

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

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Abbreviations:

SMA = Smooth Muscle Actin

CD34 = Immunohistochemical

antibody marker

IHH = Infantile hepatic

hemangioendothelioma

CT = Computer tomography

US = Ultrasonography

AFP = Alpha-feto protein

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) expertise of abdominal and retroperitoneal organs made on his first day of life showed mild hydronephrosis on both sides. On the fifth day, the kidneys ultrasound finding was normal. The baby was moved to the Habilitation department for the treatment of general body hypotony and bilateral congenital knee contractures. Two weeks after birth the abdominal US check up revealed a solid, well defined liver tumor formation measuring about 32 x 43 mm, wall thickness of 13 mm and hypoechogenic centre mostly filled with a dense content. There was neither internal calcification nor dilatation of the biliary system. Diameters of the portal vein and inferior vena cava were normal. Computed tomography (CT) 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 lesion showed early and high attenuation whereas the central zone persisted as a hypodense area (Figure 1).



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

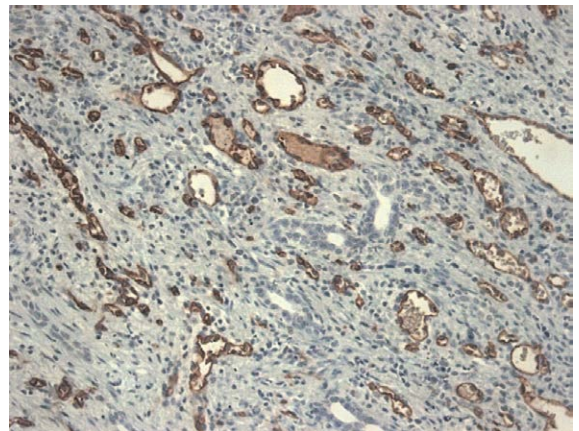


Figure 2. Microphotograph of liver tissue with tumor consisting of numerous capillary blood vessels and preserved biliary ducts (CD 34 x 200)

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 3.12×10^{12} / L, WBC 8.9×10^9 / L, HGB 86 g/L, CRP normal. Due to suspicion of IHH, the patient was prepared for surgery. During operation, a well-defined tumor formation in the sixth and seventh segment of the liver was noticed and completely removed. The histopathological finding was that the lesion consisted of a number of different size

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 $2.8 \times 10^{12} / L$. 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).

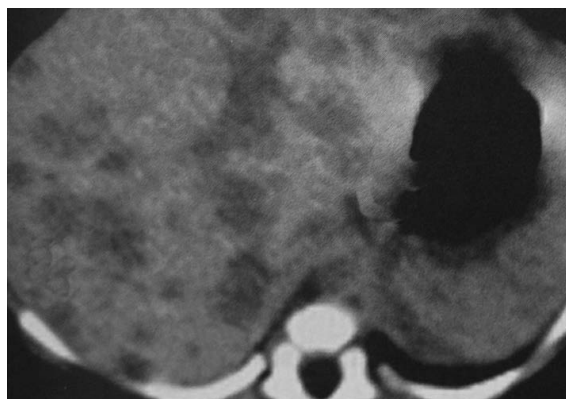


Figure 3. Conventional CT shows multiple hypodense nodules of different size in the liver

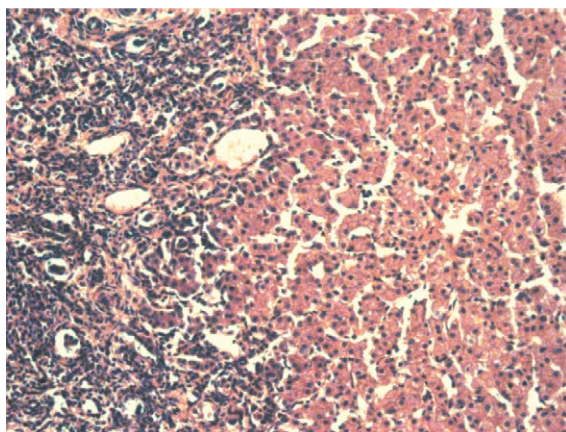


Figure 4. Microphotograph of the liver tissue (on the right): a sharp margin to tumor tissue (on the left) consisting of numerous capillary network is seen (HE x 40)

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 multilobular 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).

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 stromal 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 the ultrasound abdominal examination. A solid, well-defined heteroechoic 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 hyperechoic 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 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 hypoattenuating 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 (26).

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 obliterated 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, hypoglycemia, 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 to gastroduodenal artery 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

- Zenge JP, Fenton L, Lovell MA, Grover TR. Case report: infantile hemangioendothelioma. *Curr Opin Pediatr*. 2002;14:99-102.
- Ingram JD, Yerushalmi B, Connell J, Karrer FM, Tyson RW, Sokol RJ. Hepatoblastoma in neonate: a hypervascular presentation mimicking hemangioendothelioma. *Pediatr Radiol*. 2000;30:794-7.
- Roos JE, Pfiffner R, Stallmach T, Stuckmann G, Marincek B, Willi U. Infantile Haemangioendothelioma. *RadioGraphics*. 2003; 23(6):1649-55.
- Banks T, Podraza J. What's Your Diagnosis? Newborn with abdominal mass and distention. *Consultant for Pediatricians*. 2010;9:169-73.
- Chung-Ching L, Sheung-Fat K, Chi-Di L, Hsin-Wei K, Mao-Meng T. Infantile Hepatic Hemangioendothelioma Presenting as Early Heart Failure: Report of Two Cases. *Chang Gung Med J*. 2002;25(6):405-9.
- DiBisceglie AM, Befeler AS. Tumors and cysts of the liver. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fortran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia: Saunders Elsevier; 2010.
- Roberts LR. Liver and biliary tract tumors. In: Goldman L, Ausiello D, eds. *Cecil Medicine*. 23th ed. Philadelphia: Saunders Elsevier; 2007.
- Selby DM, Stocker JT, Waclawiw MA, Hitchcock CL, Ishak KG. Infantile hemangioendothelioma of the liver. *Hepatology*. 1994;20:39-45.
- Iyer CP, Stanley P, Mahour GH. Hepatic Hemangiomas in infants and children: a review of 30 cases. *Am Surg*. 1996;62(5):356-60.
- Tan TH, Ong KL. Multiple Haemangioma/Hemangioendothelioma. *Singapore Med J*. 2001;42(9):430-2.
- Mortel el KJ, Vanzieleghem B, Mortel el B, Benoit Y, Ros PR. Solitary hepatic infantile hemangioendothelioma: dynamic gadolinium-enhanced MR imaging findings. *Eur Radiol*. 2002;12:862-5.
- Calder CJ, Raafat F, Buckels JAC, Kelly DA. Orthotopic liver transplantation for type 2 hepatic infantile haemangioendothelioma. *Histopathology*. 1996;28(3):271-3.
- Fok TF, Chan MS, Metreweli C, Ng PC, Yeung CK, Li PK. Hepatic haemangioendothelioma presenting with early heart failure in a newborn: treatment with hepatic artery embolization and interferon. *Acta Paediatr*. 1996;85:1373-5.
- Hlatshwayo BE, Daba I, Sithole S. Infantile hemangioendothelioma. *Case Report International*. 2012;1:1-4.
- Wong DC, Masel JP. Infantile hepatic hemangioendothelioma. *Australian Radiology*. 1995;39(2):140-4.
- Wu JT, Book L, Sudar K. Serum alpha fetoprotein (AFP) levels in normal infants. *Pediatr Res*. 1981;15(1):50-2.
- Blohm ME, Vesterling Hormner D, Calaminus G, Gobel U. Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. *Pediatr Hematol Oncol*. 1981;15(2):135-42.
- Nord KM, Kandel J, Lefkowitz JH, Lobritto SJ, Morel KD, North PE, et al. Multiple Cutaneous Infantile Hemangiomas Associated With Hepatic Angiosarcoma: Case Report and Review of the Literature. *Pediatrics*. 2006;118(3):907-13.
- Horton KM, Bluemke DA, Hruban RH, Soyer P, Fishman EK. CT and MR imaging of benign hepatic and biliary tumors. *RadioGraphics*. 1999;19:431-51.
- Keslar PJ, Buck JL, Selby DM. Infantile Hemangioendothelioma of the Liver Revisited. *RadioGraphics*. 1993;13:657-70.
- Yasunaga C, Sueishi K, Ohgami H, Suita S, Kawanami T. Heterogenous expression of endothelial cell markers in infantile hemangioendothelioma: immunohistochemical study of two solitary cases and one multiple one. *Am J Clin Pathol*. 1989;91:673-81.
- Dehner LP, Ishak KG. Vascular tumors of the liver in infants and children – a study of 30 cases and review of literature. *Arch Pathol*. 1971;92:101-11.
- Gonen R, Fong K, Chiasson DA. Prenatal sonographic diagnosis of hepatic hemangioendothelioma with secondary nonimmune hydrops fetalis. *Obstet Gynecol*. 1989;73:485-7.
- Dachman AH, Lichtenstein JE, Friedman AC, Hartman DS. Infantile Hemangioendothelioma of the Liver: A Radiologic-Pathologic-Clinical Correlation. *AJR*. 1983;140:1091-6.
- Kim TJ, Lee YS, Song YS, Park CK, Shim SI, Kang CS, et al. Infantile hemangioendothelioma with elevated serum alpha fetoprotein: report of 2 cases with immunohistochemical analysis. *Hum Pathol*. 2010;41(5):763-7.
- Halefoglu AM. Magnetic resonance imaging of infantile hemangioendothelioma. *Turk J Pediatr*. 2007;49:77-81.
- Falk H, Herbert JT, Edmonds L, Heath CW, Thomas LB, Popper H. Review of Four Cases of Childhood Hepatic Angiosarcoma – Elevated Environmental Arsenic Exposure in One Case. *Cancer*. 1981;15(47):382-91.
- Becker JM, Heiliter MS. Hepatic hemangioendothelioma in infancy. *Surg Gynecol Obstet*. 1989;168:189-99.
- Kristidis P, de Silva M, Howman-Giles, Gaskin KJ. Infantile hepatic hemangioma: investigation and treatment. *J Paediatr Child Health*. 1991;27:57-61.
- Laird WP, Friedman S, Koop CE, Schwartz GJ. Hepatic hemangiomatosis. Successful management by hepatic artery ligation. *Am J Dis Child*. 1976;130(6):657-9.
- Cohen RC, Myers NA. Diagnosis and management of massive hepatic hemangiomas in childhood. *J Pediatr Surg*. 1986;21(1):6-9.
- Ezekowitz RAB, Mulliken JB, Folkman J. Interferon alpha-2a therapy for life-threatening haemangiomas of infancy. *N Engl J Med*. 1992;326:1456-63.
- Davenport M, Hansen L, Heaton ND, Howard ER. Hemangioendothelioma of the liver in infants. *J Pediatr Surg*. 1995;30:44-8.
- Woltering MC, Robben S, Egeler RM. Case report hepatic hemangioendothelioma of infancy: treatment with interferon alpha. *J Pediatr Gastroenterol Nutr*. 1997;24:348-51.
- Goldberg SJ, Fonkalsrud E. Successful treatment of hepatic hemangioma with corticosteroids. *JAMA*. 1969;208:2473-4.
- Touloukian RJ. Hepatic hemangioendothelioma during infancy: Pathology, diagnosis and treatment with prednisone. *Pediatrics*. 1970;45:71-6.

- 37 Sondhi V, Kurkure PA, Vora T, Banavali SD, Vishwanathan S, Medhi S, et al. Successful management of multi-focal hepatic infantile hemangioendothelioma using TACE/surgery followed by maintenance metronomic therapy. *BMJ Case Re.* 2012;8. doi: 10.1136/bcr.12.2011.5456
- 38 DeLorimier AA, Simpson EB, Baum RS, Carlsson E. Hepatic artery ligation for hepatic hemangiomas. *N Engl J Med.* 1967;277:333-7.
- 39 Mattioli L, Lee KR, Holder TM. Hepatic artery ligation for cardiac failure due to hepatic hemangioma in the newborn. *J Pediatr Surg.* 1974;9:859-62.
- 40 Moon SB, Kwon HJ, Park KW, Yun WJ, Jung SE. Clinical experience with infantile hepatic hemangioendothelioma. *World J Surg.* 2009;33(3):597-602.
- 41 Grabhorn E, Richter A, Fischer L, Krebs-Schmitt D, Ganschow R. Neonates with severe infantile hepatic hemangioendothelioma: limitation of the liver transplantation. *Pediatr Transplant.* 2009;13(5):560-4.
- 42 Rotman M, John M, Stowe S, Imanadar S. Radiation treatment of pediatric hepatic hemangiomas and coexisting cardiac failure. *N Engl J Med.* 1980;302:852.
- 43 Ko P, Tam A, Yuen PMP. Enlarged Liver, a Subcutaneous Nodule in the Right Arm and Congestive Heart Failure in a 3-week-old Infant. *J Hong Kong Med Assoc.* 1987;39(3):83-4.