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lymphocytic sialadenitis of Sjögren’s syndrome associated with chronic hepatitis C virus liver disease

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Viral infection has often been suggested as a possible cause of Sjögren’s syndrome or chronic lymphocytic sialadenitis, and Epstein–Barr virus has been found in the salivary glands of patients with this condition. After we had noted Sjögren’s syndrome in several patients infected with hepatitis C virus (HCV), a virus also excreted in saliva, we set up a prospective study to investigate the association of chronic lymphocytic sialadenitis, with or without symptoms, to chronic HCV liver disease.

The histological appearances of labial salivary glands in patients with proven HCV hepatitis or cirrhosis were compared with those in dead controls. Histological changes characteristic of Sjögren’s syndrome were significantly more common in HCV-infected patients (16 of 28, 57%) compared with controls (1 of 20, 5%).

Focal lymphocytic sialadenitis characteristic of Sjögren’s syndrome (though only 10 patients had xerostomia and none complained of xerophthalmia) appeared to be common in patients with chronic HCV liver disease; if this association is confirmed, identification of the underlying mechanism may improve our understanding of both disorders.

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Introduction

Sjögren’s syndrome is generally thought to be an autoimmune disease because of an associated chronic lymphocyte infiltration of salivary and lacrimal glands1 and

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the autoantibodies sometimes detected in serum. The factors which might trigger such a focal immune reaction remain unknown, but viral infections have repeatedly been suggested as a possible cause. In rats, a coronavirus infection of salivary and lacrimal glands can lead to chronic inflammation, and set up a prospective study of labial salivary glands in patients with chronic HCV hepatitis or cirrhosis.

Patients and methods

From April 1, 1990, to March 30, 1991, 29 patients with non-A, non-B hepatitis or cirrhosis were referred for hepatic biopsy and were entered into the study; 27 were anti-HCV positive by a first-generation enzyme-linked immunosorbent assay (ELISA). (Chiron/Ortho Diagnostics, Raritan, New Jersey, USA). Serum samples were retested with a second-generation anti-HCV ELISA and by recombinant immunoblot assay (RIBA, Ortho) to measure antibodies against different viral antigens. 1 patient remained seronegative and was excluded. In the other 28 patients (9 men, 19 women; mean age 60, range 32-80 years), HCV infection was considered to be the cause of chronic liver disease because of epidemiological and histological data (table I) and other causes of chronic hepatitis, particularly autoimmune hepatitis, were excluded. No patient had antimitochondrial or liver-kidney microsomal antibodies, and smooth-muscle antibodies were found in only 3 patients at a titre below 1:100; antinuclear antibodies were found by indirect immunofluorescence on rat liver and kidney sections in 12 patients, but at a low titre (table I), and always with an irregular immunofluoresence pattern. 20 patients subsequently received 3 million units a-interferon thrice weekly; transaminase concentrations at 3 months had returned to normal in 8 patients, had improved but were still raised in 8, and were unchanged in 4. The likely cause of HCV infection was blood transfusion in 13 (mean delay 13 [SE 8] years between transfusion and biopsy), acupuncture in 1, and intravenous drug injection in 1, and no clear risk factor could be identified in 13. Table I shows the activity of histological examination of labial salivary-gland biopsies are shown in table I. 16 of 28 (57%) patients with chronic HCV liver disease had histological evidence of Sjogren's syndrome compared with 1 of the 20 (5%) controls (p < 0.01). (Biopsy results for controls were: grade 0, 3; grade 1, 7; grade 2, 9; grade 3, 0; and grade 4, 1.) When the 12 patients with labial biopsy grades 3 or 4, there were no statistically significant differences with regard to sex, age, mode of contamination, y-globulin concentration, Knodell's score, or response to interferon (table II). 6 of the 10 patients with grade 3 or 4, which contained more than 1 nodular lymphocytic focus per 4 mm², were considered diagnostic of Sjogren's syndrome.

For statistical analysis we used the $\chi^2$ test for qualitative data and the Mann-Whitney test for continuous data.

Results

10 of the 28 patients with HCV complained of xerostomia, in 5 of whom symptoms were severe. No patient complained of xerophthalmia but of the 6 patients randomly assigned to ophthalmological examination, 3 had a positive Schirmer test, 1 of whom also had a positive rose-bengal test. Antinuclear antibody titres and the results of histological examination of labial salivary-gland biopsies are shown in table I. 16 of 28 (57%) patients with chronic HCV liver disease had histological evidence of Sjogren's syndrome compared with 1 of the 20 (5%) controls (p < 0.01). (Biopsy results for controls were: grade 0, 3; grade 1, 7; grade 2, 9; grade 3, 0; and grade 4, 1.) When the 12 patients with labial biopsy grades 1 or 2 were compared with the 16 who had labial biopsy grades 3 or 4, there were no statistically significant differences with regard to sex, age, mode of contamination, y-globulin concentration, Knodell's score, or response to interferon (table I). 6 of the 10 patients with

| TABLE I—PATIENT CHARACTERISTICS, XEROSTOMIA, AND LABIAL BIOPSY GRADES |
|--------------------------|--------------------------|--------------------------|--------------------------|
| Patient | Age (yr) | Knodell's score | y-globulin (g/l) | ANA (titre) | Xerostoma | Labial biopsy grade* |
|----------|-----------|-----------------|-----------------|-------------|------------|---------------------|
| 1        | 58, F     | 18              | +               | 9           | 20         | 2                   |
| 2        | 73, F     | 11              | +               | 22          | 500        | +                   |
| 3        | 61, F     | 5               | -               | 13          | 12         | -                   |
| 4        | 77, F     | 9               | +               | 20          | 500        | +                   |
| 5        | 54, M     | 7               | +               | 16          | 200        | 1                   |
| 6        | 59, F     | 7               | +               | 23          | 200        | +                   |
| 7        | 54, F     | 9               | +               | 9           | 50         | 1                   |
| 8        | 74, F     | 13              | +               | 18          | 20         | -                   |
| 9        | 64, M     | 4               | -               | 12          | 100        | +                   |
| 10       | 65, F     | 15              | +               | 23          | 200        | 2                   |
| 11       | 42, M     | 6               | +               | 18          | 200        | +                   |
| 12       | 70, F     | 7               | +               | 19          | 20         | +                   |
| 13       | 65, F     | 13              | +               | 20          | 200        | +                   |
| 14       | 52, F     | 12              | +               | 26          | 200        | +                   |
| 15       | 64, M     | 13              | +               | 13          | 200        | +                   |
| 16       | 64, F     | 14              | +               | 28          | 50         | -                   |
| 17       | 67, F     | 11              | +               | 26          | 200        | -                   |
| 18       | 54, F     | 6               | +               | 18          | 200        | -                   |
| 19       | 48, F     | 6               | +               | 13          | 200        | -                   |
| 20       | 41, M     | 6               | +               | 25          | 200        | +                   |
| 21       | 80, M     | 9               | +               | 22          | 200        | +                   |
| 22       | 57, F     | 9               | +               | 11          | 200        | +                   |
| 23       | 63, F     | 9               | +               | 30          | 200        | +                   |
| 24       | 32, F     | 8               | +               | 16          | 20         | +                   |
| 25       | 77, F     | 13              | +               | 17          | 20         | +                   |
| 26       | 60, F     | 11              | +               | 23          | 200        | +                   |
| 27       | 53, M     | 4               | +               | 13          | 200        | +                   |
| 28       | 63, M     | 7               | +               | 14          | 100        | -                   |

| TABLE II—PATIENT CHARACTERISTICS BY LABIAL BIOLOGY GRADE |
|--------------------------|--------------------------|--------------------------|--------------------------|
| LAbial biopsy grade | 1/2 (n=12) | 3/4 (n=16) | p |
| Women | 7 | 12 | 0.35 |
| Age (yr) | 60 (10) | 61 (12) | 0.85 |
| No transfused | 6 | 7 | 0.72 |
| Serum γ-globulin (g/l) | 17 (8) | 20 (5) | 0.05 |
| Knodell's score | 9 (4) | 10 (3) | 0.56 |
| No complete response to IFN | 4/8 | 4/12 | 0.90 |

Values shown as number of patients or mean (SD). IFN = α-interferon.
xerostomia had grade 3 or 4 changes on labial salivary gland biopsy; the other 4 patients had grade 2 changes.

Discussion

In Sjögren's syndrome, symptoms of xerostomia and xerophthalmia are caused by lymphocyte infiltration and destruction of lacrimal and salivary glands. The diagnostic criteria and even the definition of this condition have been the subject of much debate. Although the diagnosis was made on clinical grounds alone for many years, it is now widely accepted that the histological appearances of salivary glands can be a useful guide, and that a focus of more than 50 lymphocytes per 4 mm² of a salivary gland section is diagnostic of the condition if the biopsy specimen has been taken from normal mucosa. The sensitivity of this technique is reduced when the biopsy sample contains less than 5 salivary glands, as may occur in advanced stages of sialadenitis because of extensive atrophy and fibrosis of labial salivary glands. Some authors have suggested that patients with grade 2 lymphocyte infiltrate and extensive fibrosis could be considered to have Sjögren's syndrome, by which criteria all but 8 of our 28 patients with chronic HCV liver disease would have qualified for this diagnosis. We used the more strict criteria for statistical analysis because of their good specificity: Chisholm and Mason did not find any grade 3 or 4 changes among 60 controls. Nevertheless, because Scott found minor inflammatory changes to be common in older people, especially women, with occasional lymphocytic foci and Greenspan et al found 6 specimens with grade 3 changes (though none with grade 4) in 53 unselected necropsy specimens, and in view of the age and sex distribution of our patients with chronic HCV liver disease, we compared them with controls who had a similar sex ratio and a slightly higher mean age. Only 1 of 20 controls had grade 3 or 4 sialadenitis (5%), compared with 16 of 28 with HCV infection and chronic liver disease—which therefore seems to predispose to focal lymphocytic sialadenitis characteristic of Sjögren's syndrome. However, as only 10 of the 28 patients had xerostomia (mild in 5) and none complained of xerophthalmia (although 3 of 6 patients examined had abnormal Schirmer or rose-bengal tests), it may be more appropriate to use the terms sicca complex or chronic lymphocytic sialadenitis instead of Sjögren's syndrome.

Whatever the label, such a condition is well known in chronic autoimmune liver diseases such as primary biliary cirrhosis, autoimmune chronic active hepatitis, and cryptogenic cirrhosis, and has even been used as an additional argument to support an autoimmune pathogenesis in these diseases. Although there is a link between Sjögren's syndrome and autoimmune liver disease in the proven absence of HCV infection, it is clear that until recently some patients with chronic HCV liver disease have been thought to have autoimmune liver disease, and the occasional coexistence of Sjögren's syndrome in such patients may have been misleading. Although false-positive results for anti-HCV antibodies have been reported in autoimmune liver disease, in our patients the confirmation of anti-HCV antibodies by RIBA, the low concentrations or absence of circulating autoantibodies, and the response to interferon all support the diagnosis of chronic HCV liver disease.

We have found a striking association between HCV infection and sialadenitis, but our findings do not prove a direct link. However, there are several ways in which HCV infection might cause sialadenitis. Smooth-muscle or liver-kidney microsomal antibodies have been reported during HCV infection and interpreted as secondary immune phenomena, and antibodies against host-derived epitopes may also be detected easily in HCV hepatitis. Thus an autoimmune reaction may explain lymphocytic infiltration, even in organs not infected by HCV, if they contain a target epitope. HCV genome sequences may also be found in mononuclear cells in the blood of infected patients (C. Brechot, personal communication), and might also lead to abnormal immune responses. Another possibility is suggested by the detection of EBV in the salivary glands of patients with Sjögren's syndrome. HCV has been found in the saliva of infected individuals and there is a strikingly similar nodular pattern of lymphocyte infiltrate in salivary glands and in liver. Could HCV infection of salivary glands account for the chronic lymphocytic sialadenitis that we observed? Identification of the association between nodular chronic lymphocytic sialadenitis and chronic HCV liver disease may offer new insights into our understanding of both conditions.

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