Paucity of Sjögren-like syndrome in a cohort of HIV-1-positive patients in the HAART era.

Part II

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Objective. This study was performed in order to investigate the prevalence of Sjögren-like syndrome (SLS) in the highly active anti-retroviral therapy (HAART) era in a cohort of HIV-1-positive Greek patients.

Methods. One hundred and thirty-one unselected patients were screened by the validated European Union (EU) criteria for Sjögren’s syndrome. Of the 31 who gave a positive EU-validated questionnaire, 17 consented to undergo minor salivary gland biopsy and other tests.

Results. Only two patients had a positive salivary gland biopsy and both belonged to the non-compliant HAART group, whereas none of the compliant HAART patients had histological findings.

Conclusions. It is concluded that SLS, the prevalence of which in the pre-HAART era was 7.8%, has disappeared, possibly as a result of the protective action of HAART.

KEY WORDS: Sjögren-like syndrome, HIV infection, HAART, Pathology.

Human immunodeficiency virus (HIV) infection is often accompanied by autoimmune phenomena such as Sjögren-like syndrome (SLS), polymyositis, mixed cryoglobulinaemia [1] and autoimmune thrombocytopenia due to HIV-induced immune dysregulation. Several autoantibodies are detected in patients’ serum—though they are not always related to a specific autoimmune condition—in the setting of polyclonal hyperglobulinaemia due to persistent immunological triggering by the virus. SLS presents clinically with salivary gland enlargement, xerostomia and keratoconjunctivitis sicca.

We have described a milder form of SLS, which we have named ‘possible Sjögren-like syndrome’, characterized by subjective symptoms of xerostomia and xerophthalmia that may be accompanied clinically by unilateral or bilateral parotid gland enlargement. Ocular tests are usually negative, whereas parotid gland scanning is usually positive and minor salivary gland biopsy is similar to that in Sjögren’s syndrome. It affects 7.8% of Greek HIV-1 positive patients [2]. In a similar study conducted in a larger HIV cohort in the USA and published almost concomitantly with the above-mentioned study, a prevalence of 3% was found on the basis of a different selection questionnaire [3]. Moreover, data from a labial gland biopsy-based study of 30 unselected naïve HIV-1-positive patients in West Africa estimated the prevalence of SLS to be 48% [4]. The prevalence in African Americans is reported to be twice as high as in Caucasians [5, 6].

Although SLS generally resembles classic Sjögren’s syndrome, certain aspects have been reported to differ. Salivary gland infiltration by lymphocytes of the CD8 phenotype and the absence of anti-Ro and anti-La autoantibodies in the patient’s serum are the most prominent differences between SLS and classical Sjögren’s syndrome. Diffuse infiltrative lymphocytosis syndrome [7] is a broader term, including both sicca syndrome and extraglandular manifestations (lung, gastrointestinal tract, kidney, liver, muscle, nerves). As these studies were performed before the introduction of highly active anti-retroviral treatment (HAART), which has had a beneficial effect on the natural history of HIV infection, there are no data on
the effects of HAART on SLS. HAART is defined as a combination anti-retroviral regimen consisting of two reverse transcriptase inhibitors and a protease inhibitor, or three reverse transcriptase inhibitors. The use of zidovudine alone in a small number of patients with primary Sjögren’s syndrome (non-HIV) was reported to relieve sicca symptoms [8]. Moreover, the older anti-rheumatic agent hydroxychloroquine has been shown to decrease HIV replication and has been studied recently as an alternative anti-retroviral medication, together with zidovudine and hydroxyurea, in developing countries [9]. These two observations indicate that the immune mechanisms of HIV infection are of profound therapeutic interest. The present study was designed to assess the possible effect of HAART on SLS.

Patients and methods

Between November 1999 and January 2002, 131 consecutive unselected HIV-positive patients being followed-up in our unit were asked by the same investigator (GDP) to answer the EU-validated questionnaire about xerostomia and xerophthalmia [10]. The diagnosis of HIV infection was established by antibody testing using the enzyme-linked immunosorbent assay (ELISA) and confirmed by western blotting.

The majority of patients were of Greek (Caucasian) origin. There were 123 Greek patients, two from the USA, one from Bulgaria, one from Cuba and four from Africa. There were 113 men and 18 women. The patients belonged to all categories of HIV infection, and had a mean age of 37.3 yr (range 24–71 yr). Numbers of patients in risk groups for the acquisition of HIV infection were as follows: 106 homosexual/bisexual men, 12 heterosexuals, five homosexual/bisexual intravenous drug users (IDUs), five heterosexual IDUs and two blood transfusion recipients. Patients were divided according to the Centers for Disease Control (CDC) classification system of 1993 [11] in the non-AIDS group (categories A1, A2, B1 and B2) and the AIDS group (categories A3, B3, C1, C2 and C3). Thirty-one of the 131 patients questioned (23.7%) gave a positive answer to at least one question about ocular and one question about oral symptoms. During the period between November 1999 and January 2002, 11 patients died (nine males and two females) and two were lost to follow-up. Ten of these 13 patients gave a positive questionnaire, as defined above. Only one of the 13 patients who ceased to be available during the study completed the study protocol. Of the remaining 21 patients who had given a negative answer to the questionnaire and were HCV-negative served as controls (one woman and seven men). They consented to parotid scanning and eye testing for the detection of keratoconjunctivitis sicca.

Results

Sixteen of the 17 patients who agreed to participate were Greeks and one was Cuban. The results of the study are given in Table 1 and are summarized below.

Only two out of 17 minor labial salivary gland biopsies were classified as having a focus score of ≥1+ (at least one lymphocytic focus per 4 mm²) according to the criteria of Greenspan et al. [12]. The lymphocytic infiltrates were mainly perivascular; some were in periacinar and periductal areas. No mucoid degeneration was found.

Five patients had a positive result in Schirmer’s test (three bilaterally and two unilaterally), and two of them also had a positive BUT test result (both unilaterally). Both patients with histologically proven SLS had a positive Schirmer’s I test. No Rose Bengal staining test was positive.

Parotid gland scanning was positive in both patients with histologically proven SLS and in three patients without SLS.

Autoantibodies to Ro/SSA and La/SSB were not detected in sera.

All control patients had negative parotid scanning results and only one had a positive Rose Bengal staining test.

Discussion

Our comments on the results of the present study must be viewed in comparison with those of our previous study, which was performed in the pre-HAART era (1994–1995); the present study is a continuation of the earlier one. The research methods used were identical in the two studies and both study populations, although different in size and patient composition,
TABLE 1. Data on the 17 HIV-positive patients studied who gave positive answers in the validated EU questionnaire on Sjögren's syndrome [10]

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex, age (yr)</th>
<th>Year of initial diagnosis</th>
<th>CDC stage (1993)</th>
<th>CD4 (cells/µl)</th>
<th>Viral load (copies/ml)</th>
<th>Clinical entities included in CDC system</th>
<th>Parotid gland enlargement</th>
<th>Eye tests (Schirmer/BUT/Rose Bengal)</th>
<th>Parotid scanning</th>
<th>Minor labial gland</th>
<th>HCV serology</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 33</td>
<td>1998</td>
<td>A2</td>
<td>517</td>
<td>3848</td>
<td>–</td>
<td>Bilateral</td>
<td>–/–/–</td>
<td>+</td>
<td>–/–/–</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>M, 34</td>
<td>1992</td>
<td>C3</td>
<td>136</td>
<td>84725</td>
<td>Pulmonary TB, fever &gt;1 month</td>
<td>Bilateral</td>
<td>–/–/–</td>
<td>+</td>
<td>–/–/–</td>
<td>–</td>
<td>HAART</td>
</tr>
<tr>
<td>3</td>
<td>F, 39</td>
<td>1992</td>
<td>C3</td>
<td>541</td>
<td>50</td>
<td>HIV encephalopathy</td>
<td>Bilateral</td>
<td>–/–/–</td>
<td>+</td>
<td>–/–/–</td>
<td>–</td>
<td>HAART</td>
</tr>
<tr>
<td>4</td>
<td>F, 32</td>
<td>1990</td>
<td>B3</td>
<td>141</td>
<td>19874</td>
<td>HIV-related thrombocytopenia</td>
<td>Bilateral</td>
<td>–/–/–</td>
<td>0.8/4 mm²</td>
<td>+</td>
<td>–/–/–</td>
<td>HAART</td>
</tr>
<tr>
<td>5</td>
<td>M, 26</td>
<td>1992</td>
<td>B3</td>
<td>172</td>
<td>34832</td>
<td>Oral thrush</td>
<td>Bilateral</td>
<td>+/+/+</td>
<td>+</td>
<td>1.6/4 mm²</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>M, 66</td>
<td>1995</td>
<td>C2</td>
<td>514</td>
<td>261487</td>
<td>Parotid gland enlargement</td>
<td>Bilateral</td>
<td>–/–/–</td>
<td>+/+/+</td>
<td>Diffuse infiltration</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>F, 50</td>
<td>1992</td>
<td>A2</td>
<td>661</td>
<td>50</td>
<td>–</td>
<td>–</td>
<td>–/–/–</td>
<td>–</td>
<td>–/–/–</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>M, 42</td>
<td>1994</td>
<td>A3</td>
<td>208</td>
<td>16915</td>
<td>–</td>
<td>–</td>
<td>–/–/–</td>
<td>–</td>
<td>–/–/–</td>
<td>–</td>
<td>HAART</td>
</tr>
<tr>
<td>9</td>
<td>M, 30</td>
<td>1991</td>
<td>B2</td>
<td>284</td>
<td>217859</td>
<td>Diarrhoea &gt;1 month</td>
<td>Bilateral recurrent</td>
<td>–/–/–</td>
<td>0.15/4 mm²</td>
<td>–</td>
<td>–</td>
<td>HAART</td>
</tr>
<tr>
<td>11</td>
<td>M, 63</td>
<td>1993</td>
<td>B3</td>
<td>463</td>
<td>70</td>
<td>VZV</td>
<td>Bilateral</td>
<td>+/+</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>HAART</td>
</tr>
<tr>
<td>12</td>
<td>M, 54</td>
<td>2000</td>
<td>C3</td>
<td>22</td>
<td>173537</td>
<td>Wasting syndrome/salmonella bacteriemia</td>
<td>Unilateral</td>
<td>–/–/–</td>
<td>+</td>
<td>–</td>
<td>–/–/–</td>
<td>HAART</td>
</tr>
<tr>
<td>14</td>
<td>M, 35</td>
<td>1993</td>
<td>A2</td>
<td>235</td>
<td>41796</td>
<td>–</td>
<td>–</td>
<td>–/–/–</td>
<td>0.25/4 mm²</td>
<td>–</td>
<td>–</td>
<td>ART</td>
</tr>
<tr>
<td>15</td>
<td>M, 36</td>
<td>1997</td>
<td>B3</td>
<td>361</td>
<td>55</td>
<td>VZV</td>
<td>–</td>
<td>–/–/–</td>
<td>–</td>
<td>–</td>
<td>–/–/–</td>
<td>No</td>
</tr>
</tbody>
</table>

TB, tuberculosis; VZV, varicella zoster virus; CIN, cervical intra-epithelial neoplasia; PCP, pneumocystis carinii pneumonia; HIV-RTP, HIV-related thrombocytopenia; KS, Kaposi's sarcoma; NHL, non-Hodgkin's lymphoma; ART, anti-retroviral therapy that included two NRTIs.
The overall prevalence of SLS in the unselected HIV-1-positive population of our cohort in the HAART era was 1.53% (2 out of 131). This is significantly different from the prevalence rate of 7.8% (6/77 HIV patients) that we found in our earlier study \((P = 0.003, \text{relative risk } 5.10, 95\% \text{ confidence interval } 1.06–24.67)\). No patient compliant to HAART was found to have histologically proven SLS.

Because the prevalence of Sjögren’s syndrome among women in a closed rural Greek community has been estimated as 2.99% [13], it is evident that HAART is capable of practically eliminating HIV-related SLS. The results of this study are significant because they prove that SLS disappears histologically from the mouth after successful HAART. It is possible that anti-retroviral agents exert a direct or indirect action on the epithelial cells of the exocrine glands. When we tested retrospectively, in both studies, the effect of successful HAART on the likelihood of developing SLS in the group of patients with a positive EU questionnaire, we found a strong negative association \((P = 0.009, \text{odds ratio } 0.10, 95\% \text{ confidence interval } 0.00–0.99)\). From our data, it is likely that HAART protects against the development of SLS in HIV patients. Further studies are needed to clarify the roles of the anti-retroviral agents individually and in combination. Our findings might also indicate a wider effect of HAART on HIV-related autoimmunity. This seems an attractive hypothesis as the reduction in viral load induced by HAART decreases the persistent antigenic stimulation induced by HIV. However, further studies are needed to elucidate this.

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Conflict of interest

The authors have declared no conflicts of interest.

References