosed as having HAM/TSP and dry keratoconjunctivitis. The criteria for the diagnosis of HAM/TSP were based on the proposals of the HTLV-I research group in 1988 in Kagoshima.[6]

Neurological tests showed the coexistence of varying degrees of a pyramidal syndrome, of peripheral neuropathy, and of a polymyositis. The average duration of HAM/TSP was 6.6 years. An assessment of lacrimal secretion was made by means of the Shirmer 1 test and the Pink Bengal test. Results of the pink Bengal test are considered pathological when the total score is above 3.5 points (Van-Bijsterveld score).[7] The existence of dry keratoconjunctivitis is considered to be conclusive when two of three tests are positive.

Biological examinations for all patients included the following: erythrocyte sedimentation rate, complete blood count, typing of blood lymphocytes, rheumatoid factor tests (latex and Waaler-Rose; Funoze, Paris, France), extractable nuclear antibodies (Ro/SSA, La/SSB, Sm, RNP) (Kallestad Sanofi Diagnostic Pasteur), serum protein electrophoresis, biological liver tests, human leukocyte antigen (HLA) analysis, and detection of anti–hepatitis B virus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) antibodies. A biopsy of secondary salivary glands was also carried out. The extent of the histological lesion of the secondary salivary glands was expressed according to the Chisholm scale.[8] Because of its invasive aspect, we did not perform lacrimal gland biopsy. The pulmonary disorders were assessed by physical examination, including lung function tests and a bronchoalveolar lavage. A cellular count was made on the bronchoalveolar lavage fluid after centrifugation and May-Grunwald-Giemsa staining. The diagnosis of lymphocytic alveolitis was considered proven when the proportion of lymphocytes was greater than 15%. Gram, Papanicolaou, Grocott, and Ziehl's stainings were used to isolate bacteria.

Results

All patients had bilateral dry keratoconjunctivitis, which was proven by the Shirmer 1 test, BUT, and pink Bengal test. Total lacrimal hyposecretion of less than 10 mm was humidified in 5 minutes from BUT, showing an instability of the lacrimal film in less than 10 seconds. Functional disorders were rare, but some patients complained of pruritus. It appeared impossible to specify if the xerophthalmia took place before or after the neurological symptoms. Three cases of superficial punctate keratitis limited to the lower third of the cornea were observed. Neither filamentous keratitis, nor ulcers, nor corneal neovascularization were observed.

The histological examination of the salivary glands showed lymphoplasmocytoid infiltrations, canalicular ectasia, and a varying degree of disintegration of the secretory lobules. These lesions were comparable to the glandular changes that occur with Sjögren's syndrome. According to the Chisholm scale, the results were as follows: one biopsy grade 1, two biopsies grade 2, six biopsies grade 3, and six biopsies grade 4. Hyposialia was moderate and functional disorders were mild. Because of its invasive aspect, radionucleide scanning of the salivary glands was not performed. Erythrocyte sedimentation rate was moderately elevated but always less than 50 mm in the first hour.

The complete blood count revealed neither anemia, nor leukopenia, nor thrombopenia. The mean lymphocyte rate was 2500 per mm^3. Abnormal lymphocytes were found in the full blood counts of 7 patients, fluctuating from 1% to 11% (mean equal; 2.8%). An increase in CD3 (more than 75%) and in CD8 (more than 25%) was found in the blood of 63.6% of patients, and in CD4 (more than 45%) in the blood of 54.5% of patients.

Results of all liver biological tests were normal. Test results for antinuclear antibodies and rheumatoid factor proved negative in all cases. Total proteins were greater than 75 g/L in 73% of patients. In 9/15 (60%) patients, electrophoresis of serum protein showed a rise in immunoglobulin G (IgG) (average rate: 19.8 g/L).

Results of HLA analysis are reported in Table 1. Human leukocyte antigen-B14 antigen was found in 33% of the patients. All 15 patients had anti-CMV and anti-EBV antibodies. One patient had interstitial pneumopathy. In six patients, chest x-ray showed interstitial syndrome but no mediastinal adenopathy. Lung function tests revealed a restrictive syndrome in 73% of the patients. In 12 of 15 (80%) patients, bronchoalveolar lavage showed lymphocyte rates over 15%. All bacteriological cultures proved negative.

Three patients had a medical history of chronic uveitis. One patient (case 3) had unilateral anterior uveitis associated with hyalitis, another (case 8) had bilateral pan-uveitis, and the third (case 9) had bilateral anterior uveitis. In none of the cases were lens iris synechia, peripheral snowbanking, or chorioretinitis focus noted. The clinical course and the biological and radiological investigations in these three cases were not consistent with the usual etiologies of uveitis. The impairment of visual acuity was mild, each access responded well to local and/or general

Table 1. Clinical and Immunological Disorders in 15 Patients With Both Human T-Cell Lymphotropic Virus Type I–Associated Myelopathy/Tropical Spastic Paraparesis and Xerophthalmia

Case	Age	Gender	Chisholm Scale	% of Lymphocytes in BLF	IgG g/L	HLA Analysis	Associated Diseases
1	42	F	2	48	21.8	AW34B7DR2 DQ1	—
2	69	M	1	19	18.28	A28 B14 DR3 DQ2	Hypothyroiditis
3	63	F	4	49	35.6	A2 B14 DR5 DQ1	Uveitis
4	57	F	3	14	16.6	A1 B14 DR2 DQ1	—
5	62	M	3	14	14.8	A9 B14 DR2 DQ1	—
6	60	F	4	17	25.16	A23 B7 DR7 DQ1	—
7	58	F	2	69	24.4	A28 B7 DR5 DQ1	—
8	49	F	4	44	19.1	A28 B5 DR3 DQ2	Uveitis
9	54	F	4	58	27.4	A3 B7 B14 DR2 DQ1	Thyroiditis Uveitis polyarthralgia
10	50	F	3	36	26.7	A3 B35 DR1 DQ1	—
11	66	F	4	47	10.4	A23 B35 DR11 DQ5	—
12	70	F	4	14	14.1	A3 B44 DR11 DQ7	—
13	53	F	3	50	14.1	A3 B53 DR7 DQ8	Arthritis
14	56	F	3	45	14.9	A11 B51 DR4 DQ7	—
15	56	F	3	35	13.9	A2 B35 DR11 DQ5	—

BLF: bronchoalveolar lavage fluid; HLA: human leukocyte antigen; F: female; M: male.

corticotherapy and a full recovery was made within a few weeks. These three cases of uveitis were defined as grade 4 on the Chisholm scale. In one of these patients (case 9), uveitis was associated with thyroiditis, interstitial pneumopathy, and polyarthralgia.

Discussion

Analysis of this series of 15 patients of black origin enabled us to specify the characteristics of the xerophthalmia associated with HAM/TSP. Functional disorders were not very disabling so the onset of the disease was not easy to determine. The salivary gland biopsies showed lymphoplasmocytoid infiltrations in 80% of the patients equivalent to grades 3 and 4 on the Chisholm scale. Polyclonal hypergammaglobulinemia with a rise in IgG was found; 80% of patients had lymphocytic alveolitis. Other systems could be involved because uveitis, arthralgia, or thyroiditis were also found. One patient (case 9) had multisystemic involvement. All these features are compatible with Sjögren's syndrome, however, no characteristic immunological disorders were found. Antinuclear antibody and rheumatoid factor tests proved negative in all cases.

Epstein Barr virus, present in more than 95% of the adult population of Martinique, may be etiologically related to Sjögren's syndrome, but this has not been confirmed.[9]

Findings in patients infected by HTLV-I, who presented clinical and histological disorders very similar to those observed in Sjögren's syndrome, gave rise to the idea of an eventual link between this retrovirus and Sjögren's syndrome. In particular, lymphocytic alveolitis has been found in 80% of patients with HAM/TSP.[10] Many Japanese authors reported the presence of a high percentage of HTLV-I antibodies in patients suffering from Sjögren's syndrome.[11,12] Mariette et al showed the presence of the tax gene in salivary glands of patients with Sjögren's syndrome and this gene is seronegative to HTLV-I.[13] A special tropism of HTLV-I for the lacrimal and salivary glands has been reported, demonstrating the presence of the tax gene in these glands of transgenic mice that developed dacryosialadenitis.[14] These results suggest that HTLV-I could induce an inflammation of the lacrimal and salivary glands. The inflammation of exocrine glands, eyes,[15] lungs, muscles, and articulations could represent the many different ways of expression of a systemic disease induced by HTLV-I. This pathology could take place in a genetically determined terrain,[16] where the exact frequency of HLA-B14 antigen and a possible relationship between the existence of a type of uveitis and the degree of the lymphocytic infiltration of the salivary glands remain to be determined.

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