Successful Propranolol Treatment of a Kaposiform Hemangioendothelioma Apparently Resistant to Propranolol

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A newborn with unresectable kaposiform hemangioendothelioma associated with Kasabach Merritt phenomenon, unresponsive to vincristine and prednisone, received second-line treatment with propranolol at a dose of 2 mg/kg/day, starting at 2 months of life and continued for 13 months. There was only slight reduction in tumor mass, but measurement of propranolol levels showed extremely low plasma concentrations. The propranolol dose was progressively increased to 3.5 mg/kg/day, leading to a substantial increase in plasma levels associated with clinically relevant tumor reduction. This case highlights the importance of relating propranolol dose to its plasma concentration before considering the treatment ineffective for this vascular tumor. Pediatr Blood Cancer 0000;00:000–000. © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

Kaposiform hemangioendothelioma (KHE) is a rare vascular neoplasm, with incidence estimated 0.91/100,000 children per year and occurring typically in the first decades of life. KHE has been described as a vascular tumor with intermediate malignancy for its locally aggressive behavior and low-grade histomorphological features.[1,2] It is associated with severe complications including acute respiratory distress by airway obstruction, recurrent hemathorax, jaundice, intestinal obstruction, and characteristic consumptive coagulopathy, characterized by severe thrombocytopenia and hypofibrinogenemia, known as Kasabach Merritt phenomenon (KMP).[2,3] Retropertitoneal involvement is associated with poor outcome. Despite aggressive treatment, the mortality rate of KHE is still high due to hemorrhagic complications, hemodynamic instability, and local invasion with compression of vital tissues and organs.[3] Several therapeutic options, including corticosteroids, vincristine, α-interferon, rapamycin and/or everolimus, radiation therapy, and surgical intervention, have been described with variable success and many side effects.[2–5]

Propranolol, a nonselective β-adrenoreceptor antagonist successfully used in treating infantile hemangiomas (IH),[6] has recently been proposed as an alternative treatment for KHE associated with KMP, with variable success.[7–12] Here, we report a case of KHE apparently resistant to propranolol at standard dosage (2 mg/kg/day) that successfully responded to an increased dose. Propranolol plasma concentration was monitored to achieve the optimal dose to use with respect to the efficacy and safety of the drug.

CASE DESCRIPTION

A 7-day-old full-term newborn was admitted to our neonatal intensive care unit because of progressive respiratory distress. General physical examination was otherwise normal and initial laboratory values showed severe thrombocytopenia (3,000/μl). A consumptive coagulopathy was evident with prothrombin time slightly increased (international normalized ratio 1.92), fibrinogen 0.51 g/l (reference range, 2.0–4.0), and plasma D dimer 36.3 mg/l (normal <0.5 mg/l).

An abdominal ultrasound revealed a prevertebral hypechogenic lesion that surrounded the abdominal aorta, the emergency of the celiac trunk and the superior mesenteric artery, up to the common iliac arteries. In the thorax, the lesion displaced the inferior vena cava, surrounded the esophagus, and contacted the posterior heart wall. Computerized tomography (CT) confirmed the presence of this expansive lesion extending in the thoraco-abdominal prevertebral space and surrounding the aorta up to the renal vessels (Fig. 1A). On histologic analysis, a biopsy showed a highly vascular and hemorrhagic lesion infiltrating the skeletal muscle with a monotonous population of spindle cells. Immunohistochemical staining was positive for vimentin and CD34, and negative for CD99, alpha-smooth muscle actin and HHF35 actin, desmin, myogenin, S100 protein, synaptophysin, neurofilaments, CD56, and CD57. The initial diagnosis was infantile fibrosarcoma, and chemotherapy was started with vincristine, actinomycin D, and prednisone.[13]

Thrombocytopenia gradually resolved, but respiratory distress and coagulopathy persisted. Moreover, ultrasound imaging did not show any tumor mass reduction. On the basis of these results, 1 month later cyclophosphamide was added. When the infant was 2 months old, histological analysis of a repeat biopsy
revealed that the infiltrating lesion consisted predominantly of spindle cells fascicles with fusiform nuclei and bland chromatin pattern, without atypias, with low mitotic activity, disposed in nests with many interspersed spaces containing vascular lumen. Immunohistochemical analysis showed positive staining for CD34, CD31, and WT1, leading to the final diagnosis of KHE.

On the basis of recent reports,[7–12] second-line treatment with oral propranolol was started at a dosage of 2 mg/kg/day. Although a gradual resolution of respiratory distress was observed and coagulopathy progressively resolved, magnetic resonance imaging (MRI) performed after 4 months of treatment demonstrated only a slight reduction in tumor mass, compared with the previous CT (Fig. 1B). This treatment was continued for 7 months without observing any further radiological improvement (Fig. 1C). To evaluate the apparent resistance to propranolol, plasma propranolol concentrations on dried blood spots were measured when the patient was 15 months old.[14] Results showed extremely low plasma propranolol concentrations, on average less than 10 ng/ml. Therefore, over 2 weeks, we gradually increased the propranolol dosage, up to final dosage of 3.5 mg/kg/day, thereby inducing a major increase in plasma propranolol levels (measured 10 days after the dose increase) to approximately 40–50 ng/ml (Fig. 2). MRI performed 2 months later (when the patient was 18 months old) revealed clinically relevant tumor mass reduction of more than 30% and a substantial decrease in tumor perfusion (Fig. 1D).

Subsequently, this dosage was maintained for a further 18 months and almost complete regression of KHE was observed, without any adverse effects (e.g., neither hypotension nor hypoglycemia). Propranolol was discontinued when the patient was 3 years old. MRI performed after 6 months confirmed the virtual disappearance of the lesion without rebound. Appropriate institutional review boards approved this report and written informed consent was obtained from the patient’s parent for its publication.

**DISCUSSION**

Although complete surgical excision is the first-choice treatment of KHE, the lesions are often unresectable because of their size, anatomical sites, tissue infiltration, or bleeding complications.[9,11] Several medical treatments have been proposed,[2–5] but current knowledge is limited by the relative rarity of the disease and the lack of controlled trials. Unfortunately, treatments leading to regression of the tumor without toxicity have

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[Fig. 1. Imaging of kaposiform hemangioendothelioma at successive time points. (A) Thoraco-abdominal computerized tomography scan at disease onset. (B–D) Thoraco-abdominal magnetic resonance imaging scans performed after 4 months of propranolol at a dose of 2 mg/kg/day (B), after 11 months of propranolol at a dose of 2 mg/kg/day (C), and then after 2 months of propranolol at a dose of 3.5 mg/kg/day (D).]
not yet been identified. To date, corticosteroids and vincristine are considered the frontline treatment for KHE associated with KMP.[9,11,15,16] Vincristine achieves good response rates, although complete resolution is rare and side effects strongly limit its use.[4,16] Unfortunately, in our patient these drugs had no effect on tumor mass, even upon addition of actinomycin D and, later, cyclophosphamide.

Clinical presentation, image analysis, and histological and immunohistochemical features of KHE sometimes present similarities with other tumors, such as fibrosarcoma.[17] In this patient, at first evaluation, the diagnosis was infantile fibrosarcoma. However, MRI evaluation, more detailed immunohistochemical analysis of the second biopsy, and the presence of consumptive coagulopathy—more compatible with KHE than with fibrosarcoma—led us to the final diagnosis. MRI is universally accepted as the best diagnostic imaging technique,[2], useful both for diagnosis and evaluation of treatment efficacy, as demonstrated by this patient.

Propranolol has been reported to be effective in the treatment of benign vascular tumors, such as IH, by inducing vasoconstriction, apoptosis, and decreased expression of angiogenic factor,[18] or by modulating the renin-angiotensin system.[19] Moreover, propranolol induces apoptosis and disrupts the migration of malignant vascular tumor cells.[20] For these reasons, it was reasonable to expect a clinical benefit for KHE treatment as well. Few cases have been published concerning its use in the treatment of KHE,[7–12] with only a partial response reported. The primary tumor size and the severity of coagulopathy determine the responsiveness to treatment,[9,11] but it is also likely that drug dosage affects the clinical response.

In some patients, administration of propranolol at a dose of 2 mg/kg/day resulted in complete tumor mass regression.[7,10,11] A more extensive report showed that of 11 patients treated with propranolol at doses between 2 and 3 mg/kg/day, four patients (36%) who showed benefits from this treatment received doses between 2 and 3 mg/kg/day.[9] In another series of cases, propranolol at doses of 1–2 mg/kg/day showed no benefits.[12] In conclusion, available data show a variable response to propranolol, probably related to the dose used.

Considering the clinical history of our patient, if the treatment continued with 2 mg/kg/day, our patient would have been defined as a nonresponder, as the tumor mass was not substantially reduced after 16 months of treatment. Plasma propranolol levels were surprisingly lower than those previously reported in newborns treated with the same dose.[21] A possible explanation could be reduced absorption or increased metabolism in this patient, even though we cannot exclude the possibility that the volume of distribution or the density of β-adrenergic receptors might be increased, leading to reduction of the bioavailability of the drug. Increasing the dose to 3.5 mg/kg/day led to a large increase in plasma concentrations and was associated with a major reduction in the tumor mass and its perfusion. Our patient showed an optimal response to propranolol, although the KHE was large and associated with severe KMP, suggesting that the dosage was more important in this case than KHE dimension or KMP severity.

The link between clinical efficacy and plasma concentration of propranolol is not surprising. It has been shown that the antiangiogenic effect of propranolol is absolutely dose dependent[22] and that, for IH, propranolol was significantly more effective at a dose of 3 mg/kg/day than at 1 mg/kg/day.[7]

Although it is impossible to make definitive conclusions from a single case report, this experience suggests the importance of relating propranolol dose to its plasma concentration before considering this treatment as noneffective. Further large-scale studies are needed to confirm our findings for this difficult and sometimes life-threatening condition.

REFERENCES


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