Case Report

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Beta blocker and steroid therapy in the treatment of infantile hepatic hemangioendothelioma

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Summary **Infantile hepatic hemangioendothelioma (IHHE) is the most common benign vascular liver tumor and typically occurs during the first 6 months of life. A 4-month-old male patient presented with abdominal distention. A physical examination revealed massive hepatomegaly. Liver enzyme levels were normal. The alpha fetoprotein level was 1,323 mg/dL (6-1,000). Abdominal magnetic resonance imaging (MRI) showed multiple, well-defined and hyperintense nodular lesions in the liver. MRI findings suggested IHHE. The thyroid stimulating hormone (TSH) level was high (177.2 µU/mL). He was started on sodium levothyroxine 50 µg daily. The patient has hypoxemia due to abdominal distention during the follow-up period. Oral methylprednisolone therapy was started at a dose of 2.5 mg/kg/dose, and propranolol at a dose of 1 mg/kg/dose, bid. Fifteen days later his TSH level remained elevated at 212.3 µU/mL despite repeatedly increasing the dose of levothyroxine up to 200 µg/daily. One month after the initial presentation, his TSH level was reduced to 11.28 µU/mL. We observed a marked improvement in abdominal distention and respiratory distress within 15 days and an average reduction of 50% in the lesion diameters after a month. Despite its benign nature, IHHE may lead to development of complications. Steroid and propranolol treatment may be useful in in the management of emergency complications.**

Keywords: Infantile hepatic hemangioendothelioma, methylprednisolone, propranolol

1. Introduction

Infantile hepatic hemangioendothelioma (IHHE) represents 12% of the childhood hepatic tumors. In addition, it is the most common tumor of the liver (*1-3*). Hepatic hemangiomas are thought to result from placental angioblasts (*4*). Approximately 85% of all cases are diagnosed within the first 6 months of life and they most commonly become symptomatic during this period (*5,6*). The most commonly finding is abdominal distention. Other findings include cardiac failure, skin hemangioma, respiratory failure, fulminant hepatic failure, consumption coagulopathy and abdominal compartment syndrome (*6-8*). Recent studies report that IHHE could be associated with hypothyroidism (*9-11*). While asymptomatic lesions spontaneously regress in years, symptomatic lesions require aggressive treatment since they have fatal risk (*1*). Therefore, accurate diagnosis of the disease and appropriate treatment is important. There is no standard therapeutic approach. Steroids and propranolol are the primary treatment choices. Surgery may be required in patients with complications and no response to medical treatment (*12-14*). This case is presented to emphasize that propranolol and methylprednisolone combination therapy may be effective in combating emergency complications.

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2. Case Report

A 4-month-old male patient was brought in with

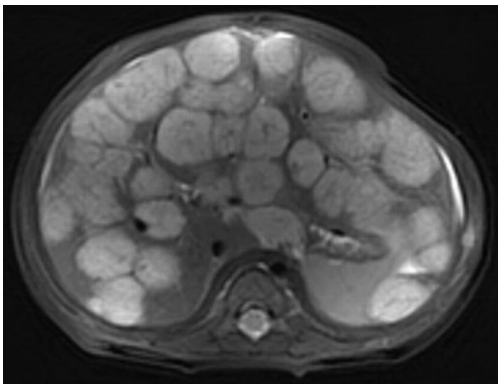

Figure 1. Before treatment T2-weighted axial MR image shows multiple hyperintense nodular lesions in the liver.

the complaint of abdominal distention. A physical examination revealed massive hepatomegaly. The liver was palpable 9 cm below the right costal margin. The liver extended towards the left of the midline and filled the splenic lodge and was palpable 5 cm below the left costal margin. The patient had a heart rate of 140 beats per minute, a blood pressure of 80/50 mmHg, and a respiratory rate of 32 breaths per minute. He had millimetric-sized hemangiomas on the trunk. Biochemistry investigation showed the following: ALT: 15 U/L, AST: 49 U/L, GGT: 495 U/L (8-61), ALP: 230 U/L (122-469), total bilirubin: 0.61 mg/dL, direct bilirubin: 0.08 mg/dL. Alpha-fetoprotein (AFP): 1,323 mg/dL (6-1,000), thyroid stimulant hormone (TSH): 177.2 μU/mL (0.73-8.35), free thyroxin (sT4): 1.29 ng/dL (0.92-1.99). Sodium levothyroxine treatment was initiated at a dose of 50 μg daily. The abdominal ultrasonography (USG) revealed an increased liver size (135 mm) and multiple hypoechoic lesions. Multiple nodular lesions covering the whole hepatic parenchyma were observed on abdominal dynamic magnetic resonance imaging (MRI) (Figure 1). The largest of these had a size of 35 × 20 mm with well defined and marked increased hyperintense vascularization on T2-weighted imaging. Doppler USG showed increased hepatic vascularization and hepatic arterial diameter. Diagnosis of infantile hepatic hemangioendothelioma (IHEE) was established based on the imaging findings. Since there was a high risk of bleeding because the tumor was of vascular origin, and USG showed increased vascularization, biopsy could not be performed. Respiratory distress developed during the follow-up period. Oxygen saturation decreased to 86% and oxygen therapy was required. Since the patient was symptomatic, oral methylprednisolone therapy was started at a dose of 2.5 mg/kg/dose, and propranolol at a dose of 1 mg/kg/dose, bid. TSH levels were 278.2 μU/mL and 212.3 μU/mL at 1 and 2 weeks after levothyroxine treatment, respectively. For this reason sodium levothyroxine dose gradually increased to 200 μg/day. On day 15 of treatment, a decrease in liver size

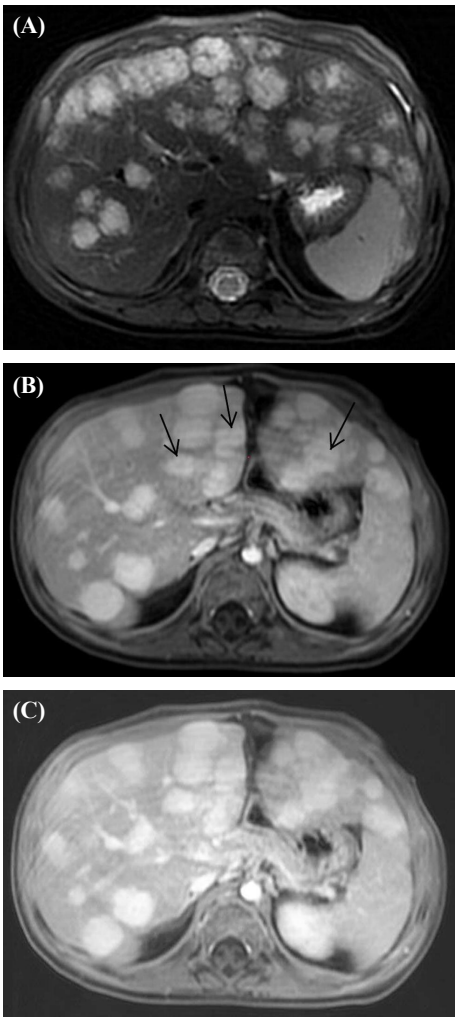

Figure 2. Follow-up T2-weighted axial MR image obtained after 9 months of therapy shows marked reduction number and size of lesions (A); after gadolinium contrast injection, there is peripheral enhancement in the arterial phase (B); and homogenous enhancement in the late phase (C).

began and the patient's additional oxygen requirement disappeared. The abdominal USG showed a decrease in the size of the largest lesion (22 × 17 mm), and the vertical length of the liver had decreased from 135 to 95 mm over the 1-month period. At that time, the TSH level was reduced to 11.28 μU/mL. The levothyroxine dose was then decreased to 75 μg daily and continued. At the third month of treatment, steroids were gradually reduced and discontinued, but propranolol therapy continued. A subsequent abdominal USG showed an increase in the size of the largest lesion (30 × 22 mm) and the vertical length of the liver increased from 95 to 124 mm in the fourth month; steroid treatment was then restarted at a dose of 0.5 mg/kg/dose, bid. The patient remained under steroid, propranolol and sodium levothyroxine treatment for nine months. At follow-up dynamic abdomen MRI showed a marked reduction number and size of all of the liver nodules (Figure 2A) which enhanced periphery post-contrast during early arterial phase (Figure 2B) with homogenous enhancement during the late phase (Figure 2C).

3. Discussion

The similarity of age between IHHE and hepatoblastomas at the time of diagnosis is interesting. Of all IHHE patients, 86% are diagnosed within the first 6 months and approximately 30-50% of patients with hepatoblastomas are diagnosed within the first year of life. Hepatoblastomas are the most common malignant liver tumor, representing 40-60% of all pediatric liver tumors (*2,15,16*). AFP is used for the differential diagnosis of pediatric liver tumors. AFP may increase up to 40,000 ng/mL at birth. After birth, it rapidly decreases; however, even at 6 months of age, it remains above adult values (*17*). In IHHE cases, high AFP values are not expected, but recent studies have shown that hepatocytes located nearby or trapped inside the tumor cells could be the source of the increased AFP levels (*15*). In our case, we considered a hepatoblastoma for a differential diagnosis; however, the AFP level was only slightly above the upper level. Ninety percent of hepatoblastoma tumors secrete a large amount of AFP due to the high level of hepatoblast cells they contain (*2,14*). Therefore, AFP levels are expected to be much higher.

Imaging methods are important in the diagnosis of liver tumors. Commonly practiced methods include tomography, MRI and ultrasound. Ultrasonographic characteristics of IHHE show variability. Well-defined hypoechoic lesions and abnormally large vascular structures are detected in the liver while color Doppler USG can define flow patterns of arteriovenous shunts in large abnormal vascular structures (*15*). The number of lesions cannot be used as a marker in differentiating between IHHE and hepatoblastomas because, in both diseases, lesions can be single or multiple (*15*). A criterion that can be used for the differential diagnosis is a venous thrombus. While this is a common finding with hepatoblastomas, it is not observed in IHHE (*3*). Contrast dynamic MRI and tomography are specific and diagnostic for IHHE. In MRI scans, IHHE lesions are observed as hypointense on T1 images and hyperintense on T2 images (*16*). In our case, there were many hypoechoic solid lesions; the hepatic artery diameter and liver vascularization increased and there was no hepatic venous thrombus. An abdominal dynamic MRI showed homogenous contrast uptake in the lesions. The patient was diagnosed with IHHE based on these findings.

In IHHE, the most common symptom is abdominal distention. In case of rapidly progressing IHHE, cardiac failure may lead to life-threatening complications such as respiratory distress and consumption coagulopathy (*6-8*). Our patient presented with the complaint of abdominal distention. During the follow up, he developed hypoxemia and needed oxygen support.

Hypothyroidism may also occur as a complication of IHHE (*11,12*). Hypothyroidism has been shown to be associated with type 3 iodothyronine deiodinase activity inside the tumor (*20,21*). This enzyme deiodinates thyroxin, thereby converting it into the biologically inactive form, triiodothyronine. A clinical manifestation, termed consumption hypothyroidism, occurs as a result of thyroid hormone inactivation exceeding the capacity of the thyroid hormone, which is synthesized by the thyroid gland (*18,19*). The biochemical features of this manifestation are very similar to the manifestations observed in primary hypothyroidism; however, the function of the thyroid hormone is normal and thyroid hormone replacement is needed to correct hypothyroidism. In our patient, we detected no structural or functional abnormalities in the thyroid gland by ultrasound or scintigraphy. Therefore, we attributed hypothyroidism to the activity of the type 3 iodothyronine deiodinase, which was secreted from the tumor tissue. The suppression of TSH along with a reduction in the tumor supported this idea.

The parameters affecting the treatment decision include the severity of the symptoms and the tumor size. There is no consensus on the mode of treatment. However, the use of systemic corticosteroids has become the mainstay of treatment (*12*). The mechanism of action for this treatment remains unclear. However, it is thought that the proliferation of endothelial cells and smooth muscle cells is inhibited and thus, reduction is achieved. Generally, prednisolone (2-3 mg/kg/day) is administered. After 2-3 weeks of medication, the drug is gradually reduced and used for 2-3 months. Recent studies have reported that complete or partial resolution is achieved in lesions with propranolol use (*13,14*). Some of the proposed hypotheses associated with propranolol's effects on hemangiomas include vasoconstriction, decreased renin production, inhibition of angiogenesis, and stimulation of apoptosis (*20,21*). Hepatic artery ligation or embolization may be performed in patients with severe symptoms and are refractory to medical treatment (*12*). Our patient had partial response to combined therapy with steroid and propranolol.

In conclusion, IHHE may manifest with massive hepatomegaly and respiratory distress during infancy and lead to life-threatening complications. Radiologic imaging is generally sufficient in making a diagnosis. Therapeutic decisions should be based on the severity of the symptoms and a propranolol and methylprednisolone combination may be useful in patients with severe symptoms.

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