The Turkish Journal of Pediatrics 1999; 41: 541-544 *Case*

HEPATITIS AS THE PRESENTING SYMPTOM OF CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS*

*R. Anıl Apak MD**, Nesrin Beşbaş MD***, Sıla Özdemir MD****, Hasan Özen MD*****, Ayşın Bakkaloğlu MD***, Ümit Saatçi MD****

SUMMARY: Apak RA, Beşbaş N, Özdemir S, Özen H, Bakkaloğlu A, Saatçi Ü. (Nephrology and Rheumatology, and Gastroenterology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Hepatitis as the presenting symptom of childhood systemic lupus erythematosus. Turk J Pediatr 1999; 41: 541-544.

We report in this article a girl with an initial diagnosis of autoimmune hepatitis who developed full-blown systemic lupus erythematosus (SLE) at her two-years follow-up. She was formerly considered as HBV-related chronic active hepatitis but due to the persistence of elevated liver enzymes, the reversal of the albumin and globulin ratio and abnormal HBV serology, she was later diagnosed as autoimmune hepatitis. With the clinical findings of arthritis, arthralgia and malar rash and supported by results of laboratory tests, she was diagnosed as a case of unusual SLE presenting with autoimmune hepatitis. We conclude, therefore, that each patient with a diagnosis of autoimmune hepatitis in childhood who exhibits abnormal HBV serology must be evaluated for a possible diagnosis of SLE. *Key words: systemic lupus erythematosus, autoimmune hepatitis, hepatitis B virus.*

Systemic lupus erythematosus (SLE) is a multisystem disease with a wide range of symptoms resulting from different antinuclear antibodies directed against one or more components of the cell nuclei. In these patients certain genetic markers are associated with distinct clinical manifestations[1].

Although 15 to 30 percent of patients have elevated liver enzymes during the course of the disease, hepatic involvement as the first manifestation is very rare in SLE[2]. More severe liver disease may also be associated, but it is almost always of infectious origin, due to misdiagnosed autoimmune hepatitis or primary biliary cirrhosis[3].

We report a girl diagnosed as autoimmune hepatitis with an abnormal hepatitis B virus serology who developed clinically full-blown SLE within three years.

* From the Nephrology and Rheumatology, and Gastroenterology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Research Assistant in Pediatrics, Hacettepe University Faculty of Medicine

*** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

**** Pediatric Nephrologist, Social Security Hospital, Ankara.

***** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine

Case Report

A nine-year-old girl was admitted with a one-month history of fever, malar rash, and redness, swelling and pain on her finger joints, elbows and knees.

She was otherwise healthy until the age of six when she developed anorexia, fatigue and jaundice, and was diagnosed as hepatitis. Physical examination findings at that time revealed her height as 112 cm (25th centile), weight as 20 kg (25th centile), and blood pressure 120/70 mmHg. She had jaundice and hepatomegaly. The remainder of the examination was normal. On laboratory evaluation, hemoglobin was 6.5 g/dl, hematocrit was 22 percent, and white blood cell count was 4,500/mm^3 with normal differential and normochrome microcytic erythrocyte morphology. Urinalysis was unremarkable. Direct Coombs' test was negative. Serum AST and ALT levels were 773 IU/L and 486 IU/L, respectively. Serum total and direct bilirubin levels were 2.2 mg/dl and 1.4 mg/dl, total protein level was 8.6 g/dl and albumin level was 4.1 g/dl. Hepatitis A virus antibody (anti HAV Ab), hepatitis B virus surface antigen (HBs Ag), HBV enzyme antigen (HBe Ag) and antibody (anti HBe Ab), HBV core IgM and IgG antibodies (anti HBc IgM and IgG) and hepatitis C virus (HCV) antibody (anti HCV) were all negative. One month later, her complaints and physical findings had not changed but AST, ALT and total protein levels rose and HBs Ag and Anti HBc IgG became positive. Two months later, her liver enzyme levels dropped about 50 percent and only HBs Ag remained positive as a serological marker. Within one year of follow-up, AST and ALT levels fluctuated between 164 and 239 IU/L. Bilirubin levels remained within normal limits. Total protein level was always high despite a normal serum globulin level. All serological markers related to HBV, including HBc IgG, became negative during the consecutive three months.

On her first year of admission, a percutaneous fine needle liver biopsy was performed due to her persistently elevated liver enzymes. Histological examination revealed disorganized hepatic architecture exhibiting portoportal bridging and increased fibrous tissue invading the liver parenchyma with mononuclear cell infiltration in portal areas. There was also evidence of suspicious nodule formation. However, these changes were not associated with a specific clinical condition.

She remained stable clinically for two years without any treatment; however, during this period her liver enzymes were persistently elevated (two-fold). At the end of second year, she started complaining of fever over 38.5°, pain, swelling and redness on her finger joints, elbows and knees. On physical examination, she had a striking malar rash, livedo reticularis, hepatosplenomegaly and fusiform swelling on her proximal interphalangeal joints. On laboratory examination, hematocrit was 32.9 percent, white blood cell cound 7,300/mm^3 with normal

differential, thrombocyte count 380,000/mm^3, and sedimentation rate 88 mm/hour. Direct Coombs' test and C reactive protein tests were positive. Anti DNA antibody level was 145 IU/L (Normal: 0-7 IU/L), complement 3 and complement 4 levels were 35.4 mg/dl (Normal: 60-120 mg/dl) and 5 mg/dl (Normal: 30-60 mg/dl), respectively. With these clinical and laboratory findings, she was diagnosed as having SLE and corticosteroid treatment was initiated. Following her first month of therapy, her complaints subsided, hepatomegaly disappeared and liver enzyme levels dropped within normal limits.

Discussion

A hepatitis-lupus connection has been recognized in adults for more than 30 years. It has not previously been considered a significant problem and is thought to be surprisingly rare[4]. However, later reports state that subclinical liver disease may be a manifestation of SLE[5]. Harvey et al.[6] reported that 35 percent of patients with SLE had palpable livers. In another report by Kofman et al.[7], 52 percent of patients with SLE had hepatomegaly, 12 percent had jaundice and 31 percent had elevated liver enzymes.

In our case, determining the etiology of chronic hepatitis was more of a problem. The patient was not taking drugs which were potentially hepatotoxic and she had negative HCV serology. Similarly, cytomegalovirus. Epstein-Barr virus and toxoplasmosis, although not directly tested in her, do not usually produce chronic hepatitis; the biopsy did not present the typical histological picture of these infections. Initial clinical presentation with abnormal transaminases levels, positive HBs Ag and anti-HBc Ab, with the support of liver histology, suggested HBV related chronic active hepatitis. On the other hand, we considered the diagnosis of autoimmune hepatitis in view of the spontaneous serologic remission following an abnormal HBV serology, the increased globulin concentration and the reversal of the albumin/globulin ratio during her follow-up. The diagnosis of SLE was established after her 1.5 year follow-up when the joint complaints appeared. The question remains whether this patient with liver disease had a coincidental serious liver disease and SLE, serious liver disease as an initial manifestation of SLE, or autoimmune liver disease with associated autoimmune phenomena suggesting the diagnosis of SLE. Our patient fulfills the ARA criteria for the correct diagnosis of SLE. Previous reports state that 10 to 20 percent of patients diagnosed as autoimmune hepatitis fulfill the ARA criteria for SLE[8]. In addition, hepatic manifestations of SLE have been considered as a significant problem in the adult population as early as four years prior to the diagnosis of SLE[9]. These data show that the former clinical presentation in our patient was the presenting symptom of an existing SLE.

However, serological markers that would have supported the diagnosis of autoimmune hepatitis were not available at that time. In fact, in a recent report by Satoh et al.[10], two cases with SLE-associated autoimmune hepatitis were found to have negative serological markers. Novel antibodies which react with transfer RNA related antigens (anti-ribosomal P antibodies) are found to be more specific for the diagnosis of SLE-associated autoimmune hepatitis[11]. Therefore, an initial positive HBV serology) recalls false-positivity resulting from an autoimmune phenomena. False-positive HCV serology in patients with autoimmune hepatitis has been reported, but this is the first case exhibiting false-positive HBV serology with autoimmune hepatitis[12].

We conclude, therefore, that in children, liver disease as manifested by autoimmune hepatitis and liver cirrhosis, even with the presence of an abnormal HBV serology, may develop in the course of SLE, and that each patient with autoimmune hepatitis in childhood must be evaluated for a possible diagnosis of SLE.

REFERENCES

1. Harley JB, Scofield RH. Systemic lupus erythematosus: RNA-protein autoantigens, models of disease heterogeneity, and theories of etiology. J Clin Immunol 1991; 11: 297-316.
2. Miller MH, Urowitz MB, Gladman DD, Blendis LM. The liver in systemic lupus erythematosus. Quart J Med 1984; 53: 401-409.
3. Hall S, Axelsen PH, Larson DE, Brurch TW. Systemic lupus erythematosus developing in patients with primary biliary cirrhosis. Ann Int Med 1984; 100: 388-389.
4. Decker JL, Steinberg AD, Gershwin ME, et al. Systemic lupus erythematosus-contrast and comparisons. Ann Int Med 1975; 82: 391-392.
5. Hoffman BI, Katz WA. The gastrointestinal manifestations of systemic lupus erythematosus: a review of the literature. Semin Arth Rheum 1980; 4: 237-247.
6. Harvey AM, Shulman LE, Trumply PA, et al. Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. Medicine (Baltimore) 1954; 33: 291-292.
7. Kofman S, Johnsan GC, Zimmerman HJ. Apparent hepatic dysfunction in systemic lupus erythematosus. Arch Int Med 1955; 95: 669-672.
8. Tamai YS, Ito K, Fukosi M. Application of the preliminary SLE criteria by the ARA to autoimmune hepatitis. Ryumachi 1974; 14: 88-90.
9. Chwalinska-Sadowska H, Milewski B, Maldyk H. Diagnostic troubles connected with differentiation of systemic lupus erythematosus against chronic hepatitis. Mater Med Pol 1977; 30: 60-63.
10. Satoh T, Hirakata M, Yoshide T, et al. Systemic lupus erythematosus associated with autoimmune hepatitis: two cases with novel antibodies to transfer RNA-related antigens. Clin Rheumatol 1997; 16: 305-309.
11. Arnett FC, Reichlin M. Lupus hepatitis: an under-recognized disease feature associated with autoantibodies to ribosomal P. Am J Med 1995; 99: 465-472.
12. Lenzi M, Ballardini G, Fusconi M, et al. Type 2 autoimmune hepatitis and hepatitis C virus infection. Lancet 1990; 335: 258-259.