Is Hepatitis C Virus a Sialotropic Virus?

To the Editor-in-Chief:

Sjögren’s syndrome (SS) is an autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. A possible relationship between SS and hepatitis C virus (HCV) was postulated in 1992 by Haddad et al., who reported the occurrence of characteristic SS histological changes in the salivary glands of patients with HCV infection. Various mechanisms may contribute to the pathogenesis of SS associated with HCV infection. These include a direct infection and proliferation of HCV in salivary glands, molecular mimicry between HCV and salivary glands, and formation of immune complexes containing HCV. A recent experimental murine model study has shown a direct link between HCV and SS. Koike et al. described the development of an exocrinopathy resembling SS in the salivary and lacrimal glands of transgenic mice carrying the HCV envelope genes, and suggested that the envelope proteins of HCV may recruit lymphocytes in the salivary glands thus leading to the formation of lymphocytic infiltrates. However, Pawlotsky et al. suggested that lymphocytic infiltration of salivary glands could be due to the presence of immune complex deposits in capillaries or to HCV replication in salivary glands or in lymphocytes infiltrating the glands.

Arrieta et al. have reported that HCV infects and replicates in epithelial cells from salivary glands of patients with SS or chronic sialadenitis, suggesting that HCV shows a specific tropism for infecting exocrine glands. This represents the first pathological evidence in humans of a direct link between HCV infection and SS. Previously, several studies have shown the existence of sicca symptomatology, positive ocular tests, lymphocytic infiltration of salivary glands, and autoantibodies in patients with HCV infection. These findings may lead to a diagnosis of SS in some HCV-patients. We recently described the clinical and immunological features of 35 patients with HCV infection who fulfilled a minimum of four of the six European criteria for the classification of primary SS. Several studies have suggested that HCV infection may account for the pathogenesis of a subgroup of patients with “primary” SS, especially in patients with evidence of liver involvement or associated cryoglobulinemia. Chronic HCV infection may remain subclinical for many years, and may be clinically expressed as the appearance of dryness of the mouth and eyes, and these HCV patients may be misdiagnosed as primary SS for a considerable period.

An interesting common feature of primary SS and HCV infection is the association with two specific conditions: mixed cryoglobulinemia (MC) and non-Hodgkin lymphoma (NHL). A strong association between MC and HCV infection is recognized, while MC in SS has been associated with a high incidence of HCV infection. In addition, the main immunological feature in the SS-HCV-related SS patients in our above-mentioned study was cryoglobulinemia which was present in 60% of the patients. This further emphasizes the strong relationship between SS, HCV, and MC. The second condition associated with both diseases is NHL, the most serious complication in the evolution of primary SS, which has also been recently described in patients with chronic HCV infection. We have described the development of NHL in two of our HCV-related SS patients (both with cryoglobulinemia), and Selva-O’Callaghan et al. have described a patient with primary SS who was subsequently diagnosed as HCV positive and who finally developed NHL. It is possible that the coincidence of HCV infection, SS, and cryoglobulinemia in the same patient may favor the development of lymphoproliferative processes.

Is HCV a sialotropic virus? The data reported by Arrieta et al. suggest that HCV may be a direct cause of sialadenitis in humans. Currently, HCV can be considered as a virus with a triple tissue tropism (hepatotropism, lymphoproliferation, and sialotropism), and this could explain a greater prevalence of sicca syndrome, cryoglobulinemia, and lymphoproliferation observed in patients with chronic HCV infection. However, the role of HCV and its viral proteins in the pathogenesis of SS is not clear at present.

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References