CASE REPORT

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Alström syndrome presenting with life-threatening variceal bleeding in an adolescent: the youngest reported case in Türkiye

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ABSTRACT

Alström syndrome (AS) is a rare autosomal recessive ciliopathy caused by pathogenic variants in the *ALMS1* gene on chromosome 2p13, with multisystem involvement including the retina, cochlea, heart, liver, and kidneys. It is characterized by progressive cone-rod dystrophy, sensorineural hearing loss, truncal obesity, insulin resistance, type 2 diabetes mellitus and cardiomyopathy. Although hepatic involvement is frequent, advanced complications such as portal hypertension and variceal bleeding are extremely rare in childhood. We report the case of a 16-year-old girl with AS who presented with hematemesis and altered mental status. Laboratory evaluation revealed chronic liver disease and diabetic ketoacidosis. Upper gastrointestinal endoscopy demonstrated grade 2-3 esophageal varices that were treated with band ligation. Genetic testing identified a homozygous pathogenic frameshift mutation (NM_001378454.1:c.10218del, p.Ser3407Valfs*12) in exon 15 of the *ALMS1* gene. This patient is the youngest reported pediatric AS case in Türkiye presenting with life-threatening variceal hemorrhage secondary to portal hypertension. The case underscores the importance of early genetic confirmation and proactive hepatic monitoring in pediatric patients with AS.

Introduction

Alström syndrome (AS) is a rare autosomal recessive ciliopathy caused by biallelic *ALMS1* mutations on chromosome 2p13, with an estimated prevalence of 1 in 1,000,000 (1,2).

It leads to progressive multiorgan dysfunction, affecting the ocular, auditory, metabolic, cardiac, renal, pulmonary, and hepatic systems. Infantile-onset cone-rod dystrophy causes early blindness with nystagmus and photophobia, while sensorineural hearing loss develops later. Metabolic features include truncal obesity, severe insulin resistance, dyslipidemia, and type 2 diabetes mellitus (T2DM). Cardiomyopathy may present in infancy or recur later, and renal or pulmonary disease manifests as chronic kidney disease, restrictive lung disease, or recurrent infections (3,4). Hepatic involvement affects up to 80% of patients, typically starting with mild steatosis or transaminase elevation in childhood and progressing to fibrosis, cirrhosis, and portal hypertension in adolescence. Insulin resistance, ciliary dysfunction, and stellate-cell activation drive fibrogenesis, which often remains subclinical until advanced stages (2,4).

Diagnosis is challenging because of gradual, overlapping features with other ciliopathies such as Bardet-Biedl syndrome. While early retinal dystrophy, hearing loss, obesity, and insulin resistance raise suspicion, confirmation requires molecular identification of biallelic *ALMS1* variants (3,4).

We report a case of a 16-year-old girl with genetically confirmed AS who developed life-threatening variceal bleeding due to portal hypertension, the youngest reported case in Türkiye. According to the literature, this is the second pediatric patient with AS requiring liver transplantation. This case underscores the importance of early genetic diagnosis and vigilant hepatic surveillance to prevent irreversible complications.

Case Presentation

A 16-year-old girl was admitted with hematemesis, melena, and altered mental status. She was the second child of healthy, non-consanguineous parents and was born at term with normal growth. In infancy, cone-rod dystrophy caused photophobia and nystagmus. During the school-age period, truncal obesity and dyslipidemia developed. At 13 years of age, she was diagnosed with T2DM and subsequently had multiple intensive care admissions for recurrent diabetic ketoacidosis (DKA). Two years before presentation, an upper endoscopy revealed esophageal varices and portal hypertensive gastropathy; however, she was subsequently lost to follow-up.

On admission, her Z-scores for weight, height, and body mass index were 0.44, -1.35, and 1.32, respectively. She was confused and disoriented, with involuntary eye movements. Abdominal examination revealed hepatomegaly and splenomegaly, each 1 cm below the costal margin, and ascites; a grade 2/6 systolic murmur was audible. Laboratory studies revealed a white blood cell (WBC) count 19.8x10^3 µL, platelets (PLT) 115x10^3 µL; PLT of 115×10^9; alanine aminotransferase 47 U/L; aspartate aminotransferase 46 U/L; gamma-glutamyl transferase 123 U/L; albumin of 3.1 g/dL; international normalized ratio (INR) 1.3; C-reactive protein (CRP) 16.4 mg/L; glucose 530 mg/dL, and marked hyperammonemia (539 µmol/L). There was no history of exposure to hepatotoxic medications, supplements, or environmental agents.

Abdominal ultrasound showed granular liver parenchyma. Differential diagnoses, including autoimmune and viral diseases, Wilson disease, α1-antitrypsin deficiency, Budd-Chiari syndrome, and extrahepatic portal vein thrombosis, were excluded. Doppler ultrasonography (USG) revealed a 12.5 mm portal vein with preserved hepatopetal flow and no thrombosis, confirming intrahepatic portal hypertension.

Echocardiography showed mild pericardial effusion, and ophthalmologic assessment confirmed retinitis pigmentosa. After stabilization with fluids, diuretics, insulin, and supportive care, urgent endoscopy revealed grade 2-3 esophageal varices with red wale signs; band ligation was performed successfully (Figure 1). No further bleeding occurred; DKA resolved by day 2; mental status normalized by day 4.

Genetic testing confirmed a NM_001378454.1: c.10218del, p.Ser3407Valfs*12 homozygous mutation in exon 15 of the *ALMS1* gene confirming AS (Figure 2).

Eight months later, the patient was readmitted with hematemesis. Laboratory evaluation revealed findings consistent with acute hemorrhagic and metabolic decompensation [WBC 16.9×10^3/µL, hemoglobin (Hb) 4.4 g/dL, PLT 101×10^3/µL, absolute neutrophil count 13.32×10^3/µL, absolute lymphocyte count 2.53×10^3/µL, glucose 472 mg/dL, albumin 2.8 g/dL, CRP 19 mg/L, INR 1.2]. Transaminase and bilirubin levels were normal. Arterial blood gas analysis revealed mild acidosis.

Abdominal USG showed coarse hepatic echotexture with irregular contours and left-lobe blunting. The main portal vein measured 12 mm, and up to 6 cm of pelvic free fluid was detected. Echocardiography was normal.

Supportive therapy with octreotide was initiated, but the Hb level continued to decline, necessitating urgent band ligation of grade 2-3 esophageal varices. After stabilization, she was transferred to a liver transplant center for recurrent life-threatening bleeding.

Written informed consent was obtained from the parents; ethics approval was not required under institutional policy.

Discussion

The unusually early hepatic decompensation in our patient may reflect the combined effects of severe insulin resistance, recurrent DKA, and a homozygous truncating ALMS1 mutation in exon 15. Although this specific

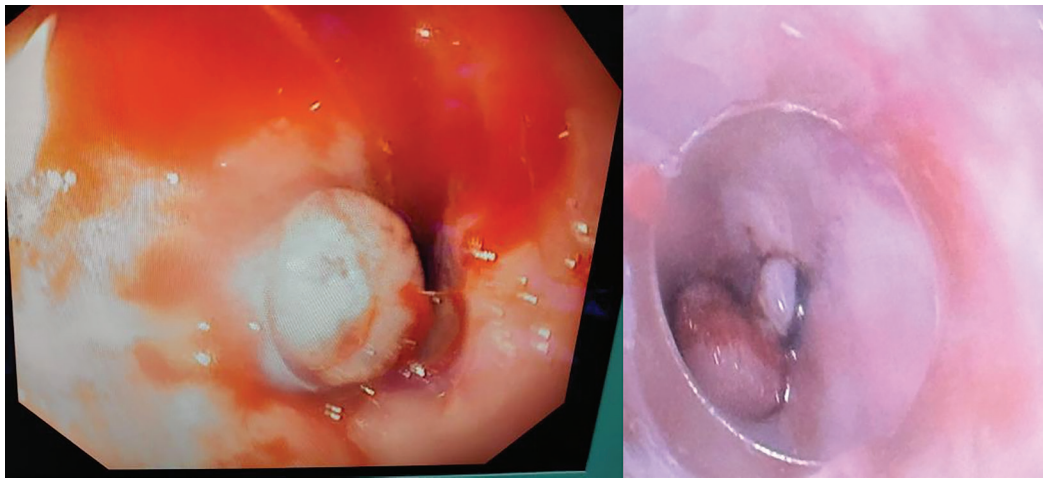

Figure 1. Endoscopic image of successful obliteration of varices following band ligation in a 16-year-old girl with Alström syndrome

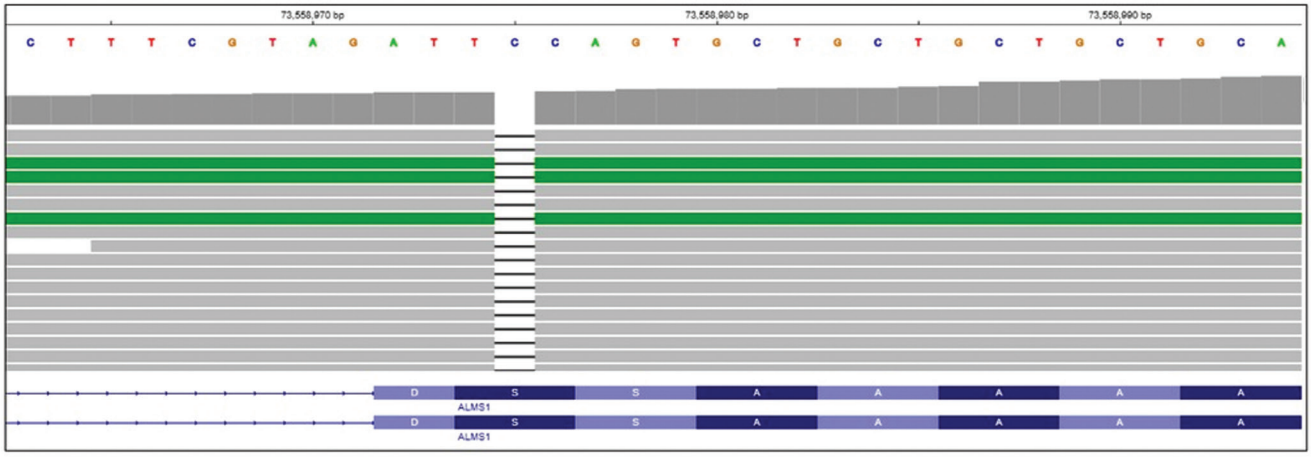

Figure 2. Genetic testing confirmed a NM_001378454.1: c.10218del, p.Ser3407Valfs*12 homozygous mutation in exon 15 of the *ALMS1* gene

variant has been rarely reported, truncating ALMS1 mutations have been associated with progressive multisystem disease and may predispose patients to earlier hepatic fibrosis and portal hypertension (5,6). Therefore, these factors could have contributed to the rapid evolution of hepatic disease in our patient. Our patient had poorly controlled T2DM from age 13, experiencing three DKA episodes over two years. Although uncommon in T2DM, DKA can occur when severe insulin resistance coexists with β-cell failure, as in AS. Recurrent metabolic and hemodynamic stress from dehydration, acidosis, and hypoperfusion may have exacerbated ongoing hepatic injury and accelerated fibrosis progression beyond what is typically expected in the steatosis-to-cirrhosis trajectory, while the concurrent marked hyperammonemia was likely due to transient perfusion-related dysfunction rather than intrinsic hepatic failure, as it resolved rapidly after correction of acidosis and fluids. Collectively, these genetic and metabolic factors could help explain the unusually young age at which our patient developed clinically significant portal hypertension and variceal bleeding.

In comparison to our findings, reported pediatric AS cases generally present with mild hepatic manifestations, such as steatosis or moderate transaminase elevation, progressing to fibrosis or cirrhosis later in life (7,8). However, exceptions similar to our case have been reported in the literature. Connolly et al. (9) reported an 8-year-old with chronic hepatitis-like changes and preserved function; Awazu et al. (10) described siblings with childhood steatohepatitis progressing to cirrhosis; and Quiros-Tejeira et al. (11) presented an 8-year-old with portal hypertension and acute liver failure, possibly triggered by metabolic or mitochondrial stress. While severe early decompensation is rare, progressive hepatic disease is a significant complication in AS, with specific truncating ALMS1 variants associated with higher prevalence and worse clinical progression (6,12).

Clinical features evolve with age, often delaying diagnosis. An average diagnostic delay of 8-10 years has been reported (4). A probable pediatric diagnosis of AS requires at least two major (e.g., visual loss, hearing deficit, metabolic abnormality) and two minor features (e.g., hepatic, renal, or endocrine involvement), while confirmation relies on identifying biallelic ALMS1 pathogenic variants. No biochemical, histologic, or imaging test can confirm the disease; thus, molecular analysis remains essential despite phenotypic overlap with other ciliopathies (3).

Lessons from this case highlight the need for structured hepatic surveillance in metabolically unstable AS patients. The following recommendations derive from pediatric portal hypertension guidelines and previously published reports, rather than from the actual follow-up course of this patient, who was lost to follow-up for extended periods. According to these guidelines, monitoring every 3-6 months with Doppler USG (± elastography) may facilitate early detection of portal hypertension. Endoscopic evaluation is generally advised when splenomegaly or thrombocytopenia develops, typically at 6-12-month intervals, depending on severity. For patients with high-risk varices, recommended schedules include re-endoscopy 1 month after band ligation and then every 1-3 months until eradication, followed by examinations every 3-6 months for two years and annually thereafter, ideally in coordination with a transplant center (13). Preventing DKA is also critical, as recurrent metabolic decompensation may aggravate hepatic injury. Early referral for transplant evaluation is recommended when signs of decompensation emerge.

The main limitation is the single-patient nature of this report, which limits generalizability. However, it provides valuable insight into the scarce pediatric data on hepatic involvement in AS.

Ethics

Informed Consent: Written informed consent was obtained from the parents.

Footnotes

Authorship Contributions

Concept: B.İ.A., S.T., N.B., Design: B.İ.A., S.T., N.B., Data Collection or Processing: B.İ.A., S.T., Y.M.E., İ.M.T., Analysis or Interpretation: B.İ.A., S.T., Y.M.E., İ.M.T., N.B., Literature Search: B.İ.A., S.T., Y.M.E., N.B., Writing: B.İ.A., S.T., Y.M.E., İ.M.T., N.B.

Conflict of Interest: The authors declared no conflict of interest.

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