Bol Med Hosp Infant Mex 2013;70(1):35-40

Clinical case

Diffuse neonatal hemangiomatosis

Jonathan Maya,[1] Gerardo Blanco,[2] Rocío Maldonado[3]

ABSTRACT

Introduction. Diffuse neonatal hemangiomatosis is a rare entity and is a serious disorder in which multiple cutaneous and visceral hemangiomas are widely distributed and sometimes may be fatal. Complications include heart failure, bleeding, and liver failure, among others. Treatment is aimed at avoiding adverse effects and complications.
Case report. We report the case of a 53-day-old male patient who presented to the hospital for skin lesions and upper gastrointestinal bleeding. During his hospital stay, visceral hemangiomas were found in the lung, spleen and gastric mucosa. He was treated with interferon alpha-2b corticosteroids and hemangiomas of gastric mucosa were treated with argon plasma coagulation.
Conclusions. Disseminated neonatal hemangiomatosis is a rare entity and can be fatal if untreated. Our patient experienced a satisfactory evolution and is currently asymptomatic.

Key words: hemangioma, skin diseases, benign neoplasms.

INTRODUCTION

Diffuse neonatal hemangiomatosis (DNH) was first described by Lister in 1938.[1] Typically it appears during the first 2 months of life. Lesions occur with greater frequency in premature children and females (4:1 ratio with respect to males).[2,3] These lesions develop during the first trimester of pregnancy between 6 and 10 weeks of gestation. Masses of rapidly dividing endothelial cells with or without lumen and a multilaminated basement membrane are formed. During the involution phase, the lumen dilates, the endothelial cells thin and fibrous tissue is deposited. Those that involute completely contain few capillaries and veins with a flattened endothelium in a stroma of fibrous tissue, collagen and reticular fibers. Immunohistochemical studies show expression of CD31, von Willebrand factor and other proteins, which indicates a proliferative vascular origin.

Vascular lesions were systematically classified by Mulliken and Glowacki in 1982.[4] Since that time, few modifications have been made to the classification. Basically, vascular alterations have been divided into malformations and tumors. Malformations are errors of morphogenesis in which normal endothelial epithelium exists. Tumors (hemangiomas) are those in which a variable endothelial hyperplasia occurs; the latter may be congenital or acquired. Hemangiomas comprise the most frequent tumors during infancy. There are five varieties: congenital, deep, telangiectatic, arteriovenous shunt and multiple hemangiomas.

Multiple congenital hemangiomas are divided into benign neonatal hemangiomas, considered when the hemangiomas are found only on the skin and DNH when, in addition to those of the skin, various internal organs are affected.[5]

DNH is a serious disorder that occurs in 1–2.6% of term infants. During the first year, the frequency can increase to 10%.[2] One in four premature babies weighing <1000 g will develop at least one hemangioma.[2] Hemangiomas are located in various organs and can occur on the skin or affect any organ. They are usually associated with a poor prognosis, although malignant transformation is rare.

Frequency of Distribution

The distribution can be seen as listed below:[2, 3]

- Skin: 100%
- Liver: 64–100% (80% mortality without treatment)
- Central nervous system: 52%

1 Former Chief Resident
2 Asistencia Quirúrgica
3 Servico de Medicina Interna

Hospital Infantil de México Federico Gómez, México D.F., México

Received for publication: 7-3-12
Accepted for publication: 11-8-12

- Lungs: Progressive dyspnea, massive hemoptysis, pulmonary arterial hypertension (diagnosed according to pulmonary angiography and biopsy): 52%
- Gastrointestinal tract: 52%
- Periocular
- Lumbosacral region

A definitive diagnosis is necessary as there are many differential diagnoses such as capillary, venous and lymphatic malformations, fibrosarcomas, rhabdomyosarcomas, myofibromatosis, nasal glioma, encephalocele, lipoblastoma, dermatofibrosarcoma, and neurofibroma, among others.

TREATMENT

Multiple treatment options have been reported and are detailed below.

- *Corticosteroids.* Used to stop the proliferation of blood vessels and induce an early involution of hemangiomas. The response rate ranges from 30–50%, depending on the dose. Usual dose is 2–3 mg/kg/day for 1 month. Doses of up to 5 mg/kg/day have been used but are associated with a high rate of adverse reactions.[6]
- *Interferon 2b alpha*. Considered as a drug that inhibits angiogenesis, endothelial cell response, smooth muscle cells and fibroblasts with their respective growth factors, preventing progression and growth and even reduction of lesions.[7] Interferon is administered subcutaneously at a dose of 3 million U/m^2 SC/day for 6–10 months, with a regression rate of up to 70%. A better response was observed when pretreatment with corticosteroids is carried out.[6] Its use can be limited by its adverse effects.
- *Vincristine/vinblastine*. Possesses inhibitory effects on angiogenesis so they are used in life-threatening hemangiomas at a dose of 1–2 mg/m^2 SC/day for 4 months. However, adverse effects have been reported such as polyneuropathy or paralytic ileus, among others.[6,8]
- *Cyclophosphamide*. Inhibitory effect on angiogenesis, in addition to many side effects. For treatment of hemangiomatoses, these are rarely used due to the low dose and short therapeutic duration.
- *Radiotherapy.* Destroys immature blood vessels of rapid proliferation but has a high index of adverse effects. Therefore, it is no longer considered a therapeutic option.
- *Embolization and surgery*. Although these have shown high mortality rates of 43% and 20%, respectively, they are available alternatives.[6]

CLINICAL CASE

We present the case of a 53-day-old male who belonged to a family of low/medium socioeconomic status and was a native and resident of Taxco, Guerrero. No hereditary family history was noted for the actual ailment. The patient had complete age-appropriate immunizations. The clinical picture became evident from the time of birth with raised, red punctate lesions predominantly on the chest and extremities that did not disappear with digital pressure. At 7 days of life the patient experienced blood-streaked vomiting that was associated with an injury to the mother's nipple. At 14 days of life he presented for a health check-up at the health center and vitamin K was administered due to persistent skin lesions. At 18 days of life he had hematemesis and was managed with multiple vitamins and cisapride. Due to persistent vomiting, at 24 days of life he was hospitalized at the Hospital del Niño Morelense (Morelense Children's Hospital) for severe anemia (4.9 mg/dL), thrombocytopenia (41,000 mm^3) and melena. He required transfusion of four units of red blood cells and platelets. He also had serology for CMV (IgG+/IgM-). Biopsy of the skin lesions was performed, reporting mixed hemangiomas. Ectopic gastric mucosa was ruled out. On endoscopy there were thick folds reported in the antrum with fresh clots. For this reason, the patient was referred to Hospital Infantil de Mexico Federico Gomez (HIMFG). On admission he had a weight of 3900 g (25^{th} percentile), height 52 cm (10^{th} percentile), cephalic perimeter 37 cm (25^{th} percentile), arterial tension 90/60 mmHg, cardiac frequency 138x', respiratory frequency 40x', and temperature 36.5°C.

Clinical examination revealed generalized pallor and the patient's appearance was consistent with his chronological age. Head was normocephalic without exostosis or depressions, eyes were symmetrical, normoreflexic isocoric pupils, patent external auditory canals, intact tympanic membrane, nares were patent, oral cavity was moist, and oropharynx

was normal. Neck was cylindrical without adenopathies, trachea midline, nontender, and pulses of good intensity. Chest demonstrated adequate inspiration and expiration, breath sounds were without alterations, lung fields were clear, well ventilated, and without aggregates. Rhythmic heart sounds had good tone and intensity, and no murmurs or added sounds were noted. Abdomen was soft, depressible, and nontender without organomegaly. There was normal peristalsis. Genitalia appeared phenotypically male. Tanner scale was I. Perianal region showed no changes. Extremities were eutrophic with adequate mobility, strength, sensitivity and normal tendon reflexes. The patient was neurologically intact without abnormal or focal movements, and there were no cerebellar or meningeal alterations. Primary reflexes were normal. Glasgow coma scale was 15/15. There was generalized skin dermatosis characterized by multiple red, elevated and palpable lesions, 1-2 mm in diameter that did not disappear upon touch and were located in the anterior and posterior chest, upper and lower extremities and buttocks (Figure 1).

CBC reported hemoglobin (15 g/L), hematocrit (43.6%), leukocytes (10,400/mm^3), segments (47%), lymphocytes (44%), and platelets (62,000/mm^3). Liver function tests were as follows: total bilirubin (7.36) mg/dL, direct bilirubin (0.31 mg/dL), indirect bilirubin (7.05 mg/dl), total protein (5.5 g/dL), albumin (3.6 g/dL), aspartate transaminase (31 U/L), alanine transaminase (30 U/L), lactate dehydrogenase (353 U/L), alkaline phosphatase (246 U/L). Renal function values were as follows: BUN (9 mg/dL), creatinine (0.4 mg/dl) and coagulation times (thromboplastin, 13.2", partial thromboplastin 43.4"). Fecal occult blood was positive with bencidine technique (++++).

Diagnostic approach was initiated. Skin biopsy was sent to pathology and reported "skin with atrophic epidermis at the dermal–epidermal junction, reticular dermis and subcutaneous tissue, numerous vascular ectasia and mixed dilation with hyperplastic vessels of the endothelial cells." During his stay at the HIMFG, the patient developed a progressive decrease in hemoglobin (8.6 mg/dL) and platelets (79,000 mm^3), requiring transfusion of packed red cells.

Because the patient presented more than five skin hemangiomas, imaging tests were ordered to to determine any visceral lesions. Abdominal ultrasound was carried out and demonstrated hypoechoic images in the spleen (Figure 2). Transfontanel ultrasound was normal. Chest and computed tomography of the abdomen reported images in the spleen (Figure 3) and lungs, suggestive of hemangiomas (Figure 4). Brain MRI was normal. Endoscopy was performed with 20 lesions (1-2 mm) reported across the gastric mucosa that appeared elevated, red in color, and without active bleeding (Figure 5). The duodenum was normal.

Due to persistent bleeding, argon plasma coagulation was again attempted. Coagulation of ~15 hemangiomas was achieved, which were located on the fundus, body and antrum. There were no complications (Figure 6).

On-demand breast feeding was initiated as well as treatment with omeprazole, domperidone and sucralfate.

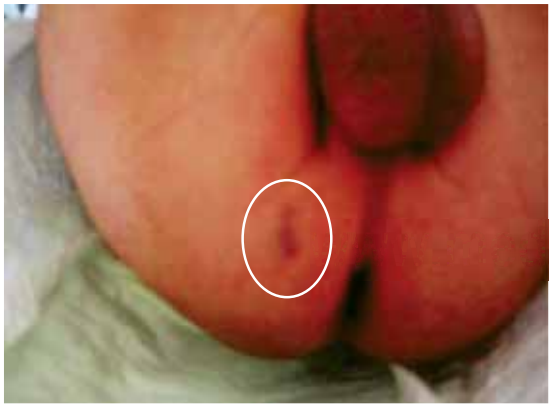

Figure 1. Hemangiomatous lesion in the gluteus.

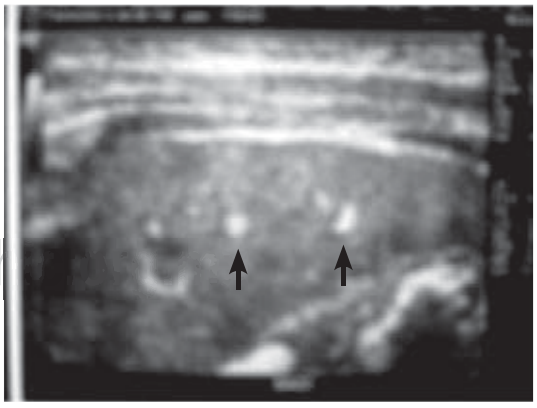

Figure 2. Abdominal ultrasound with hypoechoic images in the spleen (arrows).

Diagnosis of DNH was made and oral prednisolone (2 mg/kg/day) and interferon α-2b (1,000,000 U/m^2 SC/day for 13 days) was begun.

The patient was discharged from the hospital without signs of active bleeding. At present he continues to be treated with interferon α-2b at a dose of 3,400,000 U/m^2 SC/day and corticosteroids in reduction doses with follow-up endoscopies. The latest endoscopy demonstrated the presence of four hemangiomas without signs of active bleeding. The patient is under surveillance as an outpatient with appropriate increase in body weight, adequate psychomotor development for age, and without signs of bleeding. The mother has not reported increase in infections, despite being on immunossupressive medications.

DISCUSSION

DNH is a rare and potentially fatal disease. Death is generally associated with congestive heart failure or gastrointestinal hemorrhage. Lesions are present at birth or during the first month of life.[7] DNH is characterized by multiple skin and visceral hemangiomas. Despite their benign histology, they are associated with a high rate of mortality (between 50 and 90%) associated with cardiac failure due to arteriovenous shunts, hemorrhage, gastrointestinal and cutaneous bleeding and liver failure.[2,3,6] Due to its rapid progression, early intervention is necessary in order to avoid progression, or at least to produce regression.[6] Without treatment, the mortality rate is 77%. However, with adequate treatment mortality is reduced to 27%.[7] Treatment is focused on

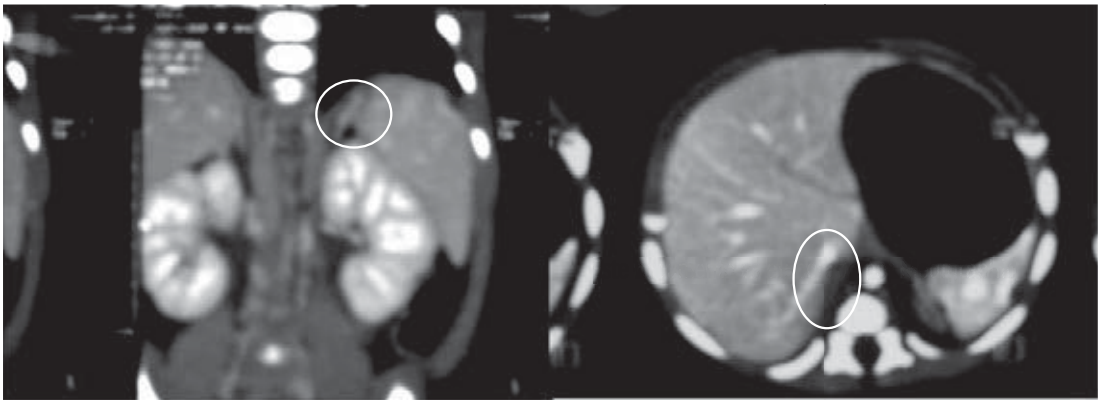

Figure 3. Abdominal tomography where hemangiomas are shown in the spleen.

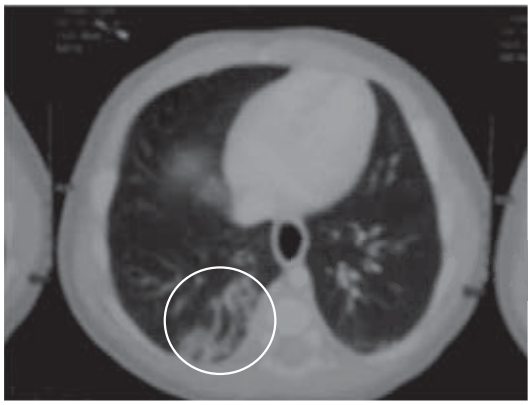

Figure 4. Thoraco-abdominal tomography where images suggestive of pulmonary hemangiomas can be seen.

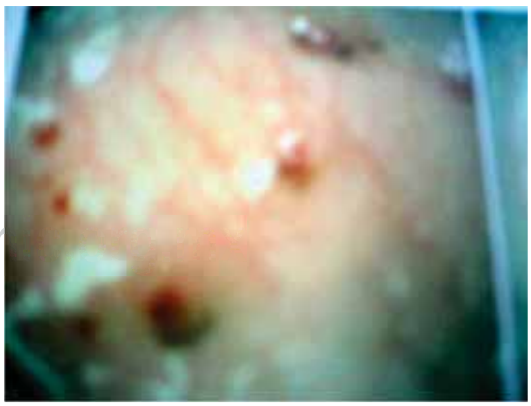

Figure 5. Gastric hemangiomas are shown on endoscopy.

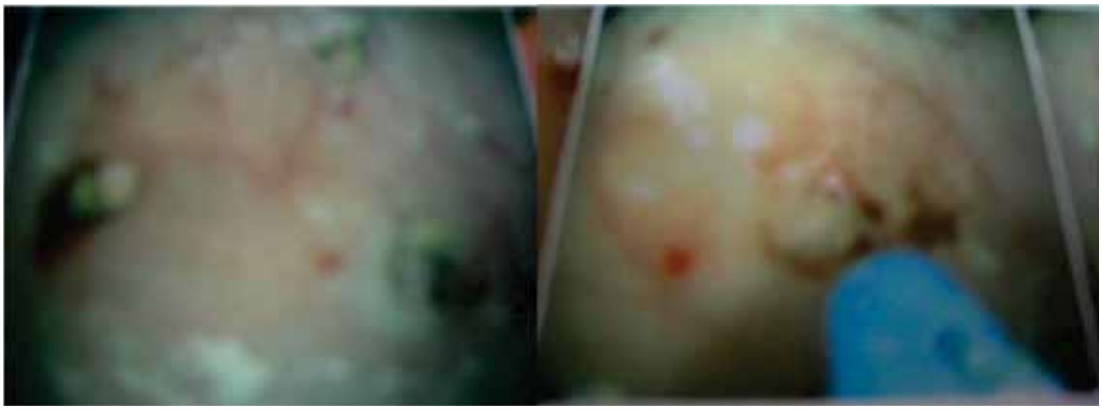

Figure 6. Argon plasma coagulation procedure using endoscopy.

avoiding adverse effects and complications. Current literature recommends the use of corticosteroids, interferon α-2b, vincristine, vinblastine, propanolol[9] or nonpharmacological treatments such as radiotherapy, embolization or surgery, with high rates of complications.[6]

Treatment should be directed to specific clinical manifestations. Corticosteroids are the principal treatment for debilitating hemorrhages or those that endanger life. The initial recommended dose is 2-3 mg/kg/day and can be increased in serious cases, although these are associated with adverse events. Hepatic embolization is recommended in focal lesions with shunts to improve cardiac insufficiency refractory to treatment.

Wananukul et al. used vinblastine with good results, although long-term follow-up of adverse events was required.[7] In another study, Vlahovic et al. used cyclophosphamide on a patient who did not respond to conventional treatments[10] and administered four courses at a dose of 10 mg/kg/day, plus mesna at 10 mg/kg/day with 10 days of separation between courses, achieving resolution of the symptoms without regression, as well as good evolution after 3 months of treatment.[10] Even though it has produced very good results, this treatment has been used in few patients because it requires further study. However, it may be an alternative after failure of other conventional treatments.

Our patient had multiple skin, lung, spleen and gastric lesions. He required argon plasma coagulation treatment of the gastric mucosa because of multiple, active bleeding hemangiomas. This procedure has shown its benefits and safety in a study by Khan et al. in pediatric patients with hemorrhage of the gastrointestinal tract.[11] Added to that, the combined treatment with prednisone and interferon α-2b has produced an appropriate response.

The patient presented here is currently asymptomatic with an adequate clinical course with regular monitoring.

Correspondence: Dr. Jonathan Maya Epelstein
E-mail: jmaya01@yahoo.com.mx

REFERENCES

1. Lister WA. The natural history of strawberry naevi. Lancet 1938;1:1429-1434.
2. Metry DW, Hebert AA. Benign cutaneous vascular tumors of infancy: when to worry, what to do. Arch Dermatol 2000;136:905-914.
3. Ohnishi S, Miyagishima T, Nakagawa M, Kamata T, Kishimoto A, Choi GH, et al. Diffuse neonatal hemangiomatosis without cutaneous lesions in an adult—a case report. Angiology 2002;53:235-237.
4. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982;69:412-420
5. Ollague J. Hemangiomatosis neonatal difusa. Folia Dermatol Peru 2007;18:28-31.
6. Gottschling S, Schneider G, Meyer S, Reinhard H, Dill-Mueller D, Graf N. Two infants with life-threatening diffuse neonatal hemangiomatosis treated with cyclophosphamide. Pediatr Blood Cancer 2006;46:239-242.

7. Wananukul S, Voramethkul W, Nuchprayoon I, Seksarn P. Diffuse neonatal hemangiomatosis: report of 5 cases. J Med Assoc Thai 2006;89:1297-1303.
8. Enjolras O, Brevière GM, Roger G, Tovi M, Pellegrino B, Varotti E, et al. Vincristine treatment for function- and life-threatening infantile hemangioma. Arch Pediatr 2004;11:99-107.
9. Mazereeuw-Hautier J, Hoeger PH, Benlahrech S, Ammour A, Broue P, Vial J, et al. Efficacy of propranolol in hepatic infantile hemangiomas with diffuse neonatal hemangiomatosis. J Pediatr 2010;157:340-342.
10. Vlahovic A, Simic R, Djokic D, Ceran C. Diffuse neonatal hemangiomatosis treatment with cyclophosphamide: a case report. J Pediatr Hematol Oncol 2009;31:858-860.
11. Khan K, Schwarzenberg SJ, Sharp H, Weisdorf-Schindele S. Argon plasma coagulation: clinical experience in pediatric patients. Gastrointest Endosc 2003;57:110-112.