CASE REPORT

Multifocal infantile haemangioma: a diagnostic challenge

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SUMMARY

We describe a case of a newborn who presented with multiple dark red macules that developed into red-to-purple papules associated with thrombocytopaenia. Abdominal ultrasound showed multiple hyperechoic papules and nodules. Endothelial cells from a skin biopsy stained positively for endothelial cell glucose transporter 1, which was consistent with a diagnosis of multifocal infantile haemangioma. At the age of 2 months, the child developed intestinal bleeding and anaemia. Upper and lower endoscopies showed no intestinal haemangiomas. Oral treatment with propranolol (3 mg/kg/day) resulted in complete involution of the skin and hepatic haemangiomas over the period of treatment, which lasted until the child was aged 15 months. This is a rare case of multifocal cutaneous haemangioma with hepatic and probable intestinal involvement, successfully treated with propranolol.

BACKGROUND

Infantile haemangioma (IH) is the most common vascular tumour in infancy, affecting 3–10% of all newborns.[1 2] Risk factors for the development of IH are sex (female ratio 3:1), race (Caucasian), prematurity, family history of IH and multiparous mothers.[1 3]

IH can be classified as localised, segmental or multifocal, the latter subtype occurring rarely, in about 3.6% of all IH.[1] Infants with multifocal IH are recognised to have a higher risk of extracutaneous disease, with the liver being the most affected organ (about 50% of cases), and there are rare cases of intestinal involvement. We describe a case of multifocal IH with hepatic and intestinal involvement that required skin biopsy for differential diagnosis with other vascular tumours, allowing appropriate treatment and successful outcome.

CASE PRESENTATION

A full-term male Caucasian newborn, with unremarkable antenatal and family history, born with Apgar score of 8 (at 1st and 5th minute), presented 20 min after delivery, with respiratory distress and multiple widely distributed millimetre-sized dark red telangiectatic macules. He was found to have moderate thrombocytopaenia and, due to the initial suspicion of neonatal sepsis, he was admitted to the neonatal intensive care unit, where he required 28% oxygen in the first 24 hours. He was treated with ampicillin and gentamicin. Although he was clinically stable, it was noted over the following days that the number of cutaneous lesions—consisting of red-to-purple papules, ranging in size from a few millimetres to 1.5 cm (figure 1A–C)—was increasing (about 30–40) and affecting the whole body surface, including palms, soles and oral mucosa. Clinically, there was no hepatosplenomegaly nor were there any neurological deficits. Antibiotics were stopped on day 5 due to persistently negative inflammatory markers and negative blood cultures. At this time, the cutaneous lesions were investigated. At the age of 2 months, the child developed intermittent, mild gastrointestinal bleeding (haematemesis and haematochezia), which resolved over a period of 3 weeks.

INVESTIGATIONS

A full blood count showed moderate thrombocytopaenia since birth (minimum of 92 000/µl), which normalised spontaneously 14 days later, with no other coagulation disorder.

A biopsy performed from one of the vascular cutaneous lesions showed small isolated dermal blood vessels with no lobular arrangement, and with conspicuous endothelial folds and small septa. Endothelial cells stained for the glucose transporter 1 (GLUT1) isoform and these were surrounded by α-smooth muscle actin-positive cells shown to be pericytes of capillary vessels (figure 2A–C). There was no expression of lymphatic markers (neither D2–40/podoplanin nor Prox1). These findings were consistent with the diagnosis of IH.

Abdominal ultrasound revealed ~20 round, hyperechoic papules and nodules in both liver lobes, with a maximum size of 20 mm, compatible with hepatic haemangiomas.

Hepatic haemangiomas were confirmed on MRI, with no involvement elsewhere.

Echocardiography and ECG performed before starting treatment were normal.

At 2 months, the child was found to have normocytic normochromic anaemia (minimum haemoglobin 8.1 g/dL), which preceded the visible gastrointestinal bleeding. Upper and lower endoscopies showed no intestinal haemangiomas.

DIFFERENTIAL DIAGNOSIS

In most cases, IH is diagnosed based on a combination of typical history and clinical examination. However, in some atypical cases, a biopsy is required to exclude other soft tissue tumours such as multifocal lymphangioendotheliomatosis with thrombocytopaenia (MLT) and kaposiform haemangioendothelioma (KHE) or neoplastic disorders such as cutaneous localisation of leukaemia (blueberry muffin baby).

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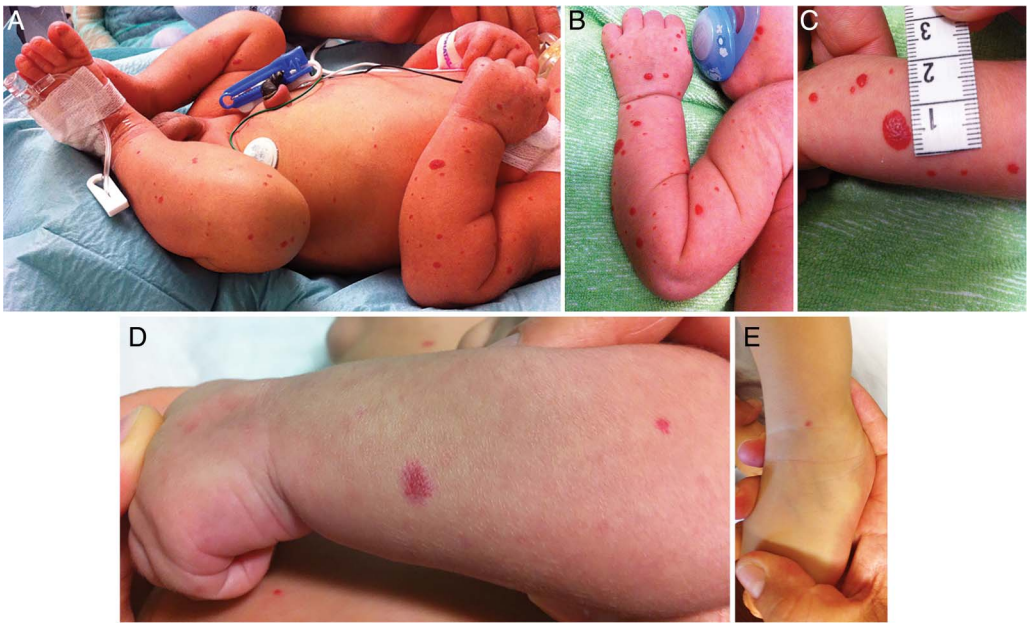

Figure 1 Multiple well-defined red-to-purple papules, of various sizes, affecting the whole body surface (A–C), with clear involution after 3 (D) and 6 (E) months of oral propranolol treatment.

MLT is a rare and recently described entity characterised by numerous variable skin lesions, ranging from telangiectatic macules or red–purple plaques 1–2 mm in size to large exophytic haemorrhagic nodules, and extracutaneous disease. Gastrointestinal involvement is common, with profuse bleeding and profound thrombocytopaenia. MLT biopsy specimens are lymphatic vessel endothelial receptor 1-positive and GLUT1-negative, and do not respond to propranolol treatment.[4] Although our case shared some manifestations with MLT, thrombocytopaenia was moderate and there was only mild gastrointestinal bleeding.

KHE is a rare GLUT1-negative vasoproliferative tumour with infiltrative nodules of vascular and lymphatic vessels that presents at or shortly after birth. Tumours can affect both superficial and deep soft tissue, arising most often in the limbs, head and neck. Cutaneous lesions appear raised and blue–red, and can be complicated by Kasabach-Merritt syndrome and coagulation disorders, a phenomenon not usually seen in IH.[5]

TREATMENT

At the age of 3 weeks, the patient was started on oral propranolol, which was titrated up to 3 mg/kg/day. No adverse effects on blood glucose, blood pressure or heart rate were noted during therapeutic monitoring. Abdominal ultrasound was repeated every 3 months.

Anaemia was treated with iron supplementation (4 mg/kg/day) for 3 months and no red blood cell transfusion was required.

OUTCOME AND FOLLOW-UP

The patient was followed in a paediatric and gastroenterology clinic. He maintained normal weight and height growth, with no haemodynamic impairment and no other complication.

Within the first days of propranolol treatment, the cutaneous lesions became paler and then progressively involuted (figure 1D, E), until their complete resolution by the age of 12 months. Ultrasonography confirmed complete resolution of the hepatic haemangiomas by the age of 15 months, when the treatment was stopped.

DISCUSSION

Historically, multifocal vascular lesions of infancy have been categorised as 'diffuse neonatal haemangiomatosis' (DNH) or 'benign neonatal haemangiomatosis'. However, recent developments in the study of vascular anomalies have highlighted the confusion in classifying these lesions, which often included MLT and other less well-characterised multifocal conditions, with varying prognosis and treatment. Glick *et al*[4] recommended abandoning the term DNH and proposed multifocal IH with or without extracutaneous disease, a terminology that we adopted.

In this case, the initial presentation of multifocal cutaneous lesions and thrombocytopaenia (not commonly found in IH) triggered investigations into extracutaneous disease and enabled a precise histopathological diagnosis. IH can be distinguished from other vascular tumours and malformations by the presence of immunohistochemical staining for GLUT1,[6 7] which was positive and determined the exact diagnosis.

Platelet count spontaneously normalised prior to starting propranolol treatment, suggesting an unrelated cause such as neonatal hypoxia.

Infants with multifocal IH have a higher risk of hepatic haemangiomatosis, which can lead to heart failure or obstructive jaundice.[8] However, most patients have an excellent prognosis and low mortality when treatment is started early, as seen in this case.[4]

Although gastrointestinal haemangiomas were suspected, upper and lower gastrointestinal endoscopy were both negative, a feature also observed in recent series, which cannot exclude intestinal involvement.[9] This is a rare complication of multifocal IH and seems to be more commonly related to segmental IH and other vascular anomalies. Moreover, the most frequent locations of gastrointestinal IH are the small bowel and mesentery,[10] which could also explain its absence on endoscopy. MR

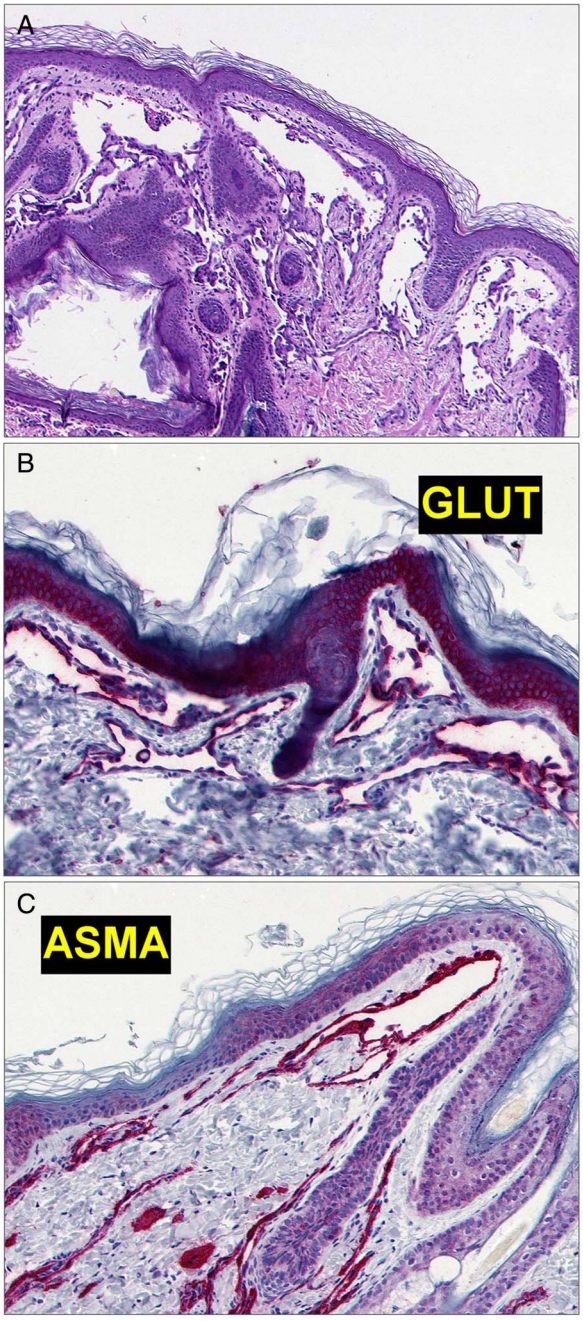

Figure 2 Infantile haemangioma. (A) Dermal capillary vessels (H&E, ×10); (B) endothelial cell glucose transporter 1 (GLUT1)-positive endothelial cells and (C) α-smooth muscle actin (ASMA) expressed by pericytes.

angiography appears to be a useful non-invasive study,[9] but the resolution of the bleeding in this case justified no further investigation.

Propranolol is widely considered to be the first-line therapy for IH, and recent evidence suggests that a dose of 3 mg/kg per day for 6 months is the most effective.[11] IH progresses mainly during the first 3 months of life, the period during which propranolol appears to have its maximal therapeutic benefit. However, some cases of IH may continue to evolve until the 6th–8th month (superficial forms), and until the 9th–12th month for cases of IH with subcutaneous manifestations.[12] In these cases, more prolonged therapy may be beneficial. In the absence of evidence regarding the appropriate duration of treatment and due to the extensive involvement, treatment in our case was continued until the child was aged 15 months, when complete resolution of hepatic haemangiomas was observed. Early treatment enabled successful prevention of life-threatening sequelae.

Our case required coordinated multidisciplinary intervention and this was crucial to achieve a successful outcome. Infants with vascular anomalies should be followed in tertiary specialist paediatric centres in order to have optimal care.

Learning points

- Children with more than five cutaneous haemangiomas should be investigated for extracutaneous disease.
- Infants with typical infantile haemangioma (IH) do not require a skin biopsy for diagnosis.
- Cases with extensive lesions present at birth, unusual cutaneous lesions or extracutaneous involvement, require a histological diagnosis.
- Propranolol is the first-line therapy for glucose transporter 1-positive multifocal IH.

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