Korean Journal of Pediatrics Vol. 51, No. 5, 2008
DOI : 10.3345/kjp.2008.51.5.528
Case report

Autoimmune hepatitis and thyroiditis associated with antituberculous medications : A case report

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= Abstract =

Drug-induced toxic hepatitis is a relatively common hepatic disease in children, and it is usually self-limiting upon cessation of the offending drugs. Antituberculous drugs are well known for inducing hepatitis. Some cases of drug-induced hepatitis with autoimmune features have been reported; in these cases, the offending drugs were usually methyldopa, nitrofurantoin, minocycline, and interferon. The authors report the first case in Korea of drug-induced autoimmune hepatitis associated with thyroiditis and multiple autoantibodies that was induced by the antituberculous drugs isoniazid and rifampin. **(Korean J Pediatr 2008;51:528-532)**

Key Words : Toxic hepatitis, Autoimmune thyroiditis, Isoniazid, Rifampin

Introduction

Drug-induced toxic hepatitis is a relatively common hepatic disease in children, and it is usually self-limiting upon cessation of the offending drugs. Usually, antituberculous drugs are the offending agents. Autoimmune hepatitis (AIH) is a chronic hepatic inflammatory process manifested by elevated serum aminotransaminase concentrations and liver-associated serum autoantibodies and hypergammaglobulinemia[1, 2]. AIH can also be induced by several drugs; however, drug-induced AIH (DIAH) is quite different from typical AIH in many aspects. Many drugs that cause DIAH have been reported. These include methyldopa, nitrofurantoin, minocycline, clometacin, and interferon, etc[3, 4]. Although antituberculous drugs commonly cause drug-induced hepatitis, DIAH associated with antituberculous medications is very rare, particularly that associated with other autoimmune features such as thyroiditis. Here, we report the first case in Korea of DIAH associated with thyroiditis and multiple autoantibodies that were induced by the antituberculous drugs isoniazid and rifampin in a 9-year-old girl.

Received : 2 November 2007, Accepted : 22 January 2008
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본 연구는 2007년 대한소아과학회 추계학술대회에서 포스터로 발표되었음.

Case report

In December 2005, a 9-year-old girl presented with signs of left axillary lymph node enlargement (2 cm×1.5 cm). Fine needle aspiration, chest computed tomography, tissue culture, and polymerase chain reaction (PCR) findings revealed tuberculous lymphadenitis and active pulmonary tuberculosis. Initially, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 8 and 26 IU/L, respectively. She had been treated with antituberculous medications until July 2006. The prescribed drugs were as follows: initially, streptomycin, isoniazid, ethambutol, pyridoxine, pyrazinamide, and rifampin for 3 months and subsequently, isoniazid and rifampin for 4 months.

From the beginning of July 2006, she had suffered from jaundice, and her oral intake was poor. On physical examination, whole body icterus and myxedematous changes of the face were noted. Hepatosplenomegaly, anemia, cutaneous telangiectasia, other musculoskeletal symptoms, and neurological abnormalities were absent. On admission, the findings of the laboratory tests were as follows: AST, 787 IU/L; ALT, 731 IU/L; white blood cells (WBC), 4,350/mm^3; hemoglobin, 11.9 g/dL; platelets, 427,000/mm^3; total protein, 8.3 g/dL; albumin, 3.9 g/dL; γ-glutamyl transpeptidase, 183 U/L (5-32 U/L); alkaline phosphatase (ALP), 188 U/L (145-420 U/L); prothrombin time (PT), INR 1.17; total bilirubin, 10.9 mg/dL; direct bilirubin, 6.6 mg/dL; ceruloplasmin, 28.7 mg/dL

(20-45 mg/dL); serum copper, 119 μg/dL (70-130 μg/dL); and immunoglobulin G (IgG), 2,382 mg/dL (608-1,572 mg/dL). Multiple autoantibodies were detected in the serological study. Anti-DNA antibodies, 26.5 IU/mL (<7.0 IU/mL) and antinuclear antibodies (ANA) at 1:640 were identified. Anti-smooth muscle antibodies (ASMA), anti-liver/kidney microsomal antibodies (LKM), and anti-mitochondrial antibodies (AMA) were not detected. The findings of a viral marker study were as follows: hepatitis B surface antigen (HBsAg), negative; hepatitis B surface antibody (HBsAb), positive; anti-hepatitis C virus (HCV) antibody, negative; hepatitis A virus (HAV) IgM, negative; cytomegalovirus (CMV) IgM, negative; CMV PCR, negative; and Epstein-Barr viral capsid antigen (EBV VCA) IgM, positive. The results of the thyroid function study were as follows: thyroid-stimulating hormone (TSH) >100 μIU/L (0.27-4.2 μIU/L); free T_4, 0.49 ng/dL (0.8-2.2 ng/dL); T3, 1.42 ng/dL (0.9-2.4 ng/dL); T_4, 5.1 μg/dL (5.8-12.8 μg/dL); anti-thyroglobulin antibody, positive; and anti-microsomal antibody, positive (Table 1, 2). The thyroid scan revealed a diffuse nontoxic goiter. The findings of abdominal sonography were consistent with those observed in acute liver disease. A liver biopsy revealed loss of hepatocytes, moderate portal inflammation, mild perivenular fibrosis, moderate inflammation, and no evidence of portal fibrosis. There was no evidence of viral infection on biopsy (Fig. 1).

For the treatment, we stopped the antituberculous medications and prescribed ursodeoxycholic acid (UDCA), levothyroxine, and silymarin. After abstinence from antituberculous drugs for 50 days, the patient's symptoms improved and the AST and ALT levels almost normalized to 42 and 24 IU/L, respectively. Other laboratory findings also normalized. For example, the total bilirubin was 1.2 mg/dL and

Table 1. Initial Findings of Laboratory Tests on Admission

Viral markers and other tests	Results
HAV IgM	Negative
HBV Ag/Ab	Negative/Positive
Anti-HCV Ab	Negative
CMV IgM, CMV PCR	Negative
EBV lgM	Positive
Ceruloplasmin (mg/dL)	28.7
Cortisol (μg/dL)	6.5
17-hydroxyprogesterone (ng/μL)	0.3
Direct Coombs test	Positive
Ig G (mg/dL)	2,382

Table 2. Summary of Autoantibodies and Thyroid Function Tests on Admission

Autoantibodies and thyroid function tests	Results
ANA	1:640
P-ANCA	Negative
Anti-ds DNA Ab (IU/mL)	26.5
Anti-SM Ab	Negative
Anti-LKM Ab	Negative
Thyroglobulin Ab	1:160
TBII	Negative
Antimitochondrial Ab	Negative
Microsomal Ab	1:160
TSH (μIU/L)	>100
T_3 (ng/dL)	1.42
T_4 (μg/dL)	5.1
Free T_4 (ng/dL)	0.49

Abbreviations: ANA, antinuclear antibody; Anti-SM Ab, anti-smooth muscle antibody; Anti-LKM Ab, anti-liver/kidney microsomal antibody; P-ANCA, perinuclear-antineutrophil cytoplasmic antibody; TBII, thyrotropin binding inhibiting antibody.

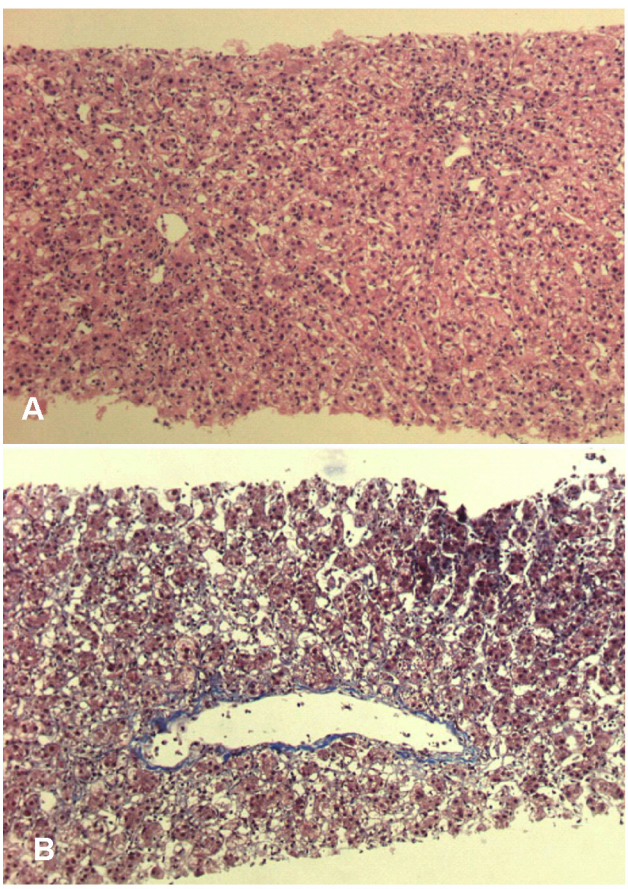

Fig. 1. (A) Clear spaces due to the loss of hepatocytes are noted around the terminal hepatic venules in zone 3. Further, moderate portal inflammation is noted (hematoxylin and eosin, ×100). (B) Mild perivenular fibrosis and moderate inflammation are noted with loss of hepatocytes in zone 3 (Masson-trichrome, ×200).

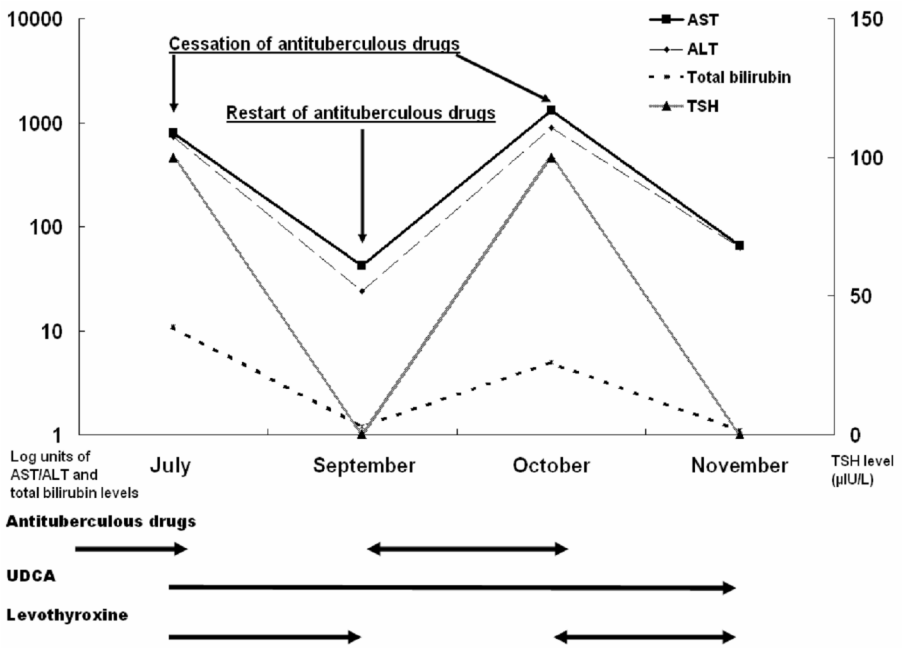

Fig. 2. Summary of clinical course and treatment of the patient.

TSH, 0.27 μIU/L. However, serum IgG remained high at 2,166 mg/dL.

To determine whether or not antituberculous treatment should be resumed after a cessation period of 2 months, the patient was re-evaluated. The Mantoux test remained strongly positive, and multiple lesions that were previously noted on chest computed tomograph were identified. We considered that further treatment with antituberculous medications would be helpful in controlling the disease thoroughly; therefore, with the full understanding and permission of the patient and her parents, we resumed the drugs isoniazid and rifampin. However, 1 month after the administration of the drugs was resumed, the following laboratory parameters were deteriorated: total bilirubin, 5.0 mg/dL; AST, 1,303 IU/L; ALT, 904 IU/L; IgG, 2,457 mg/dL; and TSH >100 μIU/L. Hence, we discontinue these 2 drugs again, and after 1 month, the AST, ALT, and total bilirubin levels improved to 65 and 63 IU/L and 1.1 mg/dL, respectively. All these clinical events are summarized in Fig 2. Currently, the patient is under observation and is doing well without medication.

Discussion

DIAH is usually associated with type 1 AIH. It is assumed that the underlying mechanism involves the binding of drug metabolites to cellular receptors or cytochrome p450 proteins, thereby forming antigen-antibody complexes which in turn trigger the autoimmune mechanism[5]. Regarding genetic linkage, DIAH is known to be associated with the complement allele C4AQO, and genetic defects in human leukocyte antigen (HLA) haplotypes B8, B14, DR3, DR4, Dw3, and C4A[6].

DIAH patients usually exhibit signs of fatigue, jaundice, poor oral intake, weight loss, and hepatosplenomegaly[7, 8]. The results of laboratory tests show increased serum AST, ALP, and IgG levels. Viral markers associated with hepatitis A, B, and C; CMV; and EBV are usually negative. Autoantibodies (ANA, P-ANCA, ASMA, LKM, etc.) are common, and other autoimmune diseases (ulcerative colitis, rheumatoid arthritis, anemia, myopathy, and thyroiditis) may be characteristically combined. The thyroid is the most commonly affected organ[9-12]. The characteristic histological picture of interface (periportal or periseptal) hepatitis consists of a predominantly lymphoplasmocytic necroinflammatory infiltrate with or without lobular involvement and portal-portal or central-portal bridging necrosis, often with the formation of liver cell rosettes and nodular regeneration[12, 13]. These findings are usually observed in patients diagnosed with classical AIH, but they may not be evident in some cases, particularly those of DIAH[14]. In our case, histological findings were not consistent with those of classical AIH.

Classical AIH may be of 2 types: definite AIH or probable AIH based on each accumulated diagnostic standard score as recommended by the International Autoimmune Hepatitis Group (IAHG) in 1992 and revised in 1999[13, 15]. However, these criteria are not always applicable to DIAH. Our DIAH patient's score prior to treatment was 6, which is too low to confirm AIH.

We performed a literature survey and found 1 article reporting AIH with autoimmune thyroiditis that was caused by antituberculous medications. It mentioned that a 25-year-old man developed AIH and autoimmune thyroiditis after 3 weeks of rifampin and pyrazinamide prophylaxis[4]. According to the literature, autoimmune thyroiditis is observed in 8-10% of all DIAH patients; however, cases associated with antituberculous drugs are very rare[16, 17].

The treatment of DIAH consists of cessation of the offending drugs and the administration of prednisolone and/or azathioprine, if clinically needed. UDCA may be helpful because it boosts immunity by decreasing intrinsic hepatotoxic bile acid, facilitating the excretion of bile juice, decreasing the expression of HLA class I by liver cell membranes, and suppressing the activation of cytotoxic T lymphocytes. This drug is safe for long-term treatment and is used in primary biliary sclerosis, primary sclerosing cholangitis, biliary atresia, etc. There have been some reports regarding the effect of UDCA on AIH; however, research regarding the role of UDCA is still in the early stage[18]. Recently, there are many studies on cyclosporine A, tacrolimus (FK-506), budesonide, cyclophosphamide, and mycophenolate mofetil (MMF) being conducted[19].

In this case, acute liver disease and hypothyroidism developed after 7 months of antituberculous medication; we therefore stopped all drugs and prescribed UDCA, levothyroxine, and silymarin. We did not administer any immunosuppressive agent. After the cessation of offending drugs, the biochemical markers and clinical symptoms improved. On recommencing the administration of the 2 previously used drugs (isoniazid and rifampin) to complete the tuberculosis treatment protocol, AIH with thyroiditis developed again. Hence, we concluded that in this patient, the DIAH and thyroiditis were caused by antituberculous drugs. According to the literature, this is very rare case worldwide. However, drug-induced hepatitis is quite common in children, and antituberculous drugs are commonly used in Korea. We encourage clinicians prescribing antituberculous drugs to children to maintain a high index of suspicion regarding autoimmunopathy, particularly in patients with drug-induced hepatitis.

한 글 요 약

항결핵약으로 유발되고 갑상선염이 동반된 자가면역간염 1례

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소아에서 약물 유발성 독성 간염은 비교적 흔하며 대부분 약을 끊으면 호전된다. 특히 항결핵약은 주요 유발 약물이다. 약물 유발성 독성 간염은 자가면역질환을 동반할 수 있으며, 이러한 원인으로 보고된 약제로는 주로 methyldopa, nitrofurantoin, minocycline, interferon 등이고, 항결핵약 보고는 드물다. 저자들은 갑상선염이 동반되고 항결핵약 isoniazid와 rifampin으로 유발된 약물 유발성 자가면역간염을 경험하였기에 국내에서 처음으로 문헌고찰과 함께 보고하는 바이다.

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