Infantile Hepatic Hemangioendothelioma Presenting as Early Heart Failure: Report of Two Cases

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Hepatic hemangioendothelioma is rare. We report on hepatic hemangioendotheliomas in 2 young infants, with initial manifestations of respiratory distress and congestive heart failure. Serum alpha-fetoprotein (αFP) level was as high as 26,343 μg/l at 14 days old in 1 case, but was only 18 μg/l in the other case. The 2 patients were treated with prednisolone and hepatic artery ligation, respectively, with no residual sequelae after 12 months of follow-up.

In this article, the clinical courses of these 2 young infants are reviewed, and the management of infantile hepatic hemangioendothelioma complicated with heart failure is discussed. In our experience, early heart failure caused by infantile hepatic hemangioendothelioma can be well controlled, especially with prednisolone therapy or by hepatic artery ligation. Spontaneous regression has been reported. However, without early recognition and therapeutic intervention, progression to decompensated heart failure may lead to death. Furthermore, it is necessary to differentiate infantile hepatic hemangioendothelioma (IHH) from hepatic malignancies. *(Chang Gung Med J 2002;25:405-10)*

Key words: hepatic hemangioendothelioma, prednisolone, hepatic artery ligation, congestive heart failure.

Infantile hepatic hemangioendothelioma (IHH) is rarely reported because of the low incidence of this tumor, which is estimated to be about 1/20,000.[1] The clinical course depends on the tumor size, localization, and its complications. IHH appears to be a histologically benign tumor that may have a poor outcome because of severe complications.[1] Congestive heart failure (CHF) was evident in 15% and liver failure in 2% of infants with this disease.[1] The tumor may be treated conservatively with corticosteroid,[2,3] cytotoxic agents,[4] interferon,[5] and irradiation.[4,6] If medical treatment fails, then radical interventions such as hepatic artery ligation,[7-9] transcatheter hepatic artery embolization,[9-11] surgical resection,[8,12,13] or even liver transplantation may be required. In general, a non-complicated tumor may spontaneously regress, but most fatalities occur in patients whose initial presentation is intractable heart failure.[1] In our experience, prednisolone or hepatic artery ligation might remit an IHH complicated with early CHF. In addition, clinical characteristics, complications, treatments, and prognosis of hepatic hemangioendothelioma in pediatric patients are reviewed.

CASE REPORT

Case 1

A female infant weighing 3630 g was born through a normal spontaneous delivery at 39 weeks

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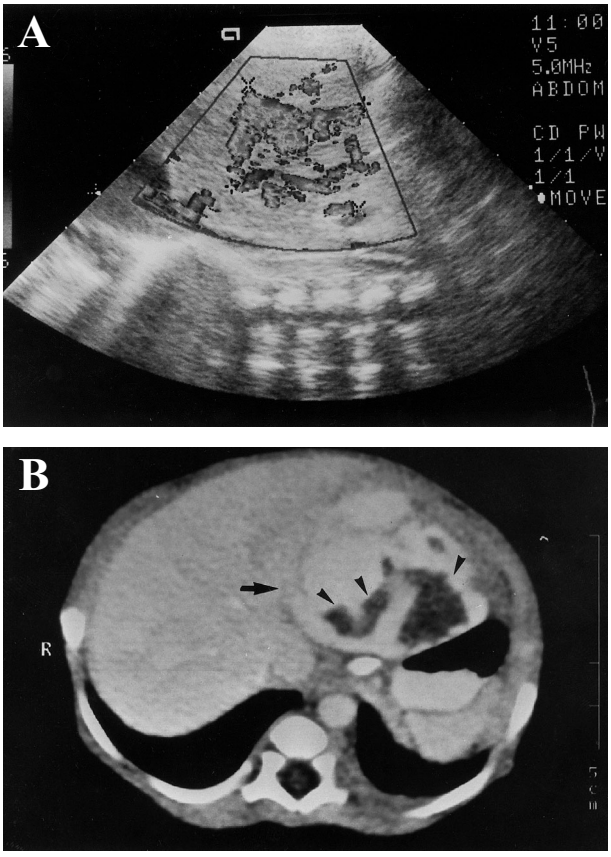
of gestation. A prenatal diagnosis of a hepatic hemangiomatous lesion on fetal ultrasound was noted. Respiratory distress with cyanosis appeared after delivery. A cardiothoracic ratio of 0.8 was measured on the chest radiograph. Auscultation revealed a loud systolic murmur. Doppler ultrasound showed a solid vascular lesion, measuring about 4.7 ¡ 3.5 cm, over the left hepatic lobe (Fig. 1A). There were no other hemangiomatous lesions detected on the skin, in the brain, or abdominal viscera. Abdominal computed tomography with contrast disclosed a well-enhanced mass with irregular central low-density cysts in the left hepatic lobe compatible with a hepatic hemangioendothelioma (Fig. 1B). Laboratory findings showed normal liver function tests, serum prothrombin time, and partial thromboplastin time. However, a reduced platelet count (6.3 ¡ 10^{10}/l) was found. A serum alpha-fetoprotein level (αFP) of 26,343 μg/l was also disclosed at 14 days old. Dopamine and low-dose prednisolone (1 mg/kg/day) were started on day 3 after birth. With a series of clinical evaluations and abdomen ultrasound follow-up, it was noted that the size of the hepatic hemangioendothelioma gradually decreased. The serum platelet count was 20.0 ¡ 10^{10}/l at 14 days old, and serum αFP declined to 20 μg/l at 6 months of age. Dopamine was discontinued 2 weeks after reduction in heart size and improvement in respiratory distress symptoms. Prednisolone was discontinued after 6 weeks; then complete regression with calcification of the tumor was noted on ultrasound after 2 months of age. Abdominal computed tomography with contrast demonstrated marked regression of the hepatic mass with a calcified lesion in the left hepatic lobe with no evident cystic part or low-density component around the lesion at 12 months of age (Fig. 1C). Her growth and development were normal after 12 months of follow-up at our outpatient clinic.



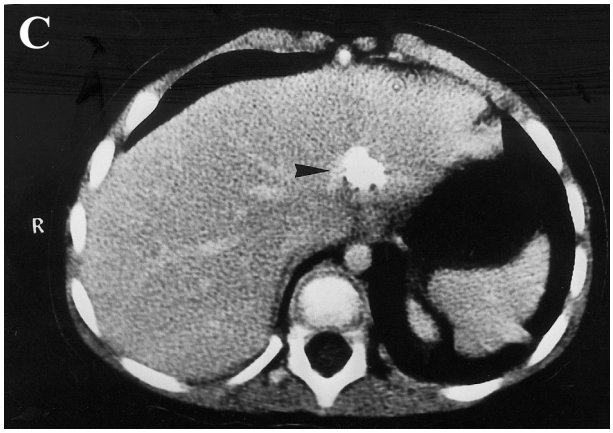


Fig. 1 (A) Doppler ultrasound showing a hyperechoic mass (4.7 ¡ 3.5 cm) with prominent vascularity in the left lobe of the liver. (B) Abdominal computed tomography with contrast disclosing a well-enhanced mass (arrow) with irregular central low-density cysts (arrowheads) in the left hepatic lobe compatible with a hepatic hemangioendothelioma. (C) Abdominal computed tomography with contrast demonstrating marked regression of the hepatic mass with a calcified lesion (arrowhead) in the left hepatic lobe with no evident cystic part or low-density component around the lesion.

Case 2

A male infant was born after 39 weeks of gestation through a normal spontaneous delivery. His birth weight was 3200 g. The entire pregnancy and delivery were uncomplicated. On the age of 10 days, he was transferred to our hospital via a local medical clinic because of tachypnea, tachycardia, and frequent vomiting.

On admission, physical examination revealed a mildly cyanotic infant with respiratory distress and a grade III/VI systolic ejection murmur over the left upper sternal border. The liver margin was palpable 4 cm below the right costal margin; no cutaneous hemangioma was noted. The chest roentgenogram showed cardiac enlargement, and the electrocardiogram disclosed biventricular hypertrophy. Laboratory studies including liver function tests (aspartate aminotransferase and alanine aminotransferase) and coagulation profile (platelet counts, PT, and PTT) were within the normal range. At 14 days old, αFP was 18 μg/l. Abdominal ultrasound revealed a giant heterogeneous mass with profuse blood flow in the right lobe of the liver. Magnetic resonance imaging demonstrated a 7-cm tumor mass, hypointense on T1-weighted and hyperintense on T2-weighted images (Fig. 2). This is compatible with hepatic hemangioendothelioma. Because the tumor enlarged rapidly with profound congestive heart failure, hepatic arteriography was arranged on the fifth day after admission. A large right hepatic artery with dilated collateral branches in the right hepatic lobe was found. Symptoms of cardiac decompensation gradually worsened, so low-dose dopamine (5 μg/kg/min), digoxin, furosemide, and prednisolone (1 mg/kg/day for 3 days then 21 mg/kg/day) were given on day 7 after admission. Prednisolone was discontinued 2 weeks later because of lack of effectiveness. Ligation of the right hepatic artery was performed on day 22 after admission due to progressive heart failure. The infant improved dramatically both in clinical and hemodynamic aspects postoperatively. The patient was discharged 2 weeks after the operation.

During monthly follow-up at our outpatient clinic, the hepatic hemangioendothelioma gradually involuted, and the liver span had decreased by 1 year of age. No evidence of recurrence was noted, and he had normal growth and development at 1 year old.

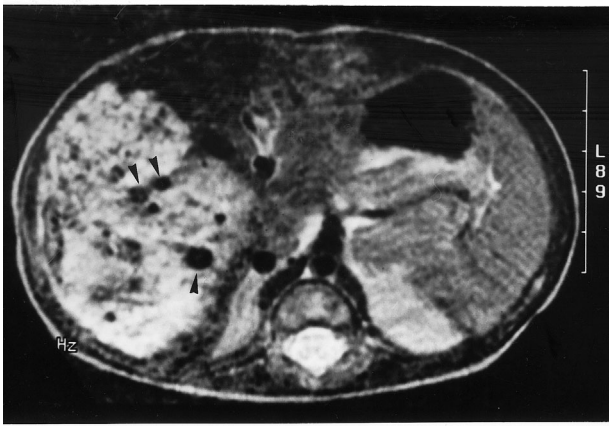


Fig. 2 Abdominal magnetic resonance image (T2 weighted) shows a high-signal hepatic mass, with engorged intratumoral vessels (arrowheads) in most of the right lobe of the liver, compatible with a hemangioendothelioma.

DISCUSSION

IHH is a type of capillary hemangioma, which consists of a network of capillary-sized and endothelium-lined vessels. There is a tendency for female predominance in gender distribution with a ratio varying from 1.3:1 to 2:1.[1] It is seen almost exclusively in children, and usually grows shortly after birth, with growth ending in the first 6 months of life.

Clinical manifestations of IHH are variable. Clinical features of IHH mainly depend on the tumor size and location,[1,5] and include hepatomegaly (83%), an abdominal mass (66%), skin hemangioma (65%), anorexia, vomiting (25%), and failure to thrive (25%).[1,5]

On abdominal ultrasound, IHH may show variable echogenicity but is predominantly hypoechoic, usually with well-defined margins. Computed tomography may demonstrate focal areas of low attenuation, which show early peripheral enhancement after injection of contrast material with variable delayed central filling-in. Magnetic resonance imaging may identify IHH as low-signal lesions on T1-weighted and high-signal lesions on T2-weighted images. According to clinical presentations, radiological evaluations and liver biopsy, the major differential diagnoses should include hepatoblastoma, mesenchymal hamartoma, hepatocellular adenoma,

focal nodular hyperplasia, and metastatic neuroblastoma.

Fork and Dens[5] reported that most cases of IHH are asymptomatic with spontaneous regression. But cases with heart failure experience a high mortality rate.[1,5] Serious complications associated with this disease include high cardiac output congestive heart failure, consumptive coagulopathy, and thrombocytopenia (Kasabach-Merritt syndrome). Rapid arteriovenous shunting through vascular channels leads to an increased cardiac output. Dilation of hepatic arteries and recirculation of blood back to right heart may lead to overt heart failure (58%).[1,5] In general, the median age of patients with hepatic hemangioendothelioma presenting with early heart failure in infancy is about 1 month old. Heart failure can cause death in up to 70% of untreated infants without adequate regression of the lesion.[3,8] Therefore, if symptoms develop, aggressive treatments are warranted.[14,15]

Corticosteroid therapy is the first step to treat complications of IHH.[14] Prednisolone[2,3] (2-10 mg/kg/day) for an average of 6 weeks or methyl prednisolone pulse-therapy[15,16] may hasten involution by inhibiting proliferation of endothelial and smooth muscle cells. The precise mechanism of action is unclear. In general, we know that prednisolone can cause such side effects as hypertension, hyperglycemia, sepsis, and pseudotumor cerebri,[8] especially when it is given to infants. Clinicians should take care and be aware of these side effects. As with the prednisolone (1 mg/kg/day) response in our case 1, although it may just have a placebo effect, we suggest that prednisolone be started from 1 mg/kg/day and gradually increased if clinical symptoms do not improve as in our case 2. Furthermore, the response to steroids can be achieved within 1 to 3 weeks, and the success rate varies from 20% to 70%.[8] When IHH is not responsive to high-dose steroids, interferon alpha-2a or alpha-2b[5,15,17] (10^6 U/m^2/day subcutaneous injection, with a therapy duration of about 3-6 months) 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.[17] In addition, radiotherapy carries variable risks of other sequelae (e.g., cirrhosis, hepatosarcoma, and leukemia) so it should not be considered for young infants unless other therapies are contraindicated or unsuccessful.[4,6,18] In addition, the experience of using cyclophosphamide for treating IHH complicated with CHF is scarce, and the striking response warrants further investigation.[4]

In rapid deterioration of cardiac status or medical therapy failure, one should consider urgent interruption of the arteriovenous shunt, such as by hepatic artery embolization.[5,10,11,19] Obliteration of the vascular channels to accelerate involution by the use of steel wire, platinum coils, and polyvinyl alcohol has been reported. Furthermore, if the large size and diffuse nature of the tumor render it unsuitable for embolization, operative hepatic artery ligation as in our case 2 can be performed. The common hepatic artery is ligated proximal to the gastroduodenal artery.[7-9,14] Localized hemangioendothelioma can be surgically resected,[8] but this was not required in our cases.

To our knowledge, serum αFP level is normal or mildly elevated in IHH.[15] As in our case 1, hepatic malignancy should be considered as a differential diagnosis[15] when serum αFP level is higher than 20,000 μg/l at 14 days old. (Normal serum αFP levels of infants between 2 weeks and 1 month of age are 9452-12,610 μg/l)[20] However, based on the age of presenting symptoms (> 85% patients under 6 months of age),[15] clinical manifestations complicated with heart failure, radiological findings, and its natural history, the possibility of a hepatoblastoma should be excluded. Otherwise, malignancy should be highly suspected.

Our experience with these 2 cases emphasizes that prednisolone (1 mg/kg/day) may be tried in treating patients with IHH complicated with early decompensated heart failure. However, its exact response in IHH needs more experience for confirmation. Hepatic artery ligation may be beneficial in cases for which prednisolone fails. Early aggressive treatment in symptomatic patients may produce a favorable outcome.

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以早期心臟衰竭爲臨床表徵之嬰兒肝臟血管內皮瘤：二例報告

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肝臟血管內皮瘤爲一罕見疾病。本文報告二例早期以呼吸窘迫和心臟衰竭表現之肝臟血管內皮瘤嬰兒，分別以低劑量類固醇和肝動脈血管結紮術治療，經過12個月追蹤，二例症狀均緩解並且沒有發生其他後遺症。

本文報告的主要目的，除了回顧這二例，早期以心臟衰竭表現之肝臟血管內皮瘤嬰兒的臨床表現及治療過程；其中第一例胎兒蛋白在第14天大時高達26,343 μg/L而另一例則正常；並強調嬰兒之肝臟其中血管內皮瘤所導致的心臟衰竭是可以由治療而得以改善，包括類固醇治療及肝動脈結紮。雖然單純的肝臟血管內皮瘤是可能自動痊癒；但症狀若無法早期改善，心臟衰竭持續惡化的結果將可能導致死亡。此外，鑑別肝臟血管內皮瘤和惡性腫瘤上是必需的。(長庚醫誌 2002;25:405-10)

關鍵字：肝臟血管內皮瘤，類固醇，肝動脈血管結紮術，心臟衰竭。

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