□ Case Report □

Successful Management with Vincristine after Failure of Prednisolone Therapy for Diffuse Neonatal Hemangiomatosis

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Hemangiomas are the most common benign tumors of infancy. Fifteen to 30% of these patients have multiple hemangiomas. Diffuse neonatal hemangiomatosis (DNH) is a disease that often has a fatal outcome if left untreated, and is characterized by multiple cutaneous and visceral hemangiomas. Corticosteroids are the commonly accepted first line treatment, but if no effect is seen, further treatment is required such as interferon, surgical excision, embolization and radiotherapy. Interferon is effective, but the neurologic sequela including spastic diplegia can be a complication. We experienced a case of DHN in a neonate. In this case, the baby presented with multiple cutaneous and visceral hemangiomas with Kasabach-Merritt syndrome (KMS) that included thrombocytopenia and consumptive coagulophthy. The baby was successfully treated with vincristine after the failure of steroid therapy. **(Korean J Pediatr 2005;48:1004-1008)**

Key Words : Diffuse neonatal hemangiomatosis, Vincristine

Introduction

Hemangiomas are the most common benign tumors of infancy, and they occur in about 10% of all full-term infants[1]. Fifteen to 30% of these patients have multiple hemangiomas[2]. Multiple hemangiomas in neonates are differentiated into benign neonatal hemangiomatosis (BNH) and the diffuse or disseminated neonatal hemangiomatosis (DNH) by their internal involvement[3]. BNH is benign when the hemangiomas are primarily confined to the skin, but their location may pose serious complications, i.e. cutaneous hemantiomas obstructing the airway or vision[2]. In DNH, the lesions may occur in the skin, liver, lungs, intestines and central nervous system (CNS). DNH carries a mortality rate of 60% to 95%, with death occurring usually from high-output cardiac failure. In addition, serious complications often arise as a result of gastrointestinal or respiratory tract hemorrhages and Kasabach-Merritt syndrome (KMS)[4, 5].

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Corticosteroids are the first-line treatment, and the response rate varies from 30-60%[6]. For those patients unresponsive to corticosteroids, several approaches have been proposed : interferon, surgical excision, embolization and radiotherapy[7, 8]. Some authors have demonstrated a favorable response to interferon alfa-2a, but a causal relationship between interferon administration and spastic diplegia has been suggested[9, 10]. The effective treatment of hemangiomas with vincristine has been reported for the cases showing life-threatening complications that have failed to respond to corticosteroids[7, 8, 11].

We report here on a case of DNH with KMS that was successfully managed with corticosteroid and vincristine.

Case Report

A two-day-old male infant was hospitalized for the treatment of respiratory difficulty and melena. He was born at 38 weeks after an uncomplicated gestation. Vaginal delivery was achieved and the birth weight was 3,060 g. The Apgar scores were 6 and 8. He had multiple hemangioma on the scalp, right arm, back and lower extremities at birth. Immediately after delivery, signs of respiratory distress and melena were noted, and the patient

was transferred to our neonatal intensive care unit.

Physical examination on admission revealed a pale and cyanotic infant with a blood pressure 45/35 mmHg, a body temperature 36.5℃, a heart rate of 155 beats/min, a respiratory rate of 80 breaths/min and the percutaneous oxygen saturation (SaO_2) was 40-50%. His weight was 3,060 g (25th to 50th percentile), his height was 49 cm (50th to 75th percentile) and his head circumference was 34 cm (50th to 75 percentile). Oxygen was supplied to him, and the SaO_2 was maintained at 90-100%. He had tachypnea, tachycardia, chest retraction and a grade 2/6-3/6 systolic murmur. His abdomen was mildly distended, but the liver and spleen were not palpable. He had multiple cutaneous cherry-red nodules that were clinically felt to represent cutaneous hemangiomas on the scalp, right arm, back and lower extremities with a 3×3 cm subcutaneous mass on the scalp (Fig. 1A, 1B).

Laboratory data revealed anemia and thrombocytopenia (hemoglobin 8.4 g/dL and platelets 142,000/mm^3). His prothrombin time (11.4 second) and partial thromboplastin time (39.8 second) were within normal limits, but the liver enzymes were elevated (AST/ALT 239/146 IU/L). On the second day, platelet counts decreased to 61,000/mm^3. On day 14, follow up data reveled aggravated anemia and thrombocytopenia (hemoglobin 6.1 g/dL and platelets 50,000/mm^3). His prothrombin time (17.4 second) and partial thrombo-

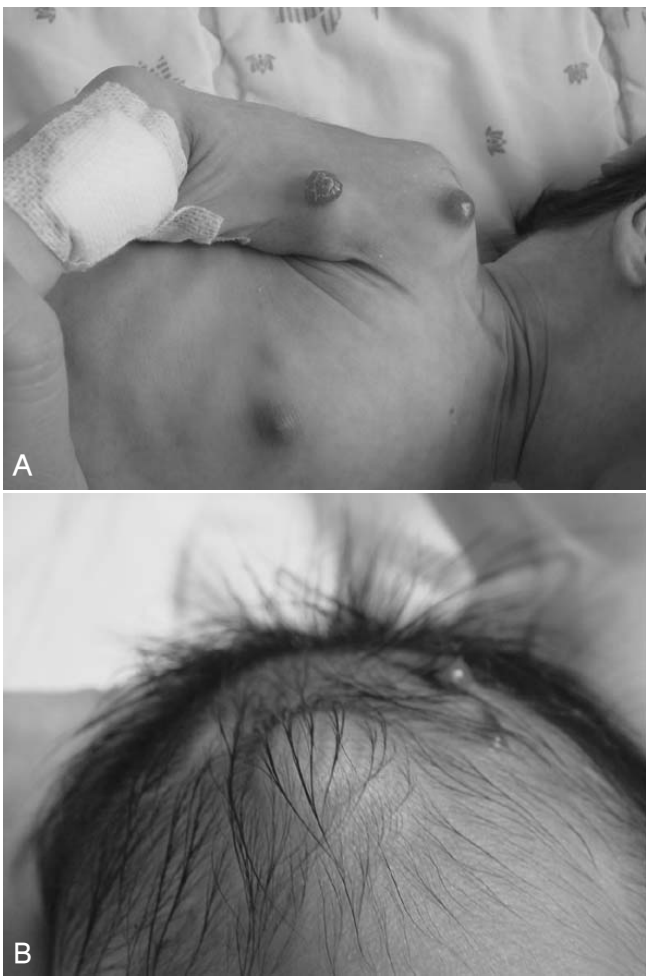

Fig. 1. (A) Two cutaneous hemangiomas are noted on the right shoulder and arm. **(B)** 3×3 cm subcutaneous mass on the scalp with two cutaneous hemangiomas.

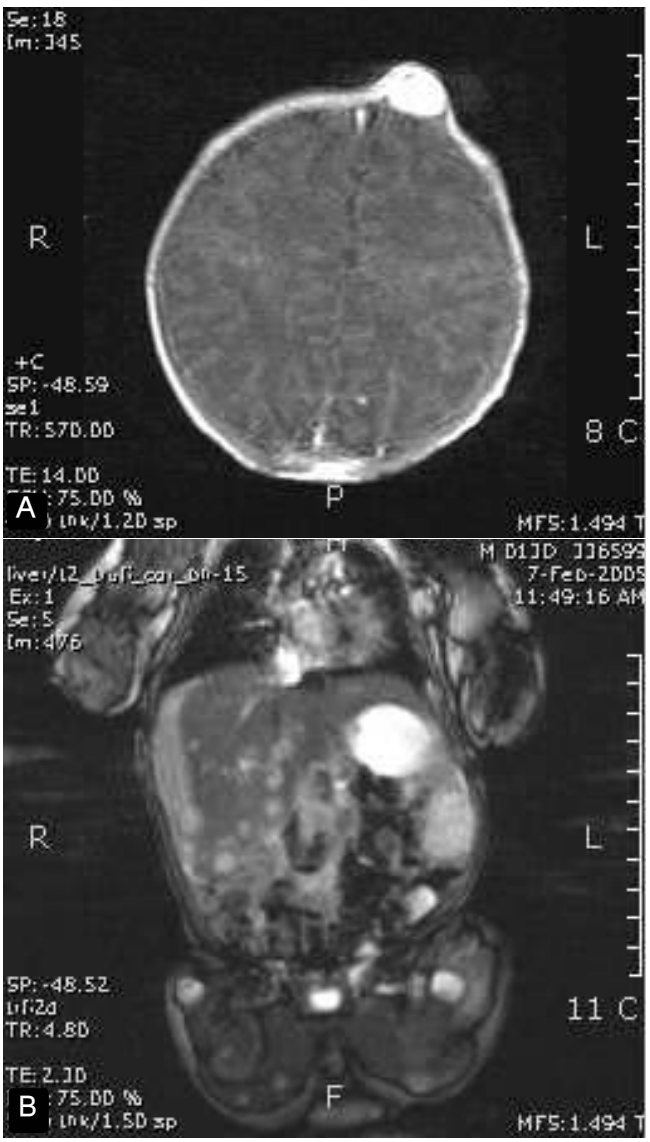

Fig. 2. (A) A axial magnetic resonance image view of the patient's head showing the well-enhancing epidural lesions without parenchymal lesion. **(B)** A coronal view showing the multiple variable sized lesions in the liver, spleen, intestine and the muscles of the extremities.

plastin time (>2 minute) were prolonged.

Chest radiography showed unremarkable findings without cardiomegaly. Abdominal ultrasonography revealed mild hepatomegaly and multiple hypoechoic rounded lesions in the liver, spleen and right kidney; the largest measured 1.2 ×1.3 cm. Brain magnetic resonance image (MRI) showed no parenchymal abnormalities, but high signal intensity was observed above the frontal area (Fig. 2A). The MRI findings of the other areas showed multiple, variable sized lesions in the liver, spleen, intestine and the muscles of neck and the extremities (Fig. 2B). Echocardiography revealed right ventricle hypertrophy, right atrium enlargement, a grade 3-4 tricuspid regurgitation, a small patent ductus arteriosus and patent foramen ovale with right to left shunting. Histopathologic finding of the skin lesion on the back revealed capillary hemangioma with extramedullary hematopoiesis.

Treatment was started with intravenous methylprednisolone (2 mg/kg/day) on day 14 and then this was changed to oral prednisolone (2 mg/kg/day) on day 21. Antibiotics administration, pack red cell, fresh frozen plasma transfusion and supportive care were provided. After one week of therapy, thrombocytopenia and consumptive coagulopathy were improved. However, despite the treatment, the hemangiomas continued to increase in size and number. Bleeding of the hematoma was also observed and this was not easily controlled. On day 10, palsy of the left facial nerve developed and persisted. On day 12, the abdominal ultrasonography revealed a mass-like lesion in the liver that suggested subcapsular hematoma and the other lesions remained unchanged. Prednisolone was continued to 2 mg/kg/day for a month, and tapered to 1 mg/kg/day. On day 28, vincristine was begun at a dose of 1.5 mg/m^2, once a week for 4 weeks. After the 3 weeks of the treatment, the skin lesions stopped growing and spreading, and they started to decrease in size. Also, the bleeding was finally controlled. On day 38, the laboratory data revealed a hemoglobin of 8.1 g/dL, leukocytes 2,610/mm^3 (neutrophils 69%), platelets 631,000/mm^3 and AST/ALT 39/20 IU/L. There were no side effects. On day 41, he was discharged and followed up at the outpatient department. Vincristine was continued at once every 2 weeks for 4 weeks, and followed by once every 3 weeks for 6 weeks at outpatient department. At present, the child is well and the hemangiomas have regressed in size and number. The regression pattern of the hemangioma is being followed-up every month.

Discussion

DNH was first described by Ramdohr[12] in 1878, and there have been four cases reported in our country[13-16]. Although DNH is a rare disorder, its mortality rate in the untreated patients is extremely high (60-95%)[5]. Therefore, the clinical evaluation of an infant with multiple cutaneous hemangiomas should include the presence and extent of the visceral involvement.

DNH is characterized by the widespread presence of cutaneous and visceral hemangiomas involving three or more organ systems. The cutaneous hemangiomas are usually generalized, they have a diameter of 0.5-1.5 cm, and they range from 50 to 100 in number[17]. These lesions are usually present at birth in 70% of the cases or they develop within the first week of life[2]. Characteristically, the hemangiomas undergo a natural course of progressive enlargement for 8-18 months, and this is followed by a phase of spontaneous regression[5]. The organs most commonly involved in DNH are the skin, liver, lungs, intestines and CNS. Death usually results from high-output congestive heart failure due to the arteriovenous shunting in the hemangiomas. In addition, serious complications often arise as a result of gastrointestinal hemorrhage, obstructive jaundice, CNS sequela due to the space-filling hemangiomas and the KMS following the consumption of the platelet and clotting factors in the hemangiomas[5]. In our patient, the multiple hemangiomas affected the skin, subcutaneous tissues, muscles, and internal organ systems including the liver, spleen and right kidney. The patient's hemangiomas increased in size and number with signs of respiratory distress and cardiac murmur, and this was followed by gastrointestinal hemorrhage, palsy of the left facial nerve, consumptive coagulopathy and KMS.

Corticosteroids are the first-line treatment, and the response rate varies from 30-60%[6]. The mechanism of corticosteroids inducing a regression of the hemangiomas is not clear. It has been suggested that the proliferating blood vessels are sensitized to endogenous circulating vasoconstrictors by the corticosteroids. Another suggested mechanism is that corticosteroids occupy receptors in the hemangioma tissue and block the factors involved in their growth[16]. The initial response to steroid therapy is usually shown within 1 to 2 weeks of their administration[10]. If no effect is seen after 2-4 weeks and the clinical situation

demands further treatment, effective alternatives are needed[5, 8].

Interferon alfa-2a has been shown in several case reports to be effective for the life-threatening hemangiomas that are unresponsive to corticosteriods[2, 4-6, 13]. Its mechanism of action remains unknown. Several mechanisms have been suggested : it inhibits endothelial cell migration and proliferation; it inhibits other steps in angiogenesis; and it down-regulates the expression of basic fibroblast growth factor (angiogenic factor)[16]. The response rate to this drug was 50-80% with a mean response time of 7 to 8 months[6, 18]. However, Barlow, et al[9] have reported that spastic diplegia developed in about 20% infants during the course of interferon alfa-2a therapy for life-threatening hemangiomas, and MRI of those infants showed leukomalacia. Therefore, the use of interferon alfa-2a should be performed for those patients with life-threatening hemangiomas that are unresponsive to corticosteroids. Careful clinical assessment of the neurodevelopmental status and performing imaging studies are also recommended during interferon therapy.

The use of vincristine has been reported in cases with life-threatening complications that have failed to respond to steroids[8, 11, 19]. Vincristine, as a vinca alkaloid, arrests cell mitosis in metaphase by preventing the tubulin polymerization that forms microtubules, and it also induces microtubule depolymerization. It has been postulated that the tubulin content of the endothelial cells is higher than it has been supposed. This has been the basis for the treatment with vincristine because the existence of a greater tubulin content in the endothelial cells and the existence of active angiogenesis would cause these cells to be more sensitive to this drug[8, 20]. This drug has long been associated with acute neurotoxcicity in adults. Neurotoxicity has also been reported in children, but is rare and usually mild[19].

In this case, the hemangiomas affected the skin, liver, spleen, kidney and the muscles of the entire body. He presented with KMS, including thrombocytopenia and consumptive coagulopathy, palsy of the left facial nerve, gastrointestinal hemorrhage and bleeding of the hemangiomas. Treatment was started with methylprednisolone (2 mg/kg/day) and then changed to prenisolone (2 mg/kg/day) for a month. During this period, the thrombocytopenia and consumptive coagulopathy were improved, but the hemangiomas increased in size and number with bleeding. We thought that the life-threatening complications improved, but the hemangiomas did not response to steroid any more. In this situation, we decided that vincristine was a more acceptable treatment than interferon. Because treatment with interferon needs a long-term period, at least 7 to 8 months, and it may be complicated with spastic diplegia, vincristine treatment may have advantage of relatively short course of treatment and fewer side effects[19]. On day 28, vincristine administration was started at a dose of 1.5 mg/m^2, once a week for 4 weeks, and then once every 2 weeks for 4 weeks; this was followed by once every 3 weeks for 6 weeks. After the three weeks of treatment, the hemangiomas regressed in size and number, and the bleeding was controlled.

At present, treatment of hemangiomas with vincristine has not been widely reported and it has been restricted to cases with life-threatening complications that have failed to respond to steroids.

We report here for the first time in Korea on a case of steroid-resistant DNH that was successfully managed with vincristine.

한 글 요 약

Vincristine 투여로 호전된 미만성 신생아 혈관종증

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이학성 · 허순영 · 김원덕

혈관종은 영아에서 가장 흔한 양성 종양으로 이 중 15-30%는 다발성 혈관종을 보인다. 미만성 신생아 혈관종증은 피부와 다수의 내부 장기를 침범하는 질환으로 치료하지 않는 경우 치명적일 수 있기 때문에 신속하고 적극적인 치료가 요구된다. 치료는 부신피질 호르몬이 1차 선택 약제로 사용되며 이에 반응하지 않으면 인터페론, 절제술, 전색술, 방사선 치료 등을 이용할 수 있다. Interferon alfa-2a는 매우 효과적이나 강직성 양마비(spastic diplegia)와 같은 심각한 합병증이 보고되고 있다. 저자들은 출생 직후 호흡곤란과 전신의 피부 혈관종을 주소로 입원하여 Kasabach-Merritt 증후군을 동반한 미만성 신생아 혈관종증을 진단 받았던 1례에서 스테로이드 치료에 대해 혈소판 감소증 및 소모성 응고장애의 호전은 있었으나 혈관종의 수 및 크기의 호전이 없어 vincristine을 투여하여 치료에 성공하였기에 문헌 고찰과 함께 보고하는 바이다.

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