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Alagille syndrome: A rare cause for xanthomatosis

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ABSTRACT

Alagille syndrome (ALGS) is a rare, autosomal dominant disorder characterized by typical facial features, cholestatic jaundice, and renal, cardiac, eye, and vertebral anomalies. Cholestasis can lead to multiple xanthomas in childhood. We report this case to emphasize the cutaneous features and the lipid abnormalities associated with ALGS. We highlight the importance of a detailed evaluation in patients with multiple xanthomas, especially children, as it may reveal an underlying serious systemic involvement.

Keywords: Alagille syndrome, Alagille-Watson syndrome, Arteriohepatic dysplasia, Childhood xanthomas, Xanthomatosis

INTRODUCTION

Alagille syndrome (ALGS)/Alagille-Watson syndrome is a rare and autosomal dominant disorder with an estimated frequency of one in 30,000–1:50,000 births.[1] It is caused by mutations in one of the two genes: *JAG1* or *NOTCH2*.[2] The paucity of bile ducts is the characteristic feature of ALGS, with almost all cases manifesting cholestatic disease, which, in turn, leads to intractable pruritus and formation of xanthomas.[1] The other organs affected are kidney, heart, eye, nervous system, and bone.[1] The affected individuals also show a distinctive facies.[1]

CASE REPORT

An 8-year-old boy, born out of a non-consanguineous marriage, presented with asymptomatic, skin-colored to slightly yellowish, raised lesions over the face, elbows, hands, buttocks, knees, and ankles of 2 years duration. The child did not give any history of seizure, unsteadiness of gait, or defective vision. The child had mild, generalized pruritus.

He had received the diagnoses of pulmonary artery stenosis and hepatomegaly with cholestasis at 5 months of age. However, these conditions were neither evaluated further, nor did he receive any treatment for the same, owing to financial constraints.

The child had no developmental delay and was immunized up to age. His elder sibling (12-year-old girl child) or parents did not give a history of similar lesions. There was no history of a similar disease in the family.

The body mass index of the child was less than 5th percentile as per the growth chart and weight for age was 55% of standard reference, indicating Grade 3 protein-energy malnutrition (weight 14 kg and height 105 cm).[3] He had a prominent forehead, deep-set eyes, bulbous nose, and

pointed chin [Figure 1]. Clinical examination revealed pallor and icterus.

Cutaneous examination revealed multiple, well-defined, discrete, skin-colored, and slightly yellowish papules, and plaques suggestive of xanthomas (eruptive, tendon, palmar, plane, and tuberous xanthomas) ranging in size from 0.2 × 0.2 cm to 3 × 3 cm distributed bilaterally symmetrically over the dorsal aspect of the lower third of forearm and wrist extending to the proximal third of hand [Figure 2a], dorsal aspect of proximal interphalangeal joints [Figure 2a], palmar aspect of all proximal and distal interphalangeal joints [Figure 2b], palmar creases, buttocks, elbows, knees [Figure 3a], and over the Achilles tendons [Figure 3b]. Skin-colored to yellowish plaques of xanthelasma palpebrarum (4 × 2 cm) were noted below both lower eyelids, extending laterally from the medial canthus [Figure 1]. Systemic examination revealed mild hepatomegaly and an ejection systolic murmer in the third, left intercostal space.

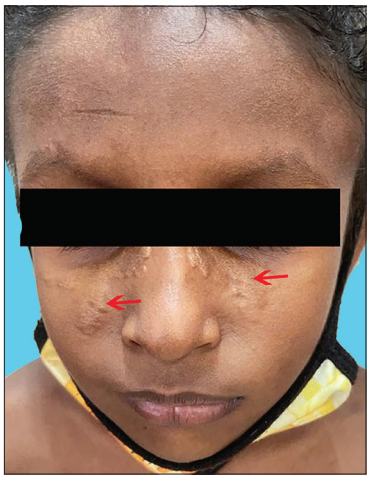

Figure 1: A child with Alagille syndrome showing broad forehead, deep-set eyes, bulbous nose, pointed chin, and xanthelasma palpebrarum (red arrow).

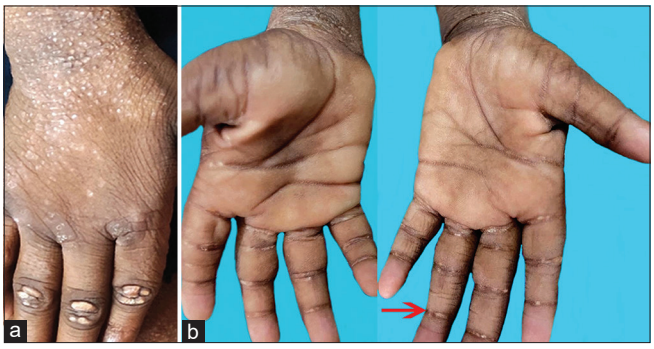

Figure 2(a): A child with Alagille syndrome showing tendon xanthomas over the knuckles and eruptive xanthomas over the dorsal aspect of forearm and hand; (b): A child with Alagille syndrome showing palmar xanthomas (red arrow).

Investigations showed anemia (9.8 g%) and conjugated hyperbilirubinemia (direct bilirubin 12.2 mg% and total bilirubin 15.2 mg%). He also had elevated serum levels of alanine (92 units/L) and aspartate (131 units/L) transaminases and alkaline phosphatase (489 units/L). Fasting lipid profile showed elevated serum levels of total cholesterol (500 mg/dl), low-density lipoprotein cholesterol (278 mg/dl), and triglyceride (190 mg/dl). High-density lipoprotein cholesterol was below normal (39 mg/dl).[4] The renal function test and thyroid function test were normal.

Histopathology from a papule on the knee showed foamy histiocytes with a peripherally pushed nucleus and a few lymphocytes in the dermis, which was consistent with the diagnosis of xanthoma [Figure 4].[5] Ultrasound sonography test of the abdomen confirmed the hepatomegaly. Serology for hepatitis B and C virus infections was negative. Parents refused consent for a liver biopsy.

Ophthalmology evaluation and skeletal survey were normal.

Considering the combination of cholestatic jaundice, pulmonary stenosis, characteristic facial features, and xanthomatosis, we made a diagnosis of incomplete ALGS.[6] The clinical evaluation did not show similar findings in parents or elder sibling. Genetic testing of the child and further evaluation of the parents and the sibling could not be carried out due to financial constraints.

He was referred to the gastroenterology and pediatric cardiology departments. The gastroenterologist advised cholestyramine resin powder (4 g/sachet) as oral suspension 3 times a day.

Follow-up after 1 month showed a slight reduction in the size of the xanthomas and serum lipid and liver enzyme levels [Table 1]. The child is currently under regular follow-up from gastroenterology and pediatrics departments.

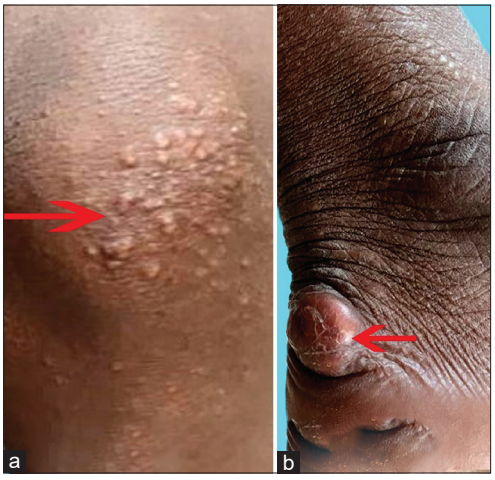

Figure 3(a): A child with Alagille syndrome showing tuberous xanthomas (red arrow) over the knee; (b): the same patient showing tendon xanthoma (red arrow) over the Achilles tendon.

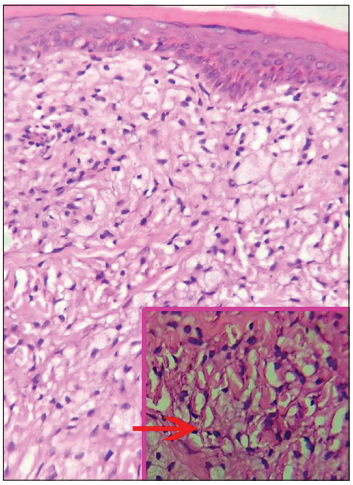

Figure 4: Skin biopsy from a papule on the knee of a patient with Alagille syndrome showing sheets of histiocytes with peripherally pushed nucleus and a few lymphocytes in the dermis, suggestive of xanthoma (H and E, ×100); inset: Higher magnification of the same showing (red arrow) foamy histiocytes (H and E, ×400).

Table 1: Liver enzymes and fasting lipid profile in a child with Alagille syndrome.

Blood parameter	At presentation	One month after starting cholestyramine
Total bilirubin	15.2 mg%	12.1 mg%
Direct bilirubin	12.2 mg%	10 mg%
Alanine transaminase	92 units/L	85 units/L
Aspartate transaminase	131 units/L	110 units/L
Alkaline phosphatase	489 units/L	402 units/L
Total cholesterol	500 mg/dl	289 mg/dl
Low density lipoprotein cholesterol	278 mg/dl	187 mg/dl
Triglyceride	190 mg/dl	190 mg/dl
High density lipoprotein cholesterol	39 mg/dl	41 mg/dl

DISCUSSION

ALGS or arteriohepatic dysplasia is an autosomal dominant disorder.[1] However, variable expressivity and reduced penetrance are common. Somatic/germline mosaicism is not infrequent in the syndrome.[6] The condition was described for the first time in 1975 by Dr. Danielle Alagille and colleagues.[7]

Underlying pathogenesis involves an impaired Notch signaling pathway (an important pathway in cell-cell-based signaling) due to mutation in either JAG1 (more common) or the NOTCH2 gene.[1] During hepatic development, Notch signaling is essential for biliary genesis.[1]

ALGS is defined by a paucity of intrahepatic, interlobular, bile ducts. The major manifestations of ALGS are cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities, and characteristic facial features. Patients manifesting all the five features are diagnosed as complete ALGS. Those who manifest three or four features are categorized as incomplete or partial ALGS.[8]

The distinct facies of ALGS is characterized by a prominent forehead, deep-set eyes with moderate hypertelorism, upslanting palpebral fissures, depressed nasal bridge, straight nose with a bulbous tip, large ears, prominent mandible, and pointed chin.[9]

Chronic cholestasis occurs in almost all cases and the child usually presents in the neonatal period or first 3 months of life with jaundice due to conjugated hyperbilirubinemia.[1,10] Liver function tests are abnormal. A liver biopsy is not mandatory for diagnosis.[2] Cholestasis leads to pruritus and dyslipidemia (which, in turn, produces xanthomas).[6] Malabsorption results in failure to thrive, growth retardation, and delayed puberty.[6,10] More than 90% of ALGS subjects show cardiovascular anomalies. Pulmonary stenosis is noted in 2/3rd of the affected.[10] Posterior embyrotoxon is the common ophthalmological abnormality noted (>80% of cases).[1] A less frequent manifestation is butterfly vertebrae, which often remains asymptomatic.[1]

Our patient had cholestatic jaundice, pulmonary artery stenosis, Grade 3 protein-energy malnutrition, prominent forehead, deep-set eyes, bulbous nose, and pointed chin which were suggestive of incomplete ALGS.[8]

Management requires a multidisciplinary approach from the pediatrician, pediatric cardiologist, ophthalmologist, and gastroenterologist. Pruritus is usually severe and resistant to treatment. Choleretic agents such as ursodeoxycholic acid or cholestyramine, rifampin, and naltrexone are tried with variable success.[6] Partial external biliary diversion may help to reduce the pruritus and the xanthoma formation, by reducing the total bile acids in the blood.[1] End-stage liver disease warrants liver transplantation.[1]

A randomized, phase 2 study {in children (1–18 years) with ALGS}, that assessed the efficacy and safety of maralixibat (an apical, sodium-dependent, bile acid transport inhibitor), concluded that the drug was able to bring out improvement in cholestasis.[11] The drug acts by inhibiting a carrier protein (apical sodium-dependent bile acid transporter/ileal bile acid transporter) that mediates the enterohepatic recirculation of bile acids. In the treatment of ALGS, the United States Food and Drug Administration has granted orphan drug designation to maralixibat and odevixibat (another ileal bile acid transporter inhibitor). However, these drugs are rather directed at inhibiting the reabsorption of bile acids in the intestine and do not address the basic cause of the syndrome (Notch signaling dysfunction).[1]

Although the pathogenesis proposes a therapeutic role for exogenous JAG1 in ALGS, this may not be a feasible option,

considering the potential of the same to produce malignancies (because of the influence of Notch signaling on cell-cell-based contact inhibition and proliferation).[1] Future therapies targeting the specific mutations that cause the defect in the Notch signaling pathway may provide a lasting benefit to the affected.

Genetic counseling should be offered to the family with an affected child as ALGS shows an autosomal dominant inheritance pattern; hence, each child of a carrier parent is at a 50% risk of inheriting the syndrome. In our case, the other family members were unaffected. This can be explained by the incomplete penetrance and the variable expressivity of the gene, parental germline mosaicism, or *de novo* mutation.[10]

CONCLUSION

Multiple xanthomas are rare, especially in children, and thus warrant further investigations. Our patient had associated pulmonary stenosis, characteristic facial features, and cholestasis; hence diagnosed as ALGS. There are only a few reports in literature regarding this syndrome which has prominent cutaneous manifestations. This case report highlights the importance of a meticulous evaluation in children with xanthomas as it can unravel an underlying serious systemic condition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

Dr. Kunjumani Sobhanakumari is on the editorial board of the Journal.

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