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CASE REPORT

Laryngeal xanthomas in alagille syndrome: A new physical finding?

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Summary Alagille syndrome (AGS) is a rare autosomal dominant disorder characterized by bile duct paucity, often with associated liver failure. Common characteristics of AGS include cholestasis with pruritus, peculiar facies, cardiovascular defects, jaundice, embryotoxon, vertebral abnormalities, and cutaneous xanthomas. The case history is presented of a 2.5-year-old female with AGS status post-orthotopic liver transplantation and stertorous breathing. Flexible laryngoscopy and bronchoscopy revealed adenoid hypertrophy along with laryngeal xanthomas. The previously undocumented finding of laryngeal xanthomas in AGS is discussed along with possible etiologies and complications.

1. Introduction

Alagille syndrome (AGS) is an autosomal dominant disorder first described in 1969 by Alagille et al. [1]. AGS has a prevalence of 1 in 70,000 to 100,000 newborns with variable expression and no sex preference [2]. AGS is caused by a mutation in the gene encoding Jagged1 (JAG1), a ligand involved in the Notch signaling pathway [3]. The Notch signaling pathway is involved in cell fate determination and is essential for normal embryonic development. In humans, Jagged1 is expressed in fetal liver, lung, brain and kidneys [4]. AGS is characterized by intrahepatic bile duct paucity with cholestasis and is also known as paucity of interlobular ducts (PBID), intrahepatic bile atresia, intrahepatic bile hypoplasia, and arteriohepatic dysplasia.

Many characteristic features of AGS include cholestasis with pruritus in 100% of patients, peculiar facies in 70—96%, cardiovascular defects (pulmonary artery stenosis, intraventricular communication, and others) in 84%, hepatomegaly in 84%, jaundice in 78%, embryotoxon in 76%, hypertriglyceridemia in 62%, vertebral abnormalities in 33—87%, xanthomas in 28—42%, splenomegaly in 51%, and renal disease in 40—73% [2,4,5]. Additional features include growth retardation, developmental delay, and intracranial bleeding [4]. Table 1 contains a list of common characteristics in AGS. Cutaneous xanthomas appear as early as the first few months of life and as late as 5 years of age. Xanthomas are benign lesions composed of lipid laden foam cells, which are histiocytes containing cytoplasmic lipid material. Xanthomas are more common in patients with severe and prolonged

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Table 1 Common characteristics [2,4,5]

Cholestasis (%)	100
Peculiar facies (%)	70—96
Cardiac defects (%)	84
Hepatomegaly (%)	84
Jaundice (%)	78
Embryotoxon (%)	76
Hypertriglyceridemia (%)	62
Vertebral anomalies (%)	33—87
Xanthomas (%)	28—42
Splenomegaly (%)	51
Renal disease (%)	40—73

cholestasis with marked serum cholesterol levels as high as >15 mmol/L [6]. Liver transplantation has been shown to be highly effective in the treatment of liver disease in AGS, often with complete resolution of xanthomata [7].

To our knowledge, there are no reported cases of pyriform sinus and laryngeal xanthomas associated with AGS in the current literature. Oral xanthomas with hypodontia, palatal and gingival xanthomas have been reported [8]. We discuss a 2.5-year-old with AGS characterized by neonatal cholestasis with marked hypercholesterolemia and laryngeal xanthomas.

2. Case report

A 2.5-year-old biracial girl with a history of AGS presented with stertorous breathing 1 month status post-orthotopic liver transplantation. She was born at 26-6/7th weeks gestation via scheduled caesarean section to a G 6 P 0-3-3-3 mother with pregnancy induced hypertension and HELLP syndrome. Her family history included hypertension and maternal hyperthyroidism but was negative for AGS. She required TPN at 3 weeks of age, which was initially thought to be the etiology of her cholestasis. She was intubated for approximately 1 month after birth and required 3 months to be weaned from CPAP to room air without nasal cannula flow. She was discharged to home at 3 months, but was readmitted approximately 2 months later for failure to thrive, hyperbilirubinemia and elevated liver enzymes.

Clinical examination revealed facial dysmorphic features including frontal bossing, triangular face with pointed chin, long philtrum, low-set ears, and deep-set eyes. She had decreased muscle mass and adiposity. She weighed 2.6 kg (<third percentile, corrected for age), head circumference was 34 cm (5th percentile, corrected for age), and blood pressure was 95/50 mmHg. She had a grade II/VI systolic murmur and a liver edge felt 1 cm below the right costal margin with no splenomegaly. She was neurological intact with no focal deficits.

Table 2 Max lipid profile pre-transplant

Cholesterol	2462
Triglycerides	347

Table 3 Max liver function tests pre-transplant

Total bilirubin	18.8
Unconjugated	1.6
Conjugated	11.0
AST	253
ALT	214
ALK	1054
GGT	2968

A liver biopsy revealed bile duct paucity. The diagnosis of AGS was also confirmed by the presence of a constellation of findings. Radiographs were taken of the spine which showed that the ninth vertebra was not completely ossified along with mid thoracic hemivertebra. Ophthalmologic exam was significant for bilateral posterior embryotoxon and mild retinal pigmentary disturbances. The patient also had hypertension. Renal ultrasound was highly suggestive of polycystic kidney disease. She did not have cardiac abnormalities by echocardiogram.

Due to her elevated lipid profile and elevated liver functions in the setting of erupting cutaneous xanthomas and enlarging liver, the patient underwent orthotopic liver transplantation at approximately 19 months of age. Her lipid profile and liver function tests prior to liver transplantation are shown in Tables 2 and 3 while her post-transplantation values are shown in Tables 4 and 5. Her metabolic panel and cell counts were unremarkable. She was maintained on immunosuppressive

Table 4 On discharge max lipid profile post-transplant

Cholesterol	128
Triglycerides	205

Table 5 On discharge max liver function tests post-transplant

Total bilirubin	0.3
Unconjugated	0.5
Conjugated	0.0
AST	31
ALT	31
ALK	137
GGT	92