**Alagille syndrome with prominent skin manifestations**

**Sujata Sengupta, Jayanta Kumar Das, Asok Gangopadhyay**  
Department of Dermatology, RKM Seva Pratishthan and Vivekananda Institute of Medical Sciences, Kolkata, India

**ABSTRACT**

Alagille syndrome, a rare genetic disorder with autosomal dominant transmission, manifests 5 major features: paucity of interlobular bile ducts, characteristic facies, posterior embryotoxon, vertebral defects and peripheral pulmonic stenosis. We report a 6-year-old male child who presented with a history of progressive jaundice since infancy, generalized pruritus and widespread cutaneous xanthomata. He was also found to have obstructive jaundice, pulmonary stenosis with ventricular septal defect and paucity of bile ducts in liver biopsy. Histopathology confirmed skin lesions as xanthomata. The child was diagnosed as a case of Alagille syndrome. This particular syndrome with prominent cutaneous manifestations has been rarely reported in the Indian literature.

**Key Words:** Alagille syndrome, Arteriohepatic dysplasia, Xanthomata

**INTRODUCTION**

Genetic diseases affecting the skin sometimes pose a diagnostic dilemma for the treating physician. We report a child presenting with jaundice, pruritus and widespread xanthomata who was finally diagnosed as a case of Alagille syndrome (AS). AS or the syndromic paucity of bile ducts, consists of 5 major features comprising paucity of interlobular bile ducts, characteristic facies, posterior embryotoxon, vertebral defects and peripheral pulmonic stenosis.\(^1,2\) It is a rare genetic disorder with autosomal dominant transmission. The mutant gene has been localized to chromosome 20p.\(^3\) This case is reported for the rarity of this entity; particularly in the Indian literature,\(^2\) and to highlight the fact that early recognition of the skin lesions may play a role in the diagnosis of this disease.

**CASE REPORT**

A 6-year-old male child born of a non-consanguineous marriage presented for evaluation of asymptomatic lesions over the face, hands and body folds for the last 4 years. The child had been well till one month of age after which he developed progressive jaundice. At the age of one-and-a-half, he developed multiple raised non-itchy lesions over the knuckles, followed by similar lesions on the eyelids, hands, and the body folds. The early lesions were slowly growing and yellowish, but later they coalesced and became skin-colored. There was associated pruritus that was generalized, moderate to severe in intensity with no diurnal variation and not relieved by treatment with oral antihistamines and topical calamine lotion and steroids. The child’s developmental milestones were delayed. His social
smile had appeared at the age of 4 months and he was not able to walk or talk till he was one-and-a-half years old. No sibling or any other family member was similarly affected.

Cutaneous examination revealed asymptomatic well-defined painless, indurated papules and plaques on the skin over the metacarpophalangeal and interphalangeal joints of the hands, eyelids, and the axillary, antecubital, inguinal and popliteal folds of both sides (Figures 1, 2 and 3). Individual lesions tended to coalesce. Newer lesions were softer and yellowish in color but older ones were mostly fibrotic and skin-colored. The mucous membranes, palms and soles, hair, nails and teeth were normal.

On general examination, the child was stunted with a height of 101 cm and weighing 14 kg. The face showed a broad forehead, deep-set eyes with hypertelorism, and a pointed chin. Mild pallor and moderate icterus were present and the vital signs were normal. A firm, non-tender hepatomegaly was present. A pan-systolic murmur was audible over the precordium. The rest of the systemic examination was normal.

On investigation, anemia, conjugated hyperbilirubinemia, raised SGPT, alkaline phosphatase and GGT were detected. Serum cholesterol level was 413 mg/dl and triglyceride 257 mg/dl. HBsAg and anti-HCV antibody were negative; chest X-ray was normal and abdominal ultrasound showed a heterogeneous parenchymal echo pattern in the liver; echocardiography revealed a sub-aortic VSD and severe pulmonary stenosis. Liver biopsy showed paucity of bile.
ducts with the ratio of bile duct to portal triad, 0.66
(N=0.8). Ophthalmologic and skeletal survey was
normal. Skin biopsy of a new lesion showed small and
large aggregates of foam-cells (Figure 4); another biopsy
from a long-standing lesion revealed fibroblasts and
collagen bundles in large numbers. The child was
diagnosed as a case of Alagille syndrome.

DISCUSSION

Alagille syndrome (arteriohepatic dysplasia) is the
syndrome of paucity of intrahepatic bile ducts. It is
probably inherited in an autosomal dominant fashion
with variable expression,[3] the incidence being 1 in
100,000 live births.[4] The disease is characterized by a
peculiar facies, with abnormalities of the liver, heart,
eye, skeleton and kidney. Mild to moderate mental
retardation may be present. Subjects commonly present
before 6 months of age for either neonatal jaundice or
cardiac murmurs; later they may present with poor
linear growth, with a broad forehead, pointed chin,
deep-set eyes and elongated nose with a bulbous tip.
Hepatic disease is the key factor in AS and the long-
standing cholestasis and the resultant
hypercholesterolemia cause cutaneous manifestations
of jaundice, pruritus, and widespread xanthomata.[3]
Generalized ecchymoses has also been reported as first
clinical presentation.[1]

A study of 92 patients of AS showed paucity of
interlobular bile ducts in 85%, cholestasis in 96%, cardiac
murmurs in 97%, butterfly vertebra in 51%, posterior
embryotoxon in the eye in 78% and characteristic facies
in 96%.[5] Our case had three of the five major features
of the syndrome with no vertebral or ophthalmologic
defects. This form of ‘partial’ or ‘incomplete’ AS has
also been reported in the Indian literature by Shendge
et al.[2] Bilateral corneal opacity was found in an Indian
girl with AS who also had mental retardation, typical
facies, cardiac murmur, xanthomatosis and cholestatic
jaundice.[7]

The long-term prognosis is uncertain with congenital
heart disease, hepatic cirrhosis, intracranial bleeding
and renal abnormalities being the commonest factors
affecting mortality.[6] Pruritus, often recalcitrant to
medical therapy, has been reported to improve with
cholestyramine (12-15 g/day).[4] Hepatic transplant is
the surgical treatment of choice. The estimated 20-year
survival rates are 80% for those not requiring liver
transplant and 60% for those requiring it.[5] Rapid
resolution of widespread xanthomata has been
reported in AS following orthotopic liver transplant.[3]

Thus Alagille syndrome is a rare and grave systemic
disorder that may be diagnosed following the clues
offered by methodical cutaneous examination.

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