Abstract

A 74-year-old woman with Sjögren’s syndrome and chronic hepatitis C (CHC) was admitted to our hospital in October 2003 for treatment of diabetes mellitus. She had the past history of recurrent thrombocytopenia, which was proven to be due to peripheral destruction. Although she had been diagnosed with hypertrophic cardiomyopathy (HCM) for 2 years, she had never felt palpitation. She suddenly died probably of fatal arrhythmia related to HCM during the last hospitalization. Although hepatitis C virus (HCV) infection has been associated with Sjögren’s syndrome, thrombocytopenia, HCM, and diabetes mellitus, all these diseases rarely occur in a single patient. It will be necessary to identify similar cases to elucidate the etiopathogenesis of extrahepatic manifestations of HCV infection.

Key words: hepatitis C virus (HCV), Sjögren’s syndrome, extrahepatic manifestation, thrombocytopenia, sudden death

Introduction

Hepatitis C virus (HCV) has become the leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (1). HCV can also cause various extrahepatic manifestations such as thrombocytopenia, cardiomyopathy, and salivary gland disorders (2–4). Although the presence of HCV at these extrahepatic organs was demonstrated (3, 5, 6), the mechanism of how HCV induce these disorders is not known.

Sjögren’s syndrome is a multisystem autoimmune disease which predominantly affects the exocrine glands, but also has extraglandular manifestations involving cutaneous, pulmonary, renal, vascular, and neurological systems. In actuality, anemia, thrombocytopenia, and leucopenia are common in patients with Sjögren’s syndrome, but they are usually mild and involvement of the cardiac muscle is quite rare (7, 8).

This report describes a 74-year-old woman with a 21-year-history of Sjögren’s syndrome who concurrently had chronic hepatitis C (CHC), thrombocytopenia, hypertrophic cardiomyopathy (HCM), and diabetes mellitus. The possible relationship of HCV infection she contracted at the age of 36 to these disorders is discussed.

Case Report

A 53-year-old woman was referred to our hospital in 1982, presenting with sicca symptom in her oral cavity and peripheral arthralgia lasting for several years. She had a past history of blood transfusion when she underwent hysterectomy for myoma uteri in 1965. Laboratory examination disclosed antinuclear antibody and mild hypergammaglobulinemia, while anti-SS-A/SS-B antibodies were negative throughout her course. Sialography showed an abnormal pooling with an apple tree-like pattern, and biopsy of the minor salivary gland revealed focal lymphocytic infiltration (Fig. 1). Based on these findings, she was given a diagnosis of Sjögren’s syndrome. She was followed up without any
specific treatments.

In 1989, elevated levels of alanine aminotransferase (ALT) were detected and a positive test for anti-HCV antibody established the diagnosis of CHC. However, the patient was lost to follow-up since 1993.

She returned to our hospital in June 2001, because she noticed occasional epistaxis. Physical examination revealed systolic ejection murmur, petechiae on her limbs (Fig. 2), and hemorrhage in conjunctivae and oral mucosae, which prompted her hospitalization. Laboratory data showed markedly decreased platelet counts (0.5×10^4/mm^3) and elevated ALT level (Fig. 3). Other hematological or biochemical data did not show any significant abnormalities except elevated platelet-associated IgG (PAIgG) at 858 ng/10^7 platelets (normal range: 9–25) and HCV RNA at 41 KU/ml (normal range: <1) (Fig. 3). Tests for rheumatoid factor, anti-double stranded DNA antibody, and anti-Sm antibody were all negative. Serum complement levels were also normal. Bone marrow examination showed an increased cell number of the megakaryocytic lineage with normal morphological appearances (Fig. 4). Splenomegaly was not detected on ultrasonogram. Based on these findings, her thrombocytopenia was ascribed to peripheral destruction as in immune thrombocytopenic purpura. Initial treatment with daily prednisolone (PSL) 0.6 mg/kg and intravenous immunoglobulin (IVIG) 17.5 g/day for 5 days did not gain any beneficial effects. After methylprednisolone pulse therapy (0.5 g/day for 3 days) followed by daily 1.0 mg/kg PSL, her thrombocytopenia gradually improved, although HCV RNA titers remained markedly increased, elevation of ALT level was mild. She was discharged symptom-free in one month.

Severe thrombocytopenia recurred that necessitated the third hospitalization on July 5, 2002. Neither PSL (increased to 30 mg/day) nor IVIG induced any favorable effects. PSL was changed to dexamethasone with an additional danazol, which increased her platelet counts gradually. Serum ALT increased slightly probably due to an adverse reaction of danazol; its withdrawal normalized her serum ALT level.

She had been in good condition and stayed asymptomatic, and dexamethasone was tapered to 1.25 mg/day by September 2003, when she was diagnosed with diabetes mellitus based on plasma glucose 239 mg/dl and HbA1c 12.1%. She was hospitalized and subcutaneous insulin injection was started immediately. Plasma glucose level gradually decreased and HbA1c was suppressed to 9.0% without any hypoglycemic episodes.

She was found dead on bed at the night of November 19, 2003. The cause of her death was not detected clinically. Serum level of creatine kinase and plasma glucose level were normal and computed tomography of her brain did not disclose any abnormal signs. Autopsy was not performed, unfortunately.

Discussion

Here, we report a patient with Sjögren’s syndrome who also had CHC, thrombocytopenia, HCM, and diabetes mellitus. The co-occurrence of CHC and Sjögren’s syndrome (9), CHC and thrombocytopenia (2), CHC and HCM (10), and
CHC and diabetes mellitus (11) have been reported. To the best of our knowledge, however, this is the first case in which all five conditions coexisted; they may have been related to the chronic HCV infection she may have suffered from during 38 years.

Diagnosis of Sjögren’s syndrome in the present case was established by typical sicca symptoms, biochemical indices, histological analysis, and sialography. She was found to be HCV-positive in 1993 and the most probable cause was the blood transfusion she received in 1965 for hysterectomy. Sjögren’s syndrome is known as one of the extrahepatic manifestations of CHC (4, 12). Sjögren’s syndrome in CHC is characterized by tenacious xerostomia, absence of systemic manifestations such as pulmonary and renal involvement sometimes observed in primary Sjögren’s syndrome, and lack of anti-SS-A or anti-SS-B antibody (13). The present case is consistent with all of these characteristics, which suggested the causal relationship between HCV infection and Sjögren’s syndrome.

Several reports have described the clinical features of thrombocytopenia observed in patients with Sjögren’s syndrome (14, 15). In the present case, the reason for the thrombocytopenia was unclear but may have been related to the chronic HCV infection.
syndrome (7, 14). The prevalence of thrombocytopenia (<10×10^4/mm^3) in Sjögren’s syndrome is reported to be 3.6% to 7.1%, which is similar to that in CHC (2, 7, 14). The degree of thrombocytopenia in Sjögren’s syndrome is usually mild without need for treatment. Even if treatment is needed, the response to PSL is generally favorable. Clinically, patients with Sjögren’s syndrome and thrombocytopenia are significantly younger and have a higher tendency to have accompanying skin eruptions and anti-SS-B antibody than those without (7). On the other hand, the majority of patients with immune thrombocytopenic purpura related to HCV need treatment such as PSL and splenectomy, with the response to PSL much poorer than those unrelated to HCV (15). Thus, we would implicate the present case’s thrombocytopenia in CHC rather than a complication of Sjögren’s syndrome based on the following reasons: high titers of serum HCV RNA, negative anti-SS-A/SS-B antibodies, severe and recurrent thrombocytopenia in spite of PSL treatment, and high age at onset.

PSL, interferon alpha (IFN-α), and splenectomy are favored in the treatment of thrombocytopenia associated with CHC (15–17). Here, we chose PSL rather than IFN-α because successful treatment with PSL for thrombocytopenia associated with HCV was reported without exacerbation of liver function (17); treatment with IFN-α per se sometimes induces thrombocytopenia in CHC (18). Splenectomy was not performed by the patient’s option. PSL was indeed effective, but its efficacy did not last long and thrombocytopenia recurred several times with concomitant increases in HCV RNA and serum ALT level. It is sometimes very difficult to select the treatment modality for thrombocytopenia associated with HCV (15–18). Under these circumstances, it is very necessary to accumulate patients like the present case to pursue safer and more effective treatments.

Recent studies have demonstrated a significantly higher prevalence of anti-HCV in HCM patients than control normal population (19), and the presence of HCV RNA in myocardial tissue from HCM was clearly documented (3). Cardiac involvement in Sjögren’s syndrome is quite rare (8), and therefore, it is highly probable that HCM was due to, or closely related to HCV infection, rather than a complication of Sjögren’s syndrome in the present case. Because there were no signs of life threatening tachyarrhythmias, no pre-

Figure 6. Possible pathways of disease progression in the present case. BTF: blood transfusion, DM: diabetes mellitus, HCM: hypertrophic cardiomyopathy, HCV: hepatitis C virus, ITP: immune thrombocytopenic purpura, SS: Sjögren’s syndrome.
ventive measure was placed to the present case (20). However, IFN-α might have been a treatment choice (21).

Many reports state that diabetes is associated with persistent HCV infection (22, 23). Because she had received high-dose corticosteroid therapies, we are not certain about the cause-effect relationship, but the possibility remains.

Finally, our hypothesis on the course and clinical outcome of this patient is depicted in Fig. 6. We are not sure whether all her symptoms and multi-organ involvement are attributable to HCV, however, the following characteristics point its possibility. First, she had received blood transfusion long before she showed sicca symptoms, recurrent and severe thrombocytopenia, HCM, and diabetes mellitus. Secondly, anti-SS-A/SS-B antibodies stayed negative throughout her clinical course. Last, all of these symptoms and organ abnormalities are known as extra-hepatic manifestations of chronic HCV infection. Should this be the case, we would have wanted to use INF-α to eradicate HCV as much as possible. IFN therapy under these circumstances, however, would have to be weighed against its immunomodulatory effects that might aggravate some symptoms of a probable autoimmune etiology.

**References**


