Clinical Case Report

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Liver heterotopia associated with congenital diaphragmatic hernia

Two case reports and a review of the literature

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Abstract

Rationale: Liver heterotopia associated with congenital diaphragmatic hernia (CDH) is a rare condition; to the best of our knowledge, only 17 cases have been reported to date. The histogenesis and clinicopathological features are largely unknown. We herein report 2 cases of liver heterotopia associated with CDH along with 17 cases described in the literature to shed light on their clinicopathological characteristics.

Patient concerns: Case 1 was a vaginally delivered male newborn who presented with respiratory distress immediately after birth. Case 2 was a female fetus who was found to have left-sided CDH during gestation.

Diagnosis: In case 1, a chest X-ray revealed left-sided CDH. In case 2, magnetic resonance imaging performed at 33 weeks of gestation revealed left-sided CDH.

Interventions: Case 1 underwent diaphragmatic patch repair surgery 3 days after birth. Histopathological examination following surgery in case 1 revealed the presence of ectopic liver tissue in the hernia sac. Case 2 was delivered by Cesarean section, and diaphragmatic patch surgery was performed 3 days after birth. During surgery, an isolated nodule was identified on the peritoneal side of the border of the defective foramen of the diaphragm. Histopathological examination following surgery in case 2 confirmed the presence of an epidermal cyst in the hernia sac. In addition, the isolated nodule was histopathologically found to be ectopic liver tissue.

Outcomes: In Case 1, CDH recurred at 6 months after surgery, and a second patch repair surgery was performed. The surgically removed hernia sac was found to contain microscopic ectopic liver tissue on histopathology. Case 1 recovered well after surgery, and there was no critical change during the 10-month postoperative period. Case 2 recovered well after surgery, and there was no critical change during the 20-month postoperative period.

Lessons: There were no secondary pathological conditions associated with the presence of ectopic liver in CDH, such as torsion, infarction, rupture, intra-abdominal bleeding, or tumorization. Our observations suggest that liver heterotopia is a rare but asymptomatic condition in patients with CDH.

Abbreviation: CDH = congenital diaphragmatic hernia.

Keywords: case report, congenital diaphragmatic hernia, epidermal cyst, liver heterotopia, malformation, recurrence, review

1. Introduction

Congenital diaphragmatic hernia (CDH) is a congenital defect of the diaphragm that permits herniation of abdominal viscera into the thoracic cavity.[1,2] The incidence is 2.7 to 4.9 in 10,000 live births.[3–5] CDH patients often have pulmonary hypoplasia and abnormal bronchial and vascular branching patterns resulting from prenatal compression of the lung and from abnormalities in lung development.[1] This abnormal development leads to increased pulmonary vascular resistance and causes pulmonary hypertension and respiratory failure. There is a controversy over the survival rate of CDH, but it seems to have improved from 50% to 80% over the past three decades owing to advances in neonatal care.[2,6]

Approximately 50% to 60% of affected individuals are known to have isolated CDH; the remainder has complex CDH, which cooccurs with other malformations or as part of a single-gene disorder or chromosome abnormality.[7] However, liver heterotopia associated with CDH has rarely been described to date. To the best of our knowledge, only 17 such cases have been reported in the literature,[8–17] except for one possible CDH case reported

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in 1936 by Ladd, who described that there were numerous duct-like structures lined by cuboidal epithelium among collagen fibers in the hernia sac but that interpretation of the histogenesis of these structures was difficult.[8] Most of these reports were presented as single case reports, and a comprehensive review of this condition has not been performed.

In this paper, we report 2 cases of CDH accompanied by liver heterotopia in newborns. Informed consent for publication of this case report was obtained from the newborns' parents. The first case was unique because ectopic liver was found in the hernia sac, and when CDH recurred at 6 months after the initial diaphragmatic surgery, ectopic liver was again found in the recurrent hernia sac. The second case was also unique because an epidermal cyst was found in the hernia sac. We also discuss the clinicopathological features of this condition based on a review of the relevant literature.

2. Case 1

2.1. Clinical summary

A male newborn was delivered vaginally at full term from a healthy mother. He subsequently underwent chest X-ray because of respiratory distress, and left-sided diaphragmatic hernia was diagnosed (Fig. 1). Patch repair surgery was performed on the fourth day of his life. During surgery, a hernia sac was found on the left side of the diaphragm, which consisted of a thin fragile membrane, protruding into the left side of the pleural cavity and containing the left lobe of the liver, stomach, spleen, small intestine, and colon. All organs were reduced back into the abdomen, and the sac was removed along with the border of the grossly normal diaphragm. The sac was histopathologically examined. The defect foramen was approximately 40×35 mm in size, and cerclage and closure of the defect foramen were performed with a patch. His postoperative course was uneventful except for the presence of gastroesophageal reflux and an awareness of left-sided cryptorchidism, and he was discharged at 52 days old from the newborn intensive care unit. At 6 months after surgery, he was hospitalized again because of respiratory syncytial viral infection. On admission, the left side of his diaphragm was found to be elevated by chest X-ray. His condition was improved by conservative management, and respiratory syncytial virus was not detectable in his body 17 days after admission. However, the left side of his diaphragm was still elevated, and the diagnosis of recurrence of diaphragmatic hernia was made. Thus, a second patch repair surgery and left orchidopexy were performed 8 months after the initial surgery. During surgery, a hernia sac was found in the dorsal portion of the patch, which consisted of a thin membrane and protruded into the left-sided pleural cavity. The sac was removed and histopathologically examined. The patient recovered well after surgery, and there was no critical change during the 10-month postoperative period.

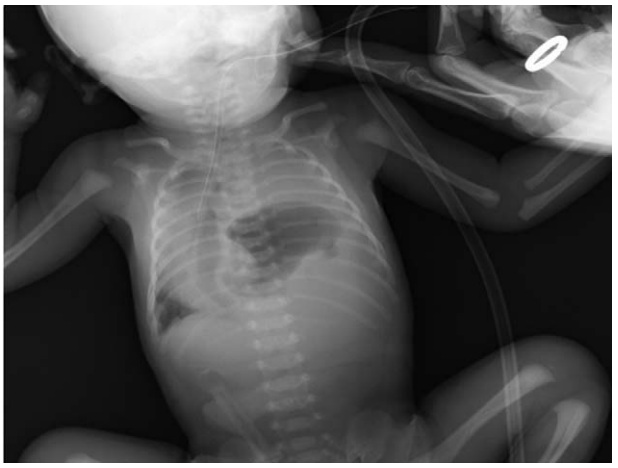

Figure 1. A chest X-ray of Case 1 shows herniating loops of the bowel and a mediastinal shift to the right side resulting from the left-sided congenital diaphragmatic hernia.

2.2. Pathological findings

Both hernia sacs removed by the initial and second surgeries were up to 130 mm in size. They consisted of thin fibrous connective tissue covered by mesothelium and accompanied by vascular congestion, in which clusters of hepatocytes and bile ducts were observed (Fig. 2A and B). Glisson's capsule-like structure was focally observed, but no cholestasis was found. No striated muscle was observed in these hernia sacs. Immunohistochemically, the hepatocytes were positive for hepatocyte-specific antigen (OCH1E5), and the bile ducts were positive for cytokeratin 19 (Fig. 2C and D). Thus, the diagnosis of ectopic liver was made for both sacs.

3. Case 2

3.1. Clinical summary

A female fetus was noted to have a left-sided CDH by chest magnetic resonance imaging at 33 weeks of gestation. She was delivered by Cesarean section at full term, and intratracheal intubation was subsequently performed. She underwent patch repair surgery on the fourth day of her life. During surgery, a hernia sac was found on the left side of the diaphragm, which consisted of a thin membrane, protruding into the ipsilateral pleural cavity and containing the spleen, small intestine and colon. All organs were reduced back into the abdomen, and the sac was removed along with the border of the grossly normal diaphragm and then histopathologically examined. An isolated nodule was attached to the peritoneal side of the border of the defect foramen of the diaphragm, which was excised and histopathologically examined. The left lung was found to be hypoplastic. The defect foramen was approximately 35×30 mm in size, and cerclage and direct closure of the defect foramen were performed. The patient recovered well after surgery, and there was no critical change during the 20-month postoperative period.

3.2. Pathological findings

An isolated nodule attached to the border of the defect foramen was $10 \times 4 \times 3$ mm in size and consisted of clusters of hepatocytes and bile ducts accompanied by vascular congestion (Fig. 3A and B). Glisson's capsule-like structures were focally observed, and no cholestasis was observed. Thus, the diagnosis of ectopic liver was made for that nodule. A hernia sac, measuring $55 \times 40 \times 15$ mm in size, contained fibrous tissue covered by mesothelium, in which an epidermal cyst was observed (Fig. 3B and D). The cyst was covered by non-atypical stratified squamous epithelium without skin appendages, and keratinous substances

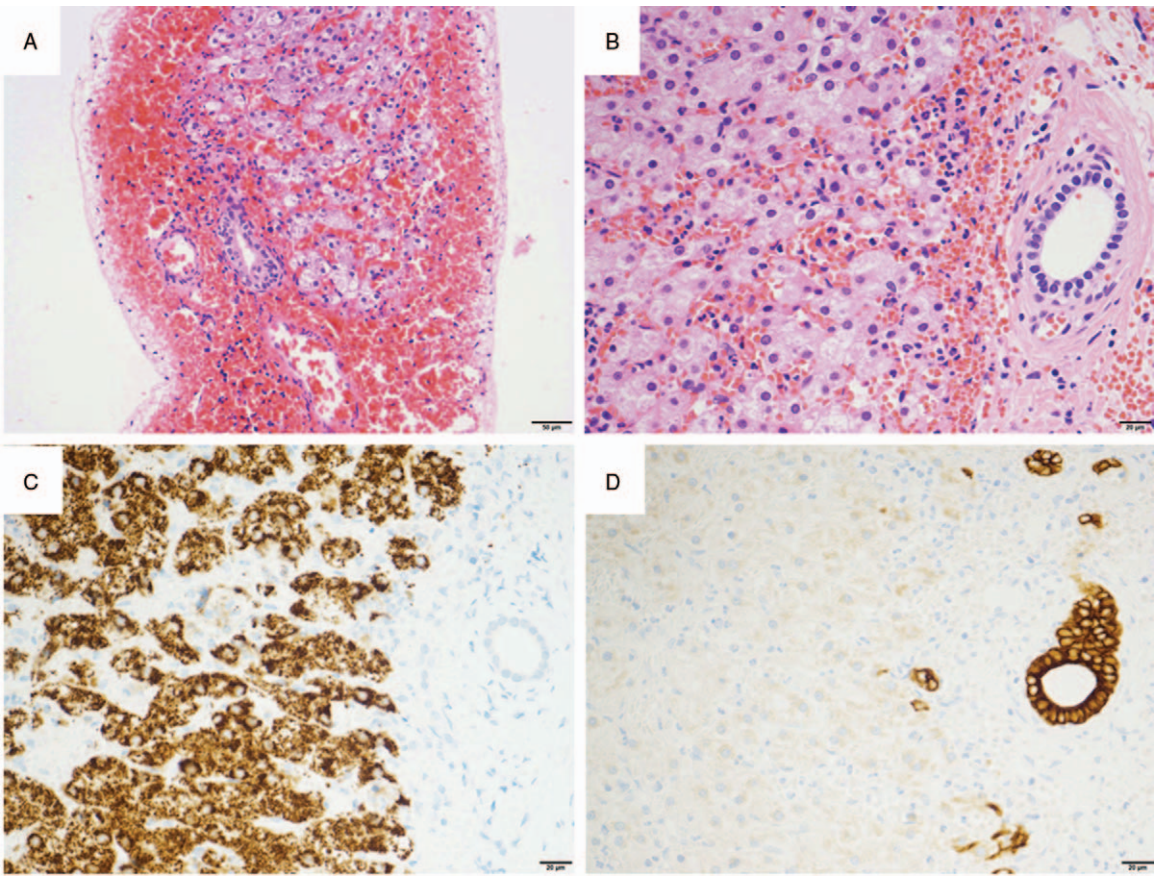

Figure 2. Photomicrographs of Case 1. A: A hernia sac resected at the initial patch repair surgery contained hepatocytes and bile ducts without atypia accompanied by vascular congestion (hematoxylin and eosin stain; the bar indicates 50 μm). B: A hernia sac resected at the second patch repair surgery for the recurrent congenital diaphragmatic hernia contained clusters of hepatocytes and bile ducts accompanied by vascular congestion (hematoxylin and eosin stain; the bar indicates 20 μm). C: Hepatocytes in the hernia sac were positive for hepatocyte-specific antigen (immunohistochemistry; the bar indicates 20 μm). D: Bile ducts were positive for cytokeratin 19 (immunohistochemistry; the bar indicates 20 μm).

were observed within the cyst. No striated muscle was observed in this hernia sac.

4. Discussion

In Case 1, it is noteworthy that both the initial and recurrent hernia sacs contained microscopic ectopic liver tissue. Saltzman et al reported that the age of CDH hernia recurrence ranged from 2 to 48 months (average, 14.8 months) and that the average period between initial repair and recurrence was 8.2 months (range, 2 to 16 months).[18] However, the mechanism of recurrence of CDH is largely unknown. The presence of liver heterotopia in the diaphragm might be associated with the disturbance of the normal development of the diaphragm, thereby leading to recurrence of herniation.[10]

In case 2, an isolated nodule was found to be ectopic liver without any connection to the main liver. In addition, an epidermal cyst was observed in the hernia sac. This combination has never been reported, to the best of our knowledge. Diaphragmatic epidermal cysts are extremely rare; only 3 cases have been reported to date.[17,19,20] Histogenesis of the diaphragmatic epidermal cyst in the current case is considered heteroplasia rather than metaplasia because the case was in a newborn.

Normally, the pericardioperitoneal canal is closed by the development of the pleuroperitoneal membrane, which is fused to the septum transversum during the fifth and seventh weeks of embryonic life. However, CDH results from failure of this closure owing to an underdeveloped pleuroperitoneal fold.[21] In human embryos, the liver bud first appears at the end of the 3rd week of embryonic life and develops in contact with the septum transversum, which appears on the 22nd day of embryonic life.[21]

Embryologically, stimulation of hepatic development is achieved by the secretion of bone morphogenetic proteins by the septum transversum and fibroblast growth factor 2 by the cardiac mesoderm.[21] Bone morphogenetic proteins enhance the competence of prospective liver endoderm to respond to fibroblast growth factor 2.[21] Then, fibroblast growth factor 2 inhibits the activity of the developmental inhibitors, thereby specifying the liver-formation field and initiating liver development.[21]

A recent targeted massively parallel sequencing study identified that approximately 10% of isolated CDH cases are shown to have possibly causative genes, namely, *ZFPM2*, *GATA4*, *NR2AF2*, *TBX1*, *TBX5*, *GATA5*, and *PBX1*.[22] In addition, mutation burden analysis identified *LBR*, *CTBP2*, *NSD1*, *MMP14*, *MYOD1*, and *EYA1* as candidate genes with

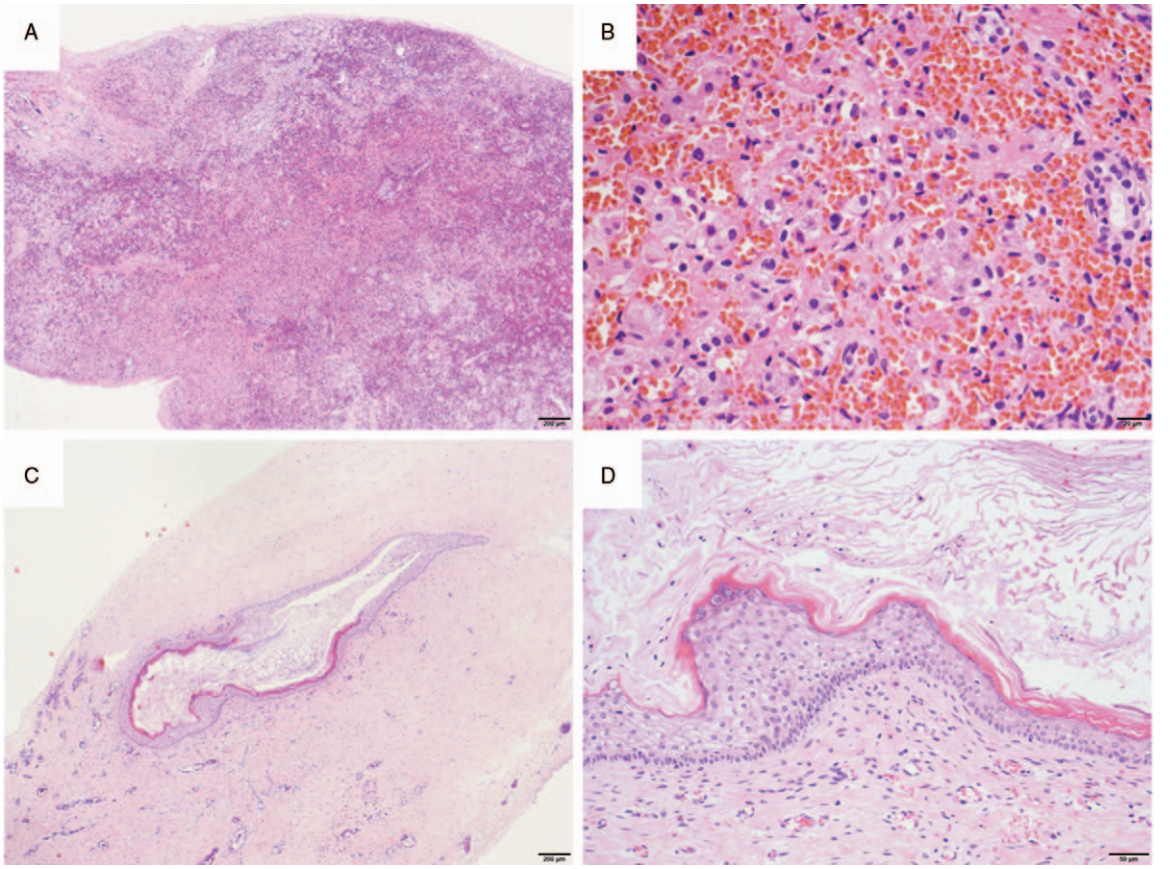

Figure 3. Photomicrographs of Case 2. A: A low-power view of isolated ectopic accessory liver lobe beneath the hernia sac (hematoxylin and eosin stain; the bar indicates 200 μm). B: A high-power view of the isolated ectopic accessory liver lobe beneath the hernia sac shows hepatocytes and bile ducts accompanied by vascular congestion (hematoxylin and eosin stain; the bar indicates 20 μm). C: A low-power view of an epidermal cyst in the hernia sac (hematoxylin and eosin stain; the bar indicates 200 μm). D: A high-power view of an epidermal cyst in the hernia sac shows a stratified squamous epithelium without atypia.

enrichment in rare variants that are predicted to be deleterious.[22] Although the exact etiology has not been elucidated, these genetic alterations in combination with other unidentified genetic, epigenetic or environmental factors may change the liver-formation field and cause liver heterotopia associated with CDH.

The clinicopathological characteristics of 19 cases of liver heterotopia associated with CDH, including the current 2 cases, are summarized in Table 1. There is a left side predominance (90%, 9/10) in cases of liver heterotopia associated with CDH, which is explained by the fact that most CDHs occur on the left side (85–95%).[21] There is a female predominance (68.4%, 13/19) in cases of liver heterotopia associated with CDH, despite the male predominance (male/female = 1.58) in cases of isolated CDH.[3] Only one patient was found to have this pathological condition in adulthood. Other frequent congenital anomalies other than the resultant ipsilateral pulmonary hypoplasia are cardiac anomalies (36.8%, 7/19), such as atrial septal defect, patent ductus arteriosus, ventricular septal defect, patent foramen ovale, and bicuspid aortic valve. Only 3 cases (15.8%, 3/19) involved absent pericardium on the ipsilateral side.

The incidence of liver heterotopia is generally low; the incidence was reported to be 0.47% among 1060 patients undergoing laparoscopic surgery.[23] Meanwhile, Cruz et al reported that the incidence of liver heterotopia was 0.04% (9/214) in their cohort with CDH, and among CDH cases with an associated space occupying lesion, the incidence of liver heterotopia was 4.2% (9/20).[17] The ectopic liver can be classified into the following four types: type I, a large accessory liver lobe attached to the liver by a connecting stalk; type II, a small accessory liver lobe attached to the liver surface; type III, ectopic liver which is situated outside the liver without any connection to it, forming a macroscopically identifiable nodule; and type IV, microscopic ectopic liver.[24] According to this classification, type IV is the most common, followed by type III and type I.

Although ectopic liver is usually asymptomatic, it can be complicated by secondary pathological conditions such as torsion, infarction, rupture, intra-abdominal bleeding, or tumorization.[25] Based on our review of the literature, no such pathological conditions are observed in cases of liver heterotopia associated with CDH. Because CDH recurrence occurred in 2 cases, there is a possibility that the presence of liver heterotopia may contribute to CDH recurrence. However, further studies are needed to clarify this hypothesis.

In summary, we have described the clinicopathological features of 2 cases of liver heterotopia associated with CDH and reviewed the relevant literature. Further clinical, genetic and experimental studies will be needed to clarify the mechanisms underlying this rare pathological condition.

Table 1

Clinicopathological characteristics of 19 cases of liver heterotopia associated with congenital diaphragmatic hernia.

Case	Reference [No.]	Sex	Age at clinical diagnosis of CDH	Clinical sympton	Age at surgery for CDH	Laterality of CDH	Findings of liver heterotopia, type	Pericardium	Other congenital anomaly	Outcome
1	Deutsch AA, et al. Br J Surg 1972;59:156–8 [9]	Female	6 months old	Feeding problem, cough, dyspnea, cyanosis	6 months old	Left side	Microscopic ectopic liver in the hernia sac, type IV	Absent	Left pulmonary hypoplasia	Discharged 17 days after admission and clinically healthy
2	Iber T, et al. J Pediatr Surg. 1999;34:1425–6 [10]	Female	0 days old	Mild respiratory distress	0 days old	Right side	Isolated intrathoracic ectopic accessory liver (8 cm in size, at the age of 6 years), type III	Present	Absent	Re-operation for recurrence of CDH at 6-yeas-old
3	Beiler HA, et al. J Pediat Surg 2001;36:E7 [11]	Male	0 days old	Respiratory distress, acidosis	0 days old	Left side	Isolated supradiaphragmatic ectopic accessory liver (5.5 cm in size), type III	Present	Absent	Uneventful for 5 years since operation
4	Salman B. J Cardiothorac Surg 2002;21:558–60 [12]	Female	6 months old	Not mentioned	6 months old	Left side	Isolated intrathoracic ectopic accessory liver lobe (8 cm in size), type I	Present	Defect of the lateral segment of the left liver lobe	Not mentioned
5	Patel Y, et al. J Pedatr Surg 2007;42:E29–31 [13]	Female	Antenatal	Not mentioned	2 days old	Left side	Microscopic ectopic liver in the hernia sac, type IV	Absent	PDA, left pulmonary hypoplasia	Complecated by delayed full enteral feeding after surgery
6	Kamath GS, et al. Ann Thorac Surg 2010;89:e36–7 [14]	Female	37 years old	Breathing difficulty, abdominal pain	37 years old	Left side	Left liver lobe adherent to the diaphragmatic defect margin and situated above the diaphragm, type I	Absent	Bicuspid aortic valve	Recovered well after surgery
7	Arafah M, et al. Patholog Res Int 2011 [15]	Male	Antenatal	Respiratory distress	14 days old	Left side	Microscopic ectopic liver in the hernia sac, type IV	Present	PDA, patent foramen ovale, VSD	Pseudomonous aeruginosa pneumonia which was successfully treated with antibiotics
8	Patel RV, et al. BMJ Case Rep 2013 [16]	Female	Antenatal	Respiratory distress	2 days old	Left side	Ectopic liver tissue in the hernia sac, type III	Present	Left pulmonary hypoplasia, abnormaly shaped hypoplastic left lobe of the liver	Well, asymptomatic and thriving well with normal chest X-ray at 7 years follow-up
9-17	Cruz SM, et al. J Pediatr Surg 2016;51:710–3 [17]	3 males 6 females	Unclear	Unclear	Unclear	Unclear	The sac was the most common location where heterotpic liver tissue was found by histology.	Absent in 2 cases	Cardiac anomalies in 4 cases (ASD, VSD or PDA), pulmonary sequestration in 2 cases	6-month overall survival rate was 88%, with the sole death being a case of right CDH with severe pulmonary hypertention.
18	Present case #1	Male	0 days old	Respiratory distress	3 days old	Left side	Microscopic ectopic liver tissue in the peritoneum around the diaphragmatic defect, type IV	Present	Left criptorchidism	Re-operation for recurrence of CDH 6 months after the initial surgery
19	Present case #2	Female	Antenatal	respiratory distress	3 days old	left side	Macroscopic isolated ectopic liver attached to the diaphragm (1 cm in size), type III	Present	Left pulmonary hypoplasia, epidermal cyst in the hernia sac, PDA	Recovered well after surgery

ASD = atrial septal defect, CDH = congenital diaphragmatic hernima, PDA = patent ductus arteriosus, VSD = ventricular septal defect. Type I, a large accessory liver lobe attached to the liver by a connecting stalk; type II, a small accessory liver lobe attached to the liver surface; type III, ectopic liver which is situated outside the liver without any connection to it, forming a macroscopically identifiable nodule; and type IV, microscopic ectopic liver.

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