Hepatic Mesenchymal Hamartoma
A Short Review

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- Hepatic mesenchymal hamartoma is a hamartomatous growth of mesenchymal tissue in the liver of uncertain etiology. It is a space-occupying lesion that can potentially compress adjacent organs resulting in various complications including death. Hepatic mesenchymal hamartoma is characterized by proliferation of variously myxomatous mesenchyme and malformed bile ducts. The differential diagnosis includes other pediatric hepatic masses. The diagnosis is typically made during infancy, and complete resection is invariably curative.

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Hepatic mesenchymal hamartoma (HMH) is an uncommon benign tumor of childhood. It makes up approximately 8% of all pediatric tumors and is second in occurrence only to hepatoblastoma when only pediatric hepatic tumors are considered. Eighty percent are found within the first 2 years of life and the remainder are detected by 5 years of age. Rare cases have been reported in adults.

Herein, we discuss the pathologic findings, pathogenesis, and differential diagnosis of this rare entity. In addition, clinical presentation and treatment options are also reviewed.

CLINICAL PRESENTATION

Typically a patient will present with an enlarging, non-tender abdominal mass. If the mass is very large, complications including ascites, jaundice, and even congestive heart failure can occur. Occasionally, the mass will expand rapidly, most likely because of rapid accumulation of fluid within cystic spaces.

No specific panel of laboratory tests is characteristic of HMH. Laboratory studies often reveal normal liver function tests and various tumor markers, including α-human chorionic gonadotropin, α-fetoprotein, and vanillylmandelic acid, are usually negative. Liver enzymes, including alanine aminotransaminase, aspartate aminotransaminase, gamma-glutamyl transferase, and alkaline phosphatase, range from normal to markedly elevated. Abdominal ultrasound can demonstrate either a multicystic or solid mass. Although not required for diagnosis, computed tomography and magnetic resonance imaging are useful for surgical planning.

Intrauterine HMHs have been well-documented in several reports. Laberge et al reviewed 12 cases, 4 of which were lethal. The remaining fetuses were diagnosed radiographically during the third trimester and the tumor was resected within the first 3 months of life. The infants for whom follow-up information was available were doing well. Of the 4 HMHs that were lethal, 1 was a neonatal demise and 3 were intrauterine demises. Intrauterine deaths are typically ascribed to the mass effect of this enlarging tumor. Adjacent structures such as the heart, lungs, kidneys, and large veins become compressed and organ failure ensues. Similarly, umbilical veins can show aneurysmal dilatation because of this distal compression.

PATHOLOGIC FINDINGS

Hepatic mesenchymal hamartomas vary greatly in size, from a few centimeters up to 30 cm. The tumor may bulge from the surface of the liver or can be pedunculated. Seventy-five percent occur on the right side, fewer occur on the left, and rarely both lobes are involved. Multiple cysts ranging from a few millimeters to several centimeters are characteristic, usually in the range of 4 to 7 cm. Cysts contain clear to yellow fluid, and occasionally gelatinous material is present. A thin rim of normal liver parenchyma is often seen at the periphery (Figure 1).

Microscopically, HMH consists of myxomatous connective tissue containing scattered bland stellate-shaped mesenchymal cells. Branching bile ducts similar to malformed ductal plates are usually present throughout and are surrounded by loose mesenchyme as well (Figure 2). The cysts often have no epithelial lining and appear to be bounded by the mesenchyme itself (Figure 3). Extramedullary hematopoiesis is noted in approximately 85% of cases. Hepatocytes may be present in single cords or in large groups, especially at the periphery of the mass (Figure 4). Atypical mitoses and invasion of adjacent liver are absent.

Although rare, malignant transformation to embryonal sarcoma (malignant mesenchymoma) has been reported. Begueret et al reported a case of a large, cystic hepatic mass in a 17-year-old girl that had areas characteristic of both embryonal sarcoma and HMH. Between the 2 distinct areas was a transition zone that contained the architectural features of a HMH but with the atypical mesenchymal features of embryonal sarcoma. In this case, immunohistochemical staining demonstrated expression of both α-smooth muscle actin and desmin.
chymal cells of an embryonal sarcoma. Flow cytometric analysis of DNA aneuploidy showed that all 3 areas had similar DNA indices suggesting a common lineage.

**PATHOGENESIS**

The pathogenesis of HMH is still debated. A handful of series have shown an association with mesenchymal stem villous hyperplasia of the placenta. Mesenchymal stem villous hyperplasia is characterized by diffuse edema of stem villi with preservation of terminal villi. Often these stem villi contain areas of large muscularized vessels. The histologic picture is similar to a partial hydatidiform mole but without the trophoblastic scalloping or proliferation. Whether these 2 entities are somehow related is still in question, but the hypothesis that they arise from synchronous abnormal mesodermal development rather than a true developmental abnormality (as originally thought) is gaining acceptance. Because placentas have seldom been examined in infants who develop large hepatic masses, the data are limited.

Several investigators have reported a balanced translocation between the long arms of chromosome 11 and chromosome 19. Rakheja et al recently reported a case of HMH in an 8-month-old boy that demonstrated a breakpoint at 19q13.4, which was similar to the previous 4 reported cases that had a documented karyotypic abnormality. Using histologic, immunohistochemical, flow cytometric, and cytogenetic data, Lauwers et al elegantly demonstrated a case of embryonal sarcoma arising from an HMH in a 15-year-old girl. The transformed component had the 19q13.4 breakpoint in addition to several other numerical and structural chromosomal abnormalities. Taken together, this raises the possibility that perhaps a subset of HMHs is truly neoplastic.

**TREATMENT**

Fetal intervention in the form of ultrasound-guided percutaneous cyst aspiration has been shown to dramatically affect outcomes. Tsao et al reported 2 fetuses with intrauterine cystic HMHs: one who underwent cyst aspiration and the other who did not. The former underwent a total of 3 antenatal aspirations. After each aspiration, fluid did
reaccumulate, but in the end, there was cyst shrinkage. The fetus was delivered vaginally at 35 weeks, and at 2 weeks postpartum both mother and child were well. The latter fetus who was not treated with prenatal cyst aspiration experienced rapid cyst enlargement, such that before appropriate intervention could be initiated, the mother had premature rupture of membranes, followed by preterm labor and delivery also at 35 weeks. Postpartum complications included intraventricular hemorrhage, cystic encephalomalacia, and renal failure, which were all thought to be related to ischemia secondary to vascular compression. The infant subsequently died.

Surgery, consisting of either enucleation or lobectomy, traditionally has been the treatment of choice in the postpartum period; however, less invasive techniques, such as laparoscopic fenestration have also been used successfully.12 Because the natural course of this tumor is to initially rapidly increase in size and subsequently decrease in size, some investigators have opted for “watchful waiting” in asymptomatic patients.14

DIFFERENTIAL DIAGNOSIS

Pediatric hepatic masses include both neoplastic and nonneoplastic proliferations as well as infectious etiologies. Radiographically, the differential diagnoses include hepatoblastoma, embryonal sarcoma, hemangioendothelioma, infantile hemangioendothelioma, and hepatic hydatid disease.15 All these entities can have varying amounts of solid and cystic areas.

Rendering a diagnosis from a needle biopsy or a fine-needle aspiration biopsy can be difficult if not approached in a systematic fashion. If the sample is hypocellular, which is not uncommon with HMH, the difficulties in arriving at a diagnosis could be compounded. Clusters of normal bile duct epithelium and hepatocytes admixed with bland mesenchymal cells in a myxoid background is highly suggestive of HMH.

Immunohistochemistry is used primarily to rule out other entities. In HMH, bile ducts and hepatocytes are cytokeratin positive, whereas the mesenchyme and pseudocysts are vimentin positive.1 Myxomatous infantile hemangioendotheliomas can resemble HMH on fine-needle aspiration biopsy, but the plump endothelium of the former is positive for factor VIII-related antigen, CD31, and CD34 immunohistochemical stains. Although a localized vascular proliferation within an HMH will stain similarly, careful attention to the amount of positive-staining cells within the entire set of aspirates will reveal the true nature of the mass.

Of the different histologic patterns of hepatoblastoma, mixed epithelial-mesenchymal hepatoblastoma is most similar to HMH. This particular type of hepatoblastoma can be composed of relatively bland appearing hepatocytes (of the fetal type) with spindle/stellate mesenchyme. In general, fine-needle aspiration biopsies of hepatoblastomas tend to be very cellular and the mixed epithelial-mesenchymal type can contain fragments of osteoid or cartilage as well. Using immunohistochemical stains for this differential diagnosis can potentially be misleading because fetal-type epithelial cells stain similar to adult-type hepatocytes (positive for cytokeratin [CK8, CK18] and hepatocyte [Hep Par 1]). In addition, the mesenchymal components of both HMH and hepatoblastoma are strongly positive for vimentin.1

Finally, distinguishing embryonal sarcoma from HMH is based on identifying atypical, pleomorphic stellate cells that are frequently set in a background of hemorrhage and/or necrosis. Within these tumor cells and occasionally in the stroma itself, periodic acid–Schiff–positive and diastase resistant hyaline globules similar to those seen in yolk sac tumor may be present. In contrast to HMH, an epithelial component is lacking in embryonal sarcoma.

SUMMARY

Hepatic mesenchymal hamartoma is a benign tumor that is typically diagnosed in childhood; its etiology has not been completely elucidated. Histologically, it is composed of bland spindled cells in a myxoid fibrous stroma with pseudocysts and normal-appearing bile ducts and hepatocytes. The differential diagnosis consists of other pediatric hepatic masses as well as select infectious cysts. Specimens with small amounts of diagnostic tissue (as in core needle biopsy or fine-needle aspiration biopsy) should be carefully examined for the histologic components described previously. Judicious use of immunohistochemical stains will help rule out other possibilities. Complications of an enlarging HMH stem from compression of adjacent vital organs and structures. Prognosis is excellent with complete resection.

References