Multifocal Infantile Hemangioma – Presentation of 4 Cases and Review of the Selected Literature

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ABSTRACT

Background: Multifocal infantile hemangiomas (IHs) are focal cutaneous lesions affecting more than 1 anatomic site. The multifocal distribution pattern is the rarest form of IH manifestation, accounting for only 3-4% of all affected infants. This type of cutaneous IHs may be a marker for extracutaneous disease, with the liver being the most frequently affected organ.

Methods: We investigated the clinical and epidemiological characteristics of a small case series of infants with multifocal IHs presenting with different clinical patterns, all diagnosed and treated in a regional tertiary-care pediatric clinic.

Results: Four infants with multifocal IHs were included in the analysis. There were 3 girls and 1 boy. Three out of 4 infants were prematurely born (2 of them very preterm), while only 1 was full-term. Clinical patterns in all cases were quite different, but more than 20 cutaneous IHs were present in each of the patients. Two infants had multifocal liver hemangioma, but without complications. In 3 out of 4 patients, systemic propranolol therapy was introduced, with excellent response in two cases (both with liver involvement).

Conclusion: With the increase in the number of cutaneous IHs, the probability of internal organ involvement, most often the liver, also increases. Evaluation for extracutaneous lesions is indicated in infants with 5 or more cutaneous IHs. Treatment of infants with multifocal IHs should be individualized and consider all relevant risk factors, including prematurity.

KEY WORDS: hemangioma, infant, premature, skin, liver, propranolol

INTRODUCTION

Infantile hemangiomas (IHs) are quite frequent vascular tumors in infancy, occurring in as many as 3-12% of infants (1-3). Most IHs are not present at birth but appear in the first few weeks or months of life. Their main characteristic is the two-stage development consisting of the proliferation phase in the first few months, followed by a gradual involution over several months to several years (4). According to the distribution pattern, morphology, and extent, they are categorized into the focal, multifocal, segmental, and indeterminate types. The majority of IHs are focal (approximately 70%). Multifocal IHs, defined as focal lesions affecting more than 1 anatomic site of the skin, are the rarest form of IH manifestation, accounting for only 3.6% of all affected infants (4). Based on the skin and soft-tissue depth, IHs can also be classified as superficial, deep, and mixed/combined (5).

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Multifocal cutaneous IHs may be a marker for extracutaneous disease, with the liver being the most frequently affected organ (6,7).

CASE REPORTS

We report a case series of 4 infants with multifocal IHs presenting with different clinical patterns. All presented infants were diagnosed, treated, and followed-up in a single regional tertiary-care university hospital.

Case 1

Our case 1 was very preterm male infant born after 29 gestational weeks (GW) and with a birth weight (BW) of 1550 g from a third spontaneously conceived pregnancy. He was born by an emergency caesarean section due to placental abruption. Numerous punctiform cutaneous IHs were detected at the postnatal age of 4 weeks. All of them were small (up to 5-6 mm), diffusely distributed, superficial (all in the skin level or slightly elevated), and round to oval in shape. On evaluation for extracutaneous lesions (abdominal ultrasound, echocardiography, and chest radiography) we found no additional internal organ involvement. Laboratory tests, including total blood count, renal and hepatic functions, coagulation status, and thyroid function, were within physiologic ranges for the age. The number of IHs was constantly increasing, and at the age of 4 months there was a total of 32 hemangiomas, all of them having similar characteristics (Figure 1). Systemic therapy with propranolol was introduced at that time. Propranolol was administered orally, with a gradual increase of the dose, to a therapeutic dose of 2 mg/kg divided in 3 equal daily doses. After reaching full therapeutic dosage of propranolol, the patient was discharged. However, unfortunately, there were no follow-up examinations for 18 months. At the age of almost 2 years, the patient was hospitalized for acute respiratory illness. It was at that point that we observed only a mild response to what amounted to be an irregularly implemented therapy.

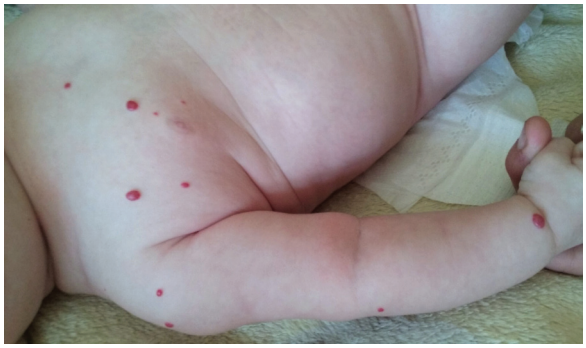

Figure 1. Case 1: Multiple round and oval infantile hemangiomas in a very preterm boy at the age of 4 months.

Case 2

Case 2 was very preterm female infant born from a first spontaneously conceived twin pregnancy in 32nd GW with BW of 2040 g. At the age of about 2 months, several IHs of varied types appeared on different body parts. Most of them were small (1-3 mm), round, and superficial, but 3 were larger (up to 1 cm), irregularly shaped, and of the combined type (Figure 2). During the next few months, many more IHs appeared on the skin of different body parts, including the palms and soles, but also on oral mucosa (a total of about 30). All new IHs were small (up to 3 mm), round, and at the level of the surrounding skin. There were no local complications resulting from IHs, nor any involvement of internal organs. The possibility of the application of oral propranolol was discussed with parents in detail, but they did not opt for it. During the follow-up period, spontaneous significant regression of all IHs was observed.

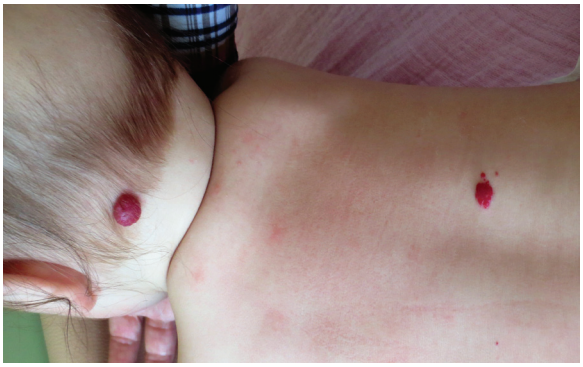

Figure 2. Case 2: Multiple IHs in a very preterm girl at the age of 7 months: round pedunculated IH on the back of the neck, several punctiform and one irregularly shaped on the back of the trunk.

Case 3

A full-term, female infant from a single, spontaneously conceived pregnancy (38th GW; BW 3350 g). More than 15 focal, small (1-3 mm), superficial IHs were noticed during the first week of life. They were diffusely distributed on the skin over the trunk, extremities, and head. Even more IHs appeared during the next few weeks. A few of them were of the mixed/combined type (Figure 3, a), and a few were located on the oral mucosa. Laboratory tests (including total blood count, renal and hepatic functions, coagulation status, and thyroid function) were within physiological parameters. Abdominal ultrasound visualized a few hypoechoic areas of up to 3 cm in diameter in the liver. Cerebral ultrasound, echocardiography, and chest radiography showed no involvement of the examined organs. Computed tomography of the abdomen at the age of 2 months demonstrated multiple

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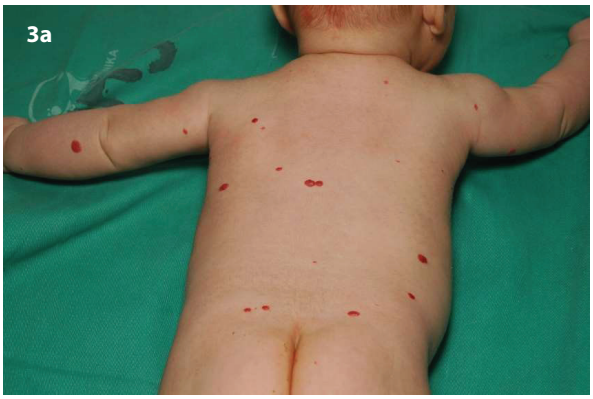

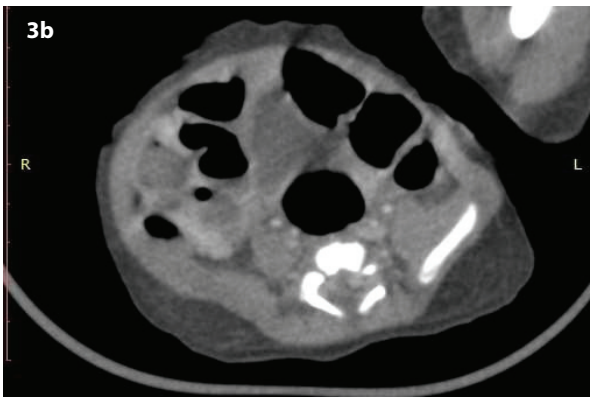

Figure 3. Case 3: full-term girl at the age of 2 months with multifocal oval and round IHs on the trunk and arms (a), and with liver IHs on abdominal computed tomography (b).

vascular malformations in the liver, more numerous than on the previously performed ultrasound examination (Figure 3, b). Thorough cardiologic investigation did not show signs of cardiac decompensation, but since the number of hepatic IHs had increased, oral propranolol was administered. The dose was gradually increased to the target of 2 mg/kg divided in 3 equal daily doses. Gradual regression of both skin lesions as well as lesions in the liver parenchyma was observed. Propranolol therapy was continued during the period of one year. During a follow-up examination (by the age of 2 years), we observed that both skin and liver lesions had completely disappeared.

Case 4

Case 4 was a preterm girl, born from a single pregnancy in the 34th GW by an elective caesarean section, with a BW of 2420 g. At the age of about 6 weeks, numerous small, round, flat IHs were noticed. They were all of the superficial type and up to 5 mm in diameter, disseminated all over the body trunk and extremities (Figure 4), with one located on the upper eyelid. Altogether, more than 20 IHs were observed. Total blood count, renal and hepatic functions, coagulation status, and thyroid function were within physiological ranges for the infant's age. At the age of 2.5 months, abdominal ultrasound revealed several hypoechoic lesions on the liver parenchyma with characteristics of hemangiomas, the largest being 26 mm in diameter. 4 weeks later, abdominal MRI revealed even more numerous multiple focal lesions of the liver that had the characteristics of infantile hepatic hemangiomas. Thorough cardiologic investigations showed no signs of cardiac failure. Systemic therapy with propranolol was introduced with a gradual increase to a therapeutic dose of 2 mg/kg divided in 3 equal daily doses. Excellent response of hepatic and cutaneous lesions was observed. By the age of 10.5 months, all cutaneous IHs completely disappeared, and liver lesions were significantly reduced.

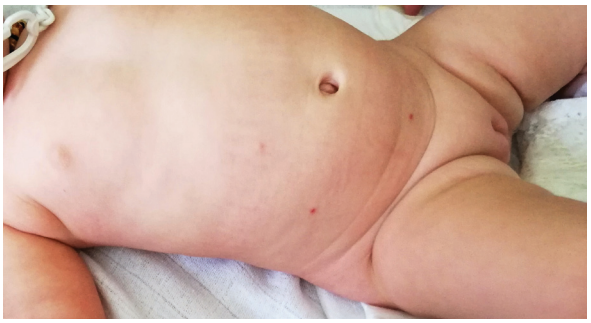

Figure 4. Case 4: a premature girl with multifocal infantile hemangiomas in the involution phase at the age of 6 months, after 3 months of propranolol therapy.

DISCUSSION

As mentioned previously, IHs are primarily solitary, but more than one IH is present in about 30% of cases. It has been reported that 3.6% of all patients have more than 5 IHs (4). However, the exact prevalence of multiple IHs has not yet been established. This is probably a consequence of the confusion regarding classification and nomenclature that is present in the current literature. Previously, in the literature, most cases of the multiple IH lesions were classified as: "diffuse neonatal hemangiomatosis" (with involvement of 3 or more internal organ systems and with higher mortality rate) or "benign neonatal hemangiomatosis" (with no involvement of internal organs, or only with liver hemangiomas, having good prognosis) (8). Today, the term "multifocal IHs" is recommended, which implies the presence of multiple cutaneous IHs on more than one anatomic site and possible liver involvement (but not of other internal organs). Multifocal IHs have a favorable outcome, and resolution of lesions occurs usually within 1-5 years (8). They should be clearly distinguished from multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT). In this, fortunately rare, entity, multifocal progressive vascular tumors are present

during the neonatal period, associated with severe thrombocytopenia, and with involvement of different organs (often associated with severe gastrointestinal bleeding). MLT is usually associated with serious complications and a high mortality rate (8).

It is known that the most common extracutaneous site of IHs involvement is the liver. Less common sites of extracutaneous involvement are the gastrointestinal tract, brain, spinal cord, mediastinum, and lungs (8,9). The severity of hepatic involvement can vary from asymptomatic to a life-threatening condition. Mortality is mostly the consequence of congestive heart failure, but liver failure may also occur if IHs are numerous enough to occupy most of the liver tissue. However, the large majority of infants with hepatic IHs remain asymptomatic, and the decision to introduce therapy should be made on a case-by-case basis. Only a small number of infants needs to be specifically treated for their hepatic hemangiomas (10,11).

It is of great importance to identify patients with IHs who are at increased risk of internal organ hemangiomas as early as possible. Several studies state that early evaluation for extracutaneous lesions is indicated in infants with 5 or more cutaneous IHs (10,12-14). Horri *et al.* conducted a multicenter prospective study on infants younger than 6 months, finding that 24 of 151 (16%) infants with five or more cutaneous IHs had solitary or multiple hepatic hemangiomas. Among 50 infants with one to four cutaneous his, no hepatic hemangiomas were found on abdominal ultrasound examination (11). A recent prospective study with a high number of participants, conducted by Ji *et al.*, suggests that an increased number of cutaneous IHs was associated with an increased risk of hepatic IHs. The incidence of liver involvement was highest in groups of subjects with 10 to 30 and with more than 30 cutaneous IHs (24.1% and 33.3%, respectively) (14). All of our cases had more than 20 IHs, and liver involvement was present in 2 out of 4 patients.

This cut-off point of 5 IHs for screening for internal organs involvement has been also debated in literature. Vredenborg *et al.* compared two groups of children with multifocal IHs. The first consisted of children with ≥10 IHs, whereas second group had 5 to 9 IHs. 33% of patients in the first group had internal hemangioma (8 liver; 1 spleen), while none in the second group displayed such lesions. Although the study sample was rather small, the authors suggest screening for internal hemangiomas (using abdominal ultrasound) only in patients with ≥10 IHs (10). Until larger studies on the association of cutaneous IHs with internal organ IHs are conducted, it is probably safer to perform appropriate laboratory and radiological investigations in all children with 5 or more cutaneous IHs.

It has been clearly confirmed that IHs occur more frequently in preterm than in full-term infants, and that the frequency of IHs rises with the decline of gestation and birth-weight (6,15). At least 2 studies (11,16) confirmed the claim that prematurity and low birth weight increase the risk not only of having an IH, but also of having a higher number of cutaneous IHs. This is consistent with data in our small case series, where 3 out of 4 infants were prematurely born (2 of them very preterm).

In the last decade, propranolol has been established as first-line therapy for IHs. Most IHs have a benign course and resolve spontaneously over time, and complications are rare. However, there are certain indications for systemic propranolol therapy for cutaneous IHs: exulcerated hemangioma; hemangioma with certain localizations (eye, nose, airway obstruction); hemangioma with a risk of scarring or serious disfigurement; and cutaneous hemangioma with liver involvement (especially with high output cardiac failure). It is estimated that about 15% of all IHs require active treatment. (17,18). As propranolol therapy has rare side-effects, indications for active intervention are have been broadened significantly, provided that therapy is instituted with all suggested age- and dosage-related precautions. Even in the presence of IHs in the liver, therapy is often not necessary, although there are no clear guidelines. The main indication for the introduction of systemic therapy for liver IHs is cardiac failure. Our presented patients with liver IHs did not have cardiac decompensation. However, since the number of liver IHs was increasing, and given that the patients were at an age when the appearance of new lesions can be expected for some time to come, we decided to introduce propranolol. In the remaining two presented cases of cutaneous multifocal IHs, the decision to apply therapy was made together with the parents – in one case the parents refused the proposal for treatment, while in the other case they wanted treatment, but it turned out that they did not implement it as prescribed. Therefore, the decision to implement therapy should be made on an individual basis, taking numerous factors into account, and in consultation with parents. Most of the guidelines recommend daily dosage of 2-3 mg/kg/day for at least 6 months (18-20).

CONCLUSION

Multifocal IHs are a rare form of IHs, but medical professionals of a wide range of specialties need to be familiar with this entity because of the risk of

association with internal organ lesions. Early evaluation for extracutaneous lesions is indicated in infants with 5 or more cutaneous IHs, regardless of their shape and size. The higher the number of cutaneous IHs, the higher the probability of internal organ involvement, with the liver being most commonly affected. Treatment of infants with multifocal IHs should be individualized, taking into account all relevant risk factors, including prematurity. Such treatment requires a multidisciplinary approach, and those patients should be followed in tertiary centers.

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