Delayed-Onset of Multiple Cutaneous Infantile Hemangiomas Due to Propranolol: A Case Report

Rocío Porcel Chacón, MDa, Javier del Boz González, MD, PhDb, Juan Navarro Morón, MDa

**abstract**

Infantile hemangiomas are the most common vascular tumors in childhood. In view of its proven effectiveness in such cases, propranolol is the drug of choice. We present the case of a male infant who started treatment with propranolol shortly after birth due to heart disease. After 7 months, when the patient had suffered various respiratory exacerbations, this treatment was suspended. One week later, multiple skin lesions (ie, multifocal infantile hemangiomas) began to appear, with no extracutaneous involvement. It was decided to resume treatment with propranolol, although at lower doses than before, and the skin lesions improved rapidly, with some disappearing completely. Treatment was definitively withdrawn at age 16 months, with only slight recurrence of the lesions. The case described is of multifocal infantile hemangiomas without extracutaneous involvement appearing beyond the neonatal period after treatment with propranolol beginning in the first days of life. The details of the case support the hypothesis that this drug is not only therapeutic but also plays a prophylactic role against infantile hemangiomas. In turn, this supports the recent proposal that this drug may be useful in preventing the growth and spread of tumors with high angiogenic potential. It is postulated that the inhibition of β-adrenergic receptors is associated with multiple intracellular processes related to the progression and metastasis of different tumors.

**Infantile hemangiomas** are the most common vascular tumors in childhood. They usually appear during the first weeks after birth, grow rapidly in the first months of life and involute (partially or completely) in a few years. Accordingly, in most cases no treatment is attempted, and physicians adopt a wait-and-see approach. However, up to 10% of hemangiomas call for treatment, with potential complications such as ulceration, bleeding, visual alterations, airway blockage, excessive growth, and even death.1-5 The first description of the value of propranolol as a treatment of infantile hemangiomas was in 2008. Since then, given its effectiveness, it has become the treatment of choice for complicated infantile hemangiomas.6 Propranolol is a noncardioselective β-blocking drug. It produces effects on vascular proliferation by inducing the apoptosis of vascular endothelial cells, thus decreasing the intravascular pressure of the lesions (vasoconstriction) and producing an antiangiogenic effect, blocking vascular endothelial growth factors and fibroblast growth factors.3 However, no previous reports have been made of cases showing the prophylactic effect of propranolol against the development of new infantile hemangiomas.

**CLINICAL CASE**

We report the case of a male infant who began to develop multiple hemangiomas at 7 months of age.
According to the personal history, gestation took place in Morocco and was uncontrolled. The mother arrived in Spain at the time of birth, which was preterm by caesarean delivery at 35 weeks’ estimated gestational age. At birth, the infant presented hydrops fetalis, respiratory distress, and pleural and pneumothorax effusion that required prolonged mechanical ventilation. Multiple complications arose, and bronchopulmonary dysplasia developed. There was also a congenital intrahepatic portosystemic shunt and an asymmetric hypertrophic cardiomyopathy associated with mild aortic regurgitation.

Treatment of the heart disease began in the second week of life with propranolol (dose of 5 mg/kg/day). The patient was discharged from hospital at 4 months of life. Despite treatment with inhaled budesonide and home oxygen therapy, the infant presented frequent respiratory exacerbations that required hospitalization, on one occasion in the PICU. During the latter admission, when the infant was 1 month of age, propranolol treatment was withdrawn. One week later, there began to appear multiple skin lesions (>20), corresponding to multifocal infantile hemangiomas affecting the face, trunk, and limbs (Fig 1), with rapid growth but no associated liver involvement, according to serial ultrasound examination. In view of the facial involvement and taking into account the previous use of propranolol for several months, it was decided to resume the application of propranolol (although at lower doses) at 9 months of age at an initial dose of 1 mg/kg/day, which was increased to 2 mg/kg/day 2 weeks later. The response to this treatment was good, with many of the lesions disappearing completely and the rest decreasing in intensity and volume (Fig 2). The patient tolerated the treatment well, and there were no respiratory exacerbations. The treatment was continued until the patient was 16 months of age. After the withdrawal of propranolol, some lesions reappeared, although in a less intense form (with a lower volume). A wait-and-see approach was then taken.

**DISCUSSION**

Historically, the term “hemangiomatosis” has generated considerable confusion because of the variety of presentations of the condition to which it has been applied. Classically, researchers differentiated between benign neonatal hemangiomatosis (affecting only the skin, although some authors also include cases with liver involvement) and diffuse neonatal hemangiomatosis (affecting ≥3 organs, although some authors include cases with only skin and liver involvement in this category). In any case, there is a consensus that the term “infantile hemangiomatosis” involves the appearance of ≥5 hemangiomas in the neonatal period.
To avoid terminological confusion, it has been proposed that this condition should be termed “multifocal infantile hemangiomas,” with or without extracutaneous involvement.7

In the present case, the fact that the lesions did not appear during the neonatal period but later, at 8 months, seems to be related to the early introduction of propranolol (in the second week of life) to treat heart disease because the hemangiomas became apparent when this medication was withdrawn. This case, therefore, can be described as late-onset multifocal infantile hemangiomas without extracutaneous involvement, delayed by propranolol.

This delayed appearance, at the conclusion of propranolol treatment, suggests that the effect of the drug on infantile hemangiomas may not only be therapeutic but also prophylactic. This in turn could support the recently postulated theory that propranolol (and other β-blockers) may be useful in preventing the growth and spread of various cancers with high angiogenic potential, such as breast cancer,8,9 melanoma,10 or prostate cancer. This hypothesis is based on various research studies, most of them observational or experiments in animal models, which have reported a decreased overall risk of cancer, reduced metastasis, and less tumor recurrence; moreover, increased overall disease-free survival has been observed among patients with cancer who were taking β-blockers for other reasons.8–11

This effect may be because β-adrenergic receptors are related to the inhibition of multiple intracellular processes involved in the progression and metastasis of different cancers, in the expression of proinflammatory cytokines, in tumor immune responses, and, presumably, in angiogenesis.8–11

Moreover, if the present case is considered multifocal infantile hemangioma, it would be the first reported case to be treated (and achieving a good response) with propranolol.

In conclusion, although further studies are needed, this exceptional case corroborates the prophylactic (and not merely therapeutic) effect of propranolol as an antiangiogenic agent, which could be related to its potential impact on cancer progression, and demonstrates the efficacy of propranolol in cases of multifocal infantile hemangiomas.

REFERENCES


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