# Biliary atresia with hyaline cartilage at the porta hepatis: a novel finding of undetermined significance: a case report

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**Biliary atresia is an important cause of liver disease and morbidity in infants with unknown etiology. To date, only five cases of biliary atresia with hyaline cartilage at the porta hepatis have been described. We present the case of a 65-day-old male child, with further insight and detailed discussion of this heterotopia of undetermined significance. *Ann Pediatr Surg* 12:122–125 © 2016 Annals of Pediatric Surgery.**

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## Introduction

Biliary atresia (BA) is the most important cause of severe liver disease of infancy, which leads to liver cirrhosis, and is also a major indication for liver transplantation in young children [1]. It is an obliterative cholangiopathy of unknown origin associated with two patterns and possibly three heterogenic presentations: embryonal/fetal, perinatal, and cystic [2,3]. Embryonal type may be accompanied by disorder of laterality and congenital malformations. Hyaline cartilage at the porta hepatis in BA is a novel finding of undetermined significance described in rare case reports (Table 1). We present an additional case with similar findings in a 65-day-old child to provide an insight to unveil the possible etiology of BA, a heterogenic enigmatic entity.

## Case report

A neonate was brought to the hospital with chief complaints of yellowish discoloration of eyes (since day 8), vomiting, high-grade fever, decreased sleep, and excessive crying since 15 days. The child was apparently well until the eighth day of life when the parents noticed yellowish discoloration of eyes accompanied by high-grade intermittent fever. No history of lethargy, hypoglycemia, nocturnal feed, constipation, or previous hospitalization was present.

Both TORCH profile and viral markers (HBsAg, HCV, HEV, and HAV) were negative. At the time of admission, his liver function tests were markedly deranged (total bilirubin, 17.9 mg/dl; direct bilirubin, 8.69 mg/dl; indirect bilirubin, 9.28 mg/dl; aspartate aminotransferase, 376.3 IU/l; alanine aminotransferase, 218.9 IU/l; alkaline phosphatase, 811.9 IU/l; and γ-glutamine transaminase, 1908.4 IU/l). Hemogram showed normocytic normochromic anemia with mild lymphocytosis (Hb 5.2 g/dl, TLC $26.2 \times 10^3$/μl, platelet $154 \times 10^3$/μl, and reticulocytes 0.5%). Direct Coomb's test was negative. Ultrasound of the abdomen revealed normal-sized liver, and no space-occupying lesion or intrahepatic biliary radicle dilatation was noted. The gall bladder was not seen. The common bile duct, portal vein, and pancreas were obscured.

On examination, the child had deep icterus. On per abdomen examination, both the liver and the spleen were palpable and measured 3.5 and 2 cm below the costal margin, respectively. On HIDA scan, there was nonvisualization of tracer activity in the small intestine 24 h after tracer was injected, which was suggestive of BA (Fig. 1).

A clinical diagnosis of neonatal cholestasis (BA) was considered. Kasai portoenterostomy was performed. Intraoperatively, the gall bladder was atretic with BA and cirrhotic liver.

**Table 1 Clinicopathological profile of cases of biliary atresia with hyaline cartilage at the porta hepatis reported in the literature**

| References | Age/sex | Associated clinical feature |
|---|---|---|
| Hassab [4] | 150 days/female | Multiple congenital anomalies |
| Mirkin and Knisely [5] | 2 days/female | None |
| | 42 days/male | None |
| Stahlschmidt [6] | 55 days/female | Cyst below the porta hepatis |
| Kashiwagi [7] | 60 days/female | cytomegalovirus infection |
| This study | 65 days/male | None |

## Pathology

The atretic gall bladder on microscopy showed columnar lining epithelium with mild chronic inflammation, occasional lymphoid aggregates, and fibrosis of the wall. The portal tissue showed few biliary radicles, the largest measuring 150 μm in diameter. The portal tissue also showed fibrocollagenous tissue displaying numerous congested blood vessels, proliferating fibroblasts, dense chronic inflammatory cell infiltrate, and few islands of mature as well as newly laid developing cartilage (Fig. 2a–d). The cartilage did not appear to obstruct the lumen of the biliary tree. Focal squamous metaplasia of bile ductules, dense chronic inflammatory cell infiltrates, and foamy macrophages within the dilated ducts were also seen (Fig. 2a and b). Many bile ductules showed expression of both cytokeratin-7 and high molecular weight cytokeratin in the lining epithelium (Fig. 2e and f).

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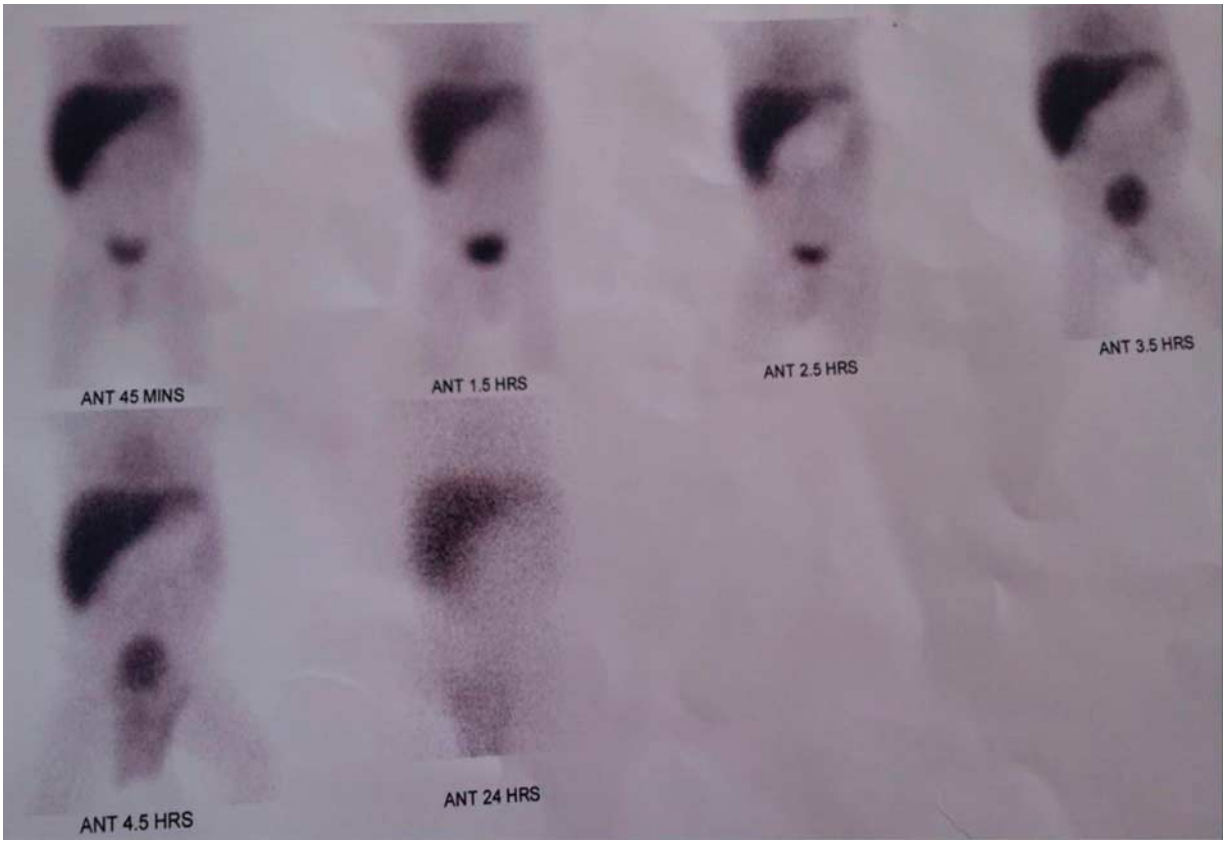
**Fig. 1**




HIDA scan showing nonvisualization of tracer activity in the intestine 24 h after tracer injection, suggestive of biliary atresia.

The liver wedge biopsy showed distortion of the lobular architecture with bridging fibrosis. The portal tracts showed expansion by moderate chronic inflammation and interface hepatitis. Marked bile ductular proliferation and diffuse cholestasis, both intracellular and canalicular, with bile plugs formation were noted. The hepatocytes also showed feathery degeneration and rosette formation.

At 1 year of follow-up, the patient was doing well, with normal developmental milestones and mild derangement of liver function tests.

## Discussion

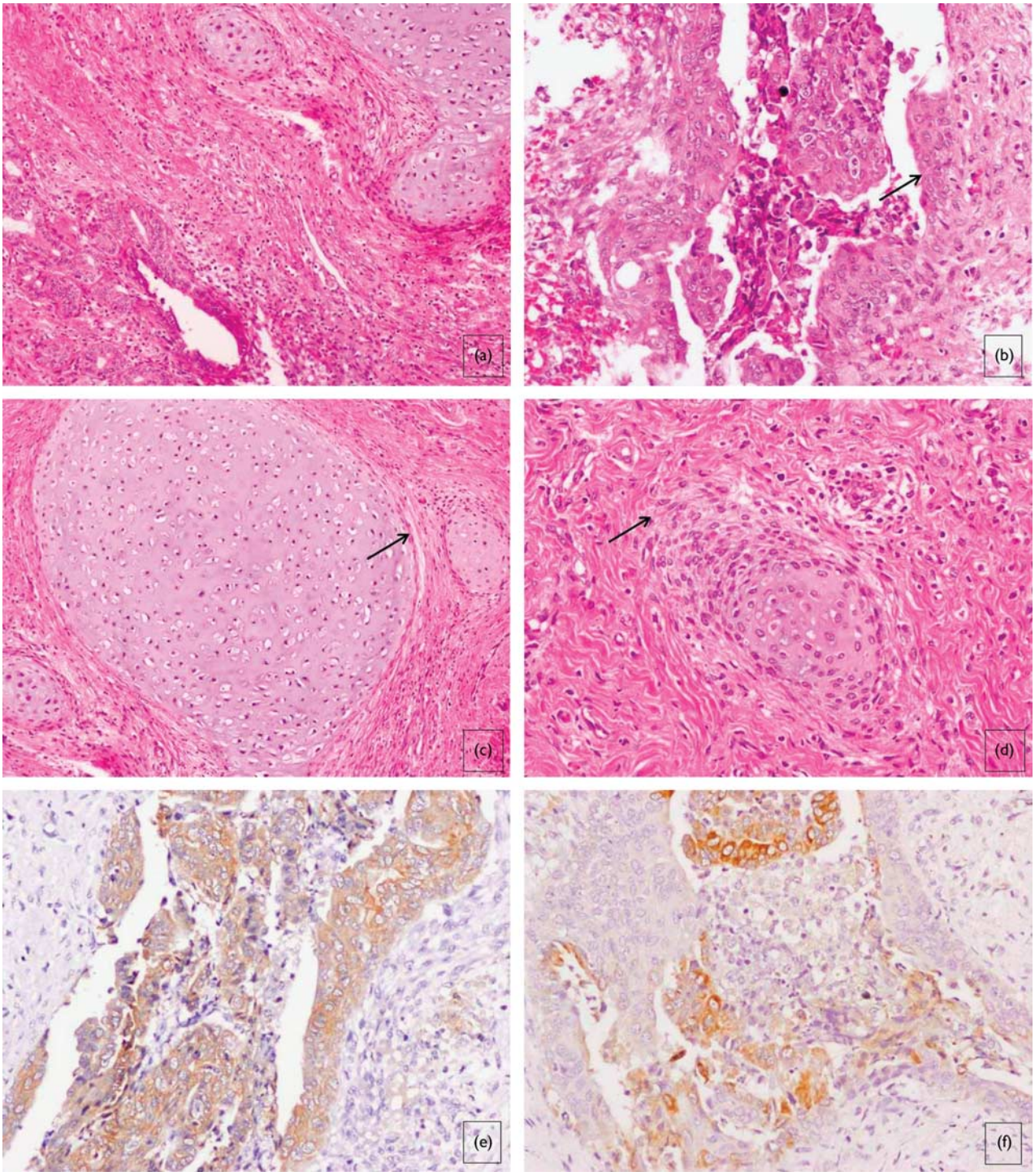
Conjugated hyperbilirubinemia in the neonatal period occurs at a frequency of 1/6000 to 1/19 000 live births [8,9]. BA is the most common hepatic surgical disorder of infancy, accounting for 30% of conjugated hyperbilirubinemia cases. The natural history of BA is markedly variable, indicating the concern to illustrate various clinicopathological factors of prognostic importance. Numerous studies have corroborated that the porta hepatis is the focal point of disordered development in BA [10,11]. However, this is a controversial prognostic factor and none of them arrived at a definitive conclusion.

Various authors have put forward different theories to explain the presence of mature cartilage at the porta hepatis. The portal plate represents the junction between the intrahepatic bile ducts and the extrahepatic biliary tree. The former develop from endodermally derived hepatoblasts within the liver. This forms the ductal plate running alongside branches of the portal vein [12]. The extrahepatic biliary tree develops from the caudal part of the hepatic diverticulum, which is also an endodermal foregut derivative.

Normally, hyaline cartilage is not an inherent structure belonging to the porta hepatis. However, as both intrahepatic and extrahepatic bile ducts are derived from the endodermal foregut derivative, heterotopia such as in foregut duplication cyst or metaplastic response to an injury may explain its presence at this unusual site. Foregut duplication cysts usually occur within the liver parenchyma and are associated with respiratory lining epithelium. In this case, no communication with the gastrointestinal tract or respiratory epithelium was seen. Well-organized mature cartilage demarcated by the perichondrium and newly laid developing band of cartilage merging with the adjacent fibrocollagenous tissue were noted. Newly developing cartilage and dense inflammation were additional finding in comparison with those described by Mirkin and Knisely [5], who concluded that bands of mature cartilage showing an abrupt transition from the surrounding connective tissue should be regarded as a developmental malformation.

Stahlschmidt *et al.* [6] suggested that hyaline cartilage at the porta hepatis and squamous epithelium might originate from the mesenchyme of the septum transversum and represent defective morphogenesis rather than a secondary phenomena. They justified that squamous metaplasia is not seen in histologic specimens taken from the hilum of the liver or within intrahepatic bile ducts in explanted liver from patients

**Fig. 2**




Photomicrographs showing histomorphology and immunohistochemistry features of the porta hepatis tissue: (a) islands of mature hyaline cartilage lying adjacent to biliary channels (HE × 100); (b) a bile duct showing denuded and multilayered metaplastic (arrow) squamous lining epithelium (HE × 200); (c) focus of mature well-organized cartilage demarcated by the perichondrium (arrow) (HE × 200); (d) immature newly laid cartilage merging with the adjacent fibrous tissue (arrow) and lacking perichondrium (× 200); (e) high molecular weight cytokeratin (HMWCK) showing positivity in multilayered metaplastic squamous epithelium (× 200); (f) cytokeratin-7 (CK7) showing positivity mainly in denuded lining epithelium (× 200).

with BA undergoing liver transplant. Squamous epithelium and cartilage were observed at the porta hepatis and not more distally within extrahepatic biliary remnants.

In our case, many bile ductules showed squamous metaplasia and expression of both cytokeratin-7 and high molecular weight cytokeratin in the lining epithelium, which supports metaplastic change. Embryonal type of BA may show additional malformations and laterality defects, which might explain the instance of cartilaginous heterotopia at the porta hepatis. Hassab *et al.* [4] described a case of embryonal type BA with hyaline cartilage and associated anomalies in the form of abdominal situs inversus, intestinal malrotation, and unilateral agenesis of the left kidney. However, they

considered hyaline cartilage at the porta hepatis as an aberrant morphogenesis unrelated to foregut cyst, teratoma, remnant of dysplastic kidney, or metaplastic change and have not explained correlation with other congenital anomalies. Kashiwagi *et al.* [7] considered that both BA and cartilage formation are likely caused by cytomegalovirus infection early in fetal life.

Altamirano and Drut [13] reported a case of BA with islets of hyaline cartilage in the wall of atretic gall bladder in a 3-month-old infant analogous to the formation of hyaline cartilage within the developing kidney in renal cystic dysplasia due to obstruction of the distal urinary tract. However, hyaline cartilage at the porta hepatis lies distal to obstruction, which is against the analogous relation as above.

## Conclusion

Hyaline cartilage and squamous epithelium within biliary ductules at the porta hepatis in a case of BA, mainly in association with dense chronic inflammatory infiltrate may result from metaplastic changes and may not be related to defective morphogenesis as described in the earlier published case reports.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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