Multiple infantile hemangiomas in a preterm infant
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Title figure:
Capillary hemangioma, H&E stain
(source: http://en.academic.ru/dic.nsf/enwiki/431790)
Hemangiomas represent the most common tumor of infancy with the highest incidence in preterm infants (1). They are usually not present at birth but develop in the first few weeks of life and proliferate in the following weeks and months. The etiology is not yet fully understood but vascular endothelial growth factor (VEGF) may play an important role. Multiple hemangiomas are defined by five or more hemangiomas, are usually smaller in size and more likely to be associated with visceral hemangiomas (2).
We present a male preterm infant born to a healthy 31-year-old G1/P1 by Cesarean section at 28 4/7 weeks due to preeclampsia.

The baby had a birthweight of 1100 g (P 25 – 50). Apgar scores were 6, 8 and 8 at 1, 5 and 10 minutes, respectively, and the arterial umbilical cord pH was 7.27. He was transferred to the neonatal intensive care unit with mild respiratory distress on nasal CPAP and required a maximal FiO₂ of 0.3. His postnatal course – apart from an episode of late-onset sepsis – was unremarkable.

At about 3 weeks of age, a few tiny hemangiomas the size of a pinhead were noted (Fig. 1–2). Over the next few weeks, the number and size of the hemangiomas increased. Abdominal ultrasound did not reveal any intestinal or liver hemangiomas. As the cutaneous hemangiomas were small and not located close to orifices, specific therapeutic interventions were not deemed necessary.

At the corrected age of 3 months, the baby was discharged home. At that time, there were a total of 83 hemangiomas, some of them having shown an impressive increase in size (Fig. 3–4).
At the age of 3 weeks, several small hemangiomas were noted (back).
At the age of 3 weeks, several small hemangiomas were noted (chest).
Multiple hemangiomas at a corrected age of 3 months (back).
Multiple hemangiomas at a corrected age of 3 months (chest and axilla).
This case report of a premature infant with multiple cutaneous hemangiomas without visceral involvement illustrates a common problem in this population. About 25% of preterm infants develop hemangiomas during the neonatal period compared to around 5% of term infants (3). Infantile hemangiomas are classified as focal or localized, segmental, indeterminate and multifocal infantile hemangiomas (4). Multiple hemangiomas are mainly located on the skin, but these infants have a higher risk of internal hemangiomas, which are particularly located in the liver. Ulceration and bleeding are the typical complications of cutaneous hemangiomas. These infants require regular clinical and sonographic follow-up including precise documentation of the lesions (5).

Infantile hemangiomas are vascular tumors. Initially, there is a proliferating phase in the first six to nine months of age, followed by an involution phase over years which ultimately leads to a residual, mostly fibrotic mass. The differential diagnosis includes other vascular tumors, as well as other vascular malformations, which in contrast to infantile hemangiomas are usually present at birth.

The exact pathogenesis of multiple infantile hemangiomas is not yet fully understood. There are different hypotheses, however, vascular endothelial growth factor A (VEGF-A), an important molecule in angiogenesis and vasculogenesis, likely plays a role. In addition, cell
embolization from the placenta, somatic mutations in a gene mediating endothelial cell proliferation, endothelial progenitor cell and hypoxia have all been implicated (6 – 9).

According to the European Propranolol In the Treatment of Complicated Haemangiomas (PITCH) study, there are three main indications for treatment: 1) periocular location with threat to vision, 2) location on the face with risk of cosmetic disfigurement and 3) risk for ulceration and bleeding, seen for example in perianal hemangiomas (10). Overall, treatment is rarely required and long-term outcome is good.

Therapeutic options include systemic or local treatment with beta blockers, cryotherapy, or laser coagulation. Since beta blocker treatment has become available, surgery is now only rarely required. Corticosteroids are generally not used in infantile hemangiomas. Modifying VEGF-A action could be a promising therapeutic option in the future, but, at this point, results of randomised controlled trials are still lacking.

Propranolol therapy for infantile hemangiomas was used in 2008 for the first time and since then has rapidly become the first line treatment. Its effect on infantile hemangiomas was discovered by chance: Léauté-Labrèze et al. used corticosteroids to treat a patient with a nasal hemangioma. During this treatment, the hemangioma stabilized in size but the
patient developed hypertrophic obstructive cardiomyopathy, which in turn was treated with propranolol. The treatment team observed rapid involution of the hemangioma (11).

Oral propranolol therapy should be started with a dose of 1 mg/kg/day in the hospital setting to monitor heart rate, blood pressure and glucose concentrations. If well tolerated, it can be increased to maintenance dose of 2 mg/kg/day (12). The main side effects are mild and include sleep disturbance and cool extremities. At higher doses, fatigue and bradycardia can occur. Treatment response depends on timing and duration of treatment. There is no consensus regarding the optimum treatment duration, but studies suggest that the risk for rebound growth decreases after 12 months (12). Rebound growth has been reported to occur in up to 20% of patients. Risk factors for rebound growth are short duration of propranolol therapy, female gender, deep infantile hemangiomas and abrupt discontinuation of therapy (13).

In summary, infantile hemangiomas are very common in premature infants. Usually, they are not present at birth but proliferate in the first few months with a peak around the age of 3–6 months, followed by a stable phase for another 2 years and a regression phase until the age of 4–5 years. The pathogenesis of infantile hemangioma is still not fully understood. Whether active treatment is required depends on
localization and size of the lesions as well as the risk for complications. Overall, only a small proportion of patients needs therapy. Local or systemic propranolol is the first line treatment. It is safe and highly effective, but compliance is important and parents should be informed about the potential and usually mild side effects.


