Ectopic liver in a five-week-old embryo

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Abstract
The first case of a placental tumor composed of benign hepatic tissue was published in 1986 and considered a placental benign hepatocellular adenoma. Since then, this lesion is better known as ectopic liver, and a total of 12 cases have been published. The ectopic liver located in the umbilical cord is an even rarer alteration, with only nine cases described to date. We report another case of ectopic liver, this time in an embryo of only five weeks of gestational age.

Keywords: ectopic liver, ectopic hepatocellular tissue, embryonic period.

Introduction
The finding of benign hepatocellular tissue in the placenta was first described in 1986 [1]. The authors believed that it was a highly specialized monodermal teratoma and termed it hepatocellular adenoma. Nowadays, there is agreement that this type of entity can arise in three different ways: an ectopic hepatic tissue, a hepatic adenoma, or a monodermal teratoma, with the most extended opinion being that its presence indicates the ectopy of normal hepatic tissue (ectopic liver). It is a rare alteration, with only 12 cases described to date [1–9].

The presence of ectopic hepatic tissue in the umbilical cord has also been described in a total of nine cases to date [10].

Aim
We are reporting a new case of ectopic hepatocellular tissue, this time in a five-week gestational age embryo, and consider that both lesions, placental and umbilical, share the same formation mechanism.

Case presentation
A woman with no clinical antecedents of interest suffered an early miscarriage. Curettage of her uterine cavity was performed, and the material obtained was sent for pathological study. Among the decidual fragments, we identified a chorionic sac, and inside, a whitish and bent embryonic structure, about 5–6 mm in crown-rump length and with an external development equivalent to five weeks of gestational age (Figure 1A).

After routine histopathological diagnosis, due to the high quality of the material and with didactic objectives, a correlative and complete slicing of the sample was carried out.

Histopathology
However, during the ulterior microscopic study and photography of the resulting histological slides, we identified a non-capsulated mass of tissue that measured 0.4×0.2 cm in its major axes and seemed to be “floating” in the chorionic cavity (Figure 1B). In some sections, this tissue appeared to be loosely attached to extraembryonic mesodermal membranes. We also observed that in the embryo, at the root level of the connection between the midgut and the yolk sac, some changes affected the vitelline duct and vitelline vessels (Figure 1C).

Under higher magnifications, we observed that cells of this tissue arranged in a trabecular pattern, with interconnecting cords, but also configured acini and small nests. They were large and polygonal cells (less often cylindrical), with large round or elliptical nuclei, conspicuous nucleoli, and discrete mitotic activity. Optically empty rounded spaces with varying diameters were also observed and reminiscent of acini with abnormal lumens or fat degeneration-like phenomena (Figure 2A).

Within the intertrabecular spaces, sinusoid vessels and hematopoietic activity were also identified (Figure 2B).

Finally, we observed the same cells integrating small nests between the vitelline duct and vitelline vessels (Figure 2C), as well as making up the vitelline duct epithelial lining (Figure 2D).

Immunohistochemical (IHC) examination
The same histological preparation which provided Figure 1 (B and C) and Figure 2 (A–D) was discolored and then used for IHC techniques with the hepatocyte paraffin 1 (HepPar1) immunomarker (Roche®). The result was positive in the extraembryonic tissue, in the embryonic...
liver, and the root of the vitelline duct (Figure 1 – left, central, and right circle, respectively).

**Discussions**

The ectopic liver is a rare disorder consisting of the presence of hepatic tissue in an extrahepatic location and without connection to the main organ [11]. The gallbladder is the most frequent extrahepatic location, although ectopic liver has been reported in other places. There are cases of ectopic liver in the placenta and umbilical cord, but they are exceptional, with only 12 and nine cases having been reported to date, respectively [1–10].

The liver begins its formation at the end of the third week of development, as a diverticular outbreak of the endoderm of the most caudal portion of the foregut, and more specifically of the ventral wall of the future duodenum. This epithelial bud is intermixed with mesenchyme which belongs to both the septum transversum and the nearby coelomic wall. In the fourth week, the cranial portion of this outbreak generates hepatic cords, which project radially and intermingle with vitelline veins to form the sinusoids. In the meantime, the caudal sector will persist without intermingling with the mesenchyme of the septum transversum and will be thinning and developing the entire extrahepatic biliary tree and ventral pancreatic bud.

![Figure 1](image-url)

**Figure 1** – Five-week-old embryo: (A) Panoramic view where a developing liver can be distinguished (1), made up of hepatocyte cords and sinusoids; (B) Extraembryonic mass of ectopic liver tissue (2), located in the chorionic cavity (3), and loosely attached to the membranes of the extraembryonic mesoderm (4 and 5); (C) Detail showing the proximity between the liver and the yolk sac pedicle root, the latter including the vitelline duct (6) and vitelline vessels (7) in its thickness. HE staining: (A and B) ×10; (C) ×25. Immunohistochemical technique (PAP) was positive for the HepPar1 marker in extraembryonic liver tissue (left circle, ×100), in the embryonic liver (center circle, ×100), and the root of the yolk duct (right circle, ×400). HE: Hematoxylin–Eosin; HepPar1: Hepatocyte paraffin 1; PAP: Peroxidase, anti-peroxidase.
Subsequently, the newly formed liver lobes grow, project ventrally and caudally through the mesenchyme of the anterior abdominal wall and reach the primitive umbilical ring. Also, the septum transversum is at this time very close to the umbilical ring, and approximately at the same time the vitelline duct (the endodermal tube connecting the midgut and the definitive yolk sac), accompanied by the vitelline vessels, passes through the umbilical ring and remains in the chorionic cavity (between the amnion and the chorionic plate).

Therefore, when the umbilical ring closes, the hepatocyte cords may accidentally remain outside the abdominal wall. Another possibility is that the endoderm undergoes aberrant differentiation towards hepatocytes in this region [12]. Regarding this latter, the endoderm can form liver, but this function is inhibited by stimuli coming from the mesoderm, ectoderm, and notochord. However, the bone morphogenetic protein (BMP), produced by the septum transversum, allows the endoderm to be sensitive to the effect of fibroblast growth factor-2 (FGF-2). This FGF-2 (secreted by the cardiogenic mesoderm) can act blocking the above-mentioned inhibitory stimuli, and the endoderm can then produce hepatocytes in this location [13].

In the present case, all these events may be directly implicated with the appearance of embryonic and fetal hepatocytes, in both the thickness of the yolk stalk and the lining of the vitelline duct (Figure 3, A–C). Therefore, the rapid growth of this tissue at these stages may allow a true ectopic hepatocellular tissue to form in the umbilical cord. In later stages, when the amniotic cavity expands rapidly and the chorionic cavity decreases in size, the amnion membrane and the chorionic plate finally meet and fuse, generating the amniochorionic membrane. In this way, the chorionic cavity is now completely obliterated, and then the ectopic liver can remain in the umbilical cord or can be displaced even more distally to be finally located in the placenta (Figure 3, A–C).

On the other hand, embryonic liver tissue that migrates to the umbilical cord or placenta in the early stages of development may not develop portal pathways, bile ducts, or the liver lobular architecture. These morphological features are more typical of ectopic hepatic tissue that originates in later stages of development [3, 7].

We contribute with the finding of ectopic liver tissue at a very early stage of development (the earliest case reported so far), and this allows us a direct relationship to be established between the proposed formation mechanisms for this alteration with the images presented here. We believe that hepatocyte sequestration occurs during the closure of the umbilical ring and/or that endodermal cells in this area are stimulated to differentiate into hepatocytes. The subsequent evolution of this ectopic tissue, and the time when its study is accessed (usually in the third trimester of gestation or after birth), have a direct relationship with the different macro and microscopic characteristics that exist between the previously published cases.
We also believe that this type of pathology occurs more frequently than it is detected [7]. Its low incidence may be due to its existence being unknown and, therefore, not recognized during a routine study, although it is also likely to be related to the fact that the sampling of the biopsied material in this type of study usually is not enough. Additionally, this type of material often presents conservation defects (usually related to bad fixations). Finally, pathologists must be aware of the existence of this type of entity to prevent misdiagnosis.

Conclusions

We present the finding of ectopic liver tissue at a very early stage of development (the earliest case). Our findings indicate that previously reported cases, both in the placenta and umbilical cord, can share the same formation mechanism. We believe that this entity occurs more frequently than it is detected and that pathologists must know its existence to avoid misdiagnosis.

Conflict of interests

The authors declare that they have no conflict of interests.

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