Infantile hepatic hemangioendothelioma: Report of two cases
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SUMMARY
We described two cases of infantile hepatic hemangioendothelioma: one with a solitary lesion and the other with multicentric lesions. Clinical presentation was with no liver symptoms in case 1, and hepatomegaly, failure to thrive, and palpable abdominal mass in case 2. Diagnostic imaging revealed single tumor formation in case 1 and multiple nodules in the liver in case 2. Dilemmas related to nature of the tumor were solved by microscopic analysis. The patient with the clinical appearance of a single lesion was successfully operated. The patient with multiple lesions in the liver tissue showed complete involution after corticotherapy.

Key words: Hemangioendothelioma; Infant; Liver Neoplasms; Case Reports

INTRODUCTION
Infantile hepatic hemangioendothelioma (IHH) is a vascular tumor originating from the mesenchymal liver tissue. It is usually considered as a tumor with a benign course. Histologically, IHH can be present in different, more or less immature types of hemangioma. It usually manifests in infants up to 6 months of age and shows rapid growth. In addition, spontaneous involution has been noticed in the period between 12 to 18 months of life, probably due to thrombosis and scar formation (1, 2). Clinical presentation of IHH is variable: parents or doctors can palpate hepatomegaly or abdominal mass, some hematologic abnormalities may be seen in laboratory investigation, or lesion may be asymptomatic and discovered incidentally (3). IHH may also be manifested as solitary or multicentric lesions. The tumor is detectable by fetal ultrasonography (4, 5).

CASE 1 – SOLITARY IHH
After 39 weeks of gestation, a boy was born with Apgar score 7/8 and body mass 3280 g. During pregnancy, mother, aged 16 years, was treated for epilepsy using valproic acid and lamotrigine. After the birth, the respiratory distress caused by the partial left sided pneumothorax was observed so the newborn was transferred to the tertiary pediatric centre where the pneumothorax was treated in the Intensive Neonatal Unit. Blood and urine analyses were suitable for diagnosing. Ultrasound (US) examination of the abdomen showed one subcapsular well-defined hypodense lesion of a 40 mm diameter in the segment 8 of the liver. After contrast media administration, the lesion showed early and high attenuation whereas the central zone showed complete involution after corticotherapy.

Figure 1. Axial CT scan with well-defined mass in the right lobe of the liver

The laboratory analysis showed: alpha-fetoprotein (AFP) 431.6 IU/mL (normal value for neonate is 48.4±34.71 IU/mL), beta-human chorionic gonadotrophin (HCG) 0.16 IU/L (normal value for male neonate is <=50 IU/L), RBC 3.12x1012/L, WBC 8.9x109/L, HGB 86 g/L, CRP normal.

The microphotograph of liver tissue with tumor consisting of numerous capillary blood vessels and preserved biliary ducts (CD 34 x 200)

Figure 2. Microphotograph of liver tissue with tumor consisting of numerous capillary blood vessels and preserved biliary ducts (CD 34 x 200)
vascular spaces with normal endothelial cells. The surrounding liver tissue contained normal connective tissue and bile ducts. Immunohistochemical staining revealed that tumor cells were CD 34 positive and smooth muscle actin (SMA) positive. The finding suggested hemangioendothelioma of the liver (Figure 2). The postoperative course in the intensive therapy unit was uneventfully good, oral intake of fluids and food was satisfactory, and the wound healed primarily.

The patient had regular clinical checkup: two years later laboratory and ultrasound findings excluded the recurrence and malignancy.

**CASE 2 – MULTIFOCAL IHH**

A six-month-old boy was admitted to the hospital for repeated bronchitis and failure to thrive. On admission the child’s body mass was 3,780 g. The clinical examination revealed palpable abdominal mass on the right side. Laboratory data showed a significant anemia with 2.8x10^{12} / L. Abdominal US showed the presence of numerous hypodense formations in his liver. CT scan confirmed the presence of a number of deposits in both lobes of the liver (Figure 3).

Anemia was treated by preoperative packed red cell transfusion and the patient was prepared for laparotomy. After upper transverse incision, the liver was observed with irregular surface with numerous nodular yellowish formations. Mesenteric lymph nodes were enlarged. There was no tumor or other lesions on the organs in the abdominal cavity and retroperitoneal space. A piece of tumor tissue and one mesenteric lymph node were removed for histopathology examination. The procedure was completed with preventive appendectomy. The postoperative period was good.

Other laboratory findings were normal and the patient began to recover quickly with adequate oral food intake. The histopathological finding showed a liver tumor: lesion consisted of vascular spaces incorporated in fibrotic stroma. Endothelial cells were edematous. Normal bile ducts were noticed. The findings indicated IHH (Figure 4). Lymph node showed no signs of malignancy. The postoperative period was successful and the child was discharged, his body mass being 4,530 g. Corticotherapy (Prednisolone 2-10mg/kg/day) was suggested for the next two months and the ultrasound check up followed. At the age of 12 months, the child's body mass was 9,990 g with a satisfactory liver function. The follow-up demonstrated the tumor’s complete regression and no complications.

**DISCUSSION**

This vascular hepatic lesion has alternative names: liver (hepatic) hemangioma, cavernous hepatic hemangioma, infantile hemangioendothelioma, multinodular hepatic hemangiomatosis (6, 7). Usually the lesion is present in the first six months of life (7-10). IHH is the most common benign hepatic tumor found in infants, but malignant transformations have been reported (1, 11, 12). Hemangiomas can present themselves as multicentric or solitary type of lesions. Tumor regression within a few months is possible particularly in asymptomatic cases (13). IHH has two growth phases: the initial rapid growth phase during first 6 to 12 months of life is followed by a period of spontaneous involution, usually within the age of 12 to 18 months (14).

Our patient with a single lesion developed tumor in his early neonatal period. Repeated US examination prior to his second week of life did not show any lesion on the liver. In the patient with multilocular hepatic lesion, the disease was detected by US examination at his sixth month.

The clinical manifestation of IHH is variable depending on tumor size, localization, and complications (5). The tumor may be asymptomatic and discovered incidentally. More often tumor is large and manifests as hepatomegaly, abdominal distention, or a palpable upper abdominal mass. Infants with IHH may have anemia, thrombocytopenia, disseminated intravascular coagulation and bleeding, and signs of heart failure (15). Arteriovenous shunting within lesions results in decreased peripheral vascular resistance and increased blood volume. High cardiac output is required to maintain vascular bed perfusion, which may lead to congestive heart failure in half of the patients (1, 2). Hematologic abnormalities include anemia and especially thrombocytopenia caused by trapping of thrombocytes within hemangioendothelioma with consumptive coagulopathy (Kasabach-Merritt syndrome) (1, 2). Other symptoms and signs such as jaundice, elevated transaminase levels, failure to thrive, respiratory difficulty, or rarely hemoperitoneum due to tumor rupture may also be present. Serum AFP levels are usually normal or slightly increased. However, reference range for AFP for healthy infants varies greatly. Although AFP levels in most healthy newborns is 48.4 ±34.71 IU/mL, they can be as high as 100 000 IU/mL or greater in the normal full term infant (16-18).
Case report

Our patient with a single lesion was completely asymptomatic and the clinical finding was accidental. The patient with multiple lesions showed failure to thrive, recurrent respiratory infection, anemia and slightly enlarged liver. Cardiac problems, consumptive coagulopathy or liver function deterioration were not noticed, and neither were cutaneous hemangiomas.

In histopathological analysis, IHH manifests as a mesenchymal tumor composed of a connecting network of predominantly small-diameter vascular channels lined by endothelial cells (19). Vascular spaces can be small, capillary, and sinusoidal type, or can be large, cavernous type (20). Areas of varying degrees of hemorrhage, necrosis, calcification, thrombosis, or fibrosis are often present in large tumors. In both our cases, the given type of lesion was considered a benign process (21). There are two histopathological types of IHH:

Type I – is often calcified; it is represented with multiple vascular channels with endothelial lining and fibrous stromal separation containing bile ductules between channels.

Type II – tissue is more disorganized and pleomorphic with hypercellular pattern; there are no stratal bile ductules (1). It is speculated to be an aggressive and potentially malignant form of IHH.

In our cases, nonmalignant cells were found in both patients, but the borderline findings in the solitary type IHH recommended regular clinical and ultrasound checkups.

Initial diagnostic procedure is usually ultrasound abdominal examination. A solid, well-defined heteroendochenegeous hepatic mass can be seen in a single type lesion as it was in our case 1. Hypoechoic rim demarcates the tumor mass from normal liver parenchyma. Vascular structures in the adjacent part of the left hepatic lobe can be compressed by the mass. Intratumoral hypoechoic structures represent small calcifications. The spleen, kidneys, and adrenal glands are usually normal. In multiple type lesions a few round lesions can be detected in the liver tissue, or the entire liver may be diffusely involved with innumerable tumor nodules as it was seen in our second case.

Prenatal ultrasound US may reveal IHH as a liver mass followed by cardiomegaly, ascites, and anasarca. Polyhydramnios caused by fetal hydrops can be associated with IHH (22,23). We have no cases diagnosed prenatally. Chest radiography is necessary to exclude congestive heart failure. Our patients had no signs of cardiac problems.

The results of abdominal CT showed low-attenuated mass and calcification in approximately 50% (20). After intravenous administration of contrast media, peripheral enhancement is present. Central portion often contains area of infarction and hemorrhage, or the necrosis appears hypodense on the delayed scans (3, 21, 24).

Distinguishing IHH as primary hepatic lesion from primary malignant liver tumor is essential. Differential diagnosis of IHH includes hepatoblastoma, metastatic neuroblastoma and mesenchymal hamartoma (1, 2). In the case of hepatoblastoma, (malignant embryonic tumor), it is often associated with persistent and markedly elevated AFP levels (1, 25). In metastatic neuroblastoma urinary levels of catecholamines are elevated, adrenal mass is present in abdomen, usually with diffusely involved liver (2, 22).

Mesenchymal hamartoma is a rare benign neoplasm, probably a congenital malformation. It usually shows a cystic or multicystic appearance. If solid components predominate, it may be difficult or impossible to distinguish these three tumors from one another (3, 26). In a histologic study it has been suggested that a congenital hamartomatous lesion may develop as: hemangioendothelioma, angiosarcoma, or tumorous lesion with three types of tissue (‘three types tumor’) (27).

Since biopsy is not always possible, the treatment decision is often made without histologic information (25).

Patients with IHH have good prognosis: a proliferative phase with rapid growth of tumor is noted in the first six months after birth and is followed by spontaneous regression up to the first year of life (28) becoming obliterate by diffuse fibrosis (27). If the child is asymptomatic there is no need for treatment. In those patients clinicians are responsible for regular follow-up imaging studies so as to have a confirmation that tumor is in spontaneous regression.

IHH is often treated conservatively, but if the conservative treatment fails, alternative methods are necessary. Procedures of treatment include medical therapy (corticosteroids, interferon or cytotoxic therapy), radiotherapy, and surgery (ligation of the hepatic artery, liver resection or liver transplantation) (29-32).

Medical therapy includes steroid and interferon alpha-2a or alpha-2b therapy to accelerate the natural involution of the tumor, and radiation therapy or chemotherapy, as well as supportive care for congestive heart failure and coagulopathy (1, 2).

Corticosteroid therapy is the first step to treat the complications: Prednisolone (2-10 mg/kg/day) for 6 weeks on the average may hasten involution by inhibiting proliferation of endothelial and smooth muscle cells. Prednisolone may cause side effects as hypertension, hyperglycemia, sepsis, especially when it is given to infants (33). Clinicians should take extra care and be aware of these side effects.

When IHH is not responsive to high-dose steroids, interferon alpha-2a or alpha-2b may be another choice to inhibit endothelial cell proliferation, migration and angiogenesis. Potential adverse effects include elevation of liver enzymes, bone marrow depression, alopecia, diminished appetite, and psychomotor regression (34).

In case of the clinical triage of congestive heart failure, hepatomegaly and associated cutaneous hemangioma, a more aggressive therapy including steroids can be applied (35, 36).

The experience of successful use of metronomic therapy with cyclophosphamide and tamoxifen has been reported (37).

In case of rapid deterioration of cardiac status or medical therapy failure, interruption of the arteriovenous shunt by hepatic artery embolization should be considered. Obliteration of vascular channels accelerates tumor involution. If a tumor is large, common hepatic artery proximal fistula can be ligated (38, 39), or surgical resection performed (33).

Transcatheter hepatic artery embolization to reduce tumor vascularity and arteriovenous shunting may be performed prior to surgical intervention in patients who fail to respond to medical treatment. Surgical resection is indicated if life-threatening symptoms are present or if the mass cannot radiologically be distinguished from malignant tumor (40).

Orthotopic liver transplantation may also be performed if all other therapies fail (41).
Complications can lead to cardiac failure, disseminated intravascular coagulopathy and thrombocytopenia; also high mortality rate has been recorded (1).

Radiotherapy carries a variable risk of sequelae like cirrhosis, angiosarcoma and leukemia, so it should not be considered suitable for infants unless other therapies are contraindicated or unsuccessful (42, 43).

IHH is believed to be a birth defect and a benign tumor. Depending on patient’s clinical status prognosis can be good or very poor and uncontrollable congestive heart failure, numerous complications, and malignant transformation to angiosarcoma may occur.

Conflicts of Interest
We declare no conflicts of interest.

REFERENCES


