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Sicca syndrome in patients infected with human immunodeficiency virus-1

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Abstract We investigated human immunodeficiency virus-1 (HIV-1)-associated sicca syndrome. The average saliva production in HIV-infected patients was 15.9 ± 6.3 ml, and the average tear production was 9.8 ± 4.5 mm. In particular, 6 patients (42.9%) showed a significant decrease in tear production. This sicca syndrome mimicked autoimmune Sjögren's syndrome (SS) because of the presence of dry eye, dry mouth, hyperamylasemia, and hypergammaglobulinemia; however, no antinuclear antibodies, anti-SS-A, or anti-SS-B were detected in sera from HIV-1-infected patients. In addition, no relationship was observed between saliva and tear production and CD4, HIV-RNA. Hepatitis C virus (HCV) and human T-lymphotrophic virus (HTLV-1) are considered to be possible causative agents of SS. However, coinfection with HCV did not affect the decrease of saliva and tear production, and only one patient was coinfected with HTLV-1. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are also potential causative agents of SS, and they are sometimes detected in the saliva of HIV-1-infected patients. However, the detection of EBV and CMV in the saliva was not related to the decrease in saliva production. Furthermore, HIV therapy (highly active antiretroviral therapy; HAART) did not affect the state of sicca syndrome.

The pathogenesis of sicca syndrome in HIV-1-infected patients is not clear, but we did find some infiltration of CD8 lymphocytes in salivary gland biopsy. Usually, CD8 lymphocytosis is found in peripheral blood in HIV-infected patients. Diffuse infiltrative lymphocytosis syndrome by predominant CD8 lymphocytes is occasionally found in HIV-infected patients. Such CD8 infiltration may induce the destruction of both the salivary and lacrimal glands.

Key words Human immunodeficiency virus-1 (HIV-1) · Sicca syndrome · Sjögren's syndrome (SS)

Introduction

Sicca syndrome, such as Sjögren's syndrome (SS), is characterized by dry mouth and dry eye. SS is one of the autoimmune diseases that often shows high titers of anti-SS-A and/or anti-SS-B autoantibodies. Although the pathogenesis of SS has yet to be elucidated, many viruses, such as human T-lymphotrophic virus (HTLV-1) and Epstein-Barr virus (EBV), are considered to be possible causative agents.[1–11] High seroprevalence of HTLV-1 infection with SS has been reported,[5] and HTLV-1 proviral DNA and HTLV-1 Tax/Rex mRNA are expressed in the salivary glands of HTLV-1-seropositive patients with SS.[1] The localization of EBV DNA and EBV-associated antigens has been found in the salivary and lacrimal glands of patients with SS.[3–11] Furthermore, cellular functions have been shown to be modulated by these viral infections.

Human immunodeficiency virus-1 (HIV-1) infects human CD4-positive T lymphocytes, and also modulates the human immune network. It has recently been reported that HIV-1-infected patients were often associated with sicca syndrome in European and American countries.[12–15] In this paper, we report the association of sicca syndrome with HIV-1 infection in Japanese patients, and the relationship of sicca syndrome with other factors.

Patients and methods

The subjects consisted of 34 HIV-infected Japanese patients. The profile of the patients are as follows: age, 20–65

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years; sex, 32 men and 2 women; 25 received highly active anti-retroviral therapy (HAART); 21 achieved a viral load less than 50 copies/ml.

Saliva and tear production was measured using the Gum test and Schirmer test. Viruses in saliva were detected using the polymerase chain reaction method (PCR). The amounts of HIV-RNA in plasma were also measured using PCR. The CD4 counts in peripheral blood were measured by flow cytometry. The titers of antinuclear antibody, anti-SS-A, and anti-SS-B were determined by enzyme-linked immunosorbent assays. EBV-encoded small RNA1,2 (EBER) in salivary gland specimens were detected by in situ hybridization, and CD8-positive lymphocytes and EBV latent membrane protein-1 (LAMP-1) were detected by immunohistochemical staining.[6,7]

Results

The average saliva production in 21 HIV-infected patients was 15.9 ± 6.3 ml, and the average tear production in 14 patients was 9.8 ± 4.5 mm (Fig. 1). In particular, 6 patients (42.9%) showed a significant decrease in tear production. These results indicate that HIV infection is thus often associated with sicca syndrome.

We also analyzed the association between saliva/tear production and clinical parameters. However, no association was observed between saliva production and CD4 counts or plasma HIV-RNA, nor between tear production and CD4 counts (Fig. 2). Statistically, tear production and plasma HIV-RNA seemed to be related, but only one of the examined patients showed a high titer of HIV-RNA. The difference of infection routes and age did not affect the decrease in saliva and tear production (data not shown).

The serum amylase level was elevated in 7 of the 27 HIV-infected patients (25.9%), and the average S isozyme of serum amylase was 61.6% ± 16.1%.

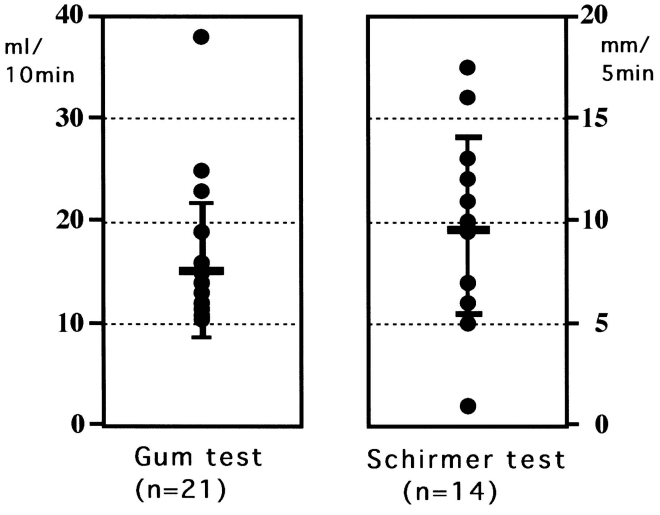

Fig. 1. Saliva and tear production of human immunodeficiency virus-1 (HIV-1)-infected patients. Saliva and tear production was measured by Gum test (ml/10 min) and Schirmer test (mm/5 min)

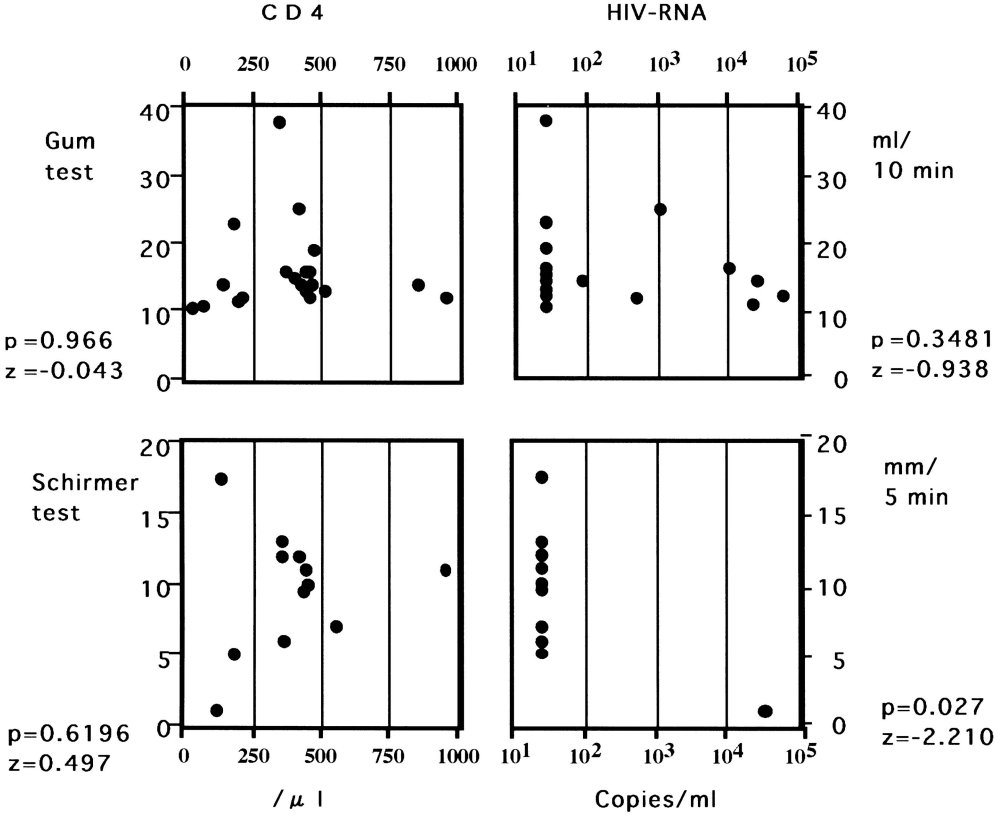

Fig. 2. Relation between saliva, tear production, and CD4, HIV-RNA. Saliva and tear production was measured by Gum test (ml/10 min) and Schirmer test (mm/5 min). CD4 counts were measured by flow cytometry, and plasma HIV-RNA was measured by polymerase chain reaction (PCR)

It has been reported that HIV-infected patients are occasionally associated with autoimmune diseases,[16–21] such as mixed connective tissue disease. Sjögren's syndrome is also characterized by autoimmune sicca syndrome, and autoantibodies, such as antinuclear antibodies, anti-SS-A, anti-SS-B, were often positive in sera from patients with primary SS. Although antinuclear antibodies, anti-SS-A, anti-SS-B were not detected in sera from 11 HIV-1-infected patients, 15 of 23 patients (62.5%) demonstrated hypergammaglobulinemia, similar to that seen in SS.

To investigate the factors that might contribute to this condition, we studied the prevalence of other viruses. Chronic hepatitis C virus (HCV) infection sometimes revealed clinical and histologic features mimicking SS.[22,23] However, coinfection with HCV did not significantly affect the decrease in saliva and tear production in HIV-1-infected patients (Fig. 3). HTLV-1 is another causative agent of SS,[1,2] but the anti-HTLV-1 antibody was detected in only one patient.

A local salivary gland infection by other viruses, such as EBV and cytomegalovirus (CMV), has often been reported to be detected in the saliva of HIV-1-infected patients.[24–26] Although we also detected EBV in the saliva of 8 HIV-infected patients (61.5%), and CMV in the saliva of 2 patients (15.4%), detection of EBV and CMV in the saliva was not associated with a decrease in saliva production (Fig. 4).

Because anti-retroviral agents have many kinds of adverse effects, it is possible that the new aggressive therapy to prevent HIV proliferation (highly active anti-retroviral therapy; HAART) may induce sicca syndrome. However, no relationship between this therapy and a decrease in saliva was found (Fig. 5).

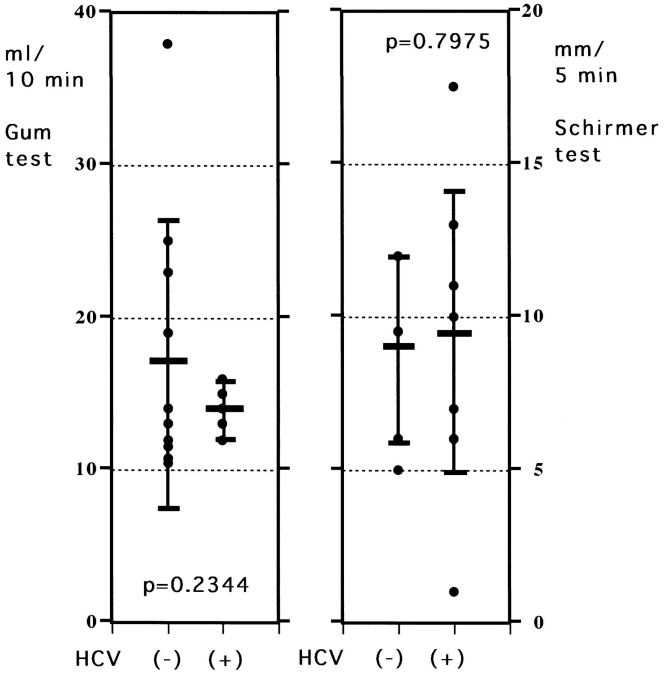

Fig. 3. Hepatitis C virus (*HCV*) coinfection and saliva, tear production

Lip biopsies (minor salivary gland biopsy) were performed on two patients. Neither of them showed any marked lymphocyte infiltration or destruction of salivary glands, which are usually found in the salivary glands of patients with SS (Fig. 6A). However, a mild infiltration of CD8-positive lymphocytes was observed (Fig. 6B). In situ hybridization using EBER and immunohistochemical staining of LAMP-1 could not demonstrate the presence of EBV in this specimen (Fig. 6C, D), despite the presence of EBV in these patients' saliva.

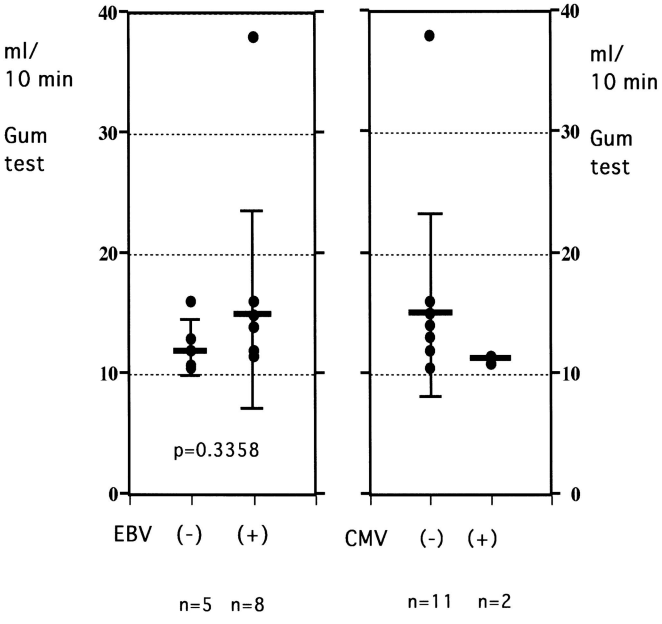

Fig. 4. Saliva production and Epstein-Barr virus (*EBV*), and cytomegalovisus (*CMV*) detection in the saliva of HIV-1-infected patients. EBV and CMV in saliva was detected using PCR

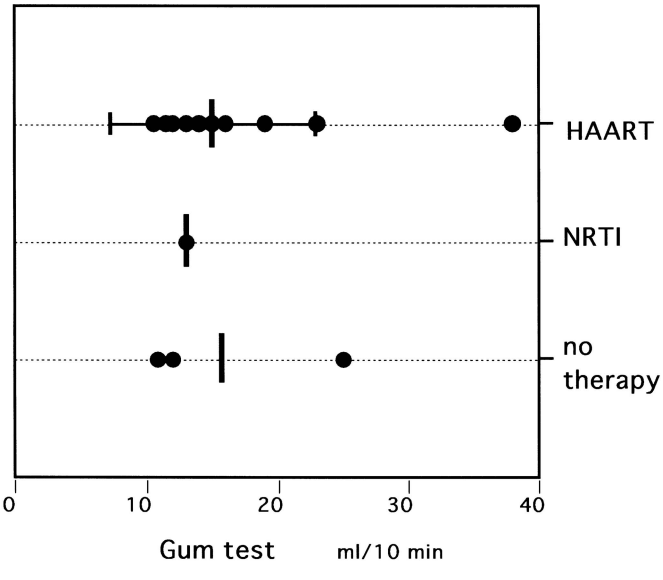

Fig. 5. Therapy and saliva production. *HAART*, Highly active antiretroviral therapy; *NRTI*, two nucleosid reverse transcriptase inhibitors

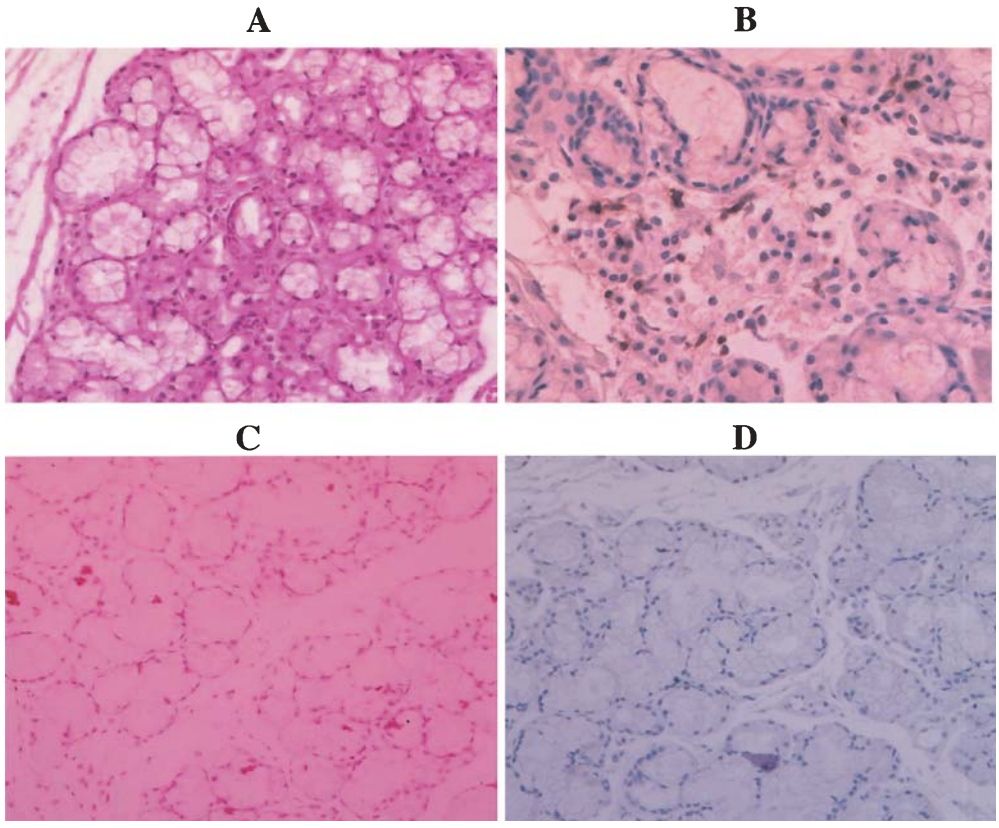

Fig. 6. Lip biopsy of HIV-1-infected patients. **A** Hematoxilin-eosin staining. **B** Immunohistochemical staining of CD8. **C** In situ hybridization using EBV-encoded small RNA1, 2. **D** Immunohistochemical staining of latent membrane protein-1

Discussion

HIV-1-infected patients have often been reported to be associated with sicca syndrome in European and American countries.[12–15] Furthermore, some researchers have also advocated that SS is related to retrovirus infection, because antigens from HIV-1 peptides react with the sera from SS.[27] In this paper, we show how Japanese HIV-1-infected patients are also associated with sicca syndrome.

The pathogenesis of sicca syndrome remains to be elucidated. We investigated the relationship with HIV disease severity, coinfection, local opportunistic infection, and therapy. CD4 counts and HIV-RNA amounts did not affect the decrease in saliva and tear production, consistent with a previous report.[13] This might indicate that the HIV itself did not induce sicca syndrome, although it has been reported that HIV-infected patients are occasionally associated with autoimmune diseases.[18–21] Sicca syndrome in HIV-1-infected patients mimicked SS because dry mouth, dry eye, hyperamylasemia, and hypergammaglobulinemia were often found in both diseases. However, antinuclear antibody, anti-SS-A, and anti-SS-B, which were known as specific autoantibodies of primary SS, were negative in the sera from HIV-1-infected patients with sicca syndrome, thus indicating sicca syndrome in HIV-1-infected patients to be a different feature from primary SS. Furthermore, there were no patients whose symptoms fulfilled the criteria of SS (San Diego criteria of SS, 1999), although we have not examined all patients in detail.

HCV and HTLV-1 are possible causative agents of SS,[1,2,22,23] and many HIV-1-infected patients were coinfected with HCV. Patients with HCV infection often have extrahepatic involvement, such as dry eyes, dry mouth, and immunological abnormalities. However, a coinfection with HCV did not affect the decrease of saliva and tear production, and only one patient was coinfected with HTLV-1, thus indicating that HCV and HTLV-1 coinfection was not responsible for this sicca syndrome.

The other viruses, such as EBV and CMV, are also candidates as causative agents of SS, and they are often detected in the saliva of HIV-1-infected patients.[3–11,26] However, the presence of EBV and CMV in the saliva did not affect the decrease in saliva. Furthermore, EBV was not detected in lip biopsy specimens using EBER in situ hybridization and LAMP-1 staining, although it was reported that EBV-associated antigens and DNA were often detected in the salivary glands of patients with SS.[6,7] A local infection of EBV and CMV, perhaps a temporary infection, did not seem to be the pathogenesis of this sicca syndrome, but it is still possible that a frequent opportunistic infection in the salivary gland and lacrimal gland might be responsible.

It remains unclear as to why EBV was not detected in the salivary gland specimens by EBER in situ hybridization and LAMP-1 staining, although EBV was detected in the saliva using PCR. Some possible explanations are (1) EBV in the saliva may be from other lymphoid tissue, such as the tonsils, in the oral cavity; (2) EBV may proliferate not in minor salivary glands, but in major salivary glands, such as the parotid glands; (3) EBV could proliferate in B lymphocytes

infiltrated in salivary glands, but EBER in situ hybridization and LAMP-1 staining could not detect them because very few B lymphocytes were detected in the specimens by CD20 staining (data not shown).

Recently many anti-retroviral agents have been used for HIV therapy, and the prognosis of HIV-infected patients has improved. But these agents have a number of adverse effects, such as the development of lipodystrophy, lactate acidosis, and insulin-resistant diabetes mellitus. It is possible that this sicca syndrome was one of the adverse events of anti-retroviral agents, but our data showed that HIV therapy did not affect the state of sicca syndrome.

Finally, the pathogenesis of sicca syndrome in HIV-1-infected patients was unclear, but we found some infiltration of CD8 lymphocytes in salivary gland biopsies. However, a marked infiltration of CD8 lymphocytes is usually found in the salivary glands in patients with SS, and it is considered that this CD8 lymphocyte infiltration is responsible for the destruction of the salivary and lacrimal glands.[28] Usually CD8 lymphocytosis is found in peripheral blood of HIV-infected patients. Diffuse infiltrative lymphocytosis syndrome, characterized by an infiltration of lymphoid tissues, salivary glands, and lungs by predominant CD8 lymphocytes, are often found in HIV-infected patients.[29] Such CD8 infiltration may induce the destruction of salivary and lacrimal glands.

The presence of an unknown retrovirus similar to HIV in the salivary gland that might be involved in the pathogenesis of a subpopulation in SS,[30] thus indicating an infection of several kinds of viruses, including HIV, has been suggested to modulate the human immune network, cause the activation of CD8 lymphocytes, and result in the destruction of salivary and lacrimal glands.

Further investigation of sicca syndrome in HIV-infected patients will allow us to better understand the pathogenesis of Sjögren's syndrome. Further studies are thus called for.

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