Familial alpha 1 antitrypsin deficiency cases that are diagnosed in adulthood

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Abstract

Alpha 1 antitrypsin (AAT) deficiency is a hereditary disorder leading to severe lung and liver diseases worldwide. An accumulation of insoluble heterodimer AAT molecules in hepatocytes is the main cause of liver disorders. The most commonly detected allele worldwide is the PIMM allele, which fulfills the AAT function. The most common missing variant is PiZZ. Serum AAT level is a beneficial but not a reliable determinant for diagnosis. Liver biopsy yields more reliable results. AAT deficiency has no specific treatment. The only treatment modality in children with end stage liver disease is the hepatic transplant. We wanted to present in our article four cases from same family, diagnosed alpha-1 antitrypsindeficiency in adulthood. (Acta gastroenterol. belg., **2016**, 79, **54-57**).

Key words : Alpha 1 antitrypsin (AAT) deficiency, liver transplantation, and Genetic Testing.

Introduction

Alpha-1 antitrypsin (AAT) deficiency is an autosomal inherited hereditary disease which may affect the lungs, liver, and rarely the skin. While it is the most common cause of inherited liver diseases in childhood, it is associated with chronic liver disease and liver carcinomas in adulthood (1). The most common genetic disorder among children who underwent liver transplantation is AAT deficiency with a frequency of 1/1600-1/1800 (2). In contrast to the pathogenesis of lung injury in deficiency, which almost certainly involves an uninhibited proteolytic attack on lung elastin, there is no evidence that the pathophysiology of liver injury in this condition is due to a deficiency of elastase inhibitory capacity. Most evidence favors the concept that the accumulation of AT in the ER is directly related to liver cell injury (3). Although serum AAT level is useful in diagnosis, is not a reliable predictor. Liver biopsy provides more reliable findings in this regard. There is no specific therapy for AAT deficiency. The only treatment for end-stage liver disease in advanced cases is liver transplantation. Here, we aimed to present our four AAT deficiency cases from the same family ; mother, father and two brothers, who were asymptomatic until adulthood.

Cases

First case

37-years-old male patient, diagnosed with chronic liver disease and followed and treated for 8 months, was admitted to our clinic with general condition disorder, abdominal distension and yellowing of skin complaints. On physical examination ; significant ascites and icterus were found. WBC : 12. 10^3/ml, hemoglobin : 11.5 g/dl, PLT : 77 10^3/mL, INR : 2.0, creatinine : 0.9 mg/dL, albumin : 2.2 g/dl, total bilirubin : 14.8 mg/dL, AST : 68 U/L, ALT : 51 U/L, alpha fetoprotein (AFP) : 5.36 IU/mL, HbsAg : negative, anti-HCV : negative, CMV IgM ; negative, anti-nuclear antibody (ANA), Liver kidney microsomal (LKM-1), anti-mitochondrial autoantibodies (AMA)) : negative, ceruloplasmin : 0.98 g/L, serum iron : 55, ferritin : 102 mg/L. Kayser fleischer ring was not observed in eye examinations, and also there was no toxic drugs, smoking and alcohol use story. AAT level of the patient was low with a value of 0.279 g/L (0.9-2.0 g/L), and genetic tests were reported as PIZZ (homozygous genotype) mutation. Liver parenchymal disease, diffuse ascites and splenomegaly were detected in the radiological images. By these findings the patient was diagnosed with chronic liver disease due to AAT deficiency. Child Pugh Turcout Score (CPTS) and model for end stage liver diseases (MELD) score of the patient were 13 and 24 respectively. Liver transplantation was planned as treatment. After the patient underwent cadaveric liver transplantation, a significant improvement in the patient's general condition and laboratory values. In liver tissue pathology, moderately active cirrhosis, positive accumulations fitting AAT (Fig. 1), and mild iron accumulation in hepatocytes were observed. In the family story ; one year ago, his mother and two years ago, his father due to AAT deficiency liver cirrhosis.

Second case

67-year-old male patient. In his story those were learned ; he admitted to our clinic with respiratory distress, acsites and weight loss two years ago and diagnosed with emphysematous lung disease, chronic liver parenchymal disease. In his computed tomography (CT) imaging, performed when he admitted with similar complaints six months ago ; 3.8 × 4.8 cm diametered, lobule

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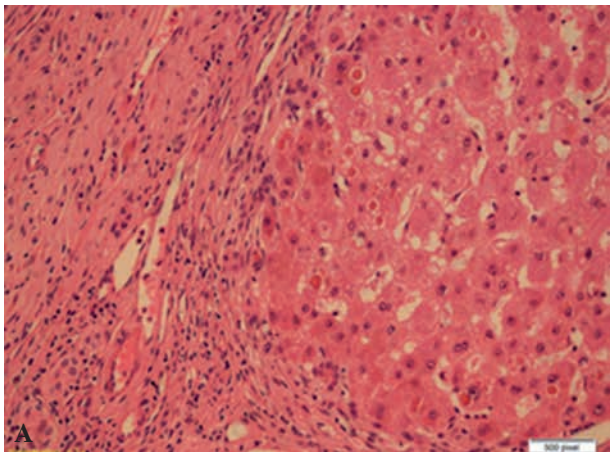

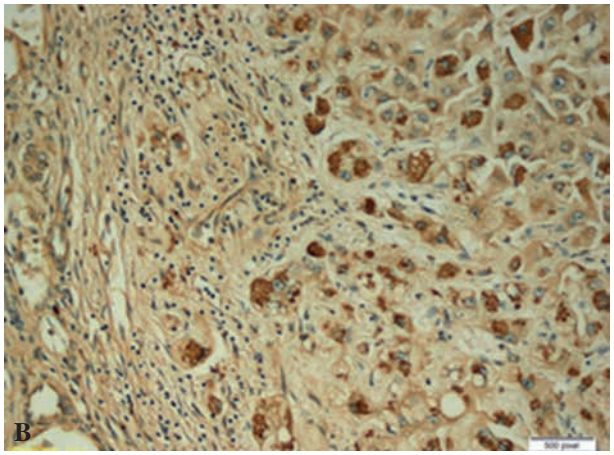

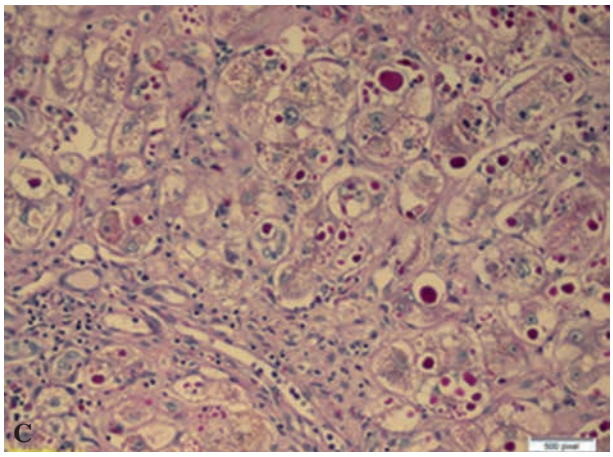

Fig. 1. — The first cases of liver pathology, d-PAS-positive intracytoplasmic eosinophilic globules into hepatocytes in the periportal area and immunohistochemical positivity for AAT in globules (A. HE ×200, B. d PAS ×200, C. AAT ×200).

contoured lesions containing hyperdense structures and showing wash-out in liver segment 2 (HCC) (Fig. 2A). It was learned that, liver transplantation had been proposed due to liver cirrhosis and HCC at that time, but the patient did not accept the operation. Therefore ; chemoembolization with a mixture of lipiodol and doxorubicin had been applied to the left hepatic vein branches, feeding lesions in liver segment 2-3, Six months after check performed CT image. A solid, space occupying lesion approximately 8 × 6 cm in diameter (HCC) (Fig. 2B). The patient admitted to emergency service with general condition disorder and confusion one week ago. While being treated in intensive care unit, the patient deteriorated to HE stage IV and his creatinine values rised to 3 mg/dL due to hepatorenal syndrome. Laboratory values ; WBC : 15 10^3/ml, hemoglobin : 8.2 g/dL, creatinine : 2.4 mg/dL, BUN : 76 platelets : 48 10^3/ml, albumin : 2.2 g/dL, total bilirubin : 1.4 mg/dL, INR : 2.1, AST : 54 U/L, ALT : 26 U/L, creatinine : 0.68 mg/dL, AFP : 94.1 IU/mL, serum iron : 55, ferritin : 106 mg/L, ceruloplasmin : 0.325 g/L, AAT : 0.444 g/L (low) (0.9-2.0 g/L), HbsAg : negative, anti-HCV : negative, CMV IgM : negative, CPTS was C-10 and MELD score was 16. On the third day of intensive care due to unresponsiveness to the treatment, the patient died.

Third case

60 year-old female patient. The patient, who has been followed-up for one year with a presumptive diagnosis of Cirrhosis of the liver due to AAT deficiency, admitted to emergency service with confusion and widespread abdominal ascites. Laboratory values were found as ; WBC : 9.4 10^3/ml, hemoglobin : 6.5 g/dL, PLT : 82 10^3/ml, INR : 2.4, creatinine : 1.4 mg/dL, albumin : 2.7 g/dL, total bilirubin : 2.33 mg/dL, AST : 61 U/L, ALT : 77 U/L, AFP : 7.73 IU/mL, autoantibodies : negative, ceruloplasmin : 0.315 g/L, ferritin : 44.4 mg/L, AAT : 0.345 (low) (0.9-2.0 g/L), HbsAg : negative, anti-HCV : negative, CMV IgM : negative, Because her CPTS was C-12 and MELD was 23, she underwent liver transplantation. In the tissue pathology of the excised liver, positive accumulations fitting AAT deficiency, cirrhosis, hepatocanalicular cholestasis and mild iron accumulation in hepatocytes were observed (Fig. 3). Laboratory results of the patient after transplantation ; total bilirubin level increased to 26 mg/dL, AST : 299 U/L, ALT : 386 U/L, fever : 38.6 degrees, blood cultures : negative, CRP : 12. While the patient was under sepsis treatment in intensive care unit, she died due to development of HE stage IV which is a form of coma and then cardiopulmonary arrest.

Fourth case

32 year-old male. The laboratory test results which were performed when he admitted to clinic in order to be a liver donor for his brother ; WBC : 6.5 10^3/ml, PLT : 25 5 10^3/ml, hemoglobin : 13.2 g/dL, AST : 62 U/L, ALT : 50 U/L, total bilirubin : 0.5 mg/dL, ALP : 87, INR : 0.9, AFP : 3.82 IU/mL, serum iron : 59, TSI : 20%, ferritin : 120 µg/L, albumin : 5.1 g/dl, autoantibodies ; negative, ceruloplasmin : 0.9 g/L, HbsAg : negative, anti-HCV : negative, CMV IgM : negative, There was no toxic drugs and alcohol use story. Kayser fleischer ring

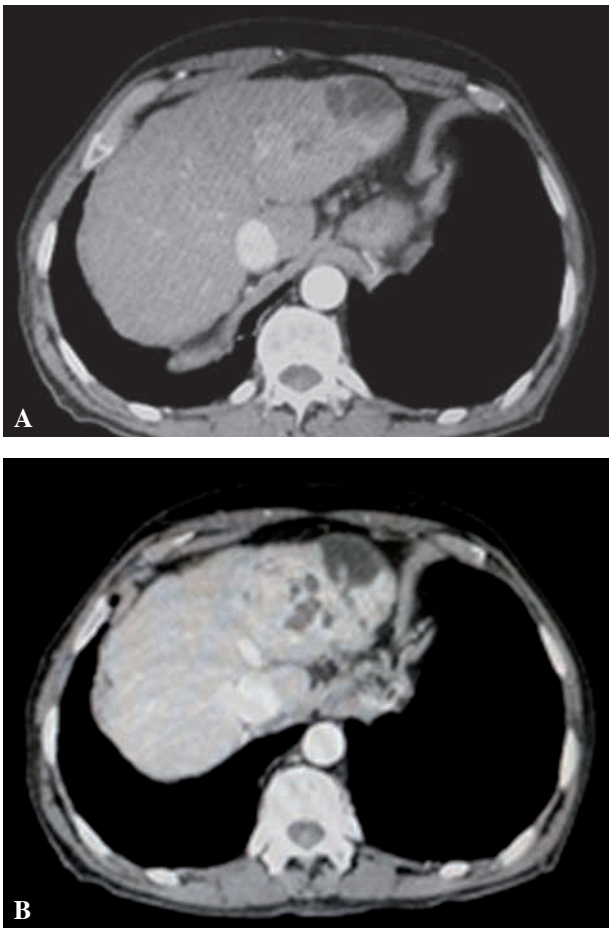

Fig. 2. — CT imaging of the second case. A. pre- images of TACE, B. an increase in the mass.

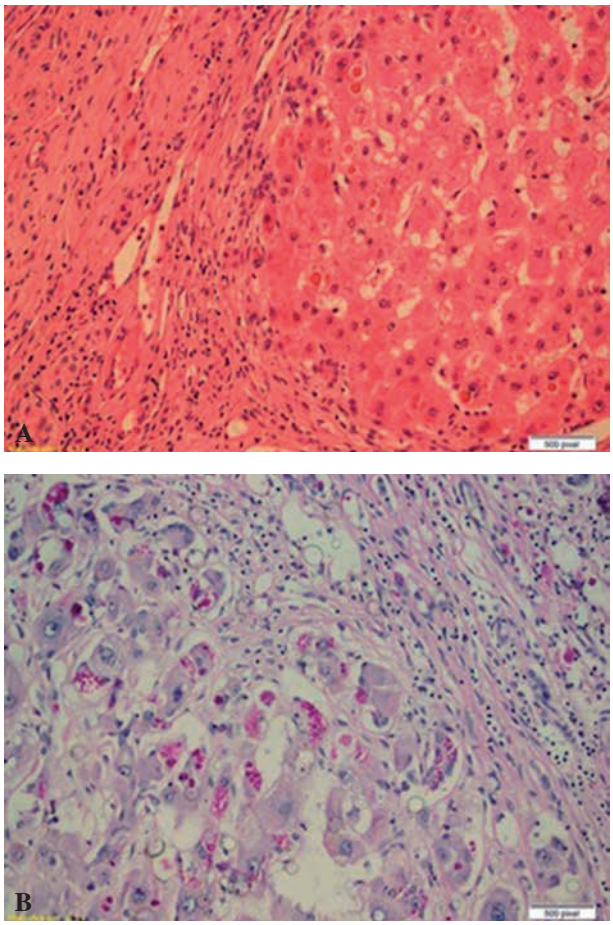

Fig. 3. — The third case of liver pathology, d-PAS-positive intracytoplasmic eosinophilic globules in the periportal area hepatocytes (A. HE ×200, B. d PAS ×200).

was not observed in eye examinations. Considering his AAT level was low with a value of 0.33 g/L (0.9-2.0 g/L), genetic tests were reported as PIZZ (homozygous genotype) mutation the patient was diagnosed with chronic hepatitis due to AAT deficiency.. In ultrasonography, liver parenchymal echo and size, spleen, portal and hepatic veins were normal. Liver biopsy was recommended, but the patient did not accept the biopsy. Regular outpatient follow-up still continues. In family story, his father, his mother, his brother was diagnosed with AAT deficiency.

Discussion

AAT deficiency is an autosomal inherited hereditary disease. Frequency varies across societies. Seres, who reviewed the cohorts of 373 AAT deficiency cases from fifty-eight countries, was calculated that there were at least 116 million carriers (PIMS & PIMZ) and 3.4 million AAT deficiency (PISS, PISZ, PIZZ) cases worldwide (4). The pathophysiology ; it is caused by mutations in protease inhibitor (PI) gene located at 14q32.19 chromosome segment (5). This mutant accumulation triggers a number of events causing hepatotoxicity (6). In a study performed in Germany, 1847 consecutive biopsy cases and 1030 autopsy cases of Caucasian adults were screened immunohistochemically for PiZ deposits. All analyzed biopsy cases were heterozygous for the PiZ mutation. The biopsy group revealed a significantly higher rate of PiZ-positive cases (3.4%) than the autopsy group (1.8%) ($p = 0.019$). The extent of PiZ deposits correlated well with the inflammatory activity and stage of fibrosis (7). Our two cases were PIZZ (Homozygous genotype) and this finding supports the frequency of it. Association of both homozygous and heterozygous AAT deficiencies with liver diseases was demonstrated previously (8). While the relative risk is 37-47% for cirrhosis and 15-30% for HCC in patients with PIZZ phenotype, the relative risk of cirrhosis is 1.8% and 5.7% for HCC in patients with heterozygous PIZZ, PISZ phenotypes ; when compared with other liver diseases (9). Considering that our first and fourth cases, who were brothers, had PIZZ, it can be thought that our other two cases, mother and father, may also had PIZZ . Taking into account that, our cases had PIZZ phenotype, two patients (first and third cases) had decompensated chronic liver disease, second case had also HCC with decompensated chronic liver disease, and severe clinical courses of the patients,

it can be said that our findings support the literature. In Larson's study on 246 individuals with Z mutation who were followed-up for 11 years, liver diseases were observed in 12.2% of the cases (cirrhosis, 11.8 ; neonatal hepatitis, 0.4 ; HCC, 3.3) (10). Liver biopsy provides reliable findings. Low serum levels of AAT and histopathology of the liver usually support each other. In our two cases laboratory impairment and histopathology of the liver were supporting each other. Five-year survival rate is 78% in liver transplantation which is reported to be similar to other metabolic diseases (11). Our two patients underwent transplantation therapy. Although, one of our patients died after transplantation (third case), the treatment of other patient still continues successfully (first case).

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