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# Mesenchymal Hamartoma of the Liver in Children Single Center Experience

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## Abstract

Mesenchymal Hamartoma (MH) of the liver is the rare congenital lesion, solid, cystic, or mixed type. It is usually recognized in early childhood (before 3 years of age). Histologically, the MH is a benign lesion but undifferentiated sarcoma in mesenchymal hamartoma was described in several cases. Some features of MH can be potentially locally malignant. Quick enlargement of the tumor may be the cause of compression of the liver, can lead to respiratory insufficiency, ileus or abdominal compartment syndrome. Differential diagnosis is difficult, especially when tumor consist of mesenchymal stroma elements. Resection of the tumor is usually the treatment of choice, but not in all cases is possible (it depends on type, size and location of the tumor). Between 1986 and 2015 we treated 21 patients with MH of the liver. Surgical treatment included cystic drainage and obliteration, marsupialisation, tumor resection (enucleation, liver resection and total hepatectomy with liver transplantation). Diagnosis of MH was confirmed in all cases, coexisting infantile hemangioma was found in one child. All patients, except one are alive in good general condition. One patient died due to secondary biliary cirrhosis after extensive tumor resection. Surgical resection of the MH is often difficult due to irregular form of the tumor and no clear border between tumor and normal liver. Complications after resection are possible especially if tumor is located in segment IV. Non-resectional treatment is usually not effective.

**Keywords: Mesenchymal hamartoma of the liver; Diagnosis; Treatment; Outcome**

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## Introduction

Mesenchymal Hamartoma (MH), of the liver is a benign liver tumor and it accounts for 3% to 8% of all liver tumors in children. The tumor is usually diagnosed before the age of 3 years (85%). It can be also recognized in prenatal examinations as well as in adults [1]. There are no convincing data about origin of MH, that could confirm whether the tumor is a congenital developmental abnormality or a benign tumor [2,3]. It occurs in three forms: cystic - mesenchymal, or with a predominance of cysts (single or multiple) or solid mesenchymal lesions. The MH lesion is more often located in the right lobe (75%), however it can be located in any part of the liver, like in liver hilum or in almost the whole organ. In many cases MH present as giant tumor with a diameter of up to 20 cm to 30 cm, filling almost the entire abdominal cavity. MH is a histologically benign lesion, consisting of a mesenchymal stroma, abnormal elements of the bile ducts, blood vessels and hepatocytes. Cysts usually develop from enlargement of bile ducts or as a result of cystic degeneration of the mesenchymal stroma [4]. Small MH usually is symptomless, can be diagnosed during abdominal ultrasonography for other causes or routine prenatal examination. Large MH are usually symptomatic, symptoms are consequence of pressure on other organs in abdominal cavity, diaphragm and secondary to diminished chest volume. Patient can present respiratory difficulties, circulation insufficiency, problems with intestinal tract and bile ducts. Sometimes haemorhage to the tumor or intra abdominal bleeding may occur due to tumor's rupture. In some cases undifferentiated sarcoma arising from MH or as coincidence with MH was described [5-7]. The aim of the study was retrospective analysis of case histories of children with MH, which were treated in our department, concerning diagnosis, treatment, complications and late results.

## Material and Methods

Between 1986 to 2015 we treated 21 children with diagnosis of hepatic mesenchymal hamartoma in the Department of Pediatric Surgery and Organ Transplantation. Diagnosis was made prenatally in one child, in 13 pts at the age below 1 year. There were 11 girls and 10 boys. Age of children at the time of treatment was between 7 days and 9 years (mean 24, 8 months, median 7, 93). Retrospective

analysis of case histories was performed. We analyzed: clinical symptoms, laboratory tests, diagnostic images, localization and tumors size, type of tumors, methods of treatment, complications, and histopathological reports, early and late follow up. Approval from the institutional Bioethical Committee of The Children's memorial Health Institute for a retrospective medical record review was obtained.

## Results

### Clinical symptoms

Clinical symptoms observed in our patients: abdominal distension (8 pts), hepatomegaly or abdominal tumor (7 pts), urinary obstruction (3 pts), respiratory distress (3), ileus (1), feeding abnormalities (3), jaundice (1), circulatory insufficiency (1), abdominal wall vessels dilatation (1). Four patients with MH were asymptomatic. In one patient diagnosis of MH was made at age of 9 years, during follow-up after treatment of sarcoma of urinary bladder. There were no abnormalities in biochemical lab tests except anemia in one patient, slight elevation of aminotransferases in another one, and elevated serum bilirubin concentration in another. Alpha-Fetoprotein (AFP) was slightly increased in one patient.

### Position, size and type of tumors

In 14 children tumors were localized in the right lobe, in 5 in the left lobe. In one patient tumors emerged from the lower segments of both lobes and in one they occupied the entire liver. Four tumors were exophytic others were located within the liver. On diagnostic imaging 12 tumors were polycystic, 5 cystic-mesenchymal and 4 solid-mesenchymal. In 14 patients tumors were huge, exceeding 10 cm in the longest dimension. In 2 patients huge cysts filled the entire abdominal cavity.

### Diagnostic procedures

All patients underwent abdominal ultrasound examination, in 19 patients computed tomography (CT scan) was performed, in 5 hepatobiliary scintigraphy and in 2 angiography (Figure 1 and 2). In 2 patients surgical biopsy of the tumor was done, which confirmed the diagnosis. Cytological examinations of fine needle biopsy (in 3 patients) and cystic fluid (in 1 patient) were non-diagnostic.

### Methods of treatment

All patients underwent surgical treatment. Primary surgical resection was performed in 16 children, including enucleation of the tumor in 7 cases and in 9 patients, various anatomical or non anatomical liver resections (Figure 3). In 5 children multiple procedures were performed including drainage, obliteration, marsupialization and resection. In one baby girl with tumor diagnosed prenatally multiple surgeries including enucleation, resection, left hemihepatectomy and drainage, obliteration, marsupialization and resection of the MH remnant were done. She was additionally diagnosed with severe hyperinsulinemic hypoglicemia and underwent subtotal pancreatic resection. In three patients initially treated unsuccessfully with drainage, obliteration or marsupialization of the cysts secondary surgery was performed. Two of them underwent hemihepatectomy and one due to involvement of the whole liver and proceeding to multiorgan failure was qualified for total hepatectomy and emergency liver transplantation. One child with single cyst was treated exclusively with its marsupialisation (Figure 4).

### Complications of the treatment

There were no complications in 16 patients after surgical treatment.

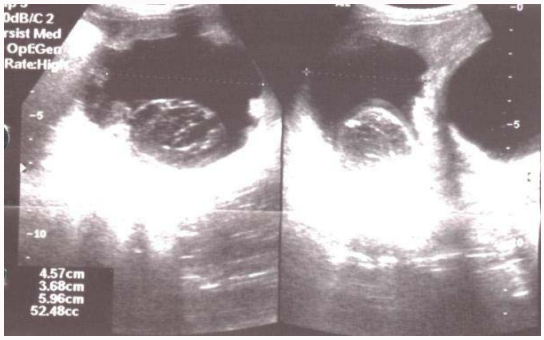


**Figure 1:** Cystic-solid lesion. Ultrasound image after drainage patient 11.

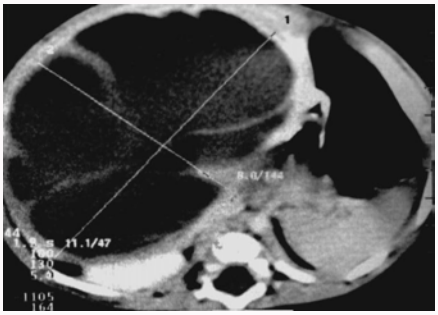

**Figure 2:** CT scan. A giant cystic lesion of the right liver lobe (patient 10).

One patient after hemihepatectomy developed biliary fistula, which was closed surgically. Three patients (two after hemihepatectomy, one after bisegmentectomy) developed cholestasis which eventually recovered and 2 of them liver cirrhosis. These two pts were qualified for liver transplantation. One of them died on waiting list for liver transplantation. Two children received liver transplantation - one due to biliary cirrhosis, and another one due to involvement of whole liver by MH and multiorgan failure.

### Follow-up

Follow up of all patients range between 4,3 years to 33,4 years (mean 14,31 yrs, median 12,93 yrs). One patient is doing well and without any symptoms after subtotal resection of the tumor. We did not observe tumor recurrence or malignancy in any case. One child died while on the waiting list for liver transplantation. In summary 20 out of 21 patients are alive and well with excellent liver function including two 18,3 years and 17,5 years after liver transplantation (Table 1).

## Discussion

The mesenchymal hamartoma of the liver is the focal growth of normal, mature cells and tissues, but of disturbed architecture. The tumor is made of loose or mucoid connective tissue containing different amount of blood vessels, cystic lymphatic spaces, bile ducts and normal hepatocytes [4]. This tumor is considered as a developmental malformation or by some authors as a benign tumor [2-4]. Developmental theories include local ischemia, bile drainage disorders, and local disorganized growth as a response to "trauma" during development. In many MH cells desmin and alpha-actin activity are detected. Under normal conditions, these substances are only detected in to cells (hepatic stellate cells). It has been shown that activated Ito cells undergo phenotypic transformation into myofibroblasts that are involved in liver fibrosis. Activation of Ito

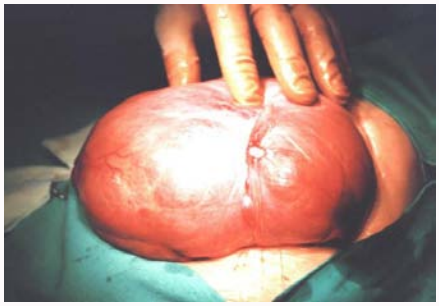

**Figure 3:** Intraoperative view on the MH in patient 3.

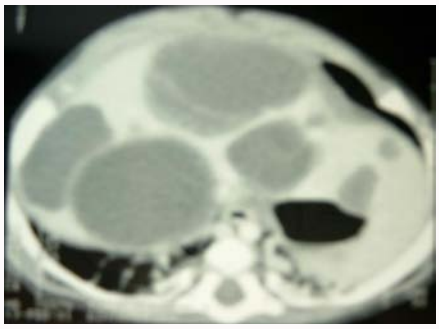

**Figure 4:** CT scan. Multicystic tumor Patient 11 eventually underwent liver transplantation due to multiorgan failure after ineffective multiple drainage attempts.

cells by some toxic agents can contribute to the development of MH [8]. The aneuploidy of DNA and translocations on the long arm of chromosome 19 found in the nuclei of some hamartoma tumors supports for cancerous origin of MH [9]. Some researchers believe that the solid tumor is a "younger" form, which is then transformed into a cystic form, which clinically is confirmed by more frequent detection of the solid form at a younger age. Other authors do not confirm this view [10]. MH is most often detected in small children, up to 2 years, it is already diagnosed during pregnancy, and it may be accompanied by generalized swelling of the fetus, placental thrombosis, placental hypertrophy or maternal toxemia. During the fetal period, both the rapid growth of the tumor and its partial regression may occur. This tumor is also, usually accidentally, found in adults. Mesenchymal hamartoma may not show any clinical symptoms, however large tumors cause compression symptoms leading to difficulty in breathing (pressure on the diaphragm), reduction of venous return (pressure on the inferior vena cava), mechanical obstruction of the gastrointestinal tract, obstruction of urinary outflow or obstructive jaundice. We have met all these symptoms in our patients. There may also occur bleeding into the tumor associated with its rapid enlargement and anemia, as well as thrombocytopenia. In some cases, the two most common benign liver tumors coexist: MH and infantile hemangioma: foci of a hemangioma within the MH cyst or as separate tumors [11]. The results of laboratory tests in children with MH are usually within the normal range. Anemia or mediocre elevation of liver function tests may occur. Increased serum Alpha-Fetoprotein (AFP) concentration along with young patient's age may lead to misdiagnosis of hepatoblastoma and initiation of chemotherapy [12,13]. In one of our patients, treated in the 1980s, such an error was made, which did not lead to a reduction of lesion. In the study of Chang et al, the level of AFP was higher in patients with solid lesions (in 4 of 13 patients AFP concentration was above the age standard) [10]. Although very uncommon, cystic or mixed lesions that look typically like MH turn out to be a rare form of fetal hepatoma (hepatoblastoma). Imaging examinations: Ultrasonography (USG), Computed Tomography (CT), Magnetic Resonance Imaging (MRI) allow in most cases for diagnosis of MH and its size and localization description. Tumors with stroma dominance (solid) have a different picture than cystic tumors, but no other clinical course is observe [10,14,15]. A typical ultrasound image of MH is a poorly vascularized polycystic formation with thin movable partitions, with hyperechogenic nodules in the septum. There are almost never any calcifications [16,17]. A typical image in computed tomography is a single or multiple cyst containing thin septum and solid elements that are not uniformly strengthened after contrast administration. In MRI, the changes are hypointense in the T1 projection and hyperintensive in the T2 projection. In imaging diagnostics, the lesion can sometimes imitate cancer metastasis to the liver. It should be taken into account when assessing the severity of the existing (other) cancer [18]. A hepatobiliary scintigraphy allows to exclude from diagnosis cystic changes in the bile ducts [1,18]. To plan the MH liver resection, the most accurate imaging diagnostics is needed to determine the tumor position relative to the liver segments, bile ducts and vessels (angio-CT, angio-MRI, and cholangio-MRI). MH should be differentiated with other nodular and cystic hepatic lesions occurring in children, such as hepatoblastoma, hepatocarcinoma, hemangiomas, sarcomas, focal nodular hypertrophy, neuroblastoma metastases, abscess, cystic echinococcosis, teratoma, lymphangioma, biliary cyst, or polycystic liver disease. Although imaging diagnostics, laboratory or serological tests allow the diagnosis or exclusion of some pathology with high probability, the histopathological examination remains the decisive one. There are reports of misleading use of chemotherapy when MH was considered to be hepatoblastoma, as well as discontinuation of treatment of cystic lesion, which later turned out to be a malignant tumor. That is why it is so important to determine the diagnosis before deciding how to proceed, especially if conservative treatment is being considered. The most reliable in this case is the surgical laparoscopic biopsy (laparoscopic). Fine-needle aspiration biopsy, both in the literature and in our experience do not allow for diagnosis [19-23]. Most authors believe that the treatment of choice for MH is complete resection due to potential tumor recurrence. In one case of recurrent tumor chromosomal translocation was found (q13, q13.3) [24]. In cases where, due to the size or location, the complete excision is impossible, it is proposed to enucleate the tumor, partial or staged excision, possibly marsupialisation or obliteration of cystic lesions [1]. In the presented material, enucleation of the tumor was performed in 6 cases and in the postoperative follow-up period of 2 years to 20 years, we did not observe recurrence in either of them after this treatment. Marsupialization or cyst drainage was performed in 4 patients. In 3 cases, tumor regrowth quickly occurred. The attempts of obliteration were ineffective. Some authors suggest observation of asymptomatic tumors. There are cases of decreasing and partial calcification of lesions during follow up, but no complete regression of change was observed [25,26]. It is worth noting, however, that asymptomatic changes are usually smaller in size and located peripherally, which gives excellent conditions for complete resection, which can now be performed also by laparoscopic method, especially in the context of the possible development of MH-based malignancy or its coexistence [5-7,27]. On the other hand, the reduction of the originally "inoperable" tumor after the observation period may give a chance of its complete removal [25]. The discussion regarding

**Table 1:** Follow up of all patients.

| Patient | Age AT primary operations (months) | Surgical treatment | Follow up (years) | Actual status |
|---|---|---|---|---|
| 1 | 6 | segmentectomy | 17,74 | Very good |
| 2 | 97 | segmentectomy | 22,28 | Very good |
| 3 | 4 | tumor enucleation | 14,86 | Very good |
| 4 | 48 | tumor enucleation | 27,78 | Very good |
| 5 | 24 | left hemihepatectomy | 21,7 | Very good |
| 6 | 36 | right hemihepatectomy | 15,39 | Very good |
| 7 | 84 | enucleation | 33,44 | Very good |
| 8 | 6 | cysts drainage - Right hemihepatectomy | 31,53 | Very good |
| 9 | 6 | bisegmentectomy | - | Dead |
| 10 | 84 | right hemihepatectomy – liver transplantation | 18,31 | Very good |
| 11 | 7 | marsupialisationa and multiple cyst drainage –liver transplantation | 17,55 | Very good |
| 12 | 4 | resection of segments 2 and 3 and tumor enucleation | 4,45 | Very good |
| 13 | 26 | tumor enucleation | 4,36 | Very good |
| 14 | 28 | enucleation and non anatomical resection of segments 4,5,6 | 5,12 | Very good |
| 15 | 0,4 | tumor resection (3 attempts) | 10,72 | Very good |
| 16 | 2,5 | segmentectomy | 6,61 | Very good |
| 17 | 4 | tumor enucleation | 8,94 | Very good |
| 18 | 37 | marsupialisation | 11,00 | Very good |
| 19 | 8 | tumor enucleation | 5,07 | Very good |
| 20 | 10 | tumor enucleation | 4,92 | Very good |
| 21 | 0,2 | tumor resection (egzophitic tumor) | 4,34 | Very good |

potential carcinogenesis within the MH remains unresolved. It was observed that there is similarity in the structure of MH and undifferentiated sarcoma, which occurs mostly at the age of 6-10 years, grows rapidly, may infiltrate diaphragm and develop lung and bone metastases. The prognosis of undifferentiated liver sarcoma is not always good [27,28]. Both MH and sarcoma contain mesenchymal tissue and benign epithelial elements. However, the mesenchymal stroma in the sarcoma shows signs of malignancy. There are also histogenetic similarities. Both in MH and undifferentiated sarcoma there is a 19q13 translocation. Although these are isolated cases, both sarcoma development after several years of MH removal has been observed [29] and coexistence of MH formation along with sarcoma [5-7,27]. This indicates the necessity of careful conclusion from the biopsy result and the consideration of each MH as a change that predisposes to the development of malignant tumor. Also cystic forms of undifferentiated sarcoma were described, treated initially as benign lesions [22]. Should, however, strive to remove MH at any price, if the probability of developing malignant neoplasm within is very low, and the risk of complications after completing surgery in some patients significant? Mesenchymal hamartoma is a tumor located quite often in the central part of the liver (segment IV), modeling the vessels and bile ducts. Its boundaries within the liver parenchyma are not macroscopically clearly visible. It results in a relatively high risk of postoperative biliary complications in these patients and its consequences. In rare situations tumor may cause life-threatening symptoms as in some patients. In one of our patients quick enlargement of the multicystic tumor resulted in obstruction of the gastrointestinal tract, in two patients in the ultrasound showed hydronephrosis, and in one the increasing respiratory effort with hypotonia and cholestatic jaundice. In these children the tumors were very large or located in the vicinity of the liver hilum, which is the most difficult for resection. As mentioned earlier in these cases attempts were initially made to reduce the symptoms by cysts drainage, but new changes quickly developed. Two of these children underwent right-sided hemihepatectomy and one had tumor resection including IV and VIII segment. In the fourth patient no resection was attempted at all because the giant tumor occupied the entire liver. This patient was directly qualified for liver transplantation. All liver resections (2 hemihepatectomies and 1 bisegmentectomy), which were later complicated by biliary cirrhosis were performed in patients with pronounced clinical symptoms. Liver transplantation in the case of a histologically benign tumor is a non-standard treatment, but sometimes it remains the only option to deal with extensive lesions that cause symptoms of abdominal tightness, and whose size and location prevent their removal [30-32].

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