

Pediatric Mesenchymal Hamartoma of Liver: A Case Report with Histomorphological Differential Diagnosis and Review of Literature

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ABSTRACT: Mesenchymal hamartoma of liver (MHL) is a benign liver tumour that occurs mainly in children, especially those under 2 years old. The pathogenesis of this tumor is still unknown. It is believed that MHL is derived from the Ito cells and either a developmental malformation of primitive hepatic mesenchyme; result of toxic or ischemic insult; or a true neoplasm. It is amenable to treatment and has a good prognosis but presents with varied clinical, imaging and histological findings. However, it can be confused with other hepatic tumors and can mimic malignancy. Therefore, it is important to recognize this rare entity to avoid unnecessary over management. We present a case of MHL in a 3-year-old boy with abdominal distension. Based on the clinical presentation, laboratory and radiological findings a diagnosis of complex cyst of liver was made. A final diagnosis of MHL was given after histopathological examination.

KEYWORDS: Mesenchymal hamartoma, liver tumor, pediatric neoplasm, hamartoma of liver.

Introduction

Primary neoplasms of the liver account to approximately 0.5% to 2.0% of all pediatric neoplasms [1].

Mesenchymal hamartoma of liver (MHL) is a rare tumor with fewer than two hundred cases reported in the literature [1].

This is considered the third most common liver tumor in children, following hepatoblastoma and infantile hemangioma [2].

It constitutes approximately 8% of all tumors in the pediatric population [3].

It mostly presents in the first two years of life [4].

Approximately 90% cases are seen in infants and fewer than 5% present after 5 years of age [5].

It has a good prognosis but can possibly recur as an undifferentiated embryonic sarcoma hence, it is considered to be a pre-malignant tumor [6].

The diagnosis requires high index of suspicion on clinical and radiological basis, but histopathology is the gold standard for the definitive diagnosis.

The histomorphological features is scarcely elaborated in literature.

We are presenting this case to stress its unique histomorphological and biological behavior and, we have laid special emphasis on the differential diagnosis and review of literature.

Case Report

A three-year-old boy, born normal at full term was brought to the hospital with a painless abdominal lump and abdominal distention.

The lump was noticed by the mother and was gradually increasing over the last eight-months.

There was also a one-month history of fever and rashes all over the body.

There was no history of vomiting or jaundice.

There was no relevant personal or family medical history.

The developmental milestones were normal.

During the physical examination, a large painless abdominal mass was observed extending across the right hypochondrium, epigastrium and umbilical region, crossing the midline and causing abdominal distension.

There was no splenomegaly.

The laboratory work-up revealed a normal hemogram, liver, and renal function tests.

Serum alpha-feto protein (AFP) level was also normal.

Viral markers for Hepatitis B and Hepatitis C were negative.

Test for Echinococcal antigen was also negative.

Abdominal ultrasound revealed an avascular hypoechoic liver mass with septations.

All other organs including kidney and pancreas were unremarkable.

For further characterization, a contrast-enhanced computed tomography (CT) of the abdomen was performed.

It showed a 10x5.9cms large, well-defined, multi-loculated, variable-sized, peripherally enhancing cystic lesion involving the left lobe of the liver (segment IV A and IV B).

Based on these findings a pre-operative diagnosis of complex cyst of liver was made.

Surgical resection of the mass was performed.

An excised 8x7x3cm partial hepatectomy specimen was received for histopathology examination.

Multiple cysts, the largest measuring 6cm in diameter were seen, and they were separated by grey white tissue. The cysts contained pale yellow colored serous fluid. No areas of necrosis, hemorrhage, solid tumor nodules or cirrhosis were noted (Figure 1A).

Microscopy revealed multiple, thin-walled cysts and the periphery showed clusters, nodules

of cytologically unremarkable hepatocytes with retained cell plate architecture. They were surrounded by myxoid and fibrous stroma. The cysts were lined by biliary epithelium.

The stroma showed spindled to stellate cells (Figure 1B-D).

Few of the close differential diagnosis based on age group and the frequency of their occurrence were Mixed epithelial-mesenchymal hepatoblastoma, Infantile hemangioendothelioma and Embryonal sarcoma.

Our case lacked features of necrosis, atypia, mitotic activity, increased vascularity or embryonal elements.

Thus, a histopathological diagnosis of MHL was given.

Parents' informed written consent was taken for publishing the case in a scientific journal.

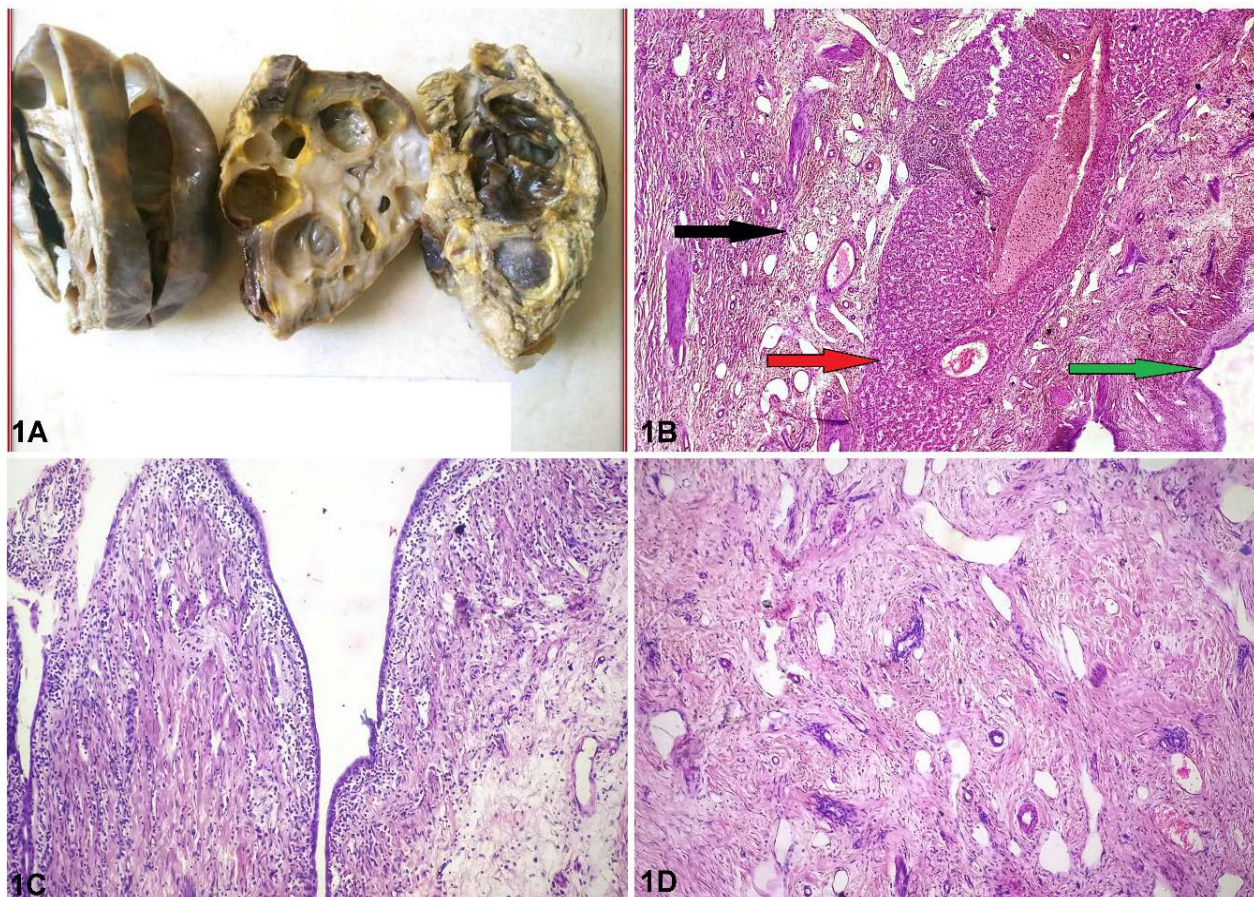


Figure 1: A. Gross photograph of the partial hepatectomy specimen showing multiple cysts with grey-white septae; B. Photomicrograph of the mass showing cysts (green arrow), islands of hepatocytes (red arrow) and fibromyxoid stroma (black arrow) (Hematoxylin and Eosin stain, 40x); C. Photomicrograph showing cyst (Hematoxylin and Eosin stain, 40x); D) Photomicrograph showing stroma with multiple blood vessels (Hematoxylin and Eosin stain, 40x).

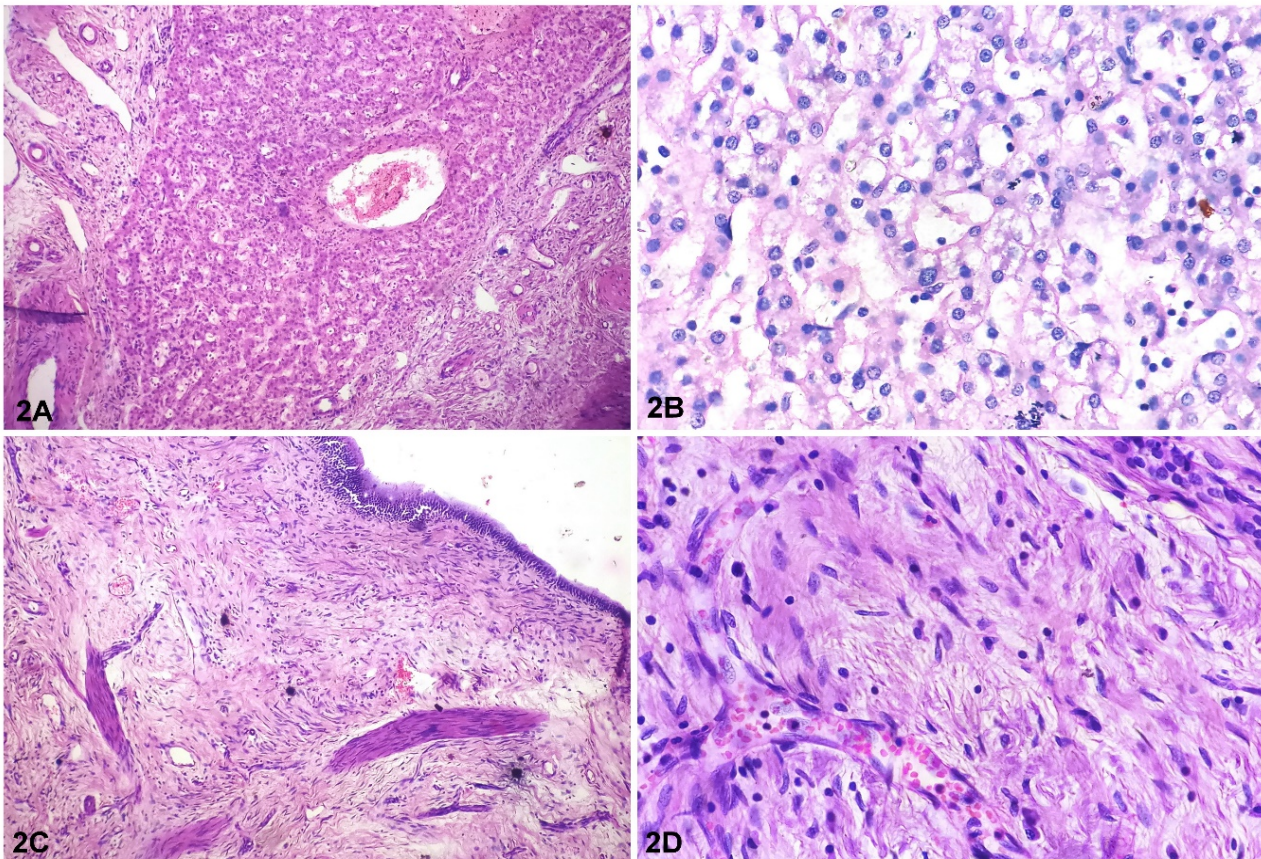


Figure 2. A. Photomicrograph of island of hepatocytes (Hematoxylin and Eosin stain, 100×); B. Photomicrograph of the banal hepatocytes with normal architecture (Hematoxylin and Eosin stain, 400×); C. Photomicrograph showing cyst with cuboidal epithelium and fibromyxoid stroma (Hematoxylin and Eosin stain, 100×); D. Photomicrograph showing stroma with spindle-shaped cells (Hematoxylin and Eosin stain, 400×).

Discussion

It is said that the first case of MHL was reported in 1903 by Mareschand, and he termed it as lymphangioma [5].

It was also known as large cavernous lymphangiomatoid lesion and large solitary bile-cell fibroadenoma [5].

The term Mesenchymal hamartoma of liver was later coined by Edmondson in 1956 [5].

Stocker and Ishak [7] suggested that in MHL, the majority of the proliferative activity occurs before or just after birth, whereas postnatal tumor growth is a result of cyst expansion.

Few reports have documented chromosomal aberrations in MHL namely, balanced translocation t [15,19] and t [11,19] (q13; q13.4) were observed to be the most frequent and recurrent anomaly [4,5].

MHL is more frequent in males.

It typically presents as an abdominal distention or an upper abdominal mass.

It may also present as vomiting, anorexia or failure to thrive.

But pain is not a typical feature of MHL.

Large tumors may increase the intra-abdominal pressure, resulting in engorgement of the anterior abdominal wall veins and cause pedal edema [4,5].

They are typically not associated with other congenital abnormalities analogous to our findings.

However, there are case reports of MHL association with congenital heart disease, intestinal malrotation, esophageal atresia, exomphalos [4,5].

Liver function test are usually normal.

Serum AFP has been found to be raised in some reported cases, and they typically reduced post excision.

The raised AFP is thought to be the result of AFP over-expression by the peritumoral hepatocytes [8] or due to secretion by the proliferating hepatocytes within the loose myxoid stroma of the tumor [9].

Most MHLs appear as hypodense and hypovascular, multilocular cystic or solid-cystic mass on imaging [4,5].

Even in the present case, the laboratory findings were normal, and imaging studies suggested a cystic mass in the liver.

However, definitive diagnosis was not possible on radiological features.

The right lobe of the liver is observed to be preferentially involved (about 75%) in MHL [4] whereas, our case showed a left lobe involvement.

It is frequently a large tumor, weighing anywhere between 400gms to 1,800gms, and reaching a diameter as large as 30cm [5].

MHL is typically a solitary, dark red to red-brown tumor with smooth surfaces.

The cut surface shows a characteristic irregular cystic appearance.

Solid and solid-cystic forms are also known.

The cysts contents are mostly clear or pale yellowish serous fluid or, more rarely, mucoid.

Larger cysts may undergo secondary changes, such as hemorrhage or empyema.

In the stromal-predominant variant, the solid component with multiple small cysts produces a Swiss-cheese appearance.

The connective tissue between the cysts is commonly gray-white to red-purple and usually appears edematous.

Although MHL is regarded as a primarily solitary lesion, but there are reports describing multifocality.

Small satellite lesions may be seen at the margin of the main tumor and have been termed as daughter nodule.

Such nodules may cause recurrence after incomplete resection.

There are also reports illustrating the presence of remote nodules at the periphery of the tumor [4,5].

Histologically, the MHL contains a mixture of various proportions of epithelial and stromal components.

It was proposed that MHL be divided into two variants, i.e., predominant cystic and predominant stromal [5].

The epithelial component consists of relatively normal hepatocytes and bile ducts, which are generally surrounded by a varying quantity of myxoid or fibrous stroma.

Hepatocytes are cytologically banal and are often arranged into small or larger groups, but retain the normal architecture of the liver cell plate.

Bile duct structures are usually arranged in a branching pattern, but may be dilated and tortuous.

They are associated with an acute inflammatory infiltrate.

Cystic spaces are lined by flattened to cuboidal epithelial cells and surrounded by fibrous tissue.

Occasionally, the cysts may lack a distinct epithelial lining.

The stroma contains mesenchymal cells, which are spindle or stellate shaped fibroblasts and myofibroblasts set within an edematous, collagenous, myxoid, or hyalinized stroma.

Numerous arteries, veins, and capillaries may be seen throughout the stroma.

Thick-walled vessels are particularly prominent at the periphery.

The normal portal tracts are generally not present.

Extramedullary hematopoiesis is commonly observed [2].

However, in our case there was no evidence of extramedullary hematopoiesis.

The cystic spaces were lined by biliary epithelium and separated by disorganized hepatic stroma.

Immunohistochemically (IHC), bile ducts in HML is cytokeratin 7 and 19 positive, whereas the mesenchymal cells are vimentin positive.

In a subset, mesenchymal cells may also express SMA, Desmin, A1AT, FGFR, Glypican-3 and Bcl2.

Hepatocytes are positive for Hep-Par1 [5].

The histomorphological features were very pathognomonic in our case; hence IHC was not required for the diagnosis.

HML can be distinguished from other differential diagnoses on the basis of certain key features as summarized in Table 1.

Table 1. Showing various differential diagnoses and their comparison with HML.

Diagnosis	Key histologic features
Mesenchymal hamartoma	Mixture of hepatocytes, cystic change, myxoid to fibrous stroma, ductules.
Hepatoblastoma (Mixed epithelial-mesenchymal)	Epithelial component has fetal and embryonal hepatocytes; mesenchymal component has spindle cells, osteoid and cartilage. Much higher cellularity; multinodularity common.
Infantile hemangioendothelioma	Small intercommunicating vascular channels of various sizes and lined by plump endothelial cells; infiltrative edges entrap ducts and hepatocytes.
Embryonal (undifferentiated) sarcoma	Anaplastic and pleomorphic tumor cells, necrosis common, eosinophilic PASD positive globules.
Bile Duct Hamartoma	These lesions are usually multiple and located in the periphery of portal tracts. Numerous, small to medium-sized, curvilinear, angular or dilated ductules. Varying degrees of dilatation that may eventually lead to cyst formation. They may contain inspissated bile. Not connected to normal biliary tree.
Caroli disease	Dilated ducts may show periductal fibrosis. Proliferation of peribiliary glands may be seen. Inspissated bile or calcareous material may be present in lumina. Cysts connect to the bile duct.
Polycystic liver disease	Diffuse liver involvement by numerous cysts lined by single layer of biliary epithelium. Cysts are not connected to the biliary tree.
Congenital hepatic fibrosis	The portal tracts are expanded by connective tissue, with wide areas of septal bridging fibrosis connecting portal tracts to each other with numerous marginally dilated and ecstatic bile ducts and ductules.

Mixed epithelial-mesenchymal hepatoblastoma is the most similar to MHL.

This also shows a biphasic pattern (epithelial and mesenchymal).

The epithelial component is composed of fetal and embryonal type hepatocytes with immature spindle/stellate to fibrous tissue as the mesenchyme.

The use of immunohistochemical stains alone in this differential diagnosis can be misleading, as both fetal and embryonal epithelial cells stain similar to adult hepatocytes i.e. positive for hepatocyte for Hep-Par1 and cytokeratin 8/18.

Furthermore, the mesenchymal components of MHL and hepatoblastoma are strongly positive for vimentin [10].

Hence, we have to heavily rely on the histomorphology to distinguish this malignant lesion from the benign MHL.

On histology the distinguishing feature is the presence of fetal/embryonal patterns, high cellularity and cartilaginous and osteoid type mesenchymal elements in hepatoblastoma which is absent in MHL.

Infantile hemangioendothelioma can be distinguished by the presence of small interconnecting vascular channels having plump endothelial cells which are positive for CD34 and CD30 (vascular markers).

Since embryonic sarcoma is known to occur in MHL it is important to make a distinction between these two lesions.

The diagnosis of embryonic sarcoma is based on the identification of atypical and pleomorphic stellar cells often observed in a background of bleeding and/or necrosis.

Within these tumour cells and occasionally within the stroma, hyaline globules which are periodic acid-Schiff positive and diastase resistant may be present.

Unlike MHL, an epithelial component is completely lacking in embryonal sarcoma [10].

In our case, both epithelial and mesenchymal components were seen. No mitotic figures, atypia, necrosis or increased vascular components were present.

In conclusion, MHL is a rare liver tumor with varied clinicopathological and radiological appearance.

It may mimic various benign and malignant neoplasms of the liver.

It has an excellent prognosis and is purely a histopathological diagnosis.

Therefore, a clear understanding of this lesion and its differentials on histopathology is important for an accurate diagnosis.

Competing Interest

We declare that we have no significant competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

The authors declare that they have no conflicts of interest.

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