Mesenchymal hamartoma of the left liver lobe in an 18-month-old female patient

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Abstract
Mesenchymal hamartoma of the liver (MHL) is a benign and rare hepatic lesion, with an uncertain etiology and a potential for developing into an undifferentiated distant embryonal sarcoma after an incomplete resection. It mainly presents as progressive abdominal distension with normal blood works. Most cases are diagnosed in the first two years of life, with a higher frequency in boys and on the right liver. We report the case of a mesenchymal hamartoma of the left liver in an 18-month-old girl, with a rough evolution and a literature review. There were performed an abdominal computed tomography (CT) scan and resection of the lesion. The macroscopic and histological examination described a 16.5×17.9×10.5 cm multicystic mass as a MHL lesion. MHLs may have a malignant potential and in the clinical presence of a “neoplastic” syndrome there requires a good diagnosis and drastic surgical treatment.

Keywords: benign tumor, child, liver, mesenchymal hamartoma.

Introduction
In 1956, Edmondson was the first one to describe a cystic mesenchymal lesion as a “mesenchymal hamartoma”, containing a great quantity of serous liquid and mainly composed of connective tissue [1]. The mesenchymal hamartoma of the liver (MHL) is a rare lesion, being the second most common benign hepatic tumor after infantile hepatic hemangioendothelioma [2, 3] and representing about 8% of all pediatric tumors [4]. Its precise etiology is still unknown. However, several theories were postulated among which a developmental abnormality, biliary obstruction, regional ischemia and disordered hyperplasia after liver injury. Moreover, MHL was described as a “true neoplasm” [5], supported by the fact that some undifferentiated embryonal sarcomas (UES) were reported eight years after an incomplete excision of MHL [6]. We report the case of a MHL with a rough evolution and rare presentation in an 18-month-old girl, altogether with a literature review.

Case presentation
An 18-month-old female patient was admitted to the Surgical Department of “Louis Țurcanu” Emergency Children Hospital, Timișoara, Romania, in May for abdominal distension, a large abdominal mass with rapid evolution (three weeks) and poor weight gain (Figure 1). The family and medical history were unremarkable. The onset of the symptoms was three weeks before the hospital admission with a distended abdomen.

On admission, the patient was in a good general health, with normal serum concentrations for all blood work, including liver function studies and tumor markers (alpha-fetoprotein – AFP).

Abdomen and pelvis computed tomography (CT) scan showed a large capsulated hepatic mass (approximately 16.5×17.9×10.5 cm – Figure 2, A–C) multiseptated, with a mixed structure, mostly liquid and a heterogeneous contrast setting. It had a compressive effect over the gallbladder and right ureter. It dislocated to the left the pancreas, the superior mesenteric artery and the upper right quadrant intestines without infiltrating them; and, thus, it shifted the two diaphragms upwards. The vascularity was fueled by a rich collateral network arising from the main elements of the left hepatic lobe. Also, there were described some abdominopelvic ascites. The description was consistent with MHL.

Before surgery, we obtained the consent of the family for surgical procedures and publication of the medical data in the chart. The authors obtained the publishing approval from the Ethics Committee of “Louis Țurcanu” Emergency Children Hospital.

Figure 1 – Clinical aspect of the abdomen before surgery. There may be noticed an excessive distension of the entire abdomen caused by the hepatic tumor.
The patient underwent complete tumor resection by atypical left hemihepatectomy.

The macroscopic aspect of the tumor described a pseudocapsulated multicystic lesion with an elastic consistency (Figure 3, A and B).

For the histopathological study, there were harvested tumor fragments that were subsequently fixed in 10% formalin solution and included in paraffin. There were performed 4 μm sections stained with Hematoxylin–Eosin (HE) and green light trichrome, Goldner–Szekely (GS) technique.

For the immunohistochemical study, the histological sections were collected on poly-L-lysine coated blades, after that they were introduced in a thermostat at 37° C for 24 hours; then, they were deparaffinized, hydrated and incubated in a 1% hydrogen peroxide solution for 30 minutes, for the blocking of the endogenous peroxidase activity. The antigen demasking was performed by boiling in a sodium citrate solution pH 6 for 20 minutes, in the microwave oven, and the blocking of the specific sites was performed by the incubation of sections in 2% skimmed milk for 30 minutes. After the washing, the sections were incubated with the primary antibodies for 14 hours (over night), in a fridge at 4°C, and the next day, there was applied the secondary biotinylated antibody for 30 minutes, at room temperature, followed by an application of Streptavidin–HRP (Horseradish peroxidase) for 30 minutes. The immunohistochemical signal was detected by 3,3’-Diaminobenzidine (DAB) under a microscopic control, the reaction being stopped by a phosphate-buffered saline (PBS) washing, when the interest structures had a maximum of staining. The contrasting was performed with Mayer’s Hematoxylin for 1–2 minutes. After that, there followed the dehydration in ethyl alcohol, xylene clarification and blade assembly by using the DPX environment (Fluka).

For the immunohistochemical study, we used the following antibodies: CD34 (monoclonal mouse anti-human-CD34, clone QBEnd 10, 1:50 dilution), vimentin (monoclonal mouse anti-vimentin, clone V9, 1:50 dilution), α-smooth muscle actin (α-SMA) (monoclonal mouse anti-human muscle actin, clone 1A4, 1:100 dilution), S100 (polyclonal rabbit anti-S100, code Z0311, 1:1000 dilution), cytokeratin (CK) 7 (monoclonal mouse anti-human-CK7, clone OV-TL12/30, 1:50 dilution), CK8 (monoclonal mouse anti-human-CK8, clone 35BH11, 1:100 dilution), CK19 (monoclonal mouse anti-human-CK19, clone RCK108, 1:50 dilution), CK20 (monoclonal mouse anti-human-CK20, clone Ks20.8, 1:25 dilution).

The microscopic study confirmed the presence of a mesenchymal hamartoma of the liver, described as a tumor proliferation of epithelial and mesenchymal elements, showing bile ducts that overlap with no atypical cells placed in a myxoid stroma of myofibroblast-like cells, associated with cyst structures without a well-defined epithelial wall. In general, the tumoral stroma had a heterogeneous aspect, with dense fibribrilary areas, rich in collagen and areas with numerous elongated, fusiform, fibroblast-like and myofibroblast-like cells, with a disordered arrangement (Figure 3, C and D). In the stroma, there were identified isolated areas of hepatocyte cords, with intense lesions of granular and vascular degeneration, with deformed sinusoid, congested, ruptured capillaries, frequently associated to microhemorrhages (Figure 4). Frequently, in the myxoid stroma there were identified canalicular structures with varying diameters, with no atypical changes, considered as remaining biliary canalicules (Figure 5). In some areas of the stroma, there were identified vascular congestions associated to microhemorrhages (Figure 6).

The immunohistochemical examinations showed that a part of the stromal cells were positive to vimentin and α-SMA (Figure 7, A and B), while the canalicular structures were positive to CK7, CK8, CK19 and negative to CK20 (Figure 8, A–D). Also, the epithelium of the biliary canalicules was intensely positive to S100 protein and moderately positive to vimentin (Figure 9, A and B).

Hepatocyte islands we identified were positive for anti-CK8 and S100. They present major injuries of granular and vascular degeneration (Figures 10 and 11). These pathological appearances demonstrate that tumor development is profoundly associated with alterations major liver parenchyma.

The investigation of the vascular component by the marking of endothelial cells with anti-CD34 antibody
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allowed us to observe that the tumor was well-vascularized, with numerous blood vessels arranged disorderly (Figure 12A), sometimes congested (Figure 12B) with a discontinuous wall, thus allowing the extravasation of blood cells in the stroma.

The patient had an uncomplicated post-operative evolution, with a complete remission of symptoms, being discharged two weeks after surgery. Three months after surgery the patient presented no clinical or imagistic (CT scan) signs of tumor relapse (Figure 2D).

Figure 3 (continued) – (C) Overall image of the tumoral stroma. There may be observed multiple cells, heterogeneously disseminated and collagen fiber septa (GS trichrome staining, ×40); (D) Image of myxoid stroma with fusiform fibroblast-like and myofibroblast-like cells surrounding the biliary ducts (GS trichrome staining, ×200).

Figure 4 – Hepatocyte cords with marked granular and vacuolar degeneration and congestion of sinusoid capillaries (HE staining, ×200).

Figure 5 – Myxoid stroma with hemorrhage areas and numerous biliary canalicules (HE staining, ×200).

Figure 6 – Image of myxoid stroma associated with vascular congestion and microhemorrhages (HE staining, ×200).
Figure 7 – (A) Stromal and canalicular cells positive to vimentin (Anti-vimentin antibody immunostaining, ×200); (B) Stromal cells positive to α-SMA (Anti-α-SMA antibody immunostaining, ×200).

Figure 8 – Biliary canalicules with epithelial cells positive to CK7 (A, ×200), CK8 (B, ×200) and CK19 (C, ×200), and negative to CK20 (D, ×200).
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Figure 9 – (A) Canalicular epithelium positive to S100 protein (Anti-S100 antibody immunostaining, ×200); (B) Canalicular epithelium moderately positive to vimentin (Anti-vimentin antibody immunostaining, ×400).

Figure 10 – Island of remaining hepatocytes with signs of granular degeneration, intensely positive to CK8 (Anti-CK8 antibody immunostaining, ×200).

Figure 11 – Cords of hepatocytes with vacuolar degeneration positive to S100 protein (Anti-S100 antibody immunostaining, ×400).

Figure 12 – (A) Tumoral stroma with a well-developed vascular network (Anti-CD34 antibody immunostaining, ×200); (B) Congested blood vessels (Anti-CD34 antibody immunostaining, ×200).

Discussion

Of all hepatic benign tumors, MHLs account for 18–29% [7, 8]. Most cases are generally diagnosed during the first two years of life, but there have also been reported during the prenatal period [9–11] and adulthood, as well [12, 13], with a male to female ratio of 3:2 [4, 14, 15]. They are rapidly growing into a “tumor-like” formation, but non-malignant malformations that are usually multicystic and more commonly reported in the right liver (right to left liver ratio 6:1) [3, 4, 15].

MHLs are variable in size from tiny lesions to large tumors (at least 8–10 cm) [3]. Kim et al. [16] found that in 85% of patients tumors are larger than 10 cm.
MHLs usually present as a progressive abdominal distension and/or a smooth abdominal mass associated with symptoms like abdominal pain, anorexia, nausea, vomiting, fever, constipation, diarrhea and poor weight gain/weight loss. In some cases due to tumor expansion, it may result in various complications such as ascites, jaundice, or congestive heart failure, engorged veins over the anterior abdominal wall and lower limb edema and/or respiratory distress [1, 4, 17–26].

Laboratory studies usually are normal, including the liver function studies. The AFP level can be moderately high and it returns to normal after resection [27, 28].

MHLs can be intrahepatic or pedunculated. Ultrasound (US), CT and magnetic resonance imaging (MRI) examinations have all been used for diagnosis. On CT and US, MHLs present as a multiseptated, multicyclic mass located in the periphery or scattered throughout the liver [2].

The management of MHLs remains controversial. A complete tumor resection, as a hepatic lobectomy or non-anatomically/atypically with a rim of normal tissue is desirable, leaving an excellent prognosis and a satisfactory long-term follow-up [17]. In massive lesions with multiple cysts, the use of ultrasound-guided, intra-operative aspiration of the cysts was reported, making it easier to resect the whole tumor [29]. Rarely, in inaccessible tumors, liver transplantation may be needed [18]. On the other hand, laparoscopic liver resection for MHL has been reported [30]. However, marsupialization and enucleating are surgical options in very large, two-lobe tumors that are not amendable to resection [26, 31, 32]. In these latter cases, the recurrence or the development of undifferentiated embryonal sarcoma may occur, thus a careful long-term follow-up is important.

Macroscopically, the cut surface reveals multiple cysts that can measure from a few millimeters to 15 cm, containing serous to gelatinous material and a gray-tan to yellow lining. Cysts increase in number with age. Microscopically, as the name suggests, the tissue consists of a mixture of bile ducts, liver cell cysts, mesenchyme, with occasional areas of extramedullary hematopoiesis. The cysts may be dilated bile ducts, or amorphous cysts surrounded by mesenchyme. Elongated or tortuous bile cysts may be dilated bile ducts, or amorphous cysts. Occasional areas of extramedullary hematopoiesis. The epithelial component was represented by islands of hepatocyte cords, with lesions of granular and vacuolar degeneration and biliary ducts. Similar to other studies, we showed that the cells of the bile canalules were positive to cytokeratins 7, 8 and 19 and negative to cytokeratin 20 [39–41].

Conclusions

An exact relationship between MHL and UES is far from being demonstrated; however, evidence suggests that MHL may indeed represent a “true neoplasm” with malignant potential and clinical presentation of such cases may bring a different view in further studies. Thus, we present a case of a MHL as a large atypical abdominal mass in the upper right quadrant of an 18-month-old girl, evolving from the left liver with a rapid evolution and asymptomatic ascites.

Conflict of interests

The authors declare that they have no conflict of interests.

References

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Received: January 16, 2016

Accepted: October 3, 2016