Cases Report

Diffuse Neonatal Hemangiomatosis: Report of 5 Cases

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Diffuse Neonatal Hemangiomatosis (DNH) is a rare, life-threatening condition associated with a few to hundreds of small, cutaneous and visceral hemangiomas. The authors reported 5 cases of DNH in which hepatic hemangioma were the most common visceral involvement. Response to prednisolone in these cases was not good, one died and four required second line therapy. Of these four cases, one case with embolisation; one with interferon and two with vinblastine. Response to vinblastine was good, but long-term follow-up of the side effects are needed.

Keywords: *Diffuse neonatal hemangiomatosis, Prednisolone, Interferon, Vinblastine*

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Hemangiomas are the most common benign tumor of childhood, and usually present at birth or during the first few months of life[1]. Benign neonatal hemangiomatosis originally proposed by Stern et al[2] consists of numerous hemangiomas occurring exclusively in the skin and following a benign course with spontaneous resolution[3]. Diffuse Neonatal Hemangiomatosis (DNH), which is characterized by multiple hemangiomas affecting the skin and visceral organs, is often associated with a poor prognosis[4]. Treatment of DNH includes high-dose systemic corticosteroids, interferon-alfa 2b and hepatic artery embolization[5-8].

The authors described five children with neonatal hemangiomatosis, four of them had hepatic involvement. Two patients who did not respond to high dose prednisolone were successfully treated with vinblastine.

Case Report

Patient 1

A 2-month-old male infant was admitted to King Chulalongkorn Memorial Hospital because of hematemesis and melena. At birth, the patient had multiple petechiae on the trunk and extremities without clinical bleeding. The physical examination was otherwise normal. The petechiae gradually developed into 50 bright red papules that varied in size from 5-10 mm on the back, the abdomen, the extremities, and the upper gum. Neurological examination and all the rest of the physical examination were within normal limits. Ophthalmic examination revealed a suprachoroidal hemangioma size of 7.7 mm in diameter in the right eye. Radiography of long bone revealed cystic lesions at metaphysis of the femur and the humerous. Skull films demonstrated many cystic lesions at the parieto-occipital region. A Computed Tomographic (CT) scan of the brain was normal. He had initial good response to prednisolone 5 mg/kg/day. While tapering off the medication slowly at 7months of age, he developed hematemesis and melena again. Predenisolone was then steps up to 2 mg/kg/day. The patient had severe GI bleeding at the age of nine months and expired.

Patient 2

A 14-week-old male infant was born with hemangiomas at the umbilicus, the buttock and the left nipple since birth. When the patient was 6 weeks of age, he was hospitalized because of pneumonia and heart failure. At the age of 12 weeks, he was referred to King Chulalongkorn Memorial Hospital because of intractable heart failure.

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On physical examination, he had respiratory distress. Hemangiomas, size 1 x 1 cm in diameter, were presented at the left nipple, 1.8 x 2.5 cm at the umbilicus and 2 x 3 cm on the buttock. Approximately 19 hemangiomas of various sizes from 0.1 to 0.5 cm in diameter were scattered over the face, the trunk and the extremities (Fig. 1). The abdomen was distended and the liver was 2 cm below the right costal margin with bruit at right upper quadrant area.

CT scan of the abdomen showed hepatomegaly with evidence of multiple hemangiomas in both lobes of the liver. CT scan of the brain showed no abnormality. Laryngoscope showed no abnormal mass. The patient had been treated with oral prednisolone (3 mg/kg/day), diuretics, and digoxin for three months without improvement. He also had pneumonia during the admission. The hemangiomas continued to increase in size and number, and the hemangiomas in both lobes of the liver showed no significant change under ultrasonography.

An angiogram revealed a large hepatic artery, 0.8 cm in diameter with generalized AVM in both lobes of the liver. Embolization was performed via a branch of the ciliac trunk. After embolization, the clinical signs of congestive heart failure were improved and the hemangiomas in both hepatic lobes were markedly decreased in size and vascularity. Corticosteroid was gradually discontinued.

Patient 3

A six-week-old female infant had discrete erythematous papules on the chest wall on the ninth day of life, and they scattered over the trunk, the extremities, the scalp and the face six days later. She had fever and dyspnea and was treated as pneumonia in the primary care center. She was referred to King Chulalongkorn Memorial Hospital because of respiratory failure. The patient developed upper gastrointestinal bleeding thereafter.

On examination, there were 284 papules, ranging from 0.1 to 0.5 cm in diameter, over the scalp, the face, the trunk and the extremities (Fig. 2). The liver was 4 cm below the right costal margin and suspected bruit on the right side.

The chest X-ray roentgenogram demonstrated cardiomegaly, and pulmonary infiltration. Echocardiogram was normal. Endoscopy revealed gastric hemangiomas.

CT scan of the upper abdomen revealed multiple hemangiomas in the liver and the spleen. Skin biopsy showed proliferation of capillaries and endothelial cells in the upper and deep dermis. There was no proliferation of endothelial cells into the tumor of blood vessels (no evidence of angioendotheliomatosis in the section).

The patient was treated with digitalis, diuretics, inotropic drugs and parenteral antibiotics. Intra-

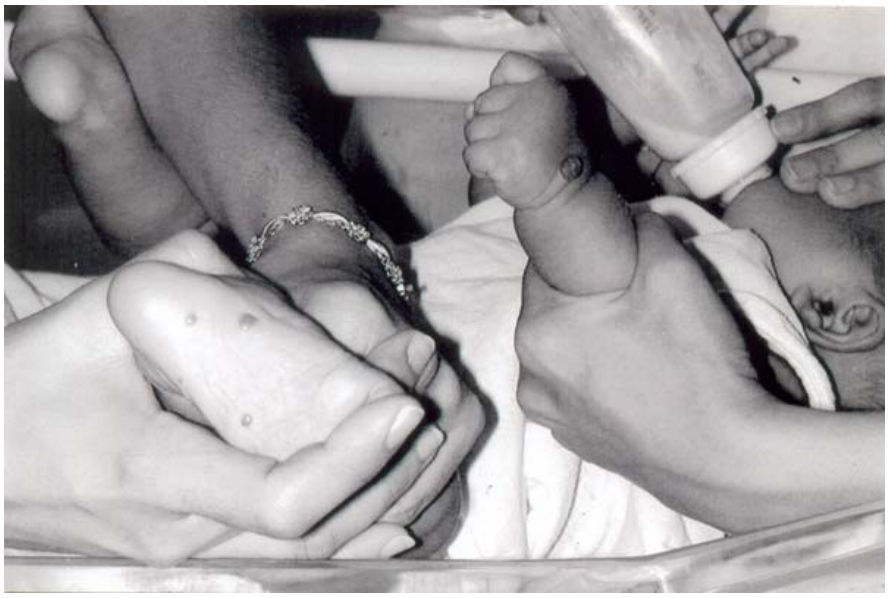


Fig. 1 Patient 2. A male infant has hemangioma at the umbilicus, left nipple, mons pubis, extremities

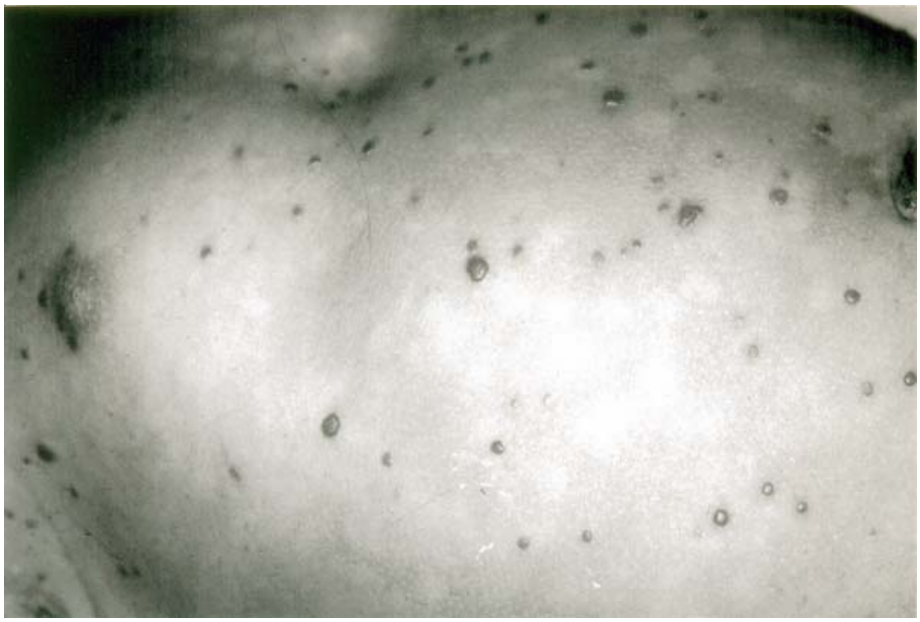


Fig. 2 Patient 3. Numerous small hemangiomas on the trunk

venous hydrocortisone was given and was later changed to oral prednisolone (2 mg/kg/day). She developed high blood pressure and there was no reduction of the liver lesion by ultrasonogram. Interferon-alfa 2b (3MU/m^2/day) was added, the clinical of heart failure was improved in 2 weeks and the skin lesions began to reduce in size. The patient was discharged from the hospital with prednisolone, interferon, diuretics and digitalis but was later lost to follow-up.

Patient 4

A female infant presented dyspnea when feeding at the age of 6 weeks. Physical examination revealed bright red papules, diameter of 3 mm, on the right side of her face, on the left chest wall, two lesions on the lower abdomen, one lesion on the right knee, a lesion on the right fifth finger, diameter 1 x 1.5 cm, and diameter 1 x 1 cm on the medial side of her left foot.

There was to-and-fro murmur grade 4 at the left parasternal border. The abdomen was distended, the liver was 3 cm below the right costal margin and the spleen was 2 cm below the left costal margin.

CT scan of the abdomen revealed diffuse well-defined hypodensity lesions, size 1 to 10 cm with dense enhancement throughout the entire liver from the peripheral sites. Marked hepatomegaly and prominent hepatic veins were also noted. CT scan of the brain showed normal study.

Chest roentgenogram demonstrated cardiomegaly with pulmonary congestion. Echocardiogram showed normal cardiac study, with multiple large hepatic hemangiomas with diastolic heart failure (high output failure).

The patient was treated with digoxin, dichlotride, aldactone and oral prednisolone (3 mg/kg/day). This regimen alleviated her symptoms, but a liver sonogram appeared unchanged. Vinblastine (0.15 mg/kg/wk) was added and prednisolone was gradually tapered off. Symptoms and signs of congestive heart failure and skin lesions improved at the second dose of vinblastine. The regression of hepatic hemangiomas was almost complete after 10 doses of vinblastine.

Patient 5

A 3-month-old female infant presented dyspnea and hoarseness of voice. Hemangiomas were noted on the trunk and extremities since the age of 2 weeks and gradually increased in size and number.

Physical examination revealed hoarseness of the voice, moderately suprasternal and mild subcostal retraction. Eighteen, hemangiomas of various sizes from 0.1 to1 cm were found over the trunk, the scalp and the extremities. All other physical findings were normal.

Abdominal ultrasonogram showed multiple hepatic hemangiomas (Fig. 3a). Echocardiography revealed a small ASD, 3 mm in diameter, with right

ventricular hypertrophy but without any evidence of congestive heart failure.

Oral prednisolone 3 mg/kg/day was started, however the patient developed congestive heart failure one month later. On examination, the liver was palpable 3cm below the right costal margin. Auscultation revealed rales in both lungs.

Chest roentgenogram demonstrated marked cardiomegaly with evidence of pulmonary venous congestion. Laryngobronchoscopy showed small supraglottic hemangiomas at the midline of posterior aryepiglottic fold and a small erythematous vascular-like nodule was observed between both corniculate tubercles.

Prednisolone was increased from 3 to 4 mg/kg/day with some improvement, but the patient developed hypertension. Calcium channel blocker was also added to control hypertension. Vinblastine (0.15 mg/kg/wk) was added. Congestive heart failure was improved and prednisolone was gradually tapered off. After nine doses of vinblastine, the cutaneous and hepatic hemangiomas had almost completely disappeared (Fig. 3b).

Discussion

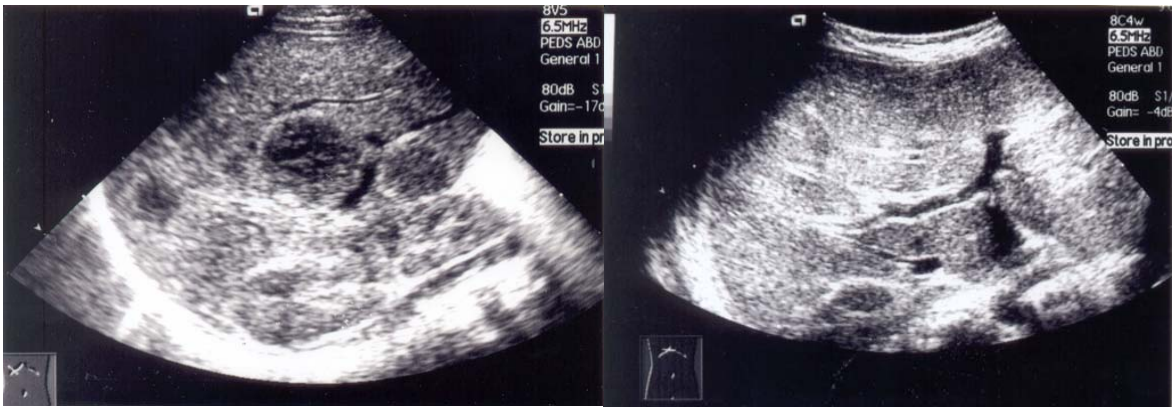
DNH is rare and frequently a fatal disorder. Death is often due to congestive heart failure or gastrointestinal hemorrhages. Typically these lesions have their onset at birth or during the first month of life. The liver is the most common extracutaneous site (64%) but virtually any organ may be affected including the brain (52%), the gastrointestinal tract (52%), the lungs (52%), the oral cavity (44%) and the eyes (32%)[1].

The majority (4/5) had hepatic hemangiomas. The gastrointestinal tract, spleen, bone, eye and larynx were also affected. Four patients with DNH (one boy and 3 girls) presented with congestive heart failure. One of the four patients also had signs of upper airway obstruction and supraglotic hemangioma was confirmed by laryngoscopy.

Like isolated hemangiomas, DNH proliferates and then involutes, but extracutaneous involvement may lead to a life threatening complication. Death usually occurs within the first 10 weeks of life as a result of AV shunting in the liver causing increased cardiac output and congestive heart failure. In addition, other complications include gastrointestinal hemorrhage, obstructive jaundice and consumptive coagulopathy may occur[10]. Without any treatment, the mortality rate was 77%[10], but with appropriate treatment the mortality was reduced to 27%. Management should be directed to its specific clinical manifestation.

Systemic corticosteroids are the main treatment for hemangiomas that are causing functional impairment or life threatening[5]. The recommended starting dose is generally 2 to 3 mg/kg/day of prednisolone. Higher doses are sometimes used for severe cases, such as hemangiomas that cause airway obstruction. Common complications include cushingoid appearance, hypertension and gastrointestinal upset.

All of the presented patients were treated with prednisolone at the dosages of 2 to 4 mg/kg/day without improvement; one patient died, four needed second line therapy.



a b

Fig. 3 Patient 5 Ultrasonography of liver before (a) and after (b) nine doses of vinblastine

Table 1. Patient's clinical data and outcome

Age of onset of hemangioma/Sex	Presenting symptoms	No.of skin lesion	Organ involvement/Investigation	Treatment	Outcome
Birth/Male	GI bleeding at 8 weeks of age	50	GI: upper gum and gastric hemangioma/Gartroscopy Eye: suprachoroidal/Fundoscopy Bone: parieto-occipital, femur, humerous/X-ray	Prednisolone (max 4 mg/kg/day), cimetidine 5 mg/kg/day, Antacid	Initial good response, after tape prednisolone to 2 mg/kg/day, GI bleeding and death at 9 months
Birth/Male	CHF at 6 weeks of age	22	Liver: multiple hemangioma on both lobes/CT	Prednisolone 3mg/kg/day, ddigoxin, iuretics, hepatic artery embolization	No recurrence for 5 years
9-days-old/Female	Pnemonia and CHF at 6 weeks of age GI bleeding at 7 weeks of age	284	GI: gastric hemangioma/gastroscopy Liver: multiple hemangioma lobes/CT Spleen: multiple hemangioma/CT	Prednisolone 3mg/kg/day, digoxin, diuretics, IFN-α 2b	Clinical improve after 2 weeks of IFN-α 2b but the patient loss to further follow-up
Birth/Female	CHF at 7 weeks of age	7	Liver: multiple hemangioma/CT	Prednisolone 3mg/kg/day, digoxin, diuretics, vinblastine	CHF improve after the second dose of vinblastine. No recurrence for 3 years
2-weeks-old/Female	CHF at 8 weeks of age Hoarseness of voice at 12 weeks of age	18	Liver: multiple hemangioma/US Supraglottic/ laryngo-bronchoscopy	Prednisolone 3mg/kg/day, digoxin, diuretics, vinblastine	CHF improve after the second dose of vinblastine. No recurrence for 3years

CHF: congestive heart failure, CT: computerized tomography, US: ultrasound, GI: gastrointestinal

Hepatic embolization is recommended for focal lesions with direct shunt as a means of controlling heart failure refractory to medical treatment[14] as in patient 3.

Interferon, a known inhibitor of angiogenesis, has been reported to treat vascular proliferation since 1989[6]. It slowly halts the growth of hemangiomas and may result in a higher rate of actual shrinkage than what is seen with corticosteroid. Interferon has been used to treat diffuse nenonatal hemangioma in a patient with congestive heart failure[8,14]. A worrisome complication is the occurrence of spastic diplegia[15] that limits the use to those infants with life-threatening hemangiomas, who have failed to respond to steroid therapy. When it is administered, neurologic status should be closely monitored. One of our patients (patient 3) was treated with interferon (3MU/m^2/day) because she did not respond to prednisolone and developed hypertension. After treatment with interferon for two weeks, her clinical status improved and was later discharged. She was lost to follow-up.

Vinca alkaloids, vincristine and vinblastine, have strong inhibition of angiogenesis. Vincristine was used successfully in 2 infants with large vascular tumors[16] and in another case of tracheal compression from vascular tumor with respiratory distress[17]. The authors successfully treated one case of Kasabach-Merritt syndrome with vincristine and another case with vinblastine[18]. Unfortunately, vincristine treatment resulted in reversible peripheral neuropathy. Vinblastine inhibits angiogenesis without cytotoxicity or cell necrosis[19]. Two of the presented patients (patient 4 and 5) responded well to weekly vinblastine without significant adverse effects. Because of its promising result, it should be further assessed as a first-line therapy for DNH.

In conclusion, the authors present 5 cases of diffuse neonatal hemangiomatosis. Treatment with prednisolone in these cases was not good, one died and four cases required second line therapy. Response to vinblastine was good, but long-term follow-up of the side effects are needed.

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Diffuse neonatal hemangiomatosis ในผู้ป่วย 5 ราย

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Diffuse neonatal hemangiomatosis (DNH) พบไม่บ่อย ผู้ป่วยอาจเป็นอันตรายถึงชีวิต ผู้ป่วยอาจมี hemangioma ที่ผิวหนังเพียงไม่กี่เม็ดจนถึงเป็นร้อยเม็ด และมี hemangioma ที่อวัยวะภายในร่วมด้วย ผู้นิพนธ์รายงานผู้ป่วย DNH 5 ราย โดยที่ 4 ราย hemangioma ที่ตับ ผู้ป่วยได้รับการรักษาด้วย prednisolone พบว่าไม่ได้ผล มี 1 รายที่เสียชีวิต และอีก 4 รายได้รับการรักษาด้วย embolization 1 ราย interferon 1 ราย และ vinblastine 2 ราย พบว่าได้ผลดี แต่ควรติดตามผลข้างเคียงในระยะยาว
