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CASE REPORT

Alagille Syndrome: Challenging Diagnosis and Prognostic Factors, A Case Report

Marwa Sameer[1*], Hadhami Ben Turkia[2]

[1]Pediatric Senior House Officer, Pediatric Department; King Hamad University Hospital. Muharraq, Kingdom of Bahrain

[2]Consultant Pediatrics/Clinical Assistant at Arabian Gulf University, Pediatric Department, King Hamad University Hospital. Muharraq. Kingdom of Bahrain

***Corresponding author:**

Dr. Marwa Sameer, B.Sc., M.D., Pediatric Senior House Officer, Pediatric Department; King Hamad University Hospital. Muharraq, Kingdom of Bahrain; Tel: + (973) 34104433; Email: marwa.sameer.6@gmail.com

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Abstract

Alagille syndrome (AS) commonly presents with cholestasis, much like other liver diseases, making the diagnosis challenging. We report a case of a patient with AS mimicking biliary atresia (BA) with a poor outcome. The infant, a product of a non-consanguineous marriage, presented with jaundice, clay stools, peripheral pulmonary stenosis, atrial septal defect, and butterfly vertebrae. Cholescintigraphy showed an absence of radiotracer excretion. Surgical exploration revealed the presence of a hypoplastic hepatic duct but a normal gallbladder, cystic, and common bile ducts. Intraoperative cholangiogram favored BA, and a Kasai procedure was performed. The liver biopsy demonstrated focal areas of ductular proliferation and periportal ballooning degeneration without bile duct paucity. The patient exhibited worsening cardiac and liver conditions, growth failure, and developmental delay. She died suddenly at home at the age of 34 months. The cholangiographic and histological abnormalities found in our patient were suggestive of BA. At the same time, she displayed four out of five diagnostic criteria for AS. Based on our experience with this case, we suggest expeditious genetic testing should be considered for any case of neonatal cholestasis with diagnostic uncertainty. This may help avoid unwarranted surgical interventions, potentially associated with worse outcomes.

Keywords: Alagille syndrome, Liver, Bile duct paucity, Cholestasis, Kasai procedure

Introduction

Alagille syndrome (AS) is the syndromic bile duct paucity (BDP) variant. It is an autosomal dominant multisystemic and progressive disorder involving the liver, heart, vertebrae, and eyes.[1,2] It is estimated to affect 1:70,000 live births globally.[3] It is caused by mutations or deletions in one of the two genes coding for proteins involved in the Notch signaling pathway: the Jagged1 (JAG1) gene or the Notch homolog 2 (NOTCH2) gene.[1] JAG1 mutations are associated with 98% of AS cases compared to the NOTCH2 gene, which only accounts for 2% of cases.[4] The microdeletion 20p12.2, encompassing the JAG1 gene, may raise suspicion of an AS

variant associated with developmental delay and hearing loss.[4]

AS is diagnosed based on clinical criteria that may not be present in early infancy, making the diagnosis challenging. Jaundice, the most common presentation in infants, is indistinguishable from other causes of cholestasis. Herein, we report a case of AS mimicking biliary atresia (BA).

Case presentation

The patient was a product of a non-consanguineous marriage, born at 36 weeks of gestation with a birth weight of 1.8 kg. She was admitted at two months of age with aspiration pneumonia and had a history of yellow discoloration of the skin with clay-colored stools since day 7 of life. She was dysmorphic with a broad forehead, deep-set eyes, hypertelorism, epicanthic folds, a flat nasal bridge, bulbous nasal tip, and a pointed chin. A systolic murmur in the pulmonary area and hepatomegaly were also observed. Her father had facial dysmorphism and a history of congenital heart disease surgery during childhood. Investigations revealed cholestasis, liver enzyme derangement, prolonged prothrombin time, and high cholesterol levels (Table 1).

Chest radiography revealed multiple thoracic butterfly vertebrae (Figure 1). Abdominal ultrasonography (US) findings were normal, and echocardiography revealed an atrial septal defect with bilateral peripheral pulmonary stenosis (PPS).

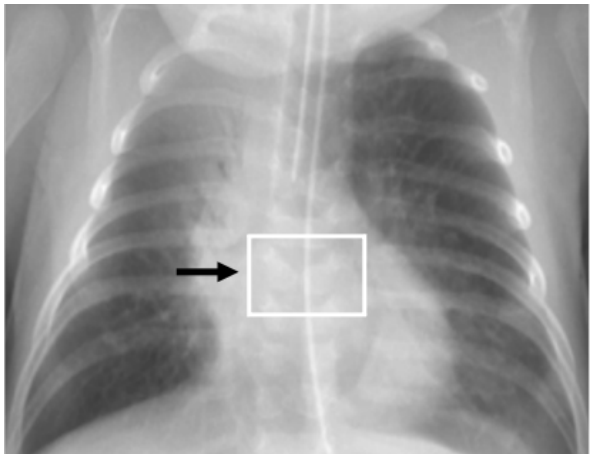

Figure 1: Chest X-ray of the patient with a labelled butterfly vertebra

The immunoreactive trypsinogen, α-1 antitrypsin, galactose-1-phosphateuridylyltransferase, tandem mass spectrometry, and TORCH screening results were normal. The slit-lamp examination ruled out posterior embryotoxon. A hepatobiliary iminodiacetic acid (HIDA) scan revealed the absence of radiotracer excretion after 24 hours. Intraoperatively, the gallbladder, cystic duct, and common bile duct appeared normal, but the common hepatic duct was hypoplastic. The cholangiogram revealed a flow reaching the duodenum; however, when obstructed distally, there was no backflow to the liver, which fit with BA type 2A (Figure 2); hence, a Kasai procedure was performed. A liver biopsy revealed a normal bile duct-to-portal tract ratio with focal areas of ductular proliferation (Figure 3).

Table 1: Laboratory Investigations at Patient's First Visit

Parameter	Value	Parameter	Value
Albumin	35.9 g/L (28-44 g/L)	Cholesterol	7.8 mmol/L (1.6-4.9mmol/L)
G-Glutamyltransferase (GGT)	1328 U/L (8-90 U/L)	Triglycerides	2.96 mmol/L (0-1.7 mmol/L)
Aspartate Aminotransferase (AST)	268 U/L (9-80 U/L)	INR	1.17 (0.61-1.17)
Alanine Aminotransferase (ALT)	201 U/L (13-45 U/L)	Activated Partial Thromboplastin Clotting Time (APTT)	21.7 seconds (28-42 seconds)
Alkaline Phosphatase (ALP)	910 U/L (90-180 U/L)	Prothrombin time (PT)	14.8 seconds (10.7-13.9 seconds)
Bilirubin Total	195.7 umol/L (23-35 umol/L)	Bilirubin Direct	175.94 umol/L (0-5 umol/L)

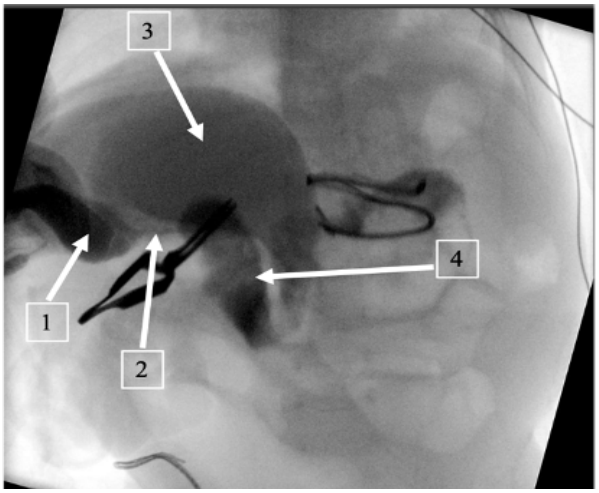

Figure 2: Intraoperative Cholangiogram. 1: Gallbladder; 2: Cystic duct; 3: Liver; 4: Duodenum

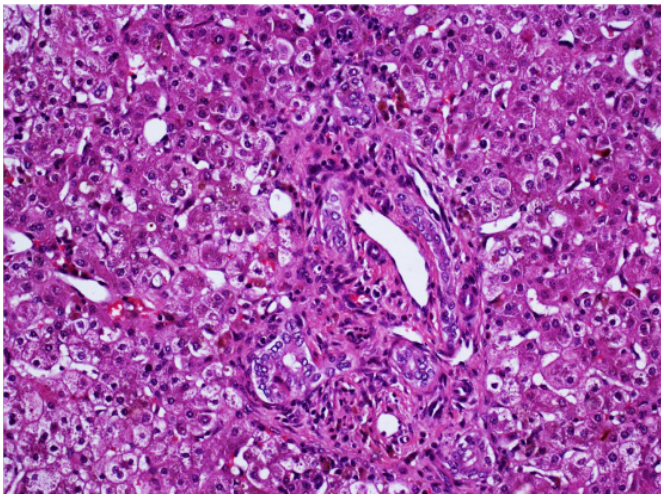

Figure 3: Liver histology showing normal bile duct-to-portal tract ratio with focal area of ductular proliferation

The patient was followed up in the general pediatric, surgical, cardiology, and dietary clinics. The liver condition rapidly deteriorated to cirrhosis and portal hypertension. Serial echocardiography revealed a progressive PPS. Magnetic Resonance Imaging (MRI) of the brain performed at the age of 2 years was unremarkable. However, her growth was severely impaired with a significant gross motor delay. Genetic testing was not performed because of financial reasons. The patient died at the age of 34 months without being previously sick. This case report was ethically approved for publication by the Scientific Research and Development Directorate at King Hamad University Hospital, a tertiary hospital in the Kingdom of Bahrain. Parental consent was also obtained.

Discussion

The classic diagnosis of AS is based on the presence of three out of the five major features: chronic cholestasis due to bile duct paucity, congenital heart disease affecting primarily the pulmonary outflow tract, butterfly vertebrae, typical facial features, and posterior embryotoxon.[1,2] AS has a variable clinical phenotype and penetrance.[5,6] Cholestasis and pulmonary stenosis are the most prevalent features, with jaundice being the presenting sign in more than 90% of cases.[2,7] Renal and vascular abnormalities are considered major criteria, though they were not found in our patient.[5] Biochemical abnormalities associated with AS, including conjugated hyperbilirubinemia, elevated G-Glutamyltransferase (GGT), cholesterol, and triglycerides, were all manifested in our patient.[4] Some studies have suggested that hypercholesterolemia may be a differentiating indicator of AS in neonatal cholestasis as it was found to be significantly higher in AS than in BA.[8] Abdominal ultrasound (US) and HIDA scan may suggest a false diagnosis of BA; both conditions are associated with abnormal gallbladder shapes, although the presence of a triangular-cord sign is not observed in AS.[9] Subramaniam et al. reported impaired bile excretion on HIDA scan in 60% of AS patients.[7] Cholangiography was also suggestive of BA in our patient as was demonstrated in 5 of 6 patients reported in the Subramaniam study.[7] Invasive biliary imaging (e.g., ERCP, PTC) should be reserved for patients showing less than three criteria and clay-colored stools. These procedures should be favored over operative cholangiography, which may worsen the prognosis of liver disease.[7]

BDP is a key histological feature of AS but was not found in our patient, which can be explained by the disease's progressive nature in that it is commonly found in late infancy. In Subramaniam's cohort, BDP was absent in 25% of the cases, even after the age of one year.[7] Additionally, ductal proliferation may be observed in young infants, leading to a misdiagnosis of BA.[3,7] Genotyping of the JAG1/NOTCH2 genes could help diagnose patients in whom a definitive diagnosis is unclear. However, no pathogenic variants were identified in 3.2% of 401

probands, although they met the diagnostic criteria for AS.[1,10] AS is inherited in an autosomal dominant pattern with variable penetrance. However, 50-70% percent of JAG1/NOTCH2 gene mutations were found to have arisen de novo.[4] Interestingly, Kohsaka et al. found JAG1 mutations in patients with proven BA who developed other signs of AS after the age of 5 years.[11]

The Kasai procedure did not prevent the progression of cirrhosis in our patient. Kaye et al. reported a higher rate of liver transplantation and mortality among patients with AS who underwent the Kasai procedure than in the control group.[12] This may be due to ascending cholangitis affecting preexisting abnormal bile ducts. Additionally, it seems that neonatal onset of jaundice and persistent elevation of bilirubin and cholesterol levels reflect poor prognostic factors, irrespective of performing Kasai surgery.[13] The cause of our patient's demise remains unclear. Brain hemorrhage related to coagulopathy is a potential cause. Neurovascular accidents have been reported in 15% of patients, accounting for 34% of mortalities.[2]

Conclusion

Alagille syndrome (AS) is a progressive, multisystem disease with clinical, radiological, and histological features overlapping with other conditions, making its diagnosis challenging in young infants. The diagnosis is mainly clinical; hence, physicians should assume a high index of clinical suspicion and adopt a low threshold for genetic testing because early diagnosis is crucial to avoid inappropriate surgical intervention. Although AS mutations most commonly arise de novo, parental genetic testing is recommended, considering the need for genetic counseling.

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Conflicts of Interest

None

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None

Ethical approval

The case report was approved by the Head of Scientific Research and Development Directorate at King Hamad University Hospital, Kingdome of Bahrain.

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