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CASE REPORT

Multifocal infantile haemangiomatosis with hepatic involvement: two cases and treatment management

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Abstract

Infantile haemangiomas (IHs) are the most common benign tumours of childhood; despite the benign histology, prognosis depends on severity of visceral involvement, with a mortality rate ranging from 50 to 90%. In this paper, we describe two infants with multifocal infantile haemangiomatosis and hepatic involvement. This condition should receive appropriate management as it can be potentially lethal due to the high risk of systemic complications such as cardiac or fulminant hepatic failure and abdominal compartment syndrome. Both cases presented with liver involvement, but only the infant who had an excellent response to propranolol is still alive. A review of current therapeutic approaches is also presented even though there are, at present, no uniform guidelines for treatment, despite the relative frequency of infantile haemangiomatosis and the potential severe complications.

Keywords: hepatic haemangioma, infant, medical treatment, multifocal infantile haemangiomatosis.

Citation

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Introduction

Infantile haemangiomas (IHs) are the most common benign tumours of childhood, occurring in approximately 5% of newborns.[1] Multiple haemangiomas are present in 15 to 30% of these neonates. The use of various names for IH has resulted in great diagnostic confusion, so the real frequency is probably underestimated.

Moreover, IHs are included in an official classification system adopted by the International Society for the Study of Vascular Anomalies in 1996, which was reviewed in 2014 and updated in 2018.[2,3] This system considers IH as a subset of vascular tumours, which are lesions characterised by abnormal proliferation of endothelial cells and aberrant blood vessel architecture and distinguished from vascular malformations, which result from alteration of vascular morphogenesis.[4]

The classification of IH is based on pattern (focal, multifocal, segmental, indeterminate), type (superficial, deep, mixed, reticular), and association with other lesions (PHACE syndrome, LUMBAR syndrome).

Several therapeutic strategies have been tested, such as steroid therapy, cytotoxic drugs, and interferon-alpha-2a, which were often ineffective. Recently, propranolol has shown efficacy for treating infantile cutaneous haemangiomas and hepatic IHs,[5,6] though its mechanism of action remains unclear. Presently the use of propranolol is increasing, and it is now considered the first-line treatment for IHs.

We report on two infants with multifocal infantile haemangiomatosis with hepatic involvement. The first one was treated before the 'propranolol era', while the second one received propranolol. Only the latter had a favourable outcome. The patients cannot be identified from the case description or any other fact published in the case reports.

Patient 1

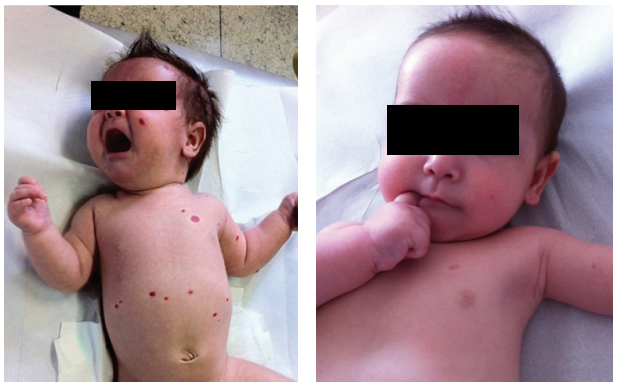
In 2003, a 20-day-old female baby, the second twin born to a 32-year-old woman, delivered vaginally at 38 weeks, presented at birth with multiple cherry red cutaneous haemangiomas. The lesions were 3–10 mm in diameter and involved the whole body, including the sole of right foot, the scalp, eyelids, lips, left hip, trunk, and right ear. Abdominal ultrasonography (US), performed at birth in another hospital, showed the presence of four haemangiomas, which increased in number and diameter at an

abdominal US repeated after 3 weeks due to clinical evidence of hepatomegaly. An abdominal computed tomography (CT) scan was performed, and it documented multiple haemangiomas that varied in diameter from 10 to 38 mm, causing disruption of normal hepatic architecture with typical characteristics of high-flow haemangiomas. The baby was transferred to our paediatric oncology unit with diagnosis of multifocal infantile haemangiomatosis. At admission, she was pale, the liver edge was palpable 3 cm below the right costal margin, while the tip of her spleen was appreciable at the left costal margin. Other congenital anomalies or dysmorphic features were not evident. Neonatal reflexes were normal. Laboratory tests documented haemoglobin of 9 g/dl, white blood count 8,000/µl, and platelets 207,000/µl. Renal and hepatic function tests and coagulation parameters were within the normal range. Thyroid function, head ultrasound, and echocardiography were normal. The second day after admission, the patient became dyspnoeic and bradycardic, and she was transferred to the paediatric intensive care unit (PICU). On arrival, the child appeared hyporeactive, severely dyspnoeic, cyanotic despite oxygen supplementation, and with poor skin perfusion. She was immediately intubated, and pressure-controlled ventilation was started. During the clinical course in PICU, several blood and plasma transfusions were given because of laboratory tests that showed severe anaemia and consumptive coagulopathy, with normal platelet count. A total-body CT scan was performed; the hepatic lesions almost completely replaced liver parenchyma. No other organ was involved. Corticosteroid treatment with intravenous methylprednisolone at a dose of 2 mg /kg/day was started, and then the dose was increased to 4 mg/kg/day after 2 days; cardiac and hepatic functions were carefully monitored. During the next 2 days, the baby's clinical conditions deteriorated. Laboratory tests suggested hepatic failure, and echocardiography disclosed normal left ventricular function and dilatation of the right cardiac sections with tricuspid regurgitation, which was treated with diuretics. Due to the absence of any response, steroid therapy was stopped, and cyclophosphamide at 8 mg/kg/day with mesna was started. After 2 days the baby became oliguric and oedematous, and echocardiography documented worsening of the cardiac failure with involvement also of left cardiac sections. A chest radiograph showed cardiomegaly and pulmonary congestion. Despite multiple supportive therapies, cardiac and hepatic failure worsened. She died 4 weeks from birth.

Patient 2

In December 2012, a full-term female infant presented at the time of delivery with multiple cutaneous lesions (at least 20) with diameters ranging from few millimetres to 1 cm and spread on the whole body surface. Liver ultrasound showed multiple roundish nodules in both liver lobes compatible with hepatic haemangiomas. A few artero-venous shunts were also seen, which caused an ectasia of the suprahepatic veins. The echocardiogram showed a left ventricular enlargement with a normal cardiac output. Complete full blood count, liver function tests, and thyroid hormones were all normal.

Figure 1. (a) Multiple haemangiomas present at delivery. (b) At the age of 1.5 months, the lesions have almost completely disappeared.



A B

Oral propranolol was given initially at a dose of 1 mg/kg/day and then increased up to 3 mg/kg/day in four daily doses. Treatment was well tolerated by the patient, with no abnormalities of hourly monitored heart rate, respiratory rate, and blood pressure. No other side effects were noted. The child was followed for the first month on a 2-weekly basis and then at monthly intervals. A significant response was noted: after 1 week of treatment, the lesions became paler, then almost disappeared at 1.5 months (Figure 1). After 7 months, cutaneous haemangiomas were no longer visible. At 9 months of treatment a hepatic ultrasound showed a significant reduction in size of the hepatic nodules and shunts with a change in appearance from hyperechogenic to hypoechogenic. Treatment was stopped after 12 months. To date, no recurrence following propranolol discontinuation has been observed after a 30-month follow-up.

Discussion

Multifocal IH with visceral involvement of the newborn, historically defined as diffuse neonatal haemangiomatosis (DNH), is a rare and potentially fatal entity in infants, present at birth or arising during the first week of life. The diagnostic criteria include the involvement of three or more organ systems. Because the outcome of patients with three organ involvement is similar to that with cutaneous and hepatic lesions, the presence of haemangiomas of the skin and liver is sufficient for diagnosis.[7,8] These lesions maintain unique patterns of growth, sequelae, and therapeutic modalities that are different from other vascular birthmarks; moreover, the differential diagnosis should include benign and aggressive cutaneous lesions.[9–11]

Haemangiomas are benign vascular tumours, and their biological behaviour is characterised by a brief first phase of rapid growth, followed by a spontaneous and slow regression that could continue for several years.[12] The life cycle can be divided into the proliferating phase (8–12 months), involution phase (1–5 years), and involuted phase (6–12 years). The vascular lesions' proliferative capacity is due to immature endothelial cells. This characteristic is maintained for a limited period during postnatal life due to various angiogenic peptides and vascular endothelial growth factor (VEGF). Hence, haemangiomas tend to increase initially during the proliferative phase, followed by regression and improvement in the involuting and involuted phases, respectively.[13]

Despite the benign histology, prognosis depends on the severity of visceral involvement, with a mortality rate ranging from 50 to 90%.[14] IHs have a worse prognosis if there are potential life-threatening complications, functional impairment, ulceration, permanent disfigurement, or association with PHACE or LUMBAR syndrome.[15] In particular, patients who developed early cardiac failure and significant vascular shunting have a poorer prognosis. In most patients, haemangiomas are limited to the skin and liver, but other sites may be involved, such as brain, lungs, intestine, and orbital region with the potential risk of visual loss or functional alteration.[16–18] The biological course can justify an initial wait-and-see approach, but some haemangiomas endangering organ functions require immediate treatment.

Despite the relative frequency of infantile haemangiomatosis and the potential severity of complications, there are currently no uniform guidelines for treatment.[19] The management of multifocal infantile haemangiomatosis with hepatic involvement includes several approaches, with variable results.[20] Systemic corticosteroids have represented for a long time the first-line of medical therapy, but response rate is variable from 30 to 60% of cases.[21,22] Moreover, a high dosage of steroids is requested to obtain an antiangiogenic effect, and its use in the neonatal period can induce several sequelae, such as cardiac hypertrophy and transient hypertrophic cardiomyopathy.[23] Different chemotherapeutic drugs, such as bleomycin, vincristine (given weekly intravenously at dosage of 0.05 mg/kg for children less than 10 kg and 1.5 mg/kg for heavier children), or cyclophosphamide (administered intravenously at dosage of 10 mg/kg/day given for 3 consecutive days), have become an alternative therapy for life-threatening corticosteroid-resistant haemangiomas.[24–25]

Specific antiangiogenic therapy with subcutaneous interferon-alpha-2a administered at dosage between 1 and 3 million U/m^2/day has been reported as effective by several authors.[26] Interferon reduces the response of endothelial cells and fibroblasts to their growth factors, and it down-regulates the genetic expression of basic fibroblast growth factor.[27] However, serious side effects due to interferon have been reported, such as irreversible spastic diplegia. Hence, this therapy requires continuous neurological surveillance.[28]

As for surgical approaches, selective embolization of intrahepatic feeding vessels in liver haemangiomas can improve prognosis, but this procedure cannot be performed in children who are haemodynamically unstable.[29] Laser therapy is also described in the literature as a successful treatment, especially for subglottic haemangiomas.[30]

After the discovery of propranolol efficacy in the treatment of IHs, many studies have confirmed the activity of the drug in inducing regression of haemangiomatous lesions without significant side effects.[31]. The drug is generally administered at a dose of 1–3 mg/kg/day, in 2–4 daily doses for a median duration of 6–12 months.

The efficacy of propranolol in reducing haemangiomas is due to its action as a non-selective inhibitor of beta-adrenergic receptors. *In vitro* studies suggest that the antiproliferative effect of propranolol on haemangiomas is due to three main mechanisms: vasoconstriction in the context of the lesion, induction of apoptosis of endothelial cells, and suppression of the angiogenetic process. Side effects related to the drug, albeit rare, include transient hypoglycaemia, bradycardia, hypotension, and bronchospasm.[32] Propranolol has shown efficacy and is well tolerated, confirming the literature data that show a positive response in more than 90% of patients treated. In recent years, propranolol has been proposed as the first-line therapy in all infants suffering from life-threatening haemangiomas and with no pulmonary or cardiovascular contraindications to the use of the drug.[33]

In conclusion, treatment of infants with multifocal infantile haemangiomatosis can benefit from multidisciplinary strategies but requires high surveillance. It is therefore still a challenge for physicians and surgeons. This report highlights that infants with multiple cutaneous haemangiomas should receive appropriate clinical and radiological investigations in order to detect visceral involvement and to assess an early specific monitoring. Prolonged treatment with propranolol may be considered in infants with multifocal infantile haemangiomatosis and hepatic haemangioma.

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