

Original article

Macrophage-dominant sialadenitis in HTLV-I-associated myelopathy post living-donor liver transplantation.

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Introduction

Both hepatitis C virus (HCV) and human T-cell virus type I (HTLV-I) have been reported to be associated with the onset of Sjögren's syndrome (SS) (1, 2). Since HCV infection demonstrates exocrine dysfunction along with sialadenitis, the American-European Consensus Group for SS excluded HCV infection in diagnosis of SS (3). We have previously reported that an epidemiologic study showed a high prevalence of SS in anti-HTLV-I antibody positive subjects (4). In this case, a complication of HAM after living-donor liver transplantation (LDLT) has recently been reported (5). Here, we additionally report the emergence of unusual sialadenitis in this patient.

Case report

The complication of HAM in this patient was already reported by Soyama et al.(5). Briefly, LDLT was performed for the patient who had suffered from decompensated liver cirrhosis due to HCV infection in August 2002. Both the patient and his younger sister as a donor were seropositive for anti-HTLV-I antibody. Immediately after LDLT in October 2002, interferon (IFN) α -2b with ribavirin were administered after recurrence of the HCV infection was confirmed,

but HAM appeared 18 months after LDLT. Though pegylated IFN α -2b with ribavirin were administered for 48 weeks against the HCV infection, no response was observed with the recurrence of active hepatitis.

When the patient was admitted to the Department of Gastroenterology for determination of the therapeutic strategy in September 2008, xerostomia was newly detected. The clinical manifestations of HAM, including spastic gait and bladder symptoms, since the last diagnosis of HAM was confirmed. Elevation of aspartate aminotransferase (53 IU/l), alanine aminotransferase (47 IU/l), and IgG (2630 mg/dl) were observed with normal total bilirubin (0.7 mg/dl). Type IV collagen and quantitative HCV ribonucleoprotein were elevated to 290 ng/ml (normal; ≤ 140) and 7.1 log IU/ml (normal; undetected) with reduced total branch chain amino acids (285 μ mol/l; normal: 379-688). A liver biopsy, which had resulted in a hospital admission in September 2008, showed chronic hepatitis with fibrous enlargement of the portal area, inflammatory cell infiltration, and piecemeal necrosis. The relative copy number of HTLV-I against β -globin in peripheral blood sample was $2.56 \times 10^2/10^4$ cells by real-time polymerase chain reaction. Along with xerostomia, both the Saxon test (1.1 g/2 minutes; < 2 g: positive) and Schirmer test (3mm/5 minutes; < 5 mm: positive) were positive with

negative results for anti-SS-A/SS-B antibodies and sialography. However, minor salivary gland biopsy (**Fig. 1A**) demonstrated more than 60 counts of mononuclear cells infiltration, which were confirmed as dominant infiltration of macrophages. Although the patient showed signs of xerostomia, positive exocrine dysfunction, and mononuclear cell infiltration into the minor salivary gland (MSG), SS was excluded according to the criteria determined by the American-European Consensus Group (**3**). Immunohistochemistry using monoclonal antibodies for MSG demonstrated positive staining of CD68 on the infiltrating mononuclear cells (**Fig. 1B**). Compared to the prevalence of CD68, the prevalence of CD4 (**Fig. 1C**) or CD8 (**Fig. 1D**) was less than that of CD68, macrophage. Major histocompatibility (MHC) class II was found in humal tonsil as a positive control (**Fig. 1E**) and MNCs in the MSG of this patient (**Fig. 1F**). Written informed consent for use of the biopsy specimen was obtained from the patient.

Discussion

HCV-related SS is reported to be characterized by a high prevalence of cryoglobulinemia with a low frequency of anti-SS-A/SS-B antibodies (**6**). In our

case, sialadenitis without SS-related autoantibodies is compatible with the characteristics of HCV-related SS. However, HCV infection usually shows infiltration of CD4+ T lymphocytes into the MSG, which is incompatible with the present macrophagic infiltration. Furthermore, it has previously been reported that IFNs have the potential to cause autoimmune diseases such as autoimmune thyroid diseases, systemic lupus erythematosus, rheumatoid arthritis, or SS (7, 8). Unoki et al reported that administration of IFN-alpha-2b for a patient with type C chronic active hepatitis induced SS with sicca symptoms and elevation of autoantibodies, suggesting IFN per se had a potential to form autoimmune disorders in patients with viral hepatitis (9).

With regard to HTLV-I infection, prognosis of HTLV-I-positive renal transplant recipients was previously reported (10), in which both living-related and cadaveric kidneys from HTLV-I carriers could be used for HTLV-I-seropositive recipients because low occurrence of adult-T cell leukemia was observed. HTLV-I is also one of the candidates for trigger of sialadenitis. We have previously reported a high prevalence of SS in patients with HAM (2). However, the phenotype of predominant mononuclear cells found in HAM-SS patients was CD4+ T lymphocytes, which was similar to the type of mononuclear

cells in HTLV-I-seronegative SS patients. Previously, Ishiguro et al (11) established a rat model of HTLV-I infection, in which massive foamy macrophages infiltrated the spinal cord and clinical manifestations of the rat resembled those of HAM patients. Meanwhile, our patient showed macrophage-dominant MNC infiltration into the MSG. Although the pathogenesis of the rat model might be different from that of human HAM because lymphocytic infiltration is an apparent characteristic of HAM patients, an unrecognized trigger might have induced infiltration of macrophages into the MSG in our patient.

Graft-versus-host-disease (GVHD) is considered to be a candidate cause of sialadenitis. Fujiwara et al (12) **have** previously reported sialadenitis in experimental GVHD in an animal model, in which the nonirradiated mice into which spleen cells were injected developed chronic GVHD. In their report, sialadenitis dominantly with CD4+ T lymphocytes was observed, although with a low frequency of macrophages, B cells, or plasma cells. However, chronic GVHD has rarely been reported after LDLT. Sun et al (13) reported a case of GVHD 4 months after cadaveric liver transplantation. In their report, the patient showed gastrointestinal symptoms, which was determined as T lymphocyte

infiltration by the colonic biopsy.

In summary, the mechanism by which sialadenitis is induced remains to be clarified. However, both active hepatitis and HAM might have the potential for viral-induced recruitment of mononuclear infiltration. Furthermore, double viral infection might provoke a strong eliminating reaction compared to single viral infection. Though an antiviral reaction is considered to be raised by innate immunity through toll-like receptors (14), intense antigen-presentation capacity might be yielded by induction of macrophages.

All authors declare no conflicts of interest in this paper.

Abbreviations; GVHD; graft-versus-host-disease, HAM; HTLV-I-associated myelopathy, IFN; interferon, LDLT; living-donor liver transplantation, MSG; minor salivary gland, SS; Sjögren's syndrome

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Figure legends

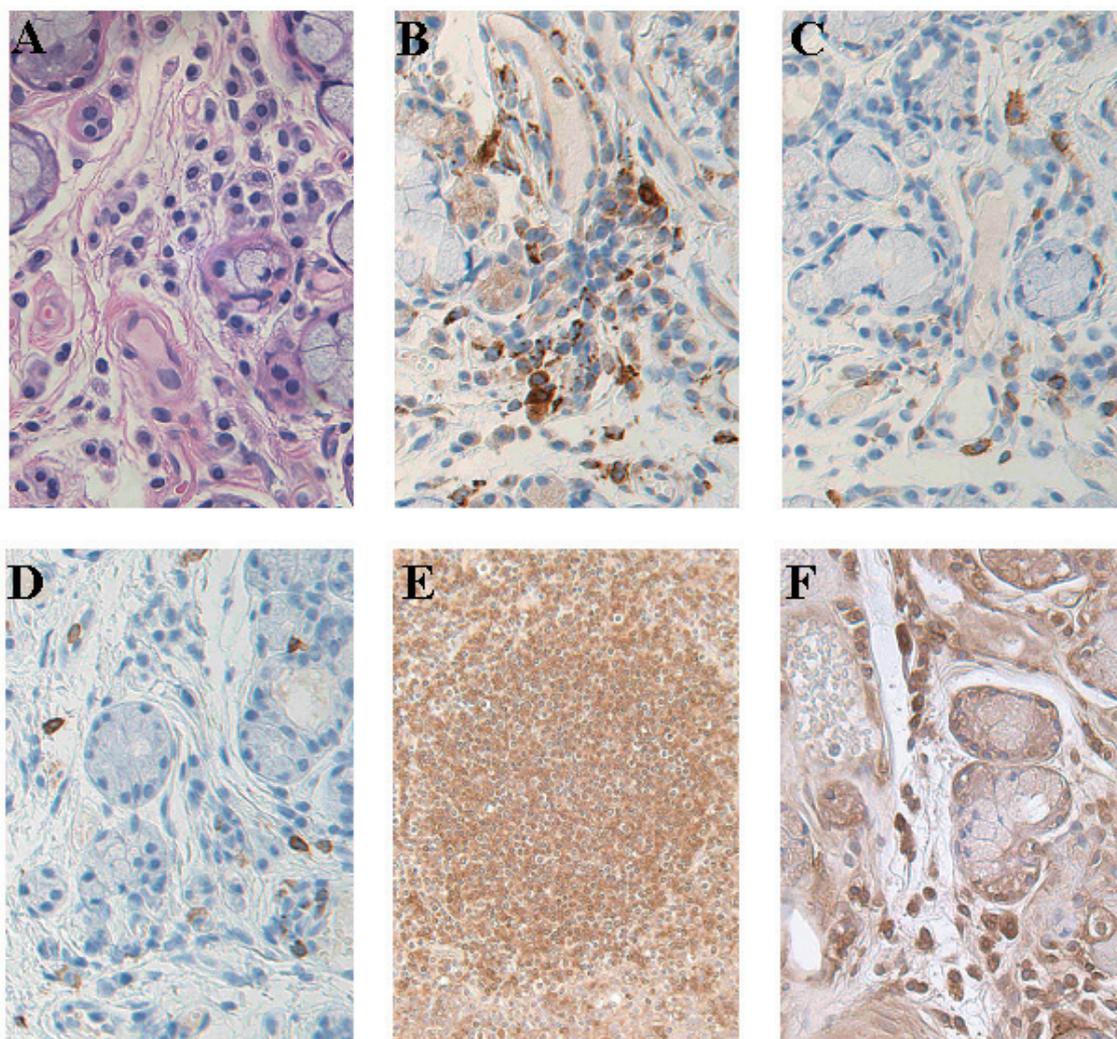


Figure 1 Phenotypic markers expressed in the minor salivary gland (MSG).

Immunohistochemistry was performed for formalin-fixed, paraffin-embedded sections (3 μ m thick) from the MSG using the streptavidin-biotin method. Primary antibodies were used as follows; A:hematoxylin eosin staining, B: CD68, C: CD4, D: CD8, E: MHC class II staining in human tonsil (positive control), F: MHC class II staining of the MSG of the patient (Original magnification; A-D, F: x200, E: x100) Hematoxylin was used as a counterstain.