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Deficiency of Adenosine Deaminase Type 2: an Unusual Clinical Presentation

Adenozin Deaminaz Tip 2 Eksikliği: Olağandışı Bir Klinik Sunum

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Deficiency of Adenosine deaminase Type 2: An Unusual Clinical Presentation

ABSTRACT

Adenosine deaminase 2 (ADA2) deficiency is a systemic autoinflammatory disease characterized by systemic inflammation, vasculitis, early-onset stroke, cytopenias, and immunodeficiency. It is caused by a loss of function due to a mutation in the ADA2 gene and is inherited in an autosomal recessive pattern. It is a disease that is difficult to diagnose and treat. In this report, we presented a case of a 14-year-old with an unusual clinical onset, where the differential diagnosis involved clinical overlap of several diseases, who was diagnosed with a homozygous mutation in the ADA2 gene, and who came with complaints of abdominal swelling and chest pain. Unlike ADA2 deficiency, which is often considered in differential diagnosis with early-onset stroke, vasculitis, immunodeficiency, and hematological abnormalities, our case contributes to the literature by presenting with liver parenchymal disease and portal hypertension findings.

Keywords: Adenosine deaminase 2 deficiency, Chronic Liver Disease, Portal Hypertension.

Adenozin Deaminaz Tip 2 Eksikliği: Olağandışı Bir Klinik Sunum

ÖZ

Adenozin deaminaz 2 (ADA2) eksikliği, sistemik inflamasyon, vaskülit, erken başlangıçlı inme, sitopeniler ve immün yetmezlikle karakterize sistemik otoinflamatuar bir hastalıktır. ADA2 genindeki mutasyon nedeniyle oluşur ve otozomal resesif bir kalıtım paterni ile geçer. Teşhis ve tedavisi zor bir hastalıktır. Bu raporda, karında şişlik ve göğüs ağrısı şikayetleriyle gelen, ADA2 geninde homozigot mutasyon saptanan, atipik bir klinik prezentasyona sahip 14 yaşındaki bir vakayı sunuyoruz. ADA2 eksikliği, erken başlangıçlı inme, vaskülit, immün yetmezlik ve hematolojik anormallikler olduğunda ayırıcı tanıda dikkate alınırken, vakamız karaciğer parankimal hastalığı ve portal hipertansiyon bulguları ile başvurmasından dolayı atipik klinik prezentasyonu ile literatüre katkıda bulunmaktadır.

Anahtar Sözcükler: Adenozin deaminaz 2 eksikliği, Kronik Karaciğer Hastalığı, Portal Hipertansiyon.

Introduction

ADA2 deficiency is a rare autosomal recessive autoinflammatory disorder characterized by systemic inflammation, vasculitis, early-onset stroke, cytopenias, and immunodeficiency (1). While ADA2 deficiency is commonly associated with neurological, vascular, immunological, and hematological involvement, hepatic manifestations are less well described. In this report, we present a pediatric case that uniquely manifested with clinical features suggestive of chronic liver disease and portal hypertension, prior to the classical signs associated with ADA2 deficiency. By sharing this case, we aim to broaden the clinical spectrum of ADA2 deficiency and highlight the importance of considering this rare diagnosis in patients with unexplained liver-related findings, particularly in the pediatric population.

Case Report

A written consent form was obtained from the family members for this publication. A 14-year-old male patient presented with abdominal and lower extremity edema, along with chest pain that started four days earlier. We learned that the swelling in his legs started after a 12-hour bus journey, and two days later, eyelid and lip swelling were added, without any associated fever. There was no history in the patient's medical history suggesting immunodeficiency. There was consanguinity between the mother and father. There was no indication of tuberculosis. Physical examination revealed periorbital edema, ascites with a fluid wave, and 4+ pitting pretibial edema in both legs. The liver was 4 cm below the costal margin, the Traube space was dull, and there was 4 cm of splenomegaly. The other system examinations were normal.

In the laboratory evaluation, the following results were obtained: white blood cells 5380/µL, neutrophils 4000/µL, lymphocytes 940/µL, hemoglobin 10.6 g/dL, mean corpuscular volume (MCV) 69.6 fL, and platelets 184,000/mm^3. Serum ammonia was 28.4 µg/dL, prothrombin time (PT) 10.2 sec, international normalized ratio (INR) 1.26, and albumin 3.4 mg/dL. Total and direct bilirubin levels were 0.7 and 0.3 mg/dL, respectively.

Aspartate aminotransferase (AST: 24 IU/L) and alanine aminotransferase (ALT: 15 IU/L) were both within normal reference ranges, supporting the absence of significant hepatocellular injury. Alkaline phosphatase (ALP: 202 IU/L), gamma-glutamyl transferase (GGT: 74 IU/L), and creatine kinase (CK: 34 IU/L) were unremarkable. Inflammatory markers were not elevated (erythrocyte sedimentation rate 9 mm/h, C-reactive protein 9 mg/L, fibrinogen 388 mg/dL).

Viral serologies were negative for HBsAg, anti-HCV, anti-HIV, and EBV IgM/IgG, while immunity markers were positive for anti-HBs and anti-HAV IgG, and anti-tetanus IgG, consistent with past immunization or exposure.

Metabolic investigations revealed a 24-hour urinary copper level of 170 µg/day and plasma ceruloplasmin of 38.4 mg/dL, both within normal ranges, thereby excluding Wilson's disease.

Abdominal ultrasound revealed an increase in heterogeneity in the liver parenchyma, multiple lymphadenopathies in the abdomen, inguinal lymphadenopathies, and an anechoic pleural effusion without septation measuring 42 mm on the right and 30 mm on the left in both hemithoraces was observed. The diameter of the portal vein was 12 mm (normal <10 mm in children), and the splenic vein diameter was 12 mm (normal <9 mm), both of which were consistent with portal hypertension. There was free fluid measuring 1.5 cm thick in the abdomen and pelvis. Evaluation with Doppler ultrasonography revealed no signs of portal vein thrombosis. Subcutaneous edema and inflammation were observed in the calf, and deep vein thrombosis was ruled out. CT angiography further supported these findings, showing a portal vein diameter of 10 mm at both intrahepatic and extrahepatic levels (normal <10 mm in children), with patent right and left portal branches. The splenic vein and superior mesenteric vein were also patent. The splenic vein measured 8 mm posterior to the pancreas (within normal limits), but was dilated to 11 mm at the splenic hilum

(normal <9 mm), confirming evidence of portal hypertension. Echocardiography was normal.

Tuberculosis, metabolic diseases (Wilson's disease, glycogen storage disease, Gaucher's disease, and lysosomal acid lipase deficiency), malignancy, autoimmune lymphoproliferative syndrome, chronic liver disease, deep vein thrombosis, systemic lupus erythematosus, brucellosis, and leishmaniasis were considered as preliminary diagnoses. The eye examination was normal, there were no findings suggestive of a storage disease. In the bone marrow smear performed with a preliminary diagnosis of malignancy, atypical cells were not detected. The autoantibodies tested for lupus were negative. In the pleural fluid obtained from a thoracentesis performed for differential diagnosis with preliminary diagnoses of tuberculosis and malignancy, pleural glucose: 107 mg/dL, protein: 20 g/l, albumin: 11 g/l, LDH: 71 IU/L, and simultaneously in the blood biochemistry, glucose: 107 mg/dL, protein: 62 g/l, albumin: 35 g/l, lactate dehydrogenase (LDH) : 180 IU/L, it was identified as reactive lymphocytic pleural fluid with a transudate nature. Pleural fluid tuberculosis PCR and culture were negative. Antiphospholipid antibody syndrome and Behçet's disease were excluded based on clinical and laboratory evaluations, and upper gastrointestinal endoscopy revealed no evidence of esophageal varices.

Due to the presence of ascites, hepatosplenomegaly, and heterogeneity in the liver parenchyma, a liver biopsy was performed, which revealed focal glycogenization, intralobular inflammation, and lobular necrosis (Figure I).

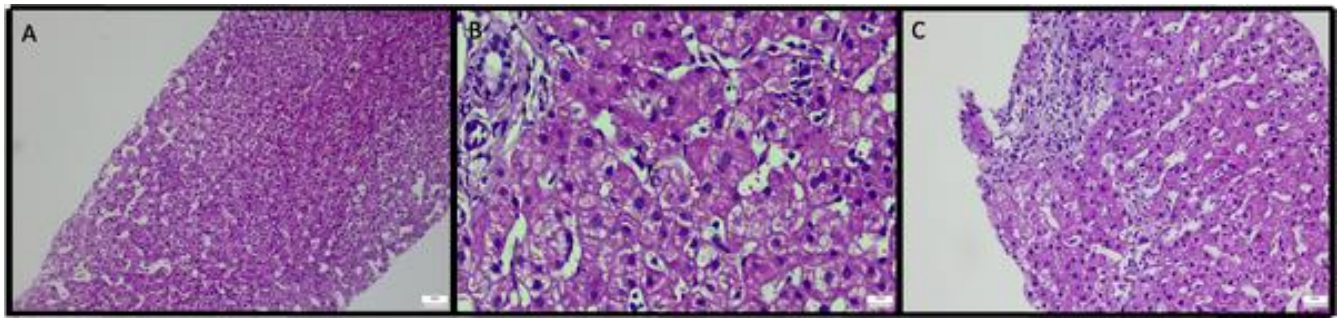

Figure I. Liver Biopsy

A) Sinusoidal congestion and dilation (H&E, X40) B) Focal glycogenization findings (H&E, X200) C) Focal intralobular inflammation and lobular necrosis (H&E, X100)

The clinical condition of the patient was consistent with portal hypertension; fluid and salt restriction were implemented, antibiotic therapy was administered, and treatment with 1 mg/kg spironolactone and 1 mg/kg furosemide was initiated. The patient responded dramatically to the antiacid treatment. On the 11th day of hospitalization, the patient's ascites symptoms regressed, and there was no swelling in the periorbital and leg areas. He was discharged with spironolactone and furosemide treatments to come for a follow-up at the pediatric gastroenterology outpatient clinic. The weight measured at discharge was 62 kg, the waist circumference was 88 cm, and a weight loss of 7 kg was detected.

In the outpatient follow-up, it was learned that the patient, who had been referred to the pediatric gastroenterology clinic at another center, had their furosemide and spironolactone treatments discontinued, and swelling in the eyes, abdomen, and legs had started again approximately 10 days later. The patient's anti-acid treatment was restarted.

The tests for Wilson's disease, severe combined immunodeficiency, and thrombophilia sent for genetic analysis returned negative results. In the whole exome sequencing analysis, a homozygous variant NM_001282225.2: c.139G>A; p.(Gly47Arg); (rs202134424) in the ADA2 gene was identified as pathogenic. A homozygous variant NM_001172477.1: c.184delA;

p.(Glu62SerfsTer2); (rs758091261) of uncertain clinical significance was detected in the RRM2B gene, which did not align with our patient's clinical findings. The patient, referred to the pediatric immunology-rheumatology outpatient clinic, is continuing etanercept treatment at an external center.

Discussion

ADA2 deficiency is an autosomal recessive systemic autoinflammatory disease characterized by systemic inflammation, fever, vasculitis, early-onset stroke, bone marrow, and immune deficiency. biallelic pathogenic mutations in the ADA2 gene (ADA2; formerly known as CECR1; Cat Eye syndrome Chromosome Region 1 gene) on chromosome 22q11 causes (1).

In humans, there are two different adenosine deaminases, ADA1 and ADA2. ADA1 plays an important role in lymphocyte function, and hereditary mutations in ADA1 cause severe combined immunodeficiency. Recently isolated ADA2 belongs to a new family of adenosine deaminase growth factors (ADGFs) that play an important role in tissue development (2).

ADA2 is mainly expressed in immune cells. Monocytes, macrophages and dendritic cells show the highest protein expression (3).

ADA2, a receptor for ADA1, binds to neutrophils, monocytes, NK cells, and B cells, facilitating the activation of immune cells (4).

The enzyme deficiency causes myeloid cells to switch to a predominant pro-inflammatory M1 macrophage with increased proinflammatory cytokine release. A key role in the pathogenesis of the disease appears to be played by tumor necrosis factor-alpha (TNF-alpha) (5).

A homozygous or compound heterozygous mutation in the ADA2 gene that causes loss of function is the cause of this rare syndrome. In a recently published systematic literature review, homozygous mutations were found in 215 out of 378 patients (5). In our patient's genetics, a homozygous mutation of the pathogen has been detected.

Recently published ADA2 deficiency management guidelines have defined four different clinical phenotypes: inflammatory/vasculitic, hematological, immunodeficient and presymptomatic (i.e. patients with biallelic variants in ADA2 who are not symptomatic, e.g. identified through family screening) (6). The phenotype of ADA2 deficiency varies from cutaneous lesions to systemic disease with central nervous system involvement and aneurysms in visceral arteries that may overlap with the spectrum of polyarteritis nodosa (PAN) (7).

In cases of early-onset vasculitis presenting with systemic PAN-like findings, ADA2 deficiency may be an underlying factor (8).

Zhou et al. reported 9 patients with recurrent ischemic strokes and fever starting before the age of 4. In three patients, there was a hemorrhagic stroke, in one patient, central retinal artery occlusion, and in one patient, left optic nerve atrophy. Urticarial papules and plaques were present in the patients. In some patients, abnormal liver enzymes, hepatosplenomegaly, hypogammaglobulinemia, pancytopenia, and leukopenia were detected (1).

ADA2 deficiency can cause cytopenia in all cell lines due to bone marrow failure (9). It can present with humoral immunodeficiency and recurrent infections (10).

Although the presence of a homozygous mutation in the ADA2 gene was sufficient to establish the diagnosis in our patient, it is noteworthy that ADA2 enzyme activity is also considered an important diagnostic parameter. In this case, enzyme activity was not assessed because the test is not routinely available in our centre and is associated with considerable cost. Nevertheless, the identification of a homozygous pathogenic variant was regarded as definitive by the treating physicians, and the diagnosis of ADA2 deficiency was confirmed on genetic grounds.

It has been published that splenomegaly is observed in 30.6% and hepatomegaly in 23.5% in ADA2 deficiency (5). Lymphoproliferation in older publications related to ADA2 deficiency has been reported in up to 30% of patients as generalized lymphadenopathy and hepatosplenomegaly (11).

However, the pathological changes in the liver caused by ADA2 deficiency and the clinical outcomes it leads to have become increasingly noteworthy as knowledge in this area has grown recently. For example, nodular regenerative hyperplasia of the liver, focal nodular hyperplasia, and non-cirrhotic portal hypertension and fibrosis have been reported (12,13,14). In our case, due to the presence of ascites, hepatosplenomegaly, and the detection of heterogeneity in the liver parenchyma, a liver biopsy was performed, which revealed sinusoidal congestion and dilation, focal glycogenization, focal intralobular inflammation, lobular necrosis, and rosette formation in the liver. The liver pathology findings in our case indicate parenchymal disease, but they do not provide specific information that can be clearly attributed to ADA2 deficiency. Unlike ADA2 deficiency, which is often considered in differential diagnosis with early-onset stroke, vasculitis, immunodeficiency, and hematological abnormalities, it is important that, as in our patient, it presents with liver parenchymal disease and portal hypertension findings. We advocate for the necessity of evaluating/screening for parenchymal liver diseases in patients diagnosed with ADA2 deficiency.

In the treatment of the disease, the phenotype is essential. Although there is no definitively defined treatment strategy, it is known that ANTI-TNF immunomodulator (etanercept) agents are particularly used in preventing stroke in the treatment of ADA2 (15). In severe cases of bone marrow failure and immune deficiency, hematopoietic stem cell transplantation is the definitive treatment option (16).

Conclusion

We presented a pediatric case diagnosed with ADA2 deficiency, atypically presenting with ascites and chronic liver disease findings, and requiring a liver biopsy. We aimed to highlight that ADA2 deficiency could be a potential cause of non-cirrhotic portal hypertension. Although patients may present with clinical findings suggestive of liver disease, liver biopsy results can often be non-specific.

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