A Case of Infantile Hepatic Hemangioendothelioma Successfully Treated with Interferon-α

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Infantile hemangioendothelioma is a rare benign, but intermediate to aggressive vascular tumor with potentially life-threatening complications such as high output congestive heart failure or Kasabach-Merritt syndrome. IHE is the most common hepatic vascular tumor and the third most common hepatic tumor in children, usually developing in infants less than 6 months of age. Serum α-fetoprotein level has been used as an important tumor marker for malignant hepatic tumors such as hepatoblastoma, hepatocellular carcinoma, and germ cell tumors. Steroids and interferon-α are two commonly used agents for medical treatment in IHE. We report a 5-month-old female infant with multiple hepatic hemangioendotheliomas associated with elevation of serum α-fetoprotein level, who was successfully treated with interferon-α. (Clin Pediatr Hematol Oncol 2010;17:69 ∼ 75)

Key Words: Infantile hepatic hemangioendothelioma, α-interferon, α-fetoprotein
cystic hepatic tumors associated with high serum $\alpha$-fetoprotein level, who was diagnosed as hemangioblastoma by ultrasonography-guided needle biopsy and then successfully treated with IFN-$\alpha$.

**Case Report**

A 5-month-old female infant was admitted to the Pediatric Department of Kangbuk Samsung Hospital for the follow up evaluation of a multiple mass in the liver. She was born in Kangbuk Samsung Hospital by vaginal delivery at a gestational age of 32 weeks with a birth weight of 1,996 g. Initial APGAR score was 8 at 1 minute and 9 at 5 minutes. She was taken care of at neonatal intensive care unit (NICU) as a low birth weight infant without mechanical ventilation. At birth, a pea sized bluish mass was examined on scalp, in left parietal area, but not on any other site (Fig. 1). One day after the birth, hypoglycemia attack developed, but serum insulin (12 $\mu$U/mL), insulin/glucagon ratio (0.4), free T4 (1.46 ng/dL), TSH (2.87 mIU/mL) levels and hepatic ultrasonography findings were normal. At one month of age, brain magnetic resonance imaging (MRI) was taken to examine the bluish mass on the left parietal scalp, and the mass was diagnosed as strawberry hemangioma with diameter about 1.5 cm. No other abnormality was found in the skull vault and brain (Fig. 2). At 3 months of age, pea sized hemangiomas newly developed on trunk and both legs (Fig. 3).

On admission at 5 months of age, weight was 7.7 kg (<3 percentile), pulse rate was 106/min and 24 breaths/min and temperature was 36.8°C. The mass was bluish, fragile,高出のようなく、触診で柔らかく、弾性を伴っていた。超音波検査で、肝臓の一部に不整形の低エコー信号を認めた。MRI では、頭蓋内に直径約 1.5 cm のストロベリーハンギオーマが見つかった。この病変は、皮膚色の腫瘍で、表面に青みがあった。血清 α-フェトプロテインのレベルが高値を示しており、肝臓に多発性腫瘍を伴っていた。新生児期に低出生体重児として管理され、出生時体重 1,996 g、出生時 APGAR スコア 8、5 分後 9 の良好な状態であった。

On admission at 5 months of age, weight was 7.7 kg (<3 percentile), pulse rate was 106/min and
respiration rate was 24/min. On skin, multiple (about 10) pea sized hemangiomas were located on face, trunk, and extremities. On abdominal examination, there was a mild abdominal distension, and the liver was 2 finger breadth palpable under right costal margin with smooth surface and blunt margin. In complete blood cell counts, hemoglobin 10.7 g/dL, white blood cell 9,600/dL, platelet 613 K/dL and normal differential counts (Seg 23.1%, Lympho 6%, Eosinophil 1.3%). Blood chemistry demonstrated normal liver enzymes (aspartate aminotransferase 28 U/L; alanine aminotransferase 19 U/L) and elevated $\alpha$ -fetoprotein level which was 10,754 $\mu$g/L. Coagulation profiles (prothrombin time 11 seconds, activated partial thromboplastin time 42 seconds) were normal. Abdominal ultrasonography showed one 5.6×4 cm sized well demarcated solid mass in left hepatic lobe, and multiple 1~2 cm sized nodules in right and left hepatic lobes, which were partly cystic and partly solid in appearance. Color Doppler imaging demonstrated that all solid tumors were highly vascular (Fig. 4). All other intra abdominal organs, including spleen, kidneys and adrenals were normal. In computed tomography (CT) scan without enhancement, scattered multiple variable sized tumors including the largest tumor with the diameter of 5.6 cm, with lower attenuation than surrounding liver, were shown in the both hepatic lobes (Fig. 5). In CT scan with enhancement, some mass showed a peripheral rim enhancement in arterial phase, other mass showed a homogenous enhancement. The 5.6 cm sized largest tumor in the left lobe (S4, S1) showed heterogenous peripheral arterial enhancement in early arterial phase, and then

Fig. 5. Abdominal CT reveals a mass with the maximum diameter of 5.6 cm in the left hepatic lobe (arrow).

Fig. 4. (A) Abdominal ultrasonography reveals 5.6×4 cm sized well demarcated solid mass in the left hepatic lobe, partly cystic and partly solid in appearance. (B) Color Doppler imaging shows highly vascular mass with variable vascularity.
showed a strong central enhancement in the portal and delayed phase. Other 2 cm sized well defined cystic tumors without enhancement were shown in S2, S8, S7 and S6. To rule out from malignant hepatic tumors, abdominal MRI was performed, and MRI showed the findings compatible with IHHE (Fig. 6). The largest vascular tumor in the left hepatic lobe showed low signal intensity in T1-weighted image and high signal intensity in T2 weighted image, and the other multiple solid tumors with diameter of 1.5 cm or less also showed T2 hyperintensity. The three cystic tumors in the right hepatic lobe with diameter of about 2 cm was showed bright signal in T2-weighted image indicating probable cystic change of hemangioendothelioma. To obtain a tissue diagnosis, an ultrasonography-guided needle biopsy of the largest lesion was performed under general anesthesia. Histological examination in combination with immunohistochemical stain with markers for vessels such as CD31 and Factor VIII showed diffuse strong posi-

Fig. 6. Abdominal MRI reveals a mass with maximum diameter of 5.6 cm in the left hepatic lobe (arrow).

Fig. 7. (A) Immunohistochemical stain of tissue with CD31 is diffuse positive, histologically confirming the diagnosis of IHHE (×400). (B) A immunohistochemical stain with factor VIII is diffuse strong positive, confirming the diagnosis of IHHE (×400).

Fig. 8. Follow-up abdominal MRI taken 4 months after the IFN-α treatment showed decrease of diameter f mass to 2.1 cm (arrow).
tivity, confirming the diagnosis of multiple IHHE (Fig. 7). Under the diagnosis of IHHE, we started IFN-α (Intron A®, multidose pen 18 MIU, Schering-Plough) therapy with the dosage of 2.4 million unit/m²/day subcutaneously daily, and then increased the dosage of IFN-α to 3 million unit/m²/day 3 weeks later. Mild fever developed from the first day of IFN-α therapy which could be controlled by acetaminophen and fever subside from the third day of therapy. There was no evidence of other side effect including neurologic sequelae during or after this therapy. One month after the start of IFN-α therapy, α-fetoprotein levels started to decrease gradually (10,754 → 2,174 → 447 → 278 → 119 ng/mL) and normalized to 30 ng/mL after 4 months of IFN-α therapy. Follow-up abdominal MRI was done serially at 1, 2, 4 month of IFN-α therapy. The maximum diameter of the largest IHHE tumor decreased from 5.6 cm to 4.4 cm after 1 month, 3.3 cm after 2 month, 2.1 cm after 4 month of IFN-α therapy. The other smaller solid and cystic hepatic tumors, as well as the multiple hemangiomas of the skin decreased in size in response to IFN-α therapy. We treated the patient for total period of 16 months. We decided to end IFN-α therapy when α-fetoprotein level was maintained in normal range, and the IHHE masses including the initially 5.6 cm sized tumor were not observed in MRI scan. She is alive and doing well for 23 months since the time of diagnosis, and the IHHE did not relapse for 10 months after the IFN-α therapy was finished.

**Discussion**

Patients with IHE are predominantly female (67%) and symptoms usually appeared before 6 months of age⁵. Most patients with IHE present with an asymptomatic abdominal mass and hepatomegaly, but these tumors may be associated with high-output cardiac failure due to arteriovenous shunts within the tumor⁸. IHE are often associated with Kasabach-Merritt syndrome, resulting in life-threatening hemorrhage due to coagulopathy and thrombocytopenia⁷. Anemia, leukocytosis, thrombocytopenia, consumption coagulopathy, tumor rupture, mildly abnormal liver function tests, jaundice, hemangioma of the skin or other organs, and, rarely, gastric outlet obstruction may also accompany IHE⁹. Hepatic lesions are usually multifocal or diffuse and solitary lesions are rare⁹. In our patient, the abnormal finding was hepatomegaly, multiple hemangioma of the skin, with an elevated serum α-fetoprotein level. In IHE cases, diagnosis of the tumor is carried out primarily by imaging studies such as ultrasonography, CT, MRI, and angiography. Ultrasound is often the initial diagnostic imaging test and appear as complex solid hepatic lesions with various hypo- and hyperechoic echogenicity. At unenhanced CT, infantile hemangioendothelioma usually manifests as a well-defined mass that is hypodense relative to the normal liver parenchyma. In about 16 ~40% of cases, the lesion is heterogeneous with central high-attenuation areas due to hemorrhage or calcifications. Contrast enhancement demonstrates peripheral pooling and central enhancement with variable delay¹⁰. In this patient, some mass showed a peripheral rim enhancement in arterial phase, other mass showed a homogenous enhancement due to multiple scattered variable sized tumors. MRI is the preferred diagnostic investigation¹¹. Typical MRI characteristics of IHHE consist of a relative hypointense T1 signal and strongly hyperintense T2 signal compared to liver tissue¹⁰. This pattern in MRI is important for differentiating IHHE from other hepatic tumors. In this patient, the MRI findings were compatible with the aforementioned MRI characteristics of the IHHE. Liver biopsy is not recommended, as it may result in life-threatening
In our case, an ultrasonography-guided needle biopsy of liver was performed to differentiate from other hepatic malignancies such as hepatoblastoma, hepatocellular carcinoma, and germ cell tumors, all of which can cause serum α-fetoprotein level elevation. Hepatoblastoma is associated with markedly elevated α-fetoprotein level and are usually solid. Calcification is common. This patient did not present coagulopathies. Serum α-fetoprotein level have been used as an important tumor marker for hepatoblastoma, hepatocellular carcinoma, and germ cell tumors. Elevation of serum α-fetoprotein level is rarely seen in case reports of IHHE. In our case, due to the presence of a multiple mass with cystic necrotic areas and elevated serum α-fetoprotein level, it was necessary to differentiate it from hepatoblastoma, hepatocellular carcinoma, and germ cell tumors with tissue diagnosis. No correlation has been reported between the level of serum α-fetoprotein level and tumor size. In our patients, α-fetoprotein level decreased from 10,754 ng/mL to 30 ng/mL after 4 months of IFN-α treatment. Known medical treatments such as steroid, IFN-α, and/or chemotherapy that includes vincristine, adriamycin, and cyclophosphamide have been used because complete resection is impossible. Although steroid can be used as the first-line treatment, a previous study showed that there were various treatment responses to steroid: total failure (30%), excellent, dramatic, rapid improvement (30%), and a moderate to doubtful response (40%) . Patient age and size of lesions are the most important factors affecting the response to corticosteroid treatment. IFN-α treatment has produced regressions of infantile angiomatous disease including IHHE. This treatment has not been favorable in all patients and has potential neurotoxic effect. In our patient, first treatment modality was IFN-α, starting at 2.4 million unit/m²/day and increased at 3.0 million unit/m²/day 3 weeks later due to multiple and large sized tumor in liver. In our patient, initial huge mass was observed, but IHHE resolved with the IFN-α monotherapy and no other treatment was required. The only side effect was slight mild fever from the first day of IFN-α with was reversible. Tumor size decreased at 5.6 cm to 2.1 cm (>75%) at 4 months. No potential neurotoxic effect and other side effects. We report a 5-month old female infant with multiple IHHE and multiple skin hemangiomas associated with elevation of α-fetoprotein level, who was successfully and completely treatment with IFN-α monotherapy.

요 약

영아 간혈관내피종은 드문 양성 종양이지만 매우 공격적인 종양으로 Kawabach-Merritt 증후군이나 울혈성 심부전 같은 생명을 위협하는 합병증을 동반할 수 있다. 영아 간혈관내피종은 가장 흔한 간혈관 종양이며 6개월 이전 영아에서 발견되는 세 번째로 흔한 간의 종양이다.혈청 α-fetoprotein 농도는 간모세포종, 간세포암종, 생식 세포종 등 악성 간종양의 중요한 종양 표지자로 사용되고 있다. 영아 간혈관내피종의 약물적 치료는 스테로이드와 인터페론 알파가 가장 보편적으로 이용되고 있다. 저자들은 피부상에 다수의 혈관종, 혈청 α-fetoprotein의 상승 등을 동반한 간혈관내피종을 가진 5개월 여아에서 인터페론 알파 치료를 통해 성공적으로 치료한 사례를 보고하는 바이다.

참 고 문 헌

2. Park EA, Seo JW, Lee SW, Choi HY, Lee SJ.