A new successful combination therapy with atenolol and prednisolone for Kasabach-Merritt syndrome

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Kasabach-merritt syndrome is a rare life-threatening syndrome associated with vascular tumors such as tufted angioma and kaposiform hemangioendothelioma. For this syndrome, there exist a few treatment modalities with variable results. For many years, corticosteroids have been employed in the first-line therapy. Nowadays, on the other hand, β blockers such as propranolol have been used owing to their acceptable efficacy and fewer side effects. In the present case report, atenolol combined with corticosteroid was, for the first time, prescribed for the treatment of the syndrome; a significant improvement was observed with no concomitant side effects.

Keywords: Kasabach-merritt syndrome; atenolol; prednisolone

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INTRODUCTION

Kasabach-merritt syndrome (KMS) is, more often than not, presented in vascular tumors such as tufted angioma and kaposiform hemangioendothelioma (KHE), yet is rarely developed in congenital hemangioma. Thrombocytopenia and consumptive coagulopathy are other clinical manifestations of this syndrome [1]. Fifty percent of the cases have been observed at birth and the incidence of the syndrome is identical in both males and females [2]. Different treatments have been proposed: corticosteroids are utilized in the first-line therapy, but in a few recent case reports, propranolol has been employed with good efficacy and low adverse effects [1]. In the present article, we report a case of congenital KMS treated with atenolol and prednisolone.

CASE REPORT

The patient was a preterm, 3-day-old boy in NICU consulted because of multiple vascular lesions on the face, neck and limbs with thrombocytopenia and tachypnea. His weight, height and head circumference were 2700 gr, 43 cm and 36 cm, respectively.The infant was resulted from a cesarean section owing to a gestational breech position at 32 weeks. His mother had mild hypertension

during pregnancy which was controlled without medication.

On physical examination, a 3×2 centimeter ecchymotic plaque was seen on the left forearm. Also observed were a 5×4.5 centimeter blue-red mass on the right hand and an enlarged mass with an approximate size of 7× 10 centimeter on the right side of the face, extending from the lateral and lower face to posterior auricular and occipital area with dilated vessels on their surface (Figures 1, 2). There were no petechiae or purpura on the other sites of the body; neither were there any other positive findings in the physical examination.

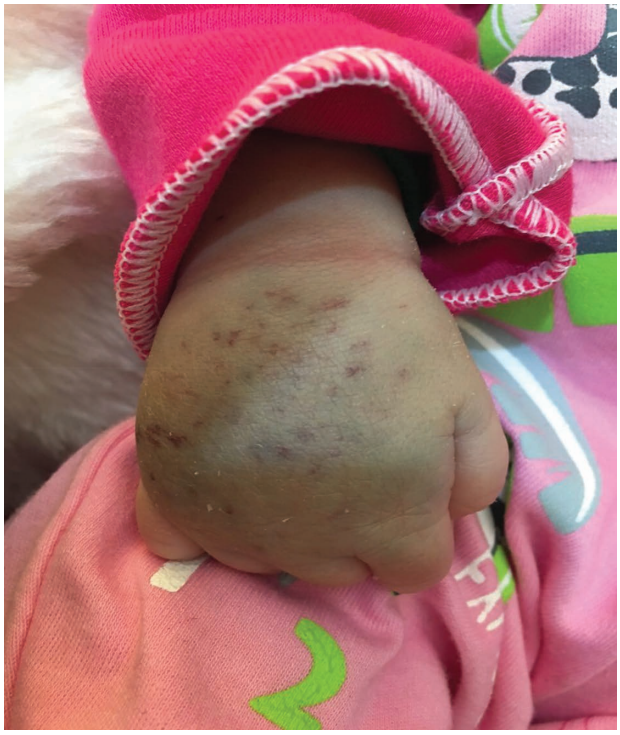

Figure 1. A 5×4.5 centimeter blue-red mass on the right hand with dilated vessels on its surface.

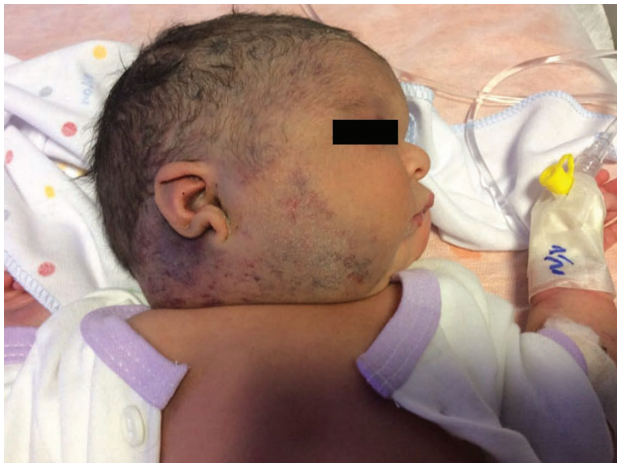

Figure 2. An enlarged mass with a size of nearly 7×10 centimeter on the right side of the face, extending from the lateral and lower face to posterior auricular and occipital area with dilated vessels on its surface.

In the first laboratory tests, the infant had a platelet count of 53×10^9/l (reduced to 37×10^9/l after 3 days), a leukocyte count of 15×10^9/l, 14.3 gr/dl hemoglobin, a total of 8.9 gr/dl bilirubin, 2.4 mg/dl D-dimer (normal range less than 0.3), 15 second prothrombin time, 41 second partial thromboplastine time and INR1.3. In the peripheral blood smear, fragmented red cells or schistocytes compatible with hemolytic anemia were reported. Thyroid function test and other lab tests were within normal limit.

Doppler sonography of vascular lesions revealed hypoechoic areas with a minimal increase in vascularity. No vascular lesions were found in the solid organs, and the brain and abdomen sonography was normal. Echocardiography demonstrated a 70% ejection fraction, 2+ mitral regurgitation, and 2+ trichuspid regurgitation with pulmonary hypertrophy.

Following consultation with cardiologist, prednisolone was administered with a dosage of 2 mg/kg/day and atenolol was employed with a dosage of 0.5 mg/kg/day, which was slowly increased to 2 mg/kg/day over 3 days. After a few days, we observed a reduction in the size and

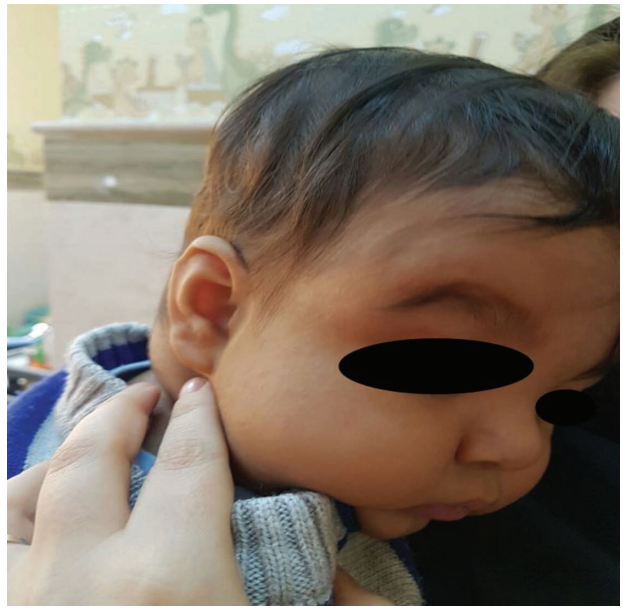

Figure 3. The complete disappearance of facial mass, 9 months after the first treatment with atenolol and prednisolone.

consistency of the lesion, changes in color from red to purple, and an augment in the platelet count to 92×10^9/l. After 3 months of follow-up sessions, the platelet count was in the normal range (230×10^9/l). And after 9 months, most of the lesions either completely disappeared or underwent a noticeable reduction in volume and size (Figure 3).

DISCUSSION

KMS, predominantly engaging the chest, back and facial zones, is most commonly diagnosed in the first year of life; however, it can appear any time between birth and a few years after. A mortality rate of up to 30% has been reported due to intracranial hemorrhage and involvement of vital internal organs [3]. In this syndrome, platelet activation, thrombosis in tumor and consumption of coagulation factors eventuate in intratumoral hemorrhage, petechiae, ecchymosis and tumor enlargement. Platelet infusion aggravates coagulopathy and leads to the enlargement of the tumor. Moreover, it can engage liver and result in heart failure secondary to high volume blood shunt [4].

Consumption coagulopathy is characterized by an increased level of D-dimer and a low amount of fibrinogen [4]. In order to corroborate the diagnosis, Doppler sonography, CT scan, magnetic resonance imaging, angiography and histology can be performed [5].

The aim of KMS treatment is tumor regression and normalization of thrombocytopenia. Previously, corticosteroid was employed in first-line therapy with a dosage of 2 to 5 mg/kg/day, functioning through vasoconstriction and inhibition of fibrinolysis. However, complications such as immunosuppression, adrenal suppression, cushingoid appearance, cataract, growth retardation and hypertension have been reported following corticosteroid therapy [2,6].

Propranolol, a nonselective beta blocker inhibiting $\beta1$andβ_2 receptors, has been recently utilized in the first-line therapy of hemangioma, owning to its fewer adverse effects and acceptable response [7]. The mechanism of action in beta blockers is through vasoconstriction, induction of apoptosis in endothelial cells, and inhibition of VEGF and FGF [8]. A few studies have employed propranolol in the treatment of KMS as monotherapy or in combination with other treatment modalities such as corticosteroids and vincristin, with favorable results [9].

Propranolol entails side effects such as bronchospasm, epilepsy, hypoglycemia, hypotension, bradicardia, sleep disorder and gastrointestinal problems [10]. Atenolol is a selective β blocker that inhibits $\beta_1$receptor. Because of its hydrophilic nature (as opposed to the lipophilic properties of propranolol), this β blocker does not cross the blood-brain barrier, hence the fact that complications such as bronchospasm, sleep disorder and hypoglycemia are either not observed or seen less frequently than propranolol [11]. In several studies, atenolol has been applied to hemangioma with an efficacy nearly equal to propranolol and fewer adverse effects [9,12].

In this article, atenolol was, for the first time, administered with prednisolone in the treatment of KMS. The lesion underwent significant changes in size, color and consistency with an elevation in platelate count, a few days following the administration of the drug.

Different studies have examined other drugs such as including interferon α, vincristine, ticlopidin, aspirin, cyclophosphamid and other surgical procedures including tumor resection, sclerotherapy, radiation therapy, compression treatment and embulization [13].

Vincristin is a vinca alkaloid which induces vascular cell apoptosis through disrupting the cell division, and entails side effects such as constipation, peripheral neuropathy, anemia, leucopenia, jaw pain, gastrointestinal upset, reversible alopecia, atonia and an increased risk of carcinogenicity in the long run [14,15].

Interferon α is a dose-independent drug with the following adverse effects: inhibition of angiogenesis, spastic diplegia (its most serious side effect), fever, skin necrosis, diarrhea, renal failure and increased liver enzymes [1].

Compression therapy, as an adjuvant therapy, is particularly applied on lesions located on the limbs, but it can be accompanied with pain. Surgery is not recommended unless the lesion is single or there exist multiple lesions in liver or spleen [5].

CONCLUSION

Recently, β blockers, such as propranolol, have

been utilized for the treatment of KMS with or without corticosteroids. Hypoglycemia, and cardiac and respiratory symptoms such as hypotension, bradicardia and bronchospasm have been proved to be more prevalent side effects of propranolol compared with atenolol. Hypoglycemia in neonates results in CNS signs such as seizures without any early signs. Accordingly, atenolol, which selectively inhibits β 1 receptors and does not cross blood brain barrier due to its hydrophilic properties, can be used as a safe and effective drug in the treatment of KMS, particularly in cases where the patient is propranolol intolerant.

Conflict of Interest: None declared.

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