Hepatitis C Virus and Sjögren’s Syndrome

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Sjögren’s syndrome (SS) is an autoimmune disease that is characterized by lymphocytic infiltration of salivary and lacrimal glands and other organs and is associated with autoantibodies such as anti-Ro/SS-A and La/SS-B (1). Although xerostomia and xerophthalmia are the most prominent symptoms of SS, a broad spectrum of systemic manifestations occurs in about half of SS patients. In the process of progression from a localized disease of salivary and lacrimal glands to a more generalized disease, many organs have lymphocytic infiltration, including hepatic, renal, pulmonary, neurologic, hematologic, dermatologic, and other systems.

Several viruses such as Epstein-Barr virus, cytomegalovirus, herpes virus, and retroviruses have been implicated in the pathogenesis of SS. Viral activation of epithelial cells and B lymphocytes in the salivary and lacrimal glands in the initiation phase of autoimmune reaction is an attractive thought to understand this disorder. Human T cell leukemia virus type I (HTLV I) could be implicated in SS in the western part of Japan (2). A possible role of hepatitis C virus (HCV) in SS has recently been suggested.

A case report in this issue of the journal (3) describes a patient with SS associated with chronic hepatitis C, thrombocytopenia, hypertrophic cardiomyopathy, and diabetes mellitus. There is some clinical and viral evidence to understand the multiple organ damage due to chronic HCV infection. See also p 657.

HCV, an RNA virus first identified in 1989, is a major cause of non-A, non-B hepatitis and the most striking feature of HCV infection is the risk of chronic hepatitis, cirrhosis and hepatocellular carcinoma. However, HCV infection affects not only the liver but also various non-hepatic tissues. Various immunologic and clinical abnormalities have been described in patients with chronic HCV infection (4); mixed cryoglobulins, autoimmune thyroiditis, pulmonary fibrosis, polymyositis, vasculitis, and recently, cardiomyopathy and diabetes mellitus. Moreover, asymptomatic immunologic changes have been reported, such as rheumatoid factor (RF) and antinuclear antibody (ANA) in these patients. The associated evidence that they result largely from immunological mechanisms, as well as from extrahepatic virus invasion and replication, lends support to the concept that HCV infection should now be viewed as a generalized disease rather than as an isolated hepatic disorder.

A relationship between HCV infection and SS was first postulated in 1992. Subsequently, several studies have demonstrated that the same clinical and histologic features seen in SS may occur in some patients with chronic HCV infection. Retrospective studies have reported the presence of antibodies against HCV in 10% of patients with sicca symptoms. In a report (5), SS patients with HCV infection showed a higher prevalence of anti-gastric parietal cell antibodies, anti-mitochondrial antibodies, cryoglobulinemia, hypocomplementemia, and a lower prevalence of anti-Ro/SS-A. HCV-RNA has been detected in saliva and salivary glands from patients with sialadenitis by polymerase chain reaction. Morphological evidence of HCV replication in salivary gland cells was also reported by in situ hybridization and immunohistochemistry (6), suggesting that HCV infects and replicates in the epithelial cells from salivary glands of patients with SS. Koike et al reported that transgenic mice carrying the HCV envelope genes developed an exocrinopathy involving the salivary and lacrimal glands and the pathology resembled SS (7). These observations suggest that HCV might be involved in the pathogenesis of sialadenitis in humans. Therefore, SS observed in some patients with HCV infection may be considered one of the extrahepatic manifestations of HCV infection. Salivary glands of patients with SS with and without chronic HCV infection probably share similar pathological changes.

Based upon our experimental findings (8), it is conceivable that there is a close interaction amongst the epithelial cells, T cells and B cells in the initial phase of autoimmune reaction in the salivary gland of SS (Fig. 1). Activated epithelial cells by viral infection can aberrantly express HLA molecules and co-stimulatory molecules such as CD80 on the cell surface, therefore these cells can present antigens with HLA molecules. The CD40L molecule expressed on the activated T cells stimulates the CD40 on the epithelial cells and upregulates their expression of the CD80 molecule. The CD80 molecule can strongly activate the CD4 T cells through the stimulation of the CD28 molecule in conjunction with TCR stimulation. Then, the activated CD4 T cells stimulate B cells through the CD40L-CD40 interaction along with the action of various cytokines and chemokines. This interaction amongst the epithelial cells, T cells and B cells is thought to allow these cells to live cooperatively against the apoptotic mechanism in the local autoimmune site, resulting in the perpetuation of the autoimmune reaction in SS.

Thrombocytopenia is one of the systemic disorders of SS
However, a number of studies have reported the presence of platelet-associated immunoglobulin G (PAIgG) in patients with chronic HCV infection. Although the presence of PAIgG is not a definitive evidence of immune thrombocytopenia, other findings support an immune mechanism. Interestingly, HCV-RNA was detected by RT-PCR in the platelets in patients with HCV infection. These data indicate that chronic HCV infection may also produce a significant autoimmune reaction to platelets, leading to thrombocytopenia.

Recently, an association of HCV infection with cardiomyopathy was reported. High incidence of positive anti-HCV antibody was present in patients with dilated cardiomyopathy. HCV RNA was detected in the hearts of patients (10). HCV may replicate in the heart and HCV infection may play a role in the development of hypertrophic cardiomyopathy.

Epidemiological studies have suggested a linkage between type 2 diabetes and chronic HCV infection. In a mouse model transgenic for the HCV core gene, the ability of insulin to lower the plasma glucose level in the HCV transgenic mice was impaired, as observed in chronic HCV patients (11). These results provide experimental evidence for the contribution of HCV in the development of insulin resistance in human HCV infection, which finally leads to the development of type 2 diabetes.

In order to elucidate the complicated pathophysiology of the interaction between viral infection and various autoimmune reactions like the cases of HCV and SS, it is absolutely necessary to accumulate such patients as the case reported in this issue (3).

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References


