Adult-Onset Still’s Disease with Submassive Hepatic Necrosis

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We present a 74-year old woman who was hospitalized because of typical spiking fever, evanescent rash, polyarthralgia, lymphadenopathy, and marked elevation of serum transaminases and lactate dehydrogenase (LDH) due to adult-onset Still’s disease (AOSD) with submassive hepatic necrosis. All of the symptoms and abnormal laboratory findings were dramatically improved after treatment with prednisolone. The clinical course of this patient indicates that AOSD with severe hepatic necrosis can successfully be treated with early administration of corticosteroid, although it remains unknown whether the disease can remain in remission with no or minimal treatment.

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Key words: fever of unknown origin, liver dysfunction, piecemeal necrosis, lymphadenopathy, corticosteroid therapy

Introduction

Adult-onset Still’s disease (AOSD) is a febrile disorder of unknown etiology characterized by typical spiking fevers, evanescent rash, arthralgia and leukocytosis. Liver function abnormalities are frequently seen in patients with AOSD, but the elevation of liver enzymes is usually mild and transient (1). We report a case of AOSD associated with submassive hepatic necrosis and marked elevation of serum transaminases, lactate dehydrogenase (LDH), serum ferritin and adenosine deaminase (ADA), which were dramatically improved after treatment with prednisolone.

Case Report

A 74-year old woman was admitted to our clinic in September 1993 because of bilateral gonalgia for the previous three weeks and fever, pruritic rash, and general malaise for one week. She underwent surgery for an ectopic pregnancy at the age of 34, and had been treated for osteoporosis with ipriflavone and alfalcacidol for the five years prior to admission. She did not have a history of blood transfusions or travelling abroad. There were no significant findings in the family history.

On admission she had fever (a double quotidian pattern) exceeding 39.0°C, lymphadenopathy in the axilla and inguinal region and anemic palpebral conjunctiva. Maculopapular pruritic salmon-pink eruptions were present on her anterior chest and extremities; these disappeared when her temperature normalized and reappeared with fever. The liver was palpable 1.5 cm below the right costal margin. The spleen was impalpable. No neurological abnormalities were found. The right knee had a little effusion without inflammatory signs.

Laboratory examination showed mild leukocytosis of 9,900/mm³ with 66% neutrophils and 16% lymphocytes, hemoglobin of 9.1 g/dl, platelet count of 271×10⁹/l, increased erythrocyte sedimentation rate of 75 mm per hour and C reactive protein (CRP) of 10.1 mg/dl. No abnormalities were found on examination of bone marrow smears and cerebrospinal fluid. Urinalysis was normal and stools were negative for blood and parasites. Serum albumin concentration was 3.5 g/dl, α₁-globulin 0.37 g/dl, α₂-globulin 1.27 g/dl, β-globulin 0.61 g/dl, γ-globulin 1.23 g/dl, aspartate aminotransferase (AST) 435 U, alanine aminotransferase (ALT) 404 U, LDH 940 U with a rise in isozymes 4 and 5. The alkaline phosphatase (ALP) was 9.8 KAU, γ-GTP 71 U, total bilirubin 0.63 mg/dl, thymol turbidity test (TTT) 1.1 Kunkel, zine sulfate turbidity test (ZTT) 6.5 Kunkel and hepaplastin test (HPT) 97%. Serum lipid levels were normal. Hepatitis B serologies showed HBsAg (−), anti-HBs antibody (+), anti-HBs antibody (-), anti-HBe antibody (−), low titers of anti-HBc antibody and IgM-anti-HBc antibody (−). Both anti-hepatitis C and IgM-anti-hepatitis A antibodies were negative. The serum ferritin was 1,794.5 ng/ml and ADA was

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57.4 U/l. Thyroid function was normal. Rheumatoid factor was negative. The antinuclear antibody was 1:40. Autoantibodies against double-stranded DNA, single-stranded DNA, smooth muscle, mitochondria and microsome were all negative. The lupus erythematosus (LE) cell phenomenon was not observed. The levels of IgG, IgA, IgM, and IgE and serum complement were normal. The skin reaction against purified protein derivative (PPD) antigen was negative. Analysis of T lymphocyte showed a slightly decreased ratio of CD4/CD8 subsets. The electrocardiogram and echocardiogram were normal. Roentgenography and CT scan of the chest revealed moderate thickening of the bronchial walls in the lower lobes bilaterally. Endoscopic examination of the stomach showed a single hyperplastic polyp.

One week after admission, pharyngitis, arthralgia of the wrists, and neck pain appeared. She had received no medication since the start of hospitalization, and high spiking fevers persisted. Repeated cultures of blood, throat, urine, stool, bone marrow and cerebrospinal fluid failed to detect any pathogenic microorganisms. Antiviral antibody titers did not show significant changes. Minocycline was administered to therapeutically rule out rickettsiosis but had no effect on the fever, polyarthralgia, or elevated transaminases and LDH.

A liver biopsy two weeks after admission demonstrated submassive hepatic necrosis in centrilobular areas (Fig. 1). Intra-hepatic bridging fibrosis, either portal-central or portal-portal, was also seen. The inflammatory infiltrates, which were composed of neutrophils and lymphocytes, greatly expanded the portal areas and caused piecemeal necrosis. A biopsy of the right inguinal lymph node revealed only reactive hyperplasia.

She received brief courses of antibiotics and then rifampicin in combination with isoniazid because some infections including tuberculosis could not be completely excluded. Despite these treatments, spiking fever and polyarthralgia further deteriorated. In addition, disseminated intravascular coagulation (DIC) occurred after the administration of cephalosporin. This reversed soon after the withdrawal of the antibiotics.

The clinical course was compatible with diagnostic criteria for adult-onset Still's disease (AOSD). After 30 mg/day of prednisolone was begun, all of the symptoms and abnormal laboratory findings were dramatically improved. She has been afebrile since day 5 of treatment with prednisolone (Fig. 2). Her stable condition has been maintained with 5–10 mg of prednisolone daily in our outpatient clinic.

**Discussion**

AOSD was initially described by Bywaters (2), and its resemblance to childhood Still's disease has been emphasized. The incidence of positive antinuclear antibody or rheumatoid factor in AOSD is somewhat greater than that seen in healthy individuals, and if present, the titer is very low (1). Because this disease lacks specific clinical and histologic features, a diagnosis of AOSD usually depends upon exclusion of other diseases such as infection, malignancy and collagen diseases. The present case was compatible with the criteria proposed by Yamaguchi et al (3), which was designed in a statistically based manner.

Among 178 patients with AOSD reviewed (1), 135 patients (75.8%) were between 16 and 35 years of age at onset while only 8 cases (4.0%) developed the disease over age 56. The present case appears to be the eldest except for an 83-year-old one (4).

When the present patient visited our out-patient clinic for osteoporosis in May 1992, sixteen months before the onset of AOSD, the laboratory data showed a slightly elevated LDH (471 U) with normal levels of transaminases and bile duct enzymes. It has been shown that LDH may be a very sensitive marker for AOSD activity, especially in its subclinical forms (5). This case may have had subclinical AOSD at this time point.

Ohta et al (6) reported that 54% of patients with AOSD had adverse drug reactions in their study. In some reports on AOSD (1), liver injury has been ascribed to drug allergies or toxicities. However, liver injury (usually mild) is often seen in patients...
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with AOSD who have not been exposed to any drugs (7). Hepatic necrosis observed in the present case was probably due to primary liver damage associated with AOSD. This is supported by the fact that liver function became normal as the disease activity of AOSD subsided with treatment.

In patients with AOSD, the liver biopsy findings have included infiltration of inflammatory cells into portal areas (1), mild interstitial hepatitis (8), mild portal fibrosis, focal hepatitis with necrosis (7), and mild chronic necro-inflammatory changes (9). Massive hepatic necrosis has been described in a case report of AOSD (11). The liver in the present case exhibited submassive hepatic necrosis with intra-hepatic bridging fibrosis and piecemeal necrosis, both of which are usually seen in severe forms of chronic active hepatitis. It has been postulated that in chronic active hepatitis, an immunologic reaction is directed against membrane constituents of the hepatocyte which serve as antigens (12). Although there has been no evidence for an underlying immune mechanism in the development of AOSD, the present findings may indicate a role of immunologic reactions in the pathogenesis of AOSD.

Because nonsteroidal antiinflammatory drugs (NSAID) alone have been unable to control the systemic symptoms in many cases of AOSD, corticosteroid has been commonly used in treatment, often with good responses as seen in the present case (1). However, a high frequency of exacerbation or recurrence following tapering or discontinuation of corticosteroid has been an important problem. Two reported patients with AOSD with severe hepatic necrosis died of hepatic failure possibly because of the delay in initiating corticosteroid in one case and recurrence of hepatic necrosis after tapering corticosteroids in another case (11, 13). The clinical course of the present patient indicates that AOSD with severe hepatic necrosis can successfully be treated with early administration of corticosteroid, although it remains unknown whether the disease can remain in remission with no or minimal treatment.

References