The association of consumptive hypothyroidism secondary to hepatic hemangioma and severe heart failure in infancy

Suna Emir¹, Filiz Ekici², Mehmet Alper İkiz¹, Sadi Vidinlisan³

¹Pediatric Oncology Unit, The Ministry of Health Ankara Children's Diseases Hematology Oncology Training and Research Hospital, Ankara, Turkey

²Pediatric Cardiology Unit, The Ministry of Health Ankara Children's Diseases Hematology Oncology Training and Research Hospital, Ankara, Turkey

³Pediatric Endocrinology Unit, Ankara Koru Hospital, Ankara, Turkey

Abstract

Although hemangiomas are the most common vascular tumors of the liver in infancy, data regarding hypothyroidism and heart failure related to hepatic hemangiomas are limited. Here, we present a 15-day-old girl who presented with prolonged jaundice at the age of 15 days. Because her TSH level was found to be 74 μ IU/mL, she was initially diagnosed with congenital hypothyroidism and L-Thyroxine replacement therapy was initiated. On follow-up examination performed two months later, it was observed that her TSH level was not suppressed and a mass was noticed in the right upper abdomen on physical examination. Abdominal ultrasonography revealed multiple masses with sizes of about 3-3,5 cm covering the whole liver. When evaluated with clinical and radiological appearance, oral methylprednisolone at a dose of 5 mg/kg/day and propranolol at a dose of 2 mg/kg were initiated with a diagnosis of hepatic hemangioma/hemangioendothelioma. Consumptive hypothyroidism due to hepatic hemangioma and congestive heart failure were considered in the patient who had findings of heart failure. The dose of L-Thyroxine was increased 2-fold. The patient received intensive care treatment for severe heart failure. Because his findings resolved, he was started to be followed up with propranolol, steroid and L-Thyroxine treatment.

(Turk Pediatri Ars 2016; 51: 52-6)

Keywords: Hypothyroidism, hepatic hemangioma, heart failure, infant

Introduction

Primary hepatic tumors occur rarely in children and constitute 0,5-2% of all childhood tumors (1). The main vascular hepatic tumors which have been reported in infancy and young children include hemangioendothelioma, cavernous hemangioma, malign epitheloid hemangioendothelioma and angiosarcoma. Hepatic hemangioma in infancy is the most common benign hepatic tumor of infancy which is manifested in the first six months of life with a rate of 85%. Some authors also use the term "infantile hepatic hemangioendothelioma" (2). It may be manifested with abdominal distension, hepatomegaly, heart failure due to arteriovenous shunt, Kasabach-Merrit syndrome, intraabdominal bleeding, cholestasis and gastrointestinal tract obstruction or

may accidentally be found on abdominal ultrasonography (3-7). Hemangioma and associated severe hypothyroidism developing secondary to increased type tree iodothyronine deiodinase was reported in 2000 for the first time (8). A patient who was found to have hepatic hemangioma on ultrasonography (USG) performed because of abdominal distension during the period when he was being followed up because of congenital hypothyroidism in the outpatient clinic of endocrinology and who developed secondary heart failure will be presented.

Case

A female baby who was born at term by normal vaginal delivery with a birth weight of 3 700 g as the

Address for Correspondence: Suna Emir E-mail: sunaemir@yahoo.com

Received: 16.08.2013

Accepted: 20.01.2014

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DOI: 10.5152/TurkPediatriArs.2016.1548

Figure 1. Abdominal magnetic resonance imaging: hyperintense masses covering the liver with markedly increased vascularization on T2-weighted imaging

Table 1. Main laboratory findings at presentation

Complete blood count	
Hemoglobin	9.4 g/dL
Leucocytes	4 800/mm ³
Hematocrite	28%
Platelets	447 000/mm ³
MCV	84/fL
Biochemistry	
Urea/Creatinine	13/0.17 mg/dL
AST/ALT	63/19 IU/L
T. Bilirubin/D. Bilirubin	18.2/1.02 mg/dL
Na/K	138/3.6 meq/dL
Thyroid function tests	
Total T3	0.7 ng/mL
Total T4	11.5 µg/dL
fT3	1.78 pg/mL
fT4	1.3 ng/dL
TSH	74.2 µIU/mL

ALT: alanine aminotransferase; AST: aspartate aminotransferase; D bilirubin: direct bilirubin; fT3: free T3; fT4: free T4; MCV: mean corpuscular volume; T Bilirubin: total bilirubin; T3: triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone

fourth child of a 24-year old mother presented to our pediatric endocrinology outpatient clinic because of prolonged jaundice when she was 15 days old. Physical examination revealed the following findings: body weight: 4 130 g (50-75 p), height: 55 cm (75 p), head circumference: 37 cm (75 p), general status:

well. The skin was icteric and the liver was palpable 2 cm below the costal margin. The other systems were evaluated to be normal. The main laboratory findings at presentation are shown in Table 1.

Thyroid USG performed because of hypothyroidism revealed that the right lobe had a size of 9x9.5 cm and the left lobe had a size of 8x10 cm and the parenchymas of both lobes and isthmus were homogeneous. No nodule was observed on ultrasonography. Levothyroxin sodium at a dose of 37.5 µg /day was initiated with a diagnosis of congenital hypothyroidism. Abdominal distention and increase in hepatomegaly was found during the follow-up visit two months later. A blue-purple vascular lesion with a size of 2x1 cm was observed on the right lumbar region in the patient whose liver was palpable 6 cm below the costal margin. A II/VI systolic murmur was heard on the left second intercostal area on cardiac auscultation. It was observed that the TSH level was not suppressed despite treatment (TSH: 49 µIU/mL, total T3: 0.849 ng/mL, free T3: 3.22 pg/mL, Total T4: 15.9 µg/dL, free T4: 2.06 ng/dL). With the recommendation of the endocrinology clinic the dose of thyroid hormone was increased to 75 µg/day.

Multiple hypo-isoechoic lesions covering the whole hepatic parenchyma the largest one having a size of 3x3.5 cm were observed on abdominal USG and masses with regular contours covering the whole liver the largest one having a size of 4 cm with marked increased hyperintense vascularization on T2-weighted imaging were observed on abdominal magnetic resonance imaging (MRI) (Figure 1). When clinical and radiological appearances were evaluated together, hepatic hemangioma/heangioendothelioma was considered and oral methylprednisolone at a dose of 5 mg/kg/day and propranolol at a dose of 2 mg/kg was initiated. It was thought that consumptive hypothyroidism related with increased type 3 iodothyronine deionidase enzyme secreted by hepatic hemangioma might be present. However, type 3 iodothyronine deionidase enzyme activity could not be demonstrated because of technical impossibilities.

On the initial transthoracic echocardiographic examination, peripheral pulmonary stenosis within physiologic limits and patent foramen ovale were found. Echocardiographic examination was repeated because peripheral cyanosis, decreased blood pressure and tachycardia were found during the follow-up.

Echocardiography revealed systolic dysfunction, third degree mitral failure and left ventricular enlargement which were considered loading findings. The patient was hospitalized and subcutaneous morphine sulphate, furosemide (2 mg/kg/day), dopamine and dobutamine were initiated. Administration of interferon was planned in the follow-up. However, this treatment was postponed, because regression up to 1 cm was found in the lesions on follow-up abdominal USG. Propranolol and steroid treatment was continued. Follow-up echocardiogram revealed that enlargement in the cardiac chambers and systolic dysfunction improved and mitral failure decreased. Intravenous positive inotropic therapy was discontinued and oral digoxin and furosemide treatment was initiated. The dose of methylprednisolone was decreased to 2 mg/kg/day and the patient was discharged to continue levothyroxine sodium treatment at a dose of 75 µg/day. At the follow-up visit one month after treatment, the laboratory findings were as follows: TSH: 4.9 µIU/mL, total T3: 0.4 ng/mL, free/T3: 1.85 pg/mL, total T4: 10.6 µg/dL and free T4: 1.26 ng/dL. On abdominal USG, marked reduction was found in the lesions which covered the whole hepatic parenchyma with the largest one in the right lobe having a size of 8x15x17 mm. The dose of methylprednisolone was decreased to 1 mg/kg/day and the patient was invited for a follow-up visit one month later. It was found that the patient did not come for follow-up visits and it was learned that he was lost at home with respiratory distress two months after discharge and steroid and thyroid hormone treatment was not given regularly because of familial problems. Verbal consent was obtained from the family.

Discussion

Hepatic hemangioma/hemangioendothelioma is the most common hepatic tumor of infancy. It is mostly manifested with abdominal mass in the first six months of life and may accompany a cutaneous hemangioma. It occurs with a two-fold higher rate in girls. On USG, it is observed as solitary or multiple hypoechoic lesions. On MRI, it is observed as a clear round mass which is hypointense on T1-weighted images and hyperintense on T2-weighted images. The diagnosis is primarily made by way of USG and MRI in cases of infantile hepatic hemangioendothelioma (IHH). Liver biopsy is generally not recommended, because it may lead to life threatening hemorrhage (2-4). Similarly, hepatic hemangioma

was considered radiologically in our patient and biopsy was not performed because of risk of bleeding. Because of abdominal distension restlessness, respiratory distress, vomiting, anemia and thrombocytopenia may be observed in these patients (4).

Congestive heart failure and consumptive coagulopathy may develop depending on the size of the hemangioma. Peripheral vascular resistance is decreased because of large arteriovenous shunts and more blood volume and cardiac output is required for perfusion of the vascular bed. This results in development of high output heart failure (6). In a study in which the clinical features of 23 patients diagnosed with hepatic hemangioma in infancy were evaluated, it was reported that high output heart failure developed in 30% of the patients and hypothyroidism developed in 22% (7). Among these patients, surgical treatment was performed in one in whom unilobar tumor was found, hepatic artery embolization and/or medical treatment was performed in three patients in whom the tumor showed a diffuse involvement and exitus was reported only in one patient.

Another complication which may be observed in IHH is development of severe hypothyroidism in relation with production of type 3 iodothyronine deiodinase enzyme (8-11). Increased thyroxine hormone catabolism in the tumor may lead to symptoms of severe hypothyroidism. Association of hepatic hemangioendothelioma and advanced hypothyroidism was reported in an infant by Huang et al. (8) for the first time. Thyroxine treatment was given at a dose higher than the routine dose to suppress TSH in this patient. Active T4 and T3 are transformed to inactive metabolites rT3 and 3'-diiodothyronine because of increased synthesis of type 3 iodothyronine deiodinase enzyme in the tumor tissue. Increased inactivation of thyroid hormone leads to hypothyroidism by exceeding the capacity of synthesis of the thyroid gland. In these patients, higher doses of L-Thyroxine are needed to provide euthyroidism (8). Euthyroid state could not be provided with a thyroid hormone dose of 37.5 µg/kg/day in our patient and the dose was increased two-fold. Similar cases were reported after the first case report of Huang et al. (8, 9-13). Çetinkaya et al. (12) reported a one-month old patient who was diagnosed with hypothyroidism during the neonatal period, whose TSH level could not be suppressed with routine thyroid hormone dose and who was found to have hepatic hemangioendothelioma during the

follow-up. It was reported that heart failure developed in the follow-up in this patient in whom methyl prednisolone and interferon were initiated for hepatic hemangioendothelioma, the patient was treated by using high dose T3 and T4 preparations in combination, the hepatic lesions were reduced and hypothyroidism improved at the end of the first year and thyroid hormone treatment was discontinued. Kalpatthi et al. (13) reported a four-year old patient who had heart failure and hypothyroidism related with hepatic hemangioma. It was reported that the TSH level was 53,3 μ IU/mL in this patient and high dose thyroid hormone (112 μ g/day) was used to suppress TSH.

Treatment of hemangiomas in infancy is still controversial. Asymptomatic patients may be monitored with serial USG until spontaneous regression occurs. Propranolol, steroid and interferon are used to provide tumor reduction. It has been shown that thyroid functions return to normal, when hepatic tumor is treated efficiently with these methods (3, 8).

The most important factors which affect the natural course of this disease and survival include presence of heart failure and/or jaundice (7). It was thought that heart failure developed in our patient in relation with decreased contraction and increased cardiac output. In addition, the negative effect of hypothyroidism on cardiac functions might also have aggravated high output heart failure. Although heart failure was successfully treated in our patient, the patient was lost, because thyroid replacement treatment and treatment for hemangioma were not given regularly by the family. In treatment of congenital hypothyroidism, it is appropriate to examine patients with six-month intervals when TSH levels decrease to normal levels, but follow-up visits should be performed more frequently in patients with consumptive hypothyroidism.

In conclusion, IHH generally has a benign prognosis, but development of heart failure and hypothyroidism may increase the morbidity and mortality. Free T4, tT4 and TSH levels should be measured in patients with large hemangiomas especially in the liver and one should be careful in terms of heart failure. In addition, an underlying hepatic hemangioma should definitely be kept in mind in patients who have been diagnosed with hypothyroidism during the neonatal period and who have not responded to high dose thyroid hormone therapy.

Informed Consent: Verbal informed consent was obtained from patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.E., F.E., A.İ.; Supervision - A.İ., S.E.; Literature Review - S.E., F.E., A.İ.; Writing - S.E., A.İ.; Critical Review - S.V.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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