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Ectopic Liver within the Placental Parenchyma of a Stillborn Fetus

Rasleen Saluja¹, MD, Ona Faye-Petersen², MD, Debra S. Heller³, MD

1) University of Hawaii, Honolulu, Hawaii 2) University of Alabama at Birmingham, Birmingham, Alabama 3)

Rutgers University-New Jersey School of Medicine, Newark, New Jersey

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Running Title: Ectopic Liver in Placenta

Abstract:

Rarely, liver tissue can be seen in the umbilical cord, where it is thought to result from ectopic localization during embryogenesis. The placental parenchyma is also a rare site for this occurrence. The exact pathophysiology of ectopic liver in the placenta is unknown. It has been considered that aberrant migration or displacement of cells from the developing hepatic buds leads to ectopic liver formation, including groups of liver cells that become entrapped in the foregut as the diaphragm closes. Additional hypotheses put forward have included monodermal teratoma and hepatocellular adenoma. While the lesions may not actually be adenomas, this term has been most utilized in the literature. Hepatocellular adenomas of the placenta are extremely rare; only nine cases have been reported thus far. We report an additional occurrence of ectopic liver in the placenta, which is the only one reported in a stillborn, and review the literature.

Key Words: ectopic liver, placenta, placental neoplasm, hepatic adenoma, monodermal teratoma

Introduction

The fetal liver develops from the caudal aspect of the foregut in the fourth week of embryonic development.¹ Entrapped hepatic cells may be found in the region of the foregut following closure of the diaphragm or umbilical rings.¹ Ectopic liver in the umbilical cord is rare, with only a few case reports, and within the placental parenchyma, rare as well. We report a case of intraplacental ectopic liver tissue, the first in a stillborn, and review the literature.

Case Report

This was a 16-week gestational age stillborn male delivered of a 30-year old G4P2021 mother. The mother had had two prior losses, one first and one third trimester loss, and had a history of asthma. The 53 gram fetus was autolyzed, with a foot length of 1.4 cm consistent with 13-14 weeks gestational age in size, but showed no other significant gross or microscopic pathology. The placenta weighted 45 grams and was grossly unremarkable. Histology showed scattered trophoblast inclusions. In addition, a microscopic well-circumscribed nodule was seen, composed of cords of hepatocytes. No portal tracts, central veins, ductules, bile pigment or extramedullary hematopoiesis were seen. The hepatic tissue stained strongly for Hep Par 1, alpha-1-antitrypsin and AE1/3 cytokeratin, and was focally positive for alpha-fetoprotein and glypican-3, consistent with the diagnosis. Based on the cytokeratin stain, the lesion appeared to be within a villus (figures 1-4).

Discussion

A few single cases of heterotopic tissue occurring in the placenta, have been reported in the literature including heterotopic adrenocortical tissue². Placental lesions composed of hepatic tissue are rare. We only found 9 prior reports of intraplacental ectopic liver tissue³⁻⁸. Our case, the first we identified in a stillbirth, appears to be an incidental finding unrelated to the stillbirth. Of the identified cases, half were in the chorionic plate, and half within the placental parenchyma, including our case³⁻⁸. Rare reported cases of ectopic hepatic tissue have occurred in the umbilical cord, and solid masses in the umbilical cord are extremely rare.^{1,9,10}

The gross appearance of placental lesions of hepatic origin has been varied. Some have been described as tan to dark-red nodules without necrosis while others are reported as tan-white, well-circumscribed discrete tumor-like lesions.^{3,4} Our case, as well as two others, were not visible grossly.⁴ All reported cases were incidental.³⁻⁸

The differential diagnoses of intraplacental hepatic tissue includes decidua⁴, ectopic adrenal cortical tissue, x-cell clusters, chorangioma and trophoblastic tumors⁵, which can be distinguished on histology. Other more rare considerations are teratomas or metastatic tumors of either maternal or fetal origin.⁶ Immunohistochemistry can be helpful. Inhibin would be expected to stain adrenal cortical tissue. Glypican-3 is normally expressed in fetal hepatocytes, affirming ectopic liver tissue or a neoplasm expressing hepatic differentiation.³ Expression of Hep Par 1 by immunohistochemistry decreases likelihood of this lesion being a yolk sac tumor.³ Benign histology as well as lack of any known primary cancer in either the fetus or mother make this lesion extremely unlikely to be a metastasis to the placenta.⁴ Early embryogenic hepatic tissue that has migrated to the placenta may not necessarily develop portal tracts, bile duct structures and classic lobular hepatic architecture that could be seen with heterotopic liver tissue that occurs later in development.⁶ The lack of portal tract structures in ectopic liver tissue has also been reported in sacrococcygeal teratomas in a fetus.¹² It has been suggested that embryonic tissue of hepatic origin that aberrantly migrates to placental and umbilical cord sites may not necessarily develop the classical lobular architecture and portal tract structures of other well-differentiated heteropias.⁶

Lack of features of malignancy makes yolk sac tumor unlikely. Primary yolk sac tumor arising in the placenta is exceptionally rare, and would be expected to stain for alpha fetoprotein.¹² Additionally, if a metastatic yolk sac tumor was under consideration, the pattern of metastatic malignancy is often multifocal and our lesion is a singular well-circumscribed nodule. Finally, the most common maternal tumors which metastasize to the placenta are melanoma, and maternal carcinomas. Fetal tumors that can affect the placenta would include congenital neuroblastoma and leukemia; our case has no features of these entities.⁶

In reviewing the literature, this lesion has appeared with several names. Theories of origin have included ectopic liver, hepatic adenoma, and monodermal teratoma. Chen, et al. first reported benign hepatic tissue in the placenta as hepatocellular adenoma.⁷ These investigators believed the lesion to be a highly specialized monodermal teratoma.⁷ Hepatocellular adenomas are believed to be benign neoplasms, found incidentally in all reported cases.³ A recent study investigated potential for malignant transformation by utilizing immunohistochemical markers known to be associated with hepatic adenomas that transformed into adult hepatocellular carcinomas as well as molecular studies investigating beta-catenin gain of function mutations correlated with malignant transformation; both of these analyses found that hepatocellular adenomas of the placenta have no known malignant potential.³ There are no reported cases of recurrence of placental hepatocellular adenoma in the literature.³

Hepatic adenomas of the placenta have been described as single well-circumscribed encapsulated nodules, composed of semidistinct lobules of cords and nests of polygonal epithelial cells resembling fetal liver.⁴ No bile pigment, ductules, portal tracts or central veins are present, and extramedullary hematopoiesis has been variable.⁴

Some investigators have considered these lesions as monodermal teratomas. Teratomas of the placenta are believed to originate in the first trimester from primordial germ cells moving from the yolk sac to the placenta, through a portion of foregut that is evaginated into the cord during embryogenesis.^{4,13} These cells then pass into the space between the amnion and chorion, which is by far the usual site for placental

teratomas.⁴ If indeed hepatic adenomas originate from yolk sac components which have migrated during embryogenesis, this could suggest that these lesions are a rare form of placental choristoma.⁴

We consider that our lesion is most likely to be ectopic liver tissue. Displacement or aberrant migration of cells from the developing hepatic bud could lead to ectopic liver formation, specifically for groups of liver cells which become trapped in the foregut when the diaphragm closes. The literature has not established how this ectopia occurs. One could postulate that liver tissue travels into the cord with the yolk sac, ends up with the yolk sac between the amnion and chorion, and perhaps is then carried out from stem villi to peripheral villi with branching. We would have expected more lesions to arise in the chorionic plate than in the parenchyma, as early migration would seem to predispose to a chorionic plate locale unless the cells are later “carried” more distally as the tree develops. However, the literature shows equal distribution of location. The morphologic features of the lesion help to differentiate it from other placental neoplasms and the immunohistochemical staining pattern help to confirm it is truly of hepatic origin. In summary, this is a rare incidental placental lesion. Since these lesions are discovered incidentally, the perceived rarity could be due to sampling.⁴

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Legends:

Figure 1-The small incidental well circumscribed lesion was appreciated microscopically.

Figure 2-The lesion was composed of cords of hepatocytes. No portal tracts, central veins, ductules, or bile pigment were present.

Figure 3-AE1/3 cytokeratin stain shows the lesion appears to be arising within a villus.

Figure 4-The hepatocytes stained for Hep Par 1.