We present a case of a 41-day-old girl with diffuse hemangiomatosis on her chin, right thigh, occipital area, and liver. She also had hepatomegaly, heart failure, and hypothyroidism. Hemangiomatosis did not respond to 2 weeks of oral administration of prednisolone, but was successfully treated with propranolol. After 2 years of propranolol treatment, the lesions of hemangiomatosis nearly disappeared. Hypothyroidism was controlled by levothyroxine replacement. As hemangiomatosis regressed, thyroid function was normalized. Propranolol may have adverse effects including hypotension, hypoglycemia, bronchoconstriction, and restlessness, but she did not experience such adverse effects. Propranolol could be the first choice for diffuse neonatal hemangiomatosis (DNH). Our case also suggests that thyroid function test is needed in patient with DNH.

Key Words: Diffuse neonatal hemangiomatosis, Propranolol, Liver hemangioma

Introduction

Hemangioma is a common vascular tumor in infant, and its prevalence is about 5-10% of all infants [1]. Most of the lesions are restricted to skin, which is considered benign [1]. But some infants may have other visceral organ involvement of hemangioma [2]. Diffuse neonatal hemangiomatosis (DNH) is a condition of multifocal cutaneous hemangiomas with or without involvement of other visceral organs, usually the liver [2]. Obstructive jaundice with hepatomegaly and large shunt causing heart failure are well-known complications [3]. Central nervous system involvements such as brain hemangioma with hemorrhage, cystic change, and perivascular edema have also been reported [3]. Traditionally, systemic corticosteroid is the main treatment, while surgical resection can be performed in refractory cases [4]. Other pharmacologic drugs including interferon alpha-2b and vincristine/vinblastine are also treatment options [5]. Recently, propranolol has been shown to be effective with less adverse effects [5]. We present a case of DNH accompanied by hypothyroidism which was successfully treated with propranolol and levothyroxine replacement.
Case Report

A 41-day-old girl was referred from the department of dermatology for the evaluation and treatment of multiple hemangiomas on scalp, right thigh, and left chin (Fig. 1). Hepatomegaly and cardiomegaly were also noted. She was the first child and born by normal vaginal spontaneous delivery after an uncomplicated pregnancy except preterm birth. Her gestational age was 36+5 weeks and birth weight was 2.6 kg. Neonatal screening tests showed normal range of thyroid-stimulating hormone (TSH) level (4.8 μIU/mL).

On her visit, body weight was 4.4 kg. She had no family history of hemangiomas, tumors, or congenital malformation. Her mother found erythematous nodule on right thigh at birth, and additional erythematous nodules on left chin and right occiput 4 days after birth. On physical examinations, her liver was palpated about 5 cm below the costal margin. Grade 2-3 of systolic murmur was audible on her left chest. Ultrasonography of the liver revealed multiple variable sized hemangiomas. Chest X-ray showed cardiomegaly and pulmonary congestion (Fig. 2). Echocardiography revealed secundum atrial septal defect sized 1.8 mm and mild mitral regurgitation with normal heart function. Laboratory tests showed mild anemia (Hb 8.0 g/dL), normal platelet count (317,000 /μL), normal free T4 (1.12 ng/dL, normal range: 0.9-2.6 ng/dL), normal total T3 (62.62 ng/dL, normal range: 60-159 ng/dL), and elevated TSH (100.0 μIU/mL, normal range: 1.7-9.1 μIU/mL). Otherwise, no significant abnormalities were found. Whole body magnetic resonance imaging (MRI) showed multiple well-enhanced lesions in the liver, pleural cavity, and the skin (right thigh, left lower leg, left forearm, back area, left mandibular area, and scalp), which was compatible with DNH (Fig. 3). Besides cardiomegaly and pulmonary congestion, she had symptoms suggesting heart failure such as poor oral intake and decreased physical activity. To control heart failure, digoxin, furosemide, and spironolactone were started. Although oral prednisolone (2.0 mg/kg/day) was given for 2 weeks in the department of dermatology before referral to our department, there was no improvement of hemangiomas. Propranolol was started at a dose of 1.0 mg/kg/day, and then increased to 1.5 mg/kg/day at 5 days, while oral prednisolone was tapered over a month. During administration of propranolol, her blood pressure, heart rate, respiration rate, and serum glucose were closely monitored and maintained in the normal range. To replace thyroid hormone, levothyroxine was started at a dose of 10 μg/kg/day.

Two months later, hemangiomas on occipital area disappeared, while skin lesions on chin and thigh decreased in size. Three months later, thyroid function test showed euthyroid state and the dose of levothyroxine was de-

Fig. 1. Hemangiomas in left chin and right thigh with hepatomegaly at the age of 41 days. She had been prescribed oral prednisolone for about 2 weeks.

Fig. 2. Cardiomegaly with pulmonary congestion on chest X-ray.
creased to 5 μg/kg/day. At this time, the medications for heart failure were also discontinued, since cardiomegaly was improved on chest X-ray. Four months later, follow-up ultrasonography revealed a marked improvement of hepatic lesions. Two years later, propranolol was tapered over 2 months and then finally discontinued (total duration of administration: 25 months). Levothyroxine was maintained until 3 year of her age (total duration of administration: 34 months).

On the imaging study at 3 years of annual follow-up, further decrease of hepatic hemangiomas was noted. The skin lesions almost disappeared, and no additional treatment was required.

**Discussion**

Infantile hemangioma (IH) is usually a benign disorder, presenting within a few weeks after birth [4]. It rapidly grows between 1 and 2 months of life, and then slowly regresses by age 5 to 7 [4]. The pathophysiology remains unknown. Histologically, it is the proliferation of benign endothelial-like cells that have GLUT-1, Lewis Y antigen, FcyRII, and merosin markers [6]. A hypothesis suggested that it originates from placenta, and the placental theory explains its natural history of a rapid growth followed by a gradual involution [6]. It is also supported by the histochromatographic and genetic similarities between IH and placenta [6]. Although most hemangiomas are presented with cosmetic problems such as disfiguration of skin, severe complications can be accompanied depending on its location or involvement of other organs. Periorbital lesions can cause amblyopia or visual loss [7]. Airway complications have also been reported in a patient with airway IH such as subglottic IH [8]. In case of lumbosacral IH, it may involve intraspinal area and requires evaluation with spinal ultrasonography [9].

DNH is characterized by neonatal onset, no evidence of malignancy, and multiple organ involvement [2]. Liver is the most common organ that is involved [2]. Hepatic hemangioma is the most common infantile hepatic tumor [10]. Most of them are asymptomatic, but large shunt can cause high-output heart failure and failure to thrive [10]. Consumptive hypothyroidism can also be associated with a large vascular lesion. Type 3 iodothyronine deiodinase prevents T4 activation and inactivates T3. The overexpression of type 3 iodothyronine deiodinase in the hemangioma tissue is considered to be the cause of hypothyroidism [11]. Hypothyroidism may not be detected in neonatal screening program as in our case, because it develops after tumor size is increased. Thyroid hormones are critical for the development of child, especially in infant. Both heart failure and hypothyroidism can lead to the delay of growth and neurological development. Thus, careful evaluation including thyroid function test is needed in case of patient with DNH.

Many medications have been used for DNH, including corticosteroid, interferon, and vincristine [5]. Although these drugs had been shown to be effective, they are sometimes associated with significant adverse effects such as growth
retardation, spastic diplegia, or hematologic toxicity [12]. Propranolol, a non-specific beta-blocker, is becoming one of the main therapeutic agents for DNH. Many literatures showed its efficacy with minimal adverse effect [5,12]. Although precise mechanisms are yet to be investigated, it may act by inducing vasoconstriction or suppressing vascular endothelial growth factor or other proangiogenic cytokines such as matrix metalloproteinase [13]. Other hypothesis is that propranolol prevents immature progenitor cells from differentiating into endothelial cell or pericytes [13]. Known adverse effects of propranolol are bradycardia, hypotension, hypoglycemia, and bronchoconstriction, presented by lethargy, restlessness, delayed capillary refill time, dyspnea, etc [14]. In a systemic review, (asymptomatic) hypotension was the most common serious adverse effect (13.1%) followed by hypoglycemia (11.4%), (asymptomatic) bradycardia (8.7%), and pulmonary symptoms (8.0%) [14]. Even though the optimal dose and treatment duration have not yet been determined, propranolol was used at doses of 1.5-2.0 mg/kg/day in the reported cases [15]. Further studies are needed to figure out the optimal dosing and duration according to the extent and severity of the disease.

Our case showed a successful treatment of DNH using propranolol with no adverse effect. There was no progression or exacerbation of the tumor after discontinuing the drug. As hemangioma regressed, cardiomegaly improved and the need for thyroid hormone replacement decreased. Propranolol could be the first choice for diffuse neonatal hemangiomatosis. Our case also suggests that thyroid function test is needed in patient with DNH.

References