A Case of Kasabach-Merritt Syndrome Successfully Treated with Interferon-alpha 2b and Propranolol

Jung-Won Lee, M.D.¹, Hye Lim Jung, M.D.¹, Jae Won Shim, M.D.¹, Deok Soo Kim, M.D.¹, Jung Yeon Shim, M.D.¹, Moon Soo Park, M.D.¹ and Hee Jin Park, M.D.²

Departments of ¹Pediatrics and ²Radiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Kasabach-Merritt syndrome (KMS) is a rare, life-threatening disease characterized by rapidly enlarging hemangioma and consumptive coagulopathy. We report a case of KMS in a 28-day-old female neonate with a huge mixed type hemangioma on her right thigh with muscle involvement and severe venous engorgement, who was refractory to prednisone therapy, but was successfully managed with the interferon (IFN)-α 2b and propranolol combination therapy. By the third week of IFN-α 2b treatment, hematological parameters had normalized and the hemangioma size had dramatically decreased, and after 5 months of the treatment, complete resolution was observed visually. We also measured serum levels of cytokines including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), monocyte chemotactant protein-1 (MCP-1) and platelet-derived growth factor-BB (PDGF-BB), at diagnosis and serially during treatment but the levels did not correlate with the clinical response. The patient has not shown relapse after 20 months of follow up.

Key Words: Kasabach-Merritt syndrome, Hemangioma, Cytokine, Interferon

Introduction

Kasabach-Merritt Syndrome (KMS) is a rare but life-threatening disease, characterized by profound thrombocytopenia, microangiopathic hemolytic anemia and consumptive coagulopathy in the presence of a large vascular lesion [1]. This syndrome develops in early infancy and vascular lesions present most commonly on extremities, trunk, and face or neck. Retroperitoneal and intrathoracic lesions are less common but are frequently associated with KMS [2]. Heart failure can be complicated by arteriovenous malformation within the lesion. The pathogenesis of hemangioma and KMS has not been established but might be related to increase in cytokines and growth factors associated with angiogenesis [3]. Management of KMS is challenging due to its infiltrating nature of hemangioma, risk of bleeding due to consumptive coagulopathy, and high mortality rates in newborns [4]. There are multiple modalities of treatments including prednisolone, vincristine, antiangiogenic agents
such as interferon (IFN)-α-2, laser photocoagulation, local radiation therapy, surgical excision, and embolization. But among these modalities, standard treatment has not been established. We report a case of successfully managed refractory KMS with the IFN-α 2b and propranolol therapy, and the serially checked serum levels of cytokines including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), monocyte chemoattractant protein-1 (MCP-1), and platelet-derived growth factor-BB (PDGF-BB).

### Case Report

A prematurely born (gestational age 36 weeks, birth weight 2,150 g, the first twin) 28-day-old female neonate was transferred because of a huge hemangioma with size of circumferential length 12.5 cm × longitudinal length 8 cm (Fig. 1) on her right thigh with profound thrombocytopenia. Her prenatal and natal histories were normal. Surface of the lesion was dark red and intact without ulceration, hemorrhage, or secondary infection. Ultrasonography and magnetic resonance imaging (MRI) demonstrated a huge hemangioma involving subcutaneous fat layer of the right medial thigh, right vastus medialis and intermedius muscles (Fig. 2). Marked venous engorgement in right inguinal area draining from hemangioma to right superficial femoral vein was also detected. Upon admission, anemia (9.9 g/dL), severe thrombocytopenia (11,000/μL), prolonged activated partial thromboplastin time (aPTT: 49.2 sec, normal value 25–45 sec), elevated D-dimer (33,829.7 ng/mL, normal value <500 ng/mL), and low fibrinogen (98 mg/dL, normal value 125–300 mg/dL) were recorded (Fig. 3). She was examined with echocardiography and brain ultrasonography, and those results were normal, except a small size atrial septal defect.

Before she was transferred to our institution, she had been administered propranolol (Indenol, 2 mg/kg/day, orally, every 8 hours) for 12 days, but clinical response was poor. We continued propranolol (Indenol, 2 mg/kg/day, orally, every 8 hours) treatment, and added prednisolone (Solondo, 2-5 mg/kg/day, orally, every 8 hours). The propranolol and prednisolone were given for 28 days, but the thrombocytopenia (5,000/μL) did not improve (Fig. 3), and the size of hemangioma increased to circumferential length 14 cm × longitudinal length 7 cm × depth 3.2 cm (Fig. 2). We added IFN-α 2b therapy (Intron A Pen 18MIU, 3 million units/m²/day, daily, subcutaneous injection) while prednisolone was tapered off for a month. After 3 weeks of combination treatment of IFN-α 2b and propranolol, the platelet count (168,000/μL), aPTT (42.9 sec) and fibrinogen (183 mg/dL) were normalized (Fig. 3) and the hemangioma size was visually decreased. After 30 days of the treatment, we confirmed markedly decreased size of the hemangioma.

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**Fig. 1.** (A) Hemangioma in the right inner thigh at the age of 55 days, before treatment. (B) Significant improvement could be seen after 3 weeks of interferon-α 2b treatment. (C) With fading of surface color and shrinkage of lesion, near-complete clearance achieved after a year of termination of interferon-α 2b.
on ultrasonography. So IFN-α 2b was decreased to an alternate-day schedule for 4 months. At 4 months of IFN-α 2b treatment, the hemangioma size on MRI was longitudinal length 3.5 cm x depth 1.3 cm (Fig. 2). After 5 months of the treatment, the hemangioma was not grossly visible and then we discontinued IFN-α 2b, but continued with propranolol therapy. Propranolol was administered for 9 months in total. Two months after the termination of IFN-α 2b, she had received laser therapy which was performed 6 times in 6 weeks interval.

We also measured serum levels of VEGF, bFGF, MCP-1 and PDGF-BB at diagnosis, during treatment and follow-up.

Fig. 2. The right thigh mass shows hyposignal intensity on T1-weighted images and strong enhancement after contrast injection. Color Doppler reveals numerous arteriovenous shunts within the hemangioma. The hemangioma size is decreased dramatically after IFN-α 2b treatment. Before the treatment of IFN-α 2b, its longitudinal length was 7 cm and depth was 3.2 cm. And the size was decreased to longitudinal length 3.5 cm and depth 1.3 cm after 4 months of IFN-α 2b. After a year of termination of IFN-α 2b, its longitudinal length was 3.5 cm and depth was 1 cm.
period. The cytokines were measured by multiplex assay (Luminex, R&D system, Minnesota, USA). These levels rather increased after several months of IFN treatment, but the levels, excluding PDGF-BB, eventually decreased compared to the initial levels. But the serial serum levels of these cytokines did not correlate to clinical responses (Fig. 3).

At one year follow up, the hemangioma was further resolved on MRI to size of longitudinal length 3.5 cm × depth 1.0 cm (Fig. 2). At this time, hemangioma was not grossly visible but showed atrophy of thigh muscle and shrinkage of overlying skin (Fig 1). She have been followed up regularly for 20 months after the end of IFN-α 2b treatment, and she is now 26 months old showing normal development and growth, and without showing any side effects or relapse.

Fig. 3. Sequential changes of hematologic parameters and cytokines. aPTT, activated partial thromboplastin time; FGF-β, fibroblast growth factor-β; IFN, interferon; MCP-1, monocyte chemoattractant protein-1; PL, prednisolone; PDGF-BB, platelet-derived growth factor-BB; VEGF, vascular endothelial growth factor.

Discussion

KMS was first described in 1940 by Kasabach and Merritt in a 2-month-old boy who presented with a capillary hemangioma with profound thrombocytopenia and hypofi-brinogenemia [2]. KMS most commonly develops in infancy, and mortality and morbidity rates are as high as 30% because of hemodynamic instability, local invasion, and compression of vital structures. And spontaneous regression without treatment is rare.

The pathogenesis of hemangioma and KMS are not completely understood but many cytokines and growth factors are reported to be involved in pathogenesis [3]. The most well-known cytokine that plays the pivotal role in angiogenesis is VEGF which is known to stimulate the proliferation of vascular endothelial cells promoting the formation of blood vessels, and increase the permeability of
blood vessels, particularly microvessels [5]. The plasma VEGF levels have been reported to correlate with a successful clinical response in hemangioma [3]. Another angiogenic cytokine bFGF is an autocrine growth factor for endothelial cells, reported to be expressed in the cytosol of the hemangioma endothelial cells during the proliferative phase [6]. The bFGF is known to be elevated in patients with active angiogenesis and in the urine of infants with proliferating endotheliomas, which fall dramatically in cases with good clinical response to therapy [7]. MCP-1 was shown to promote hemangioendothelioma proliferation by recruiting macrophages to stimulate vessel sprout formation in vitro [8]. PDGF has been shown to induce vessel formation and to promote tumor growth by stimulation of angiogenesis, PDGF-BB was also shown to be elevated significantly high in the supernatant of hemangioma stem cell cultures [9]. In the case of our patient, serum levels of VEGF, bFGF and MCP-1 started to decrease 6 months after the end of IFN treatment, but the serial serum levels did not correlate with the clinical responses. And PDGF-BB level rather increased during and after the IFN therapy. FU et al. observed increased VEGF concentration in the peripheral blood one week after the pure alcohol injection to hemangioma. They assumed it is because of the stimulation of local oxidants, resulting in the synthesis and secretion of compensatory VEGF [5]. We observed increase in serum levels of VEGF, bFGF, MCP-1 and PDGF-BB in our KMS patient during IFN-α and propranolol treatment and for 6 months after the successful cease of treatment. As KMS is a very rare disease, we need a collaborative study to evaluate cytokine levels to find their involvements in pathogenesis of KMS.

Our KMS case had a huge hemangioma infiltrating muscle with a severe venous engorgement, who did not respond to corticosteroid, but responded completely to IFN-α 2b only after 3 weeks of therapy. We are assuming that propranolol therapy had additive effects, IFN exerts both an anti-proliferative and anti-angiogenic effect. The two forms of IFN-α 2a and IFN-α 2b, are probably identical in efficacy, and both forms have been used in KMS and life-threatening hemangiommas of infancy at a dosage of 3 million IU/m²/day, with favorable results. The adverse effects of IFN include fever, neutropenia, mild anemia, mild elevation of liver function test, and neurotoxicity, especially spastic diplegia [10,11]. Our patient experienced only fever on second day of IFN and the fever subsided spontaneously. Propranolol is known as vasoconstrictor, down-regulator of angiogenetic factors such as VEGF and bFGF, and up-regulator of apoptosis of capillary endothelial cells [12].

In conclusion, we successfully treated a case of refractory KMS with IFN-α 2b and propranolol combination therapy, showing hematologic remission and marked decrease in hemangioma size after 3 weeks of therapy and grossly complete resolution of hemangioma after 5 months of therapy, without serious side effects of therapy, complications or relapse after 20 months of follow up. So we recommend IFN-α 2b and propranolol combination therapy as the first line therapy for KMS. We also suggest future collaborative studies to elucidate the role of angiogenic cytokines in the pathogenesis and prognosis of KMS and hemangioma.

References

1. Economou M, Papagianni A, Tsigka A, et al, Successful management of a small infant with Kasabach-Merritt phenomenon using vincristine: a case report, Blood 2014;25;777-9.
2. Tlougan BE, Lee MT, Drolet BA, Frieden IJ, Adams DM, Garzon MC, Medical management of tumors associated with Kasabach-Merritt phenomenon: an expert survey, J Pediatr Hematol Oncol 2013;35:618-22.
3. Saito M, Gunji Y, Kashii Y, et al, Refractory kaposiform hemangioendothelioma that expressed vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3: a case report, J Pediatr Hematol Oncol 2009;31:194-7.
4. Nakib G, Galleta V, Quaretti P, et al, Chemotherapy and surgical approach with repeated endovascular embolizations: safe interdisciplinary treatment for kasabach-merritt syndrome in a small baby, Case Rep Oncol 2014;7:23-8.
5. Fu ZJ, Li CM, Wang TH, Jiang ZL, Fu ZC, Vascular endothelial growth factor expression and pathological changes in the local tissue of facial hemangiomas following injections with pure alcohol, Oncol Lett 2015;9:1099-103.
6. Dosquet C, Coudert MC, Wassef M, Enjolras O, Drouet L, Importance of bFGF ("basic fibroblast growth factor") for diagnosis and treatment of hemangiomas, Ann Dermatol Venereol 1998;125:313-6.
7. Hall GW, Kasabach-Merritt syndrome: pathogenesis and management, Br J Haematol 2001;112:891-62.
8. Gordillo GM, Onat D, Stockinger M, et al, A key angiogenic
role of monocyte chemoattractant protein-1 in hemangiendothelioma proliferation. Am J Physiol Cell Physiol 2004;287:C866-73.

9. Roach EE, Chakrabarti R, Park NI, et al. Intrinsic regulation of hemangioma involution by platelet-derived growth factor. Cell Death Dis 2012;3:e528.

10. Acharya S, Pillai K, Francis A, Criton S, Parvathi VK. Kasabach-Merritt syndrome: management with interferon, Indian J Dermatol 2010;55:281-3.

11. Yoo NH, Park SM, Lyu CJ, Yang CH, Sohn YM, Kim KY. A case of Kasabach-Merritt syndrome with involvement of airway obstruction treated with interferon alfa-2a, Korean J Pediatr Hematol Oncol 1998;5:182-7.

12. Xiao Q, Li Q, Zhang B, Yu W. Propranolol therapy of infantile hemangiomas: efficacy, adverse effects, and recurrence, Pediatr Surg Int 2013;29:575-81.