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Ductular Reaction, Late-Onset Bile Duct Deficiency, and Cirrhosis: A Case Report Highlighting Misleading Histological Morphology in Alagille Syndrome

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Aim: to highlight the diagnostic challenges of Alagille syndrome (AGS), which can mimic other cholestatic diseases like biliary atresia. We aim to emphasize the importance of integrative diagnostic approaches, including genetic testing, to avoid misdiagnosis and unnecessary surgical procedures in cases where histological findings, such as ductular proliferation, do not follow typical patterns of AGS.

Key points. Diagnosing Alagille syndrome AGS is quite complex as it shares symptoms similar to those of other cholestatic diseases, especially biliary atresia. Bile duct paucity is the major pattern of AGS. Infants more than six months of age usually already show a visible bile duct paucity. However, in this case, our patient, who was more than six months old, didn't show bile duct paucity and ductular reaction was the major pattern. A four-year-old girl presented with chronic cholestasis, congenital heart disease, skeletal anomalies, ocular abnormalities, and facial deformity. Her liver biopsy at the age of one year predominantly showed ductular proliferation. Initially, we diagnosed her with biliary atresia. However, subsequent examination of a total hepatectomy sample at the age of four revealed bile ducts were difficult to identify in most portal tracts. Genetic testing in 2022 identified a heterozygous likely pathogenic variant in the *JAG1* gene, confirming AGS. The patient underwent liver transplantation.

Conclusion. We report the histology findings in AGS that can potentially be mistaken for other cholestatic diseases. We also highlight the importance of integrative diagnostic approaches to avoid misdiagnosis and unwarranted surgical procedures.

Keywords: Alagille syndrome, bile duct paucity, neonatal cholestasis, *JAG1* gene, case report

Conflicts of interest: the authors declared no conflicts of interest.

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Дуктулярная реакция, недостаточность желчных протоков с поздним началом и цирроз: клинический случай, свидетельствующий о ложной гистологической морфологии при синдроме Алажиля

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Цель: акцентировать внимание на сложностях диагностики синдрома Алажиля, способного имитировать другие холестатические заболевания, такие как билиарная атрезия. Авторы стремились подчеркнуть, что для постановки точного диагноза необходимо применять комплексные методы, включая генетическое тестирование. Это позволит избежать ошибок в диагностике и предотвратить ненужные хирургические вмешательства в случаях, когда гистологические данные, например пролиферация протоков, не соответствуют типичным проявлениям синдрома Алажиля.

Основные положения. Диагностика синдрома Алажиля может быть затруднена из-за сходства его симптомов с проявлениями других холестатических заболеваний, особенно билиарной атрезии. Ключевым признаком синдрома Алажиля является небольшое количество желчных протоков. Обычно у младенцев старше шести месяцев уже наблюдается явная недостаточность желчных протоков. Однако в описанном случае у пациентки, которая была старше шести месяцев, не было выявлено малочисленности желчных протоков, а основным симптомом была дуктулярная реакция. У четырехлетней девочки наблюдались хронический

холестаз, врожденный порок сердца, аномалии скелета, глаз и деформация лица. Биопсия печени, проведенная в возрасте одного года, выявила преимущественно протоковую пролиферацию. Первоначально у пациентки диагностировали билиарную атрезию. Однако последующее исследование образца, полученного после тотальной гепатэктомии в возрасте четырех лет, показало, что желчные протоки трудно идентифицировать в большинстве портальных трактов. Генетическое исследование, проведенное в 2022 г., выявило гетерозиготный, вероятно патогенный вариант в гене *JAG1*, подтвердив наличие синдрома Алажиля. Пациентке была проведена трансплантация печени.

Заключение. Представлены результаты гистологического исследования при синдроме Алажиля, которые потенциально могут быть ошибочно приняты за другие холестатические заболевания. Авторы обращают внимание на необходимость комплексного подхода к диагностике, позволяющего избежать ошибок и необоснованных хирургических вмешательств.

Ключевые слова: синдром Алажиля, недостаточность желчных протоков, неонатальный холестаз, ген *JAG1*, клинический случай

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Introduction

Alagille syndrome (AGS) is a genetic disorder caused by mutations in two genes: Jagged 1 (*JAG1*) or Neurogenic Locus Notch Homolog Protein 2 (*NOTCH2*) [1, 2]. Having the potential to affect multiple organs, AGS is considered a serious condition with significant repercussions for a child's growth, development, and overall quality of life. Timely management of AGS can be challenging for clinicians, as early intervention is crucial for improving outcomes [3]. Additionally, AGS is relatively uncommon, with reported incidence rates of 1 in 70,000 to 100,000 live births worldwide [4]. Between 2012 and 2024, there were only five AGS patients at Dr. Cipto Mangunkusumo Hospital (Rumah Sakit Umum Pusat Nasional Dr. Cipto Mangunkusumo, RSCM). This lack of exposure may contribute to the inexperience and unawareness among some medical practitioners [5].

Diagnosing AGS is quite complex, as it shares symptoms with other cholestatic diseases, particularly biliary atresia. A retrospective study reported that 13 % of AGS patients were misdiagnosed and underwent the Kasai procedure [6]. Bile duct paucity, defined as a reduced ratio of interlobular bile ducts to portal tracts with a ratio of less than 0.5, is crucial for distinguishing AGS histologically [7, 8]. This bile duct paucity is considered age-related and tends to increase over time. Infants older than six months typically exhibit visible bile duct paucity [9].

Our patient's liver biopsy examination at one year of age predominantly showed ductular proliferation, which we initially regarded as indicative of biliary atresia. Three years later, a second histopathological examination revealed bile duct paucity and biliary cirrhosis; however, ductular proliferation was still observed in other areas of the portal tracts. We aim to report these histological findings, which can be mistaken for other cholestatic diseases, and to highlight the importance of integrative diagnostic approaches to avoid misdiagnosis and unwarranted surgical procedures.

Case presentation

This is a case of a four-year-old girl referred to the gastroenterology clinic at RSCM with an initial diagnosis of biliary atresia. The patient was born at term with a borderline low-normal birth weight of 2,500 grams. She is the second child of two siblings, and her living elder sibling is asymptomatic (Fig. 1). She experienced delayed developmental milestones and malnutrition starting in early childhood. At two months old, she began showing signs of jaundice, accompanied by fever and elevated bilirubin levels. Her urine was dark brown, and her stool was pale. Phototherapy was administered in the perinatology intensive care unit. Although her bilirubin levels decreased, scleral icterus persisted, so treatment continued for another month. She was eventually referred to a (RSCM) after showing no significant improvement.

In November 2018, she was suspected of having AGS based on her clinical presentations. She had a triangular face with a head circumference of 40 cm, a wide and protruding forehead, deeply set eyes, a saddle nose with a rounded tip, a small, pointed chin, and prominent ears. Her eyes were icteric, with posterior embryotoxon and normal intraocular pressure. A cardiac examination revealed a grade III/6 holosystolic murmur. Her abdomen was distended, with an enlarged liver palpable 7 cm below the costal arch and 6 cm below the xiphoid process. The spleen was also palpable and firm, extending 4 cm below the left costal margin. Xanthoma, measuring 1.5 × 0.4 cm, was present in the subcutaneous tissue of the back, at the level of the second and third lumbar vertebrae. There were no pedal edema, purpura, palmar erythema, or spider nevi.

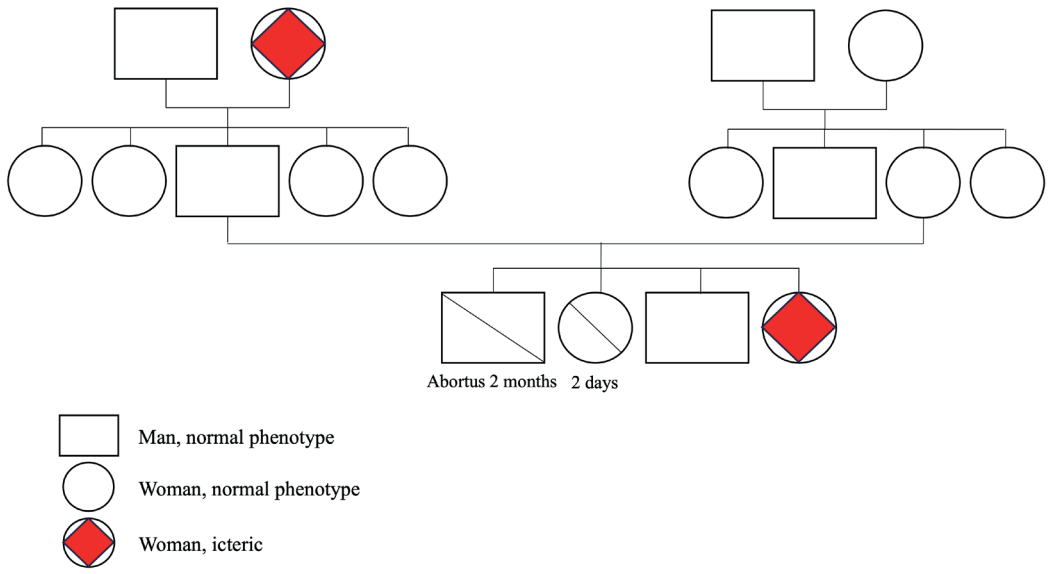

Figure 1. Pedigree of the patient. There is a history of jaundice in her lineage — which is her grandmother from her father's side of the family

Рисунок 1. Родословная пациентки. Желтуха в анамнезе имеется у ее родственников (у бабушки по отцовской линии)

Her bilirubin concentration was high at 30.96 mg/dL, with a direct fraction of 22.44 mg/dL, a high aspartate transaminase (AST) level of 168 U/L, a high alanine transaminase (ALT) level of 150 U/L, a low albumin concentration of 3.48 g/dL, and high gamma-glutamyl transpeptidase (GGT) levels of 46 U/L. Her urine was yellow and cloudy, containing bacteria, and was positive for 3+ bilirubin. Virology tests showed reactivity in EBV IgG, anti-Rubella IgG (640 IU/mL), and anti-CMV IgG (726.9 IU/mL). Meanwhile, anti-toxoplasma, anti-HAV IgM, HBsAg, anti-HBs, anti-HBe, anti-HBc total, and anti-HCV tests were all non-reactive. The patient had been vaccinated against hepatitis A virus,

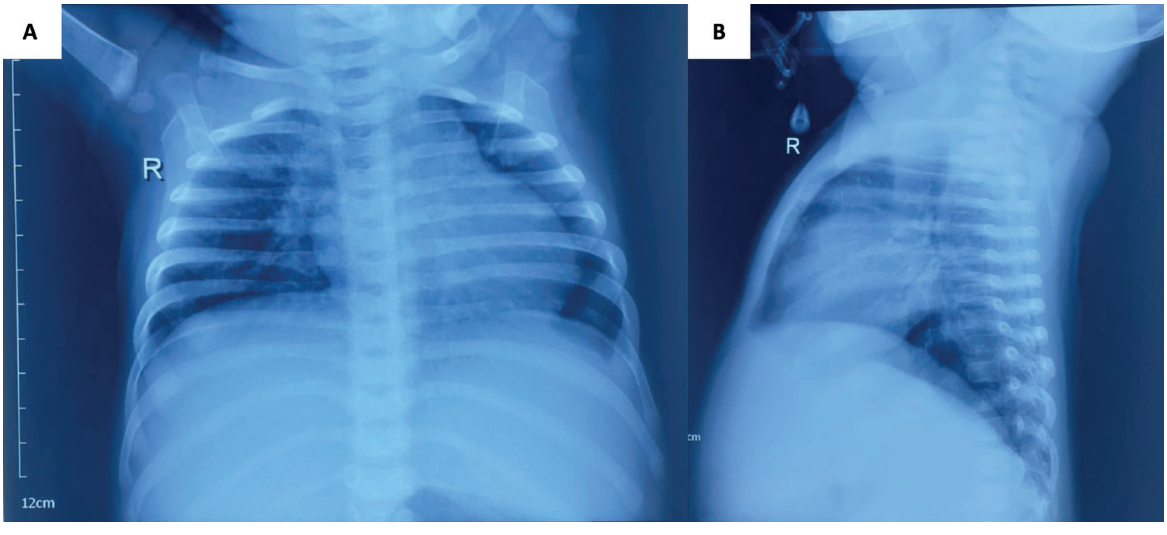

Figure 2. Imaging: A — chest X-ray in 2022 showed an enlarged heart and pulmonary infiltrate; B — whole spine X-ray showed butterfly vertebrae on T_{IV}–T_{XII}

Рисунок 2. Рентгенограмма: А — снимок грудной клетки в 2022 г., увеличенное сердце и легочный инфильтрат; В — снимок позвоночника, бабочковидные позвонки на уровне T_{IV}–T_{XII}

hepatitis B virus, tuberculosis, polio, diphtheria, influenza virus, pneumonia, mumps, typhoid, and varicella.

The results of her chest X-ray in 2019 showed a normal heart size and minimal infiltrates in the right paracardial region. However, a chest X-ray evaluation in 2022 revealed an enlarged heart with infiltration in the upper, middle, and lower fields of the right lung (Fig. 2A). The X-ray of her spine showed butterfly vertebrae from the fourth to the twelfth thoracic vertebra (Fig. 2B). An ultrasound examination revealed portal hypertension and no visible gallbladder contractions, both when fasting and after drinking. A multi-slice computed tomography scan of the abdomen confirmed hepatosplenomegaly

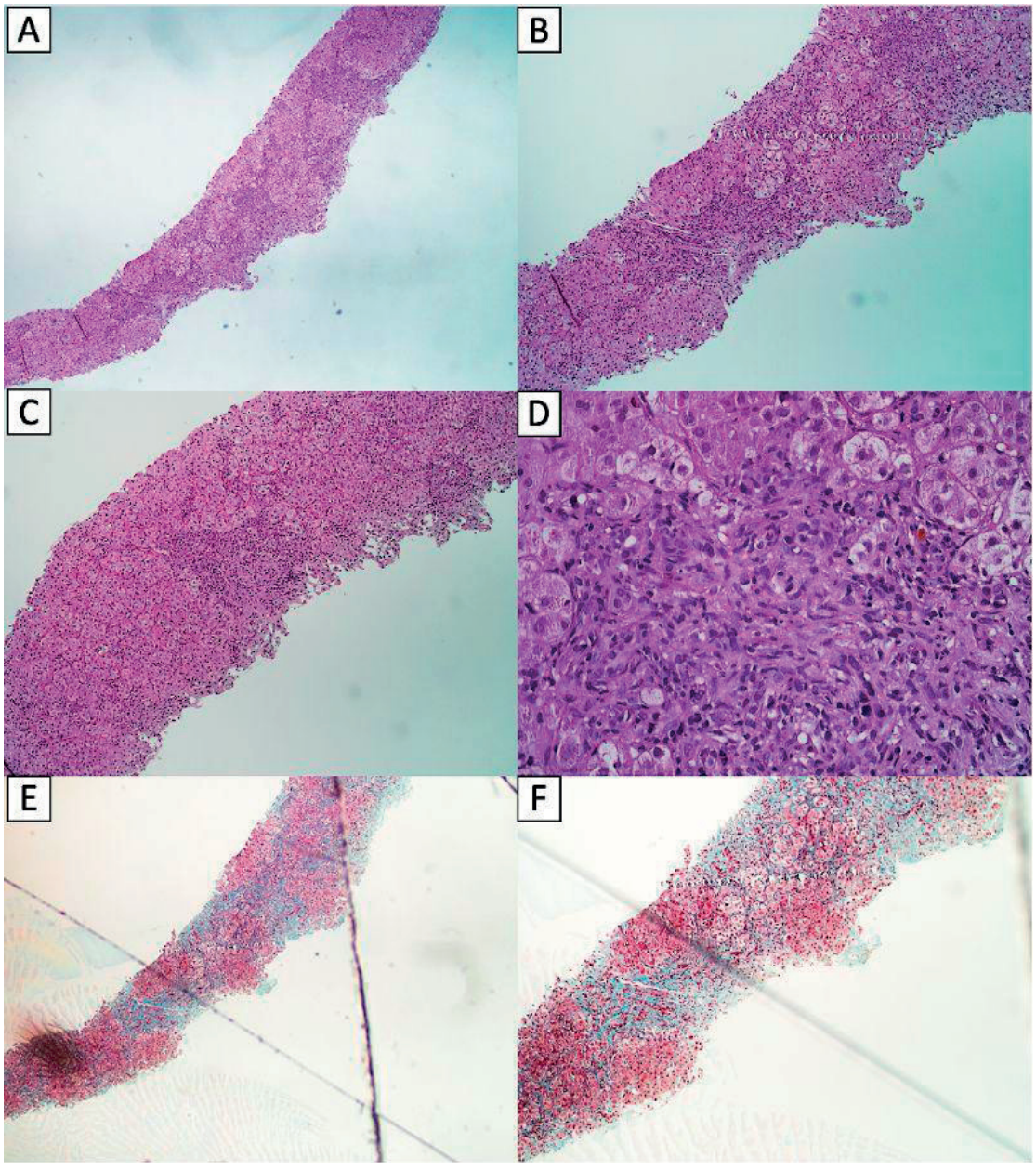

Figure 3. Liver biopsy in 2019, histopathology: A — portal tract expansion (hematoxylin and eosin, ×40); B — portal tract expansion (hematoxylin and eosin, ×100); C — ductular proliferation (hematoxylin and eosin, ×100); D — bile deposit (hematoxylin and eosin, ×40); E — fibrosis F3 (trichrome, ×40); F — fibrosis F3 (trichrome, ×100)

Рисунок 3. Биопсия печени 2019 г., гистопатология: A — расширение портального тракта (гематоксилин-эозин, ×40); B — расширение портального тракта (гематоксилин-эозин, ×100); C — протоковая пролиферация (гематоксилин-эозин, ×100); D — желчные отложения (гематоксилин-эозин, ×40); E — фиброз F3 (трихром, ×40); F — фиброз F3 (трихром, ×100)

Table. Frameshift mutation of *JAG1* gene revealed by genetic testing
Таблица. Мутация со сдвигом рамки считывания гена *JAG1*, выявленная при генетическом тестировании

Gene	Subject	Variant Coordinates	Zygosity	Allele	Type and classification
JAG1	Patient	Exon 25 NM_000214.2:c.3061_3064del, p.(lle1021Glyfs*14)	Het	ATAC/del	Frameshift likely pathogenic
JAG1	Mother		Hom		

and sagittal cleft bone deformity, with the gallbladder visualized in normal size and shape. She also underwent echocardiography, which showed a patent ductus arteriosus. Gastroduodenoscopy revealed esophageal varices grade I–II without any bleeding. Fiberoptic endoscopic evaluation of swallowing revealed 70 % adenoid hypertrophy.

Her first liver biopsy was performed in 2019 when she was one year old. The sample was a 2 cm long, thread-like shape. We found six portal tracts. The liver cells had a trabecular appearance; some appeared degenerated and swollen. There were intra-cytoplasmic and intra-canalicular bile deposits. Acute and chronic inflammation was seen in the periportal and lobular areas. In almost all portal tracts, mild ductular proliferation and an intraepithelial inflammatory reaction in the ductules were found. The portal area was dilated with slight fibrosis, suggesting early cirrhosis (Fig. 3). We initially concluded that it may be biliary atresia as a differential diagnosis. However, molecular testing in 2022 revealed a four-nucleotide deletion in exon 25 of the *JAG1* gene, leading to a premature termination codon, supporting the diagnosis of AGS. After a board meeting, a joint decision was made that the patient was eligible for liver transplantation.

Our patient underwent genetic testing in 2022. A heterozygous variation was found. A four-nucleotide deletion, c.3061_3064del, p.(Ile1021Glyfs*14), was identified in exon 25 of the *JAG1* gene. This deletion changes the codon reading frame, leading to the formation of a premature termination codon, which results in the production of a truncated protein (Table). The deletion is classified as likely pathogenic according to the guidelines from the American College of Medical Genetics and Genomics. This finding is consistent with autosomal dominant Alagille Syndrome Type 1. The heterozygous variation in exon 25 (c.3061_3064del) of the *JAG1* gene was not found in the mother.

An examination of the liver resection sample from when the patient was four years old in December 2022 revealed a liver with a soft consistency and a greenish-brown color. The total liver size was 18.5 × 12.0 × 6.0 cm. The outer surface was smooth with some nodular areas. The gallbladder was present, measuring 3.5 × 1.2 × 1.0 cm, white in color, springy, with a wall resembling a thin white membrane, and its lumen was filled with clear mucus. The cystic duct was difficult to identify. We did not find any velvety mucosa, erosion, ulceration, or gallstones (Fig. 4).

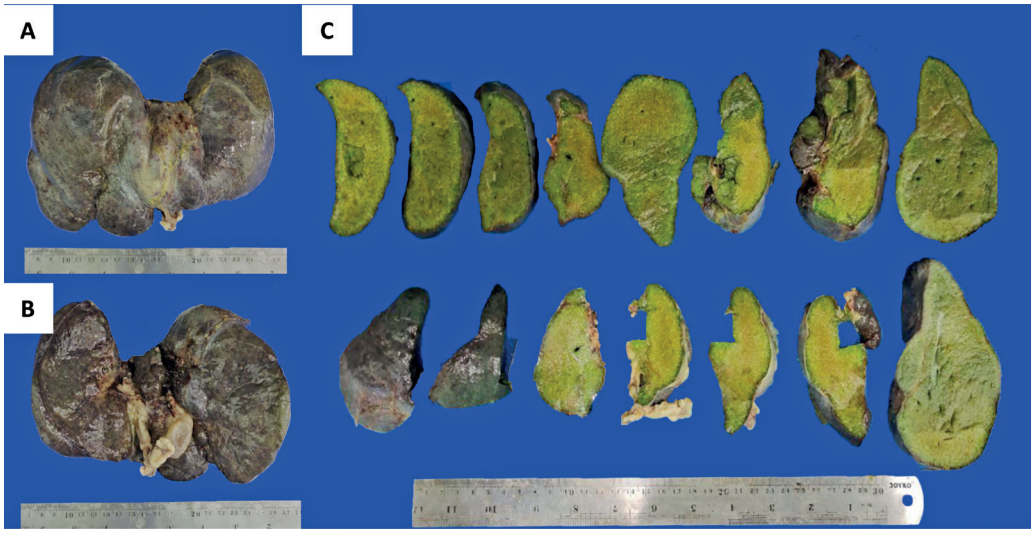

Figure 4. Liver resection in 2022: A–B — gross examination showed an 18.5 × 12.0 × 6.0 cm liver with gallbladder present; C — on the cut surface, there was no mass
Рисунок 4. Резекция печени в 2022 г.: A–B — макроскопическое исследование, печень размером 18,5 × 12,0 × 6,0 см с наличием желчного пузыря; C — на поверхности разреза образований не обнаружено

Histologic examination of total hepatectomy showed partially degenerated and swollen liver cells. Bile deposits were found in hepatocytes and canaliculi. There was mild steatosis. The bile duct was difficult to identify in most portal tracts. In other areas of the portal tract, ductular proliferation and chronic inflammatory cells were found. The gallbladder tissue showed a mucosa lined with single-layered columnar epithelial cells and lightly covered with chronic inflammatory cells. Bridging fibrous activity was found and coiled with the regenerating nodule formation (Fig. 5). We concluded it was in accordance with bile duct paucity which can be caused by AGS with Laennec scores 4A–4B suggesting biliary cirrhosis.

After a total hepatectomy was performed and the conclusion of AGS was obtained, the patient underwent liver transplantation in 2022. To date, the patient is alive and undergoing regular check-ups.

Discussion

This is a case of a four-year-old female diagnosed with AGS [7]. AGS is inherited in an autosomal dominant pattern [10]. There was a history of jaundice in our patient's lineage, specifically in her paternal grandmother. If a parent has AGS, the offspring have a 50 % chance of inheriting the gene mutation. Regardless of whether she had a first-degree relative with the disorder, individuals who exhibit one or more clinical characteristics should be suspected of having AGS [7].

AGS is caused by mutations in the genes encoding *JAG1*, a ligand of the NOTCH receptors, or the NOTCH2 receptor itself. More than 97 % of patients have a mutation in the *JAG1* gene, while less than 1 % have a mutation in the *NOTCH2* gene. Under physiological conditions, four NOTCH receptors interact with Jagged and Delta-like ligands, which

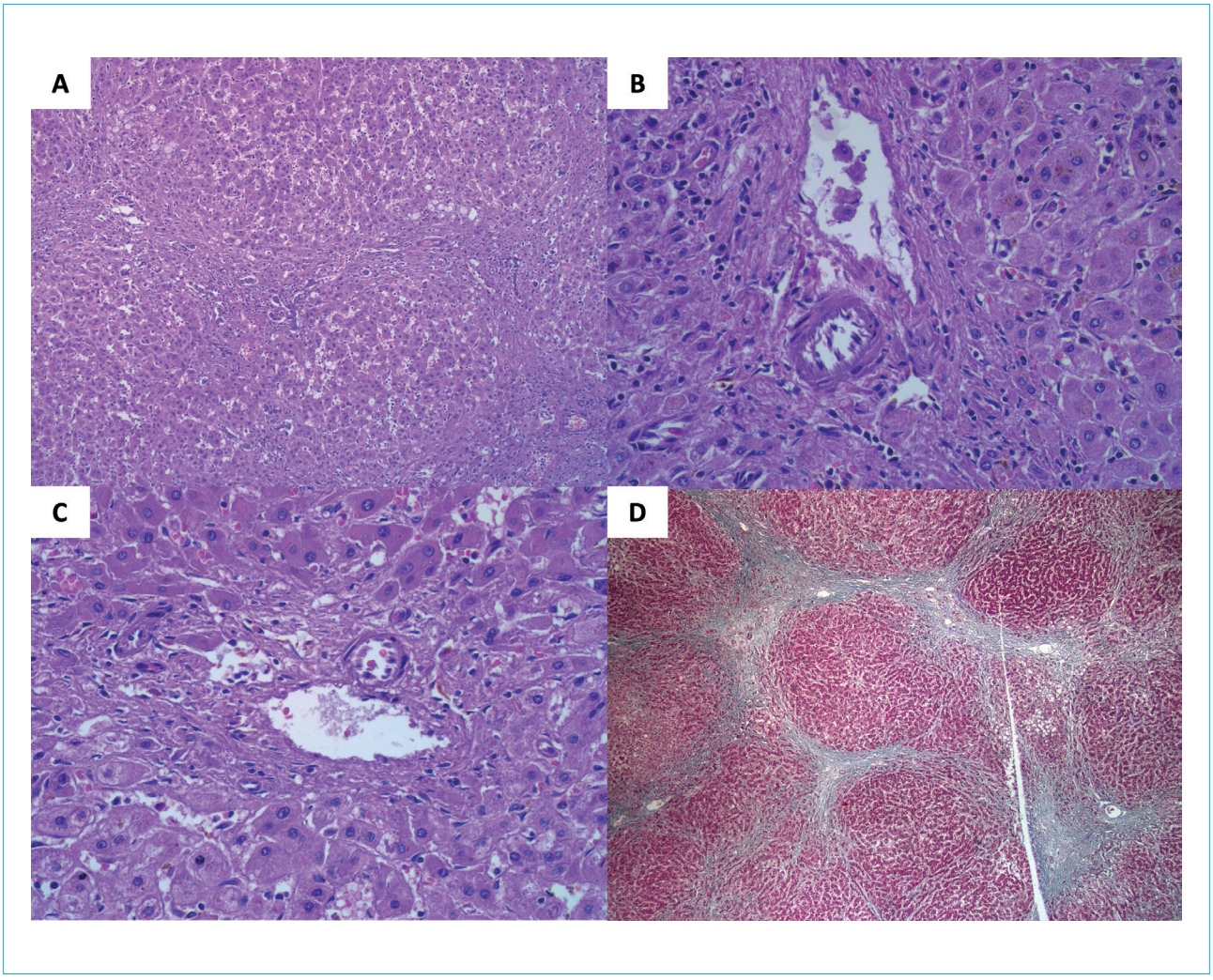

Figure 5. Liver resection in 2022, histopathology: A — bile duct paucity (hematoxylin and eosin, ×100); B–C — bile duct loss (hematoxylin and eosin, ×400); D — Laennec score 4A–4B (trichrome, ×100)

Рисунок 5. Резекция печени в 2022 г., гистопатология: A — скудность желчных протоков (гематоксилин-эозин, ×100); B–C — отсутствие желчных протоков (гематоксилин-эозин, ×400); D — оценка по Лаэннеку 4A–4B (трихром, ×100)

regulate intracellular pathways that specialize cells during embryonic organ development. While a misstep in this process can lead to other clinical conditions, AGS is considered one of the most prominent manifestations [11]. *JAG1* mutations may also disturb postnatal liver growth. Postnatal liver growth is thought to occur by increasing the number of mainly peripheral lobules and branching and elongating the accompanying portal tracts [9, 12].

The clinical presentation of AGS usually becomes visible during infancy and can vary greatly from patient to patient [7, 9]. Our patient was suspected of having AGS because she exhibited all five primary symptoms: chronic cholestasis, congenital heart disease, skeletal anomalies, ocular abnormalities, and facial deformity [7]. However, each of these symptoms is not exclusive to AGS, leaving room for the possibility of other diagnoses.

Cholestasis affects over 90 % of those with AGS. It is a major clinical presentation of hepatic involvement and most often manifests as conjugated hyperbilirubinemia [4]. The onset of conjugated hyperbilirubinemia can occur as early as two weeks of life, though it usually occurs within the first three months. In our case, it was marked by jaundice, dark brown urine, and pale stools starting at two to three months old [4, 13]. Laboratory examination showed elevated levels of direct and total bilirubin, ALT/AST, and GGT [4].

Cardiovascular diseases in AGS most often manifest as peripheral pulmonary artery stenosis, with 30 % involving structural defects such as pulmonary atresia, tetralogy of Fallot, ventricular septal defect, or atrial septal defect. Our patient was found to have a grade III/6 holosystolic murmur, cardiomegaly on chest X-ray, and patent ductus arteriosus on echocardiography [14]. As for ocular abnormalities, we found posterior embryotoxon with normal intraocular pressure. Posterior embryotoxon is characterized by a prominent Schwalbe's ring at the junction of the cornea and iris [8, 13]. However, without additional symptoms, embryotoxon alone cannot be a diagnostic indicator of AGS, as it occurs in 15 % of the general population without AGS, as well as in 70 % of patients with a deletion in 22Q11 [4]. Her facial deformity was characteristic of AGS, with features such as a broad forehead, straight nose with rounded tips, pointy chin, deep-set eyes, and a generally triangular facial appearance with prominent ears [13]. However, it should be noted that these facial characteristics are more subtle in neonates due to adipose tissue deposition, making the signs less noticeable [4].

In most cases, patients with AGS may also experience severe pruritus, xanthomas, and impaired growth or malnutrition [15]. Pruritus and growth failure occur at a higher rate in AGS compared to biliary atresia [14]. Our patient had both pruritus and growth failure. Minor clinical manifestations such as kidney disease, mental retardation, pancreatic insufficiency, or intracranial abnormalities were not present [3]. While these findings do not heavily impact the diagnosis, they can be helpful for the physician in forming a more precise diagnosis based on the frequency of symptoms.

Another method that may increase the precision of AGS diagnosis is radiological imaging. However, it is not recommended to rely solely on radiological imaging to diagnose AGS due to the significant resemblance of imaging findings, such as non-visualization of the biliary tree and the presence of a small gallbladder. Histological analysis remains necessary to establish the diagnosis [16, 17].

Butterfly vertebrae can be assessed using radiographic modalities such as anteroposterior X-rays and multi-slice computed tomography [18, 19]. We found butterfly vertebrae from the fourth to the twelfth thoracic vertebra on the patient's spine X-ray. However, butterfly vertebrae are occasionally found in asymptomatic patients [4]. On ultrasound evaluation, AGS is distinguished from biliary atresia by the absence of triangular cord signs, smaller hepatic artery diameter, a lower incidence of gallbladder wall irregularities, and a lack of portal hypertension [3, 16]. AGS also has a narrower portal septum, fewer hepatic parenchymal changes, smaller portal vein diameters, larger hepatic artery diameters, and less severe hepatic cirrhosis compared to biliary atresia, especially in end-stage biliary atresia [20].

Histopathological examination is considered an essential step in diagnosing AGS [1, 16, 17, 21, 22]. Through this examination, a pathologist can identify a histological pattern and correlate it with clinical parameters, such as GGT levels, which provide guidance for diagnosis [5]. The major histological finding in AGS is bile duct paucity, defined as a bile duct/portal tract (BD/PT) ratio of less than 0.5 [2, 7]. However, it is important to be cautious when interpreting the presence of bile duct paucity in premature infants, as a BD/PT ratio of less than 0.9 may be considered physiological [5]. There is also debate, as some papers list ductular response as a sign of liver disease in AGS patients. This difference of opinion arises because newborns under six months old may not exhibit visible bile duct paucity or may instead show ductular proliferation [9].

This case report presents a patient with histopathological findings of mild ductular proliferation at one year of age. We also observed intraepithelial inflammatory reactions in the ductules, along with intra-cytoplasmic and intra-canalicular bile deposits in almost all portal tracts. The porta was dilated with slight fibrosis, suggesting early cirrhosis. Initially, based on histopathological examination alone, we had very little suspicion that this case could be AGS, as bile duct paucity is the only feature considered the major histopathological indicator of AGS. Although AGS may present with a few histopathological features, such as ductular proliferation, fibrosis, and giant hepatocytes, these are not the main indicators

of the condition [9]. Furthermore, histologic patterns that overlap, such as bile duct proliferation, are more common in AGS infants younger than six months [23]. We suspected this patient had biliary atresia due to the similar features observed under the microscope [7, 8, 23].

An examination of a total hepatectomy sample at the age of four years showed that the bile ducts were difficult to identify in most portal tracts. However, in other areas of the portal tracts, ductular proliferation and chronic inflammatory cells were still present. There was also evidence of bridging fibrous activity. We noted cirrhosis with broad fibrous septae forming regenerative nodules. A similar case reported by G.H. Deutsch indicated that ductular proliferation observed in the initial biopsy at six months transformed into a characteristic pattern of bile duct paucity when the patient was re-evaluated at two years of age [24]. Some ductules and cells in the canals of Hering within the periportal parenchyma of portal tracts may become more visible after CK7 immunostaining [9].

Different methods and timing of sampling in this case — namely, a biopsy when the patient was one year old and a total hepatectomy when the patient was four — might contribute to the differing histological findings. The assessment of incomplete portal tracts from the initial inspection is a significant concern with needle biopsies from neonates. We also suspect that the first liver examination revealed a spontaneous appearance of bile ducts because it was performed further toward the liver center. In contrast, the second liver examination sampled more peripheral hepatic parenchyma. This distinction may be explained by the fact that the liver's center experiences a ductular response, while the liver's periphery does not. This occurs when the bile ducts in AGS patients fail to branch and elongate during postnatal liver growth shortly after delivery. A lack of bile duct branching and elongation leads to progressively severe bile duct paucity when sequential needle liver biopsies are obtained from the peripheral liver area in AGS patients [9]. However, it is also possible that the interlobular bile ducts shrank as the patients aged. *JAG1* haploinsufficiency in AGS interferes with the branching and differentiation of biliary epithelium in newly formed hepatic lobules, as *JAG1* is required for the development of biliary epithelium [24].

Our patient underwent genetic testing in 2022, which revealed a heterozygous likely pathogenic variant in the *JAG1* gene [9]. Genetic testing, including next-generation sequencing, can be very helpful in cases where there is significant morphologic and clinical overlap, as the vast majority of patients with AGS have mutations in *JAG1* (approximately 90 %), with a minority having mutations in *NOTCH2* [5, 7]. Although *JAG1* has been reported by T. Kohsaka et al. to be associated with extrahepatic biliary atresia due to six missense *JAG1* mutations identified in about 100 patients, it is still considered sporadic [7, 25]. Apart from diagnosing the patient, the purpose of genetic testing in this case is also to evaluate the potential donor, in this case, the mother. A potential related liver donor should be assessed for AGS to exclude the diagnosis in the donor. If the pathogenic variant in the proband is known, targeted genetic testing for that variant should be performed on the potential donor [26].

Some AGS patients misdiagnosed as having biliary atresia may undergo Kasai portoenterostomy [4]. Since this procedure does not compensate for the loss of bile ducts within the liver, surgical repair of the extrahepatic bile duct system is not a viable treatment option for AGS patients. The already compromised intrahepatic bile ducts may sustain further damage due to the inflammatory processes triggered by exposure to intestinal contents [3]. Instead, liver transplantation is the preferred management for AGS [27, 28]. By the age of 18, over 75 % of children with AGS who present with cholestasis require liver transplantation [29]. In this case, our patient underwent this procedure at the age of four.

It is difficult to predict disease progression based solely on histologic or clinical features due to the involvement of multiple organs. This underscores the importance of early and accurate detection of AGS. Various studies have confirmed that the progression of AGS often leads to critically poor outcomes. Generally, these outcomes are linked to the severity of liver abnormalities or cardiac complications, as these two organs account for patient mortality in approximately 25 % of cases [11, 14, 16].

Conclusion

Alagille syndrome presents with various clinical signs of differing severity. Accurate and early diagnosis is crucial for appropriate patient management and improved prognosis. While various papers agree on the importance of histopathological examination, there is always a chance that histological features observed under the microscope can be misleading. This poses a potential risk for misdiagnosing Alagille syndrome as other cholestatic diseases, such as biliary atresia. It is essential to integrate a variety of diagnostic approaches, including patient anamnesis, physical examination, laboratory testing, histopathology, radiological imaging, and genetic testing. These integrated diagnostic methods, especially early genetic testing, should be employed for suspected patients, particularly when multiple "grey areas" are identified throughout the process.

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