remains unexplained in the index case, possibility of early hemorrhagic transformation of an underlying embolic ischemic infarction could not be ruled out as the probable pathophysiologic mechanism where cardiac tumours were the potential source of emboli [10].

Contributors: RP: diagnosed, worked up the case and wrote the manuscript; SB and BR: managed the case and reviewed the literature; RP and RB: prepared the final manuscript and followed up the case.

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Alagille Syndrome with a Previously Undescribed Mutation

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Background: Alagille Syndrome is a rare genetic disease characterized by abnormalities of the intrahepatic biliary ducts with cholestasis along with multisystem anomalies. **Case characteristics**: An 8-year old child with persisting jaundice, severe itching and failure to thrive. **Observation**: Diagnosis of Alagille syndrome was made on the basis of clinical features, typical facies and liver biopsy showing bile duct paucity. Genetic analysis revealed a novel de novo mutation in the JAG 1 gene. **Outcome:** The child was started on ursodeoxycholic acid following which the itching improved. **Message**: A novel *de novo* mutation in JAG 1 gene is described in this child with Alagille Syndrome.

Keywords: *Arteriohepatic dysplasia, Mutation, Posterior embryotoxon.*

Alagille syndrome (AGS) has been classically identified with paucity of bile ducts in the liver, along with involvement of the heart, vertebrae, eyes and typical facial features. AGS has only rarely been described from India [1-4]. We describe a young boy with Alagille syndrome with a previously undescribed mutation in the *JAG1* gene.

CASE REPORT

This 8-year-old boy presented with complaints of persisting jaundice and itching for past 6 years. The parents also complained of the child failing to thrive. For last two years, he was having difficulty in distant vision. He also had history of one episode of blood-tinged vomitus not associated with melena. There was no history of bleeding from any other site or any features of encephalopathy in past. There was no history suggestive of recurrent loose stools or malabsorption. Child was developmentally normal for his age. He was product of non-consanguineous parentage, had two elder siblings

who were alive and healthy.

His weight was 13 kg (z-score <-3) and height was 99 cm (z-score <-3). Child had mild pallor, icterus, clubbing and scratch marks. There were no petechial or purpuric spots, palmer erythema, spider nevi, telangiectasia, gynecomastia or testicular atrophy. Child had peculiar facial features in form of prominent forehead, deep set eyes, a pointed chin, and a saddle nose with bulbous tip. Respiratory and neurological examination was normal. A grade III ejection systolic murmur was audible in left 2nd intercostal space with normal S1 and S2. Liver was palpable 2 cm below costal margin with a span of 8 cm with normal consistency and smooth surface. Spleen was not palpable. There was no ascites.

On investigations, his hemoglobin was 8.7 g/dL with normocytic normochromic peripheral smear; ESR was 25 mm in 1st hour. Prothrombin time was 14 seconds with control of 11 seconds (INR 1.3). Renal function tests were normal. Total bilirubin was 4.4 mg/dL with conjugated fraction of 2.9 mg/dL. AST and ALT were 363 IU/L and 311 IU/L, respectively with serum alkaline phosphatase of 733 IU/L. His GGTP was 103 IU/L. Total serum proteins were 6.9 g/dL with serum albumin 3.2 g/dL. Hepatitis-B surface antigen (HbsAg) and anti-HCV antibodies were negative. Anti-nuclear antibodies, anti-smooth muscle antibodies and anti-LKM1 were negative. Serum ceruloplasmin was 45.1 mg/dL, and 24-hour urinary copper was less than 50 µg/day. On evaluation of eyes, child had posterior embryotoxon in both eyes with both eyes also showing KF rings. Visual acuity in right eye was 6/60 and in left eye was 6/FCCF (finger close- to-face); intraocular pressure was normal with normal posterior chamber. Chest *X*-ray and *X*-ray spine did not show any abnormality. On ultrasound examination of abdomen, liver and gall bladder were normal; portal vein was of normal size, both kidneys were normal with normal urinary bladder. Echocardiography showed normal biventricular function, normal right pulmonary artery, and ostial stenosis in left pulmonary artery with a pressure gradient of 22 mm Hg. On UGI endoscopy, there were no esophageal varices with normal stomach and duodenal mucosa. There was mild esophagitis in lower one-third of esophagus. Biopsy from lower esophagus showed mucosal fragments with ulceration and fibrin. Liver biopsy showed paucity of bile ducts with periportal ballooning degeneration and cholestasis. Portal tract showed inflammation and fibrosis. Immunostaining for CK19 did not show bile ducts.

A blood sample from the index case and both the parents was analyzed for mutations in the *JAG* 1 gene. All 26 exons and intron-exon boundaries of the *JAG*1 gene were amplified under standard PCR conditions and sequenced in both directions. All identified mutations were confirmed on a second PCR product. The mRNA reference sequence was NM_000214 with base 1 corresponding to the first base of the initiation ATG codon. It was identified as a *de novo* mutation "c.1395+3_1395+4dupAT" in *JAG1* gene in a heterozygous state.

The final diagnosis was Alagille syndrome. Child was started on ursodeoxycholic acid, after which itching decreased. Vision improved after correcting refractory errors.

DISCUSSION

Over 500 cases of AGS have been described since its initial description [5,6]. This is an autosomal dominant syndrome, with the gene (*JAG1*) being traced to chromosome 20 [7]. AGS is diagnosed if 3 or more of the following 5 major features are present: cardiac murmur, posterior embryotoxon, butterfly-like vertebrae, renal abnormalities and characteristic facies in the presence of bile duct paucity [8]. The prevalence of the syndrome in India is not known; only few cases are reported [1-4]. The novel mutation is designated "c.1395+3_1395+ 4dupAT". It describes a duplication of two bases (AT) in intron 11 at position c.1395+3. The mutation leads to an alteration of splicing resulting in production of an abnormal RNA and protein product. This mutation has not been reported in other AGS patients and has also not been reported as a normal variation. Thus, c.1395+3_1395+4dupAT is likely to be a causative mutation for AGS, although functional studies have not been done to prove this conclusively. Moreover, the mutation was not found in parents.

To conclude, c.1395+3_1395+4dupAT is assumed to be the cause of Alagille syndrome in this patient. As the mutation was not found in either parent, it was most likely a *de novo* mutation. However, because of the possibility of germline mosaicism in either parent, the risk of recurrence in further offspring of the parents, though low, is greater than that of the general population.

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Pemphigus Vulgaris in a Neonate and his Mother

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Background: Neonatal pemphigus is a rare, transient blistering condition due to transplacental transfer of maternal autoantibodies. **Case characteristics**: A male neonate born to a mother with oral pemphigus was noticed to have multiple lesions. **Observation**: Multiple flaccid bullae were noticed on the face, scalp, trunk and extremities with clear fluid and few areas of erosions. **Outcome**: All lesions resolved at the end of one week with conservative management. **Message**: Maternal pamphigus may rarely involve her newborn infant; it resolves on its own.

Keywords: *Autoimmunity, Neonatal pemphigus vulgaris, Transplacental transfer.*

Pemphigus is a group of autoimmune blistering disease of skin and mucous membranes [1]. Incidence rates between 0.1 and 0.5 per 100,000 people per year have been reported [2]. Neonatal pemphigus is a transient autoimmune blistering disease caused by transfer of maternal IgG autoantibodies to desmoglein-3 through the placenta when the mother is affected with pemphigus [3,4].

CASE REPORT

A 1-day-old boy weighing 2900 grams, born after full term pregnancy, was noticed to have multiple flaccid bullae on the face, scalp, trunk and extremities with clear fluid and few areas of erosions. All lesions showed a rim of erythema and abrupt demarcation from the surrounding normal skin (***Fig.* 1**). These lesions were not restricted to trauma-prone areas. A few lesions had profuse serous discharge. Nails and oral mucosa were not involved. Mother of this infant was diagnosed to have oral pemphigus vulgaris 8 months before conception, documented by incisional biopsy from buccal mucosa and direct immunofluorescence test (DIF), and was on daily oral steroids. The child was suspected to have neonatal pemphigus vulgaris based on the morphology

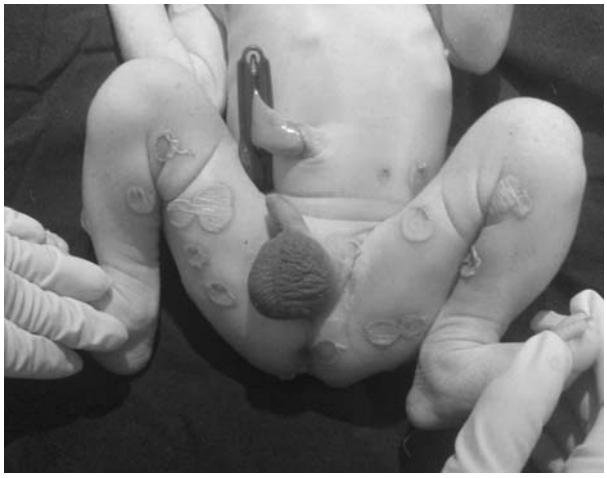

FIG.1 *Flaccid bullae and crusted erosions with an erythematous rim distributed over the groin area in the neonate.*