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Autoimmune Hepatitis as an Initial Presentation of SLE

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Abstract

An 11-year-old female patient with autoimmune hepatitis (AIH) was referred to our rheumatology clinic due to her current musculoskeletal manifestations. The patient had been diagnosed with AIH 3 months previously, based on jaundice and impaired liver function tests, and she had been treated with low-dose prednisolone and azathioprine. She presented with malaise, arthritis, a malar rash on the face, and oral ulcers. Laboratory tests revealed a positive ANA/anti-dsDNA test. Liver biopsy showed chronic hepatitis with severe inflammatory activity, in favor of a diagnosis of definite AIH. She fulfilled the international criteria for both SLE and AIH. The clinical symptoms and laboratory findings of SLE improved with ongoing treatment with corticosteroids and azathioprine, accompanied with hydroxychloroquine sulfate. The present case indicates that AIH can be the first manifestation of SLE in children.

Keywords: Autoimmune Hepatitis, Pediatric Lupus, Liver Disorder

1. Introduction

Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disorder, more prevalent in females, that is associated with high liver transaminase and immunoglobulin G levels, and histological changes due to inflammation in hepatocytes and liver tissue (1). It usually presents in children with nonspecific symptoms, such as malaise, lethargy, and arthralgia without arthritis. It can present either very acutely or more insidiously, but can progress rapidly and lead to cirrhosis in a relatively short period of time in untreated severe disease (2). AIH reflects a complex interaction between triggering factors, autoantigens, genetic predisposition, and immune regulatory mechanisms (3). Systemic lupus erythematosus (SLE) is a systemic autoimmune disease classically involving the skin, kidneys, and central nervous system. Several previous reports showed the manifestation of AIH in adult lupus patients (4-6); however, there are no reports of such an association between AIH and SLE in children. Both AIH and SLE have an autoimmune basis and hence can occur simultaneously or masquerading as presentations of each other. In this case report, we report AIH as the first manifestation of SLE in an 11-year-old girl.

2. Case Presentation

After obtaining IRB approval from our center's ethics board, we decided to report this special case. An 11-year-old female patient was referred to the rheumatology department with complaints of anorexia, malaise, weight loss, pain in the sacroiliac joint accompanied by carpal joint swelling, and remarkable motion limitations. The patient had had icteric sclera for 3 months prior to her current presentation. Her parents did not agree for her to undergo liver biopsy at that time. Laboratory data revealed liver dysfunction, suggesting autoimmune hepatitis, and she underwent treatment for hepatitis (prednisolone 2 mg/kg daily with azathioprine 1 mg/kg). However, with the elimination of jaundice and decreased hepatic enzyme levels, the prednisolone dose was tapered. Low-dose prednisolone had been continued until she was referred to our clinic.

On her review of systems, she had photosensitivity (malar rash), oral ulcers, morning stiffness for about 1 hour, intermittent constipation and diarrhea, and hair loss. She also had a recent weight loss of about 2 kg. She is the third child of her family and was born via vaginal delivery. There was no consanguinity between the parents. Family history was negative for rheumatic or inherited liver disease, including systemic lupus erythematosus (SLE) and autoimmune hepatitis (AIH). On physical exami-

nation, we found malar rash, oral ulcers, slight tenderness of the sacroiliac joint, and swelling and limitation of movement in the carpal joints. There was no organomegaly.

Laboratory tests showed lymphopenia, mild Coomb's-positive anemia, and high hepatic enzyme levels, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase. Serological tests were positive for serum nuclear antigen antibodies (ANA) and double-stranded DNA antibodies (anti-dsDNA) (0.868 and 28.7 IU/mL, respectively), and decreased levels of serum C4 (0.147 gr/L). Anti-smooth muscle antibody (ASMA) was greater than 1/80 and serum globulin was 3.5 g/dL. The liver needle biopsy showed bridging fibrosis and the presence of few plasma cells in portal tracts, in favor of AIH. These paraclinical results together with the clinical findings strongly suggested systemic lupus erythematosus (SLE) as the definitive diagnosis. Indeed, in this case, AIH was associated with SLE.

With the diagnosis of SLE, 30 mg/kg/day of methylprednisolone pulse was begun, with a rapid clinical improvement in arthritis, malaise, and general condition. Azathioprine was continued at the same dose as before (1 mg/kg/day). In addition, daily hydroxychloroquine sulfate, folic acid, and vitamin E were added to her medication list, to control SLE more precisely. This aggressive treatment continued for 3 days, then the methylprednisolone dose was changed to 1.5 mg/kg/day orally. This treatment continued for 2 months, after which the prednisolone dose was tapered and continued to the present.

This treatment directed against SLE resulted in both clinical and laboratory test improvements. At the 6-month follow-up, the patient had no malaise, morning stiffness, joint pain, or limitations in carpal joint range of motion. A complete blood count revealed a hemoglobin of 13.6 g/L, white blood cell count of 17,400/mm^3 (diff: neutrophils 77%, lymphocytes 21%, and eosinophils 2%), and a red blood cell count of 5,250,000/mm^3, showing marked improvement in lymphopenia and anemia. Biochemistry testing showed a serum creatinine of 0.8 and a normal BUN. All liver function tests were normal, except for slightly high AST of 55 IU/L. Therefore, the treatment against SLE resulted in marked improvement in SLE symptoms and signs, as well as in liver function (Table 1).

3. Discussion

Two types of childhood AIH are described based on seropositivity: smooth muscle antibody (SMA) and/or antinuclear antibody (ANA), which is AIH type 1, and antibodies to liver-kidney microsome type 1 (anti-LKM1), which is AIH type 2. There is a female predominance in both (7).

There is no characteristic feature that distinguishes hepatic involvement of SLE from AIH based on their clinical and biochemical profiles. Although rare, there are documented reports of liver involvement in SLE patients. The more confounding issue is that patients with AIH may be at an increased risk of developing systemic connective tissue diseases and vice versa (8). Since the treatment strategies are different in these two conditions, the challenge is whether to treat the patient as an SLE case with secondary liver involvement or as an AIH case with primary liver disease (8-13).

The diagnosis of AIH is based on laboratory and liver histology features, in addition to the exclusion of conditions that resemble AIH (14). Periportal (interface) hepatitis is the hallmark of AIH syndrome, and portal plasma cell infiltration is typical of the disorder. Although the International Autoimmune Hepatitis Group scoring system is designed for adults, it can also be used for children to support the diagnosis of AIH in the presence of periportal hepatitis (15). The diagnosis of SLE is based on the criteria defined by the American College of Rheumatology (16).

It is not possible to use the serologic criteria (such as hypergammaglobulinemia and positive tests for ANA, SMA, anti-ribonucleoprotein antibody, and anti-cardiolipin antibodies) alone in order to make the definitive diagnosis, because both AIH and SLE-associated hepatitis have features of autoimmune disorders. What can lead to a definitive diagnosis are several histological and clinical features that can differentiate AIH from SLE (17, 18). The presence of cirrhosis or periportal hepatitis, periportal piecemeal necrosis associated variably with lobular activity, and rosette formation of liver cells support the diagnosis of AIH, but do not exclude SLE. In contrast, liver histology in SLE usually shows changes attributable either to drug toxicity or non-specific liver involvement, e.g., fatty degeneration or hydropic hepatocytes (19-21).

Our patient was evaluated for hereditary (Wilson's disease, α-1 antitrypsin deficiency, genetic hemochromatosis) and infectious (hepatitis A, B, C; CMV; EBV) liver injuries. All of the related diagnostic features were negative. The liver biopsy showed fibrosis of hepatocytes accompanied by plasma cell infiltrations. The patient met several criteria of the revised scoring system for diagnosis of AIH, including female gender, negative viral hepatitis markers, elevated serum globulins, ANA and ASMA titers, formation of liver histology, and the presence of another autoimmune disease (SLE in this case) (22). Even more interesting is that she met the American College of Rheumatology criteria for SLE as well as the criteria for AIH. She had the characteristic common SLE clinical features (photosensitivity, malar rash, arthritis, and oral ulcers) and was positive for ANA and anti-dsDNA, which are sufficient to diagnose SLE (22,

Table 1. Follow-Up Laboratory Testing of Patient After Treatment for a Combination of SLE and AIH

Lab Test	Result	Normal range
CBC		
RBC count	5,250,000/mm^3	3.72 - 5.30 x 1,000/mm^3
Hemoglobin	13.6 of 100 g/L	11 - 15.5 g/L
WBC count	17,400/mm^3; (neutrophils 77%, lymphocytes 21%, eosinophils 2%)	4,000 - 11,000 /mm^3
Biochemical analysis		
Serum creatinine	0.8 mg/dL	0.5 - 1 mg/dL
BUN	12 mg/dL	13 - 43 mg/dL
Liver Function Tests:		
PT	12 seconds	12 seconds
PTT	38 seconds	28 - 48 seconds
ALT	28 IU/L	Up to 41 IU/L
AST	55 IU/L	Up to 31 IU/L
Alkaline phosphatase	138 IU/mL	64 - 306 IU/mL
Total bilirubin	0.7 mg/dL	0.1 - 1.2 mg/dL
Conjugated bilirubin	0.2 mg/dL	0.1 - 0.4 mg/dL
Albumin	4.8 gr/dL	3.5 - 5.5 gr/dL
Serological analysis		
ESR	40	
ANA	0.868 IU/mL	< 1 IU/mL
ds DNA	28.7 IU/mL	< 16 IU/mL
C3	135 mg/dL	10 - 80 mg/dL
C4	14.7 mg/dL	10 - 40 mg/dL
CH50	99.89	51 - 150
Pathological Analysis		
Liver biopsy	Bridging fibrosis and few plasma cells in portal tracts	

23).

We believe that our patient had AIH in association with SLE. Her first clinical and laboratory presentations were suggestive of AIH, while over the following 3 months, obvious clinical and serologic manifestations of SLE emerged, such as photosensitivity, malar rash, arthritis, and oral ulcers, as well as positive ANA and anti-dsDNA (24). By continuing her past treatment and adding new drugs, we saw rapid clinical improvement in her arthritis, malaise, and general condition, as well as her hepatitis (25, 26).

Patients with SLE have a 25% - 50% chance of developing abnormal liver tests in their lifetime. The frequency of liver dysfunction and the associated portal inflammation support the view that subclinical liver disease is a concomitant feature of SLE (27). Several previous reports indicated the manifestation of AIH in adult lupus patients. However, except for one case report indicating an overlap syndrome of AIH/SLE, there has been no article discussing AIH in association with SLE.

In conclusion, we suggest that children with liver dysfunction as an autoimmune disease, such as AIH, should be investigated for SLE since its first manifestation can be AIH. Doing so can help the physician begin the appropriate treatment sooner, saving time as well as reducing complications and improving the prognosis of SLE. Both AIH and SLE have been reported to respond rapidly to steroid therapy, and with appropriate treatment, the prognosis is generally good for both conditions. However, if left untreated, AIH can progress rapidly and lead to cirrhosis in a relatively short period of time.

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