CASE REPORT

Adult-onset Still’s Disease Complicated by Autoimmune Hepatitis: Successful Treatment with Infliximab

Kenji Fujii, Ryo Rokutanda, Yasuhiro Osugi, Yoshinobu Koyama and Toshiyuki Ota

Abstract

A 17-year-old woman was previously diagnosed with autoimmune hepatitis (AIH) by liver biopsy. Adult-onset Still’s disease (AOSD) was subsequently diagnosed on the basis of high fever, arthralgia, erythema, leukocytosis (>80% granulocytes), cervical lymph node swelling, splenomegaly, and hyperferritinemia. Her symptoms and liver dysfunction improved with prednisolone of 60 mg daily and subsequently methotrexate was added. However her symptoms and liver dysfunction relapsed when prednisolone was tapered to 20 mg/day. Therefore infliximab was introduced additionally and her symptoms and liver dysfunction subsided. To our knowledge, this is the first reported case of AOSD with AIH diagnosed by liver biopsy.

Key words: adult-onset Still’s disease, autoimmune hepatitis, Sjögren’s syndrome, IgG4-related disease, TNF inhibitor


Introduction

Adult-onset Still’s disease (AOSD) is a rare systemic inflammatory disorder, and the associated liver dysfunction is frequent with AOSD patients. AOSD-associated liver dysfunction is sometimes useful as a marker of disease activity and also as supplementary information for diagnosis (1). However, many reported cases of AOSD with liver dysfunction are drug-induced AOSD. On the other hand, AOSD with autoimmune hepatitis (AIH) is extremely rare (2, 3) and histological examination of the liver was not performed in the previous reports. To our knowledge, this is the first report of AOSD complicated by AIH diagnosed by liver histopathology, and a case of successful treatment with anti-tumor necrosis factor (TNF) blocker for AOSD with AIH.

Case Report

In January 2007, a 17-year-old woman presented at our hospital with left lacrimal gland swelling that lasted 7 months. However she had no dryness of the eyes. Laboratory analysis revealed a positive titer of antinuclear antibodies (ANA) (1:1,280), elevated immunoglobulin (IgG) (1,829 mg/dL), and extensive inflammatory cell invasion of the salivary glands (Fig. 1); and Sjögren’s syndrome (SS) and IgG4-related disease were suspected. However, a definitive diagnosis was not determined because she was serologically negative for anti-Ro and anti-La antibodies, and her IgG4 levels were not elevated (41.7 mg/dL). Eventually, her symptoms spontaneously improved. We followed her without medication for 1 year. However, in January 2008, the patient developed liver dysfunction [aspartate aminotransferase (AST): 1,040 IU/L, alanine aminotransferase (ALT): 1,124 IU/L, lactate dehydrogenase (LDH): 615 IU/L, and alkaline phosphatase (ALP): 821 IU/L] and hyperferritinemia (3,043 ng/mL) without any symptoms (e.g., lacrimal gland swelling, sicca symptoms, erythema, fever, sore throat, and arthralgia). Laboratory analysis showed a positive titer of ANA (1:1,280) and elevated IgG (2,139 mg/dL), but her IgG4 levels were not elevated (62.9 mg/dL). Furthermore, liver biopsy showed mild to moderate lymphocytic infiltration and partial piecemeal necrosis (Fig. 2). Although SS still seemed like a possibility, she was definitively diagnosed with AIH after obtaining a score of 16 points using the diagnostic criteria of the International Autoimmune Hepatitis Group (4). The symptoms and liver dysfunction improved with the administration of an initial daily dose of 30 mg
prednisolone (PSL), followed by tapering of PSL to 10 mg/day. In August 2008, she was admitted to our hospital with a high fever (39°C) (which continued for more than 2 weeks), bilateral knee arthralgia, and erythema of the extremities. Physical examination revealed evanescent salmon-pink maculopapular erythema on the neck and extremities, along with the Koebner phenomenon. Mild swelling of lymph nodes was noticed in the cervical region but not in the subclavicular, axillary, or inguinal regions. Lacrimal gland enlargement and sicca symptoms were not seen on admission. Laboratory tests showed leukocytosis (13,300/μL) with more than 80% granulocytes, liver dysfunction (AST: 69 IU/L, ALT: 81 IU/L, LDH: 462 IU/L, and ALP: 216 IU/L), elevated erythrocyte sedimentation rate (47 mm/h), elevated C-reactive protein (4.41 mg/dL), hyperferritinemia (18,306 ng/mL), and elevated total complement activity (CH50) (63.8 U/mL). Tests for rheumatoid factor, anti-Ro antibody, anti-La antibody, anti-smooth muscle antibody, and anti-liver-kidney microsomal type 1 antibody were negative. In addition, tests for hepatitis B and C antibodies, human immunodeficiency virus antibody, cytomegalovirus antibody, Epstein-Barr virus antibody, and herpes simplex virus antibody were negative. Serum soluble interleukin (IL)-2 receptor was mildly elevated at 827 U/mL (normal value: <500). Further, only mild hepatosplenomegaly was found on abdominal computed tomography (CT), with any accompanying significant abnormality such as abdominal lymphadenopathy. Blood, urine, and throat cultures were sterile. Therefore, infection and malignancy were excluded and AOSD was diagnosed according to the criteria of Yamaguchi et al (5). After PSL was increased to 60 mg/day, her symptoms improved and her liver dysfunction went down to normal. Following this, her PSL was tapered to 40 mg/day. And then methotrexate was added for a steroid-sparing effect at 6 mg/week with careful attention of preventing liver function from becoming worse. However, when PSL was further tapered to 20 mg/day, the patient developed AOSD flare with the reappearance of fever, erythema, and liver dysfunction (AST: 52 IU/L, ALT: 48 IU/L, LDH: 458 IU/L, and ALP: 244 IU/L), and hyperferritinemia (3,234 ng/mL). We considered replacing or adding another immunosuppressant drug, but the patient rejected this proposal because of the risk of fertility problems. And we presented an introduction of anti-TNF blocker or anti-IL-6 receptor antibody to control her diseases, she consented to an introduction of infliximab because of an extended-interval dosing regimen of infliximab and the risk of liver dysfunction by tocilizumab. Subsequently, infliximab (3 mg/kg) was administered and her clinical course improved. She did not develop AOSD flare and AIH even after we tapered PSL to 5 mg/day (Fig. 3).

**Discussion**

AOSD is a rare systemic inflammatory disorder, and the associated liver dysfunction and elevated serum ferritin levels are useful as markers of disease activity and also as supplementary information for diagnosis (1, 6).

In the present patient, AIH was initially diagnosed on the basis of her clinical course of liver dysfunction without fever and erythema, accompanied by the typical findings of liver pathology. The prevalence of concomitant SS and AIH has been reported to be 1.7-4% (7, 8); however, the present patient was not definitively diagnosed with SS at that point of time. On the other hand, to the best of our knowledge, SS with severe hyperferritinemia or AOSD has not been reported previously. In addition, the appearance of hyperferritinemia in our patient was not coincident with lacrimal gland swelling and sicca symptoms, the presence of which would have indicated SS. Therefore, her hyperferritinemia did not occur as a result of the latent presence of SS.

Here IgG4-related disease was suspected because of lacrimal gland enlargement and pathological inflammatory cell invasion of the salivary glands (9). However, immunostaining with anti-IgG4 antibodies was not performed, repeated measurements of serum IgG4 did not show any elevation, and other clinical conditions associated with IgG4-related diseases (such as autoimmune pancreatitis, interstitial nephritis, and retroperitoneal fibrosis), were not evident in the clinical course. Therefore, an IgG4-related disease was not the most likely cause in our case.

In the few reports of AOSD complicated by AIH (2, 3), histological examination of the liver was not performed (Table 1). This is the first report of AOSD complicated by AIH diagnosed by liver histopathology. Ferritin levels in AOSD patients are usually higher than those found in patients with other autoimmune or inflammatory diseases (1), and several cytokines-namely IL1β, IL18, TNFα, and IL6-appear to regulate the increased production of ferritin (10). Recently, it has been reported that a predominance of Th1 cytokines was shown in the peripheral blood and tissues of patients with active untreated AOSD (11), and also that IL18 was predominantly expressed in the liver tissue of AOSD patients (12). On the other hand, hyperferritinemia accompanied by liver dysfunction occurs in AIH, which is also char-
Figure 2. Pathological findings of the liver. Mild to moderate lymphocytic infiltration and partial piecemeal necrosis were recognized in portal region as interface hepatitis. Rosette formation of hepatocytes was also recognized. a) Low-power microscopic examination (Hematoxylin and Eosin staining ×100). b) Magnified view of A (Hematoxylin and Eosin staining ×400).

Figure 3. Clinical course

characterized by hepatocellular destruction. Regarding the pathogenesis of AIH, candidate target molecules for autologous hepatocytes have been identified and the participation of humoral immunity has been suggested (13). However, since very high ferritin levels are not common in AIH, the present case suggests the coexistence of different pathological conditions, namely AIH and AOSD.

Recently, the pathomechanism of autoimmune-associated hemophagocytic syndrome (HPS) was reported to be hyperferritinemia accompanied by an underlying collagen disease, which is different from infection- and/or malignancy-associated HPS (14). In that report, autoantibody-mediated, immune-complex-mediated, and cytokine-mediated mechanisms were proposed as the possible mechanisms of autoimmune-associated HPS. Further, HPS was accompanied by collagen diseases with specific autoantibodies, such as systemic lupus erythematosus, mixed connective tissue disease, and rheumatoid arthritis, in all cases and occurred as a result of an autoantibody-mediated mechanism. The ferritin levels in these cases were 34-496 ng/mL, unlike the severe hyperferritinemia in the present case. On the other hand, most of their cases of AOSD with HPS were due to a cytokine-mediated mechanism. In the present case, though the immune-complex levels were not measured, specific autoantibodies and hypocomplementemia were not detected in the clinical course. Therefore, hyperferritinemia in our patient could have occurred due to a cytokine-mediated mechanism despite the absence of a hemophagocytic condition. The AIH in this case did not show specific autoantibodies; therefore, her AIH may have been a heterogeneous type different from typical AIH. Further, her symptoms, including those of AIH, may have been due to an atypical
manifestation of AOSD itself.

With respect to the therapeutic approach to AOSD complicated by AIH, there exist reports of both a treatment-resistant fatal case despite steroid pulse and intravenous Ig therapy (2) and a successful case treated with steroids and plasma exchange (3); the former may have been a severe treatment-resistant case (Table 1). The usefulness of biological and TNF agents for AOSD has been reported (15, 16). The present case also suggests the usefulness of TNF inhibitors for AOSD with AIH.

We reported a very rare case of AOSD complicated by AIH. However, in a report on the pathological findings of 306 cases of rheumatic disease with liver dysfunction, 2/3rd cases were diagnosed as definite or probable AIH based on the diagnostic criteria of the International Autoimmune Hepatitis Group (17). Currently, distinguishing AIH from AOSD on the basis of specific liver pathology may not be possible. Further research, including the identification of specific cytokines and/or new specific antibodies for determining pathological differences between the diseases, is needed.

The authors state that they have no Conflict of Interest (COI).

References


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