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Is the identification of multiple infantile cutaneous haemangiomas always a definitive diagnosis? A case report of an infant with multifocal hepatic haemangioma

Czy rozpoznanie skórnych mnogich naczyniaków niemowlęcych to zawsze ostateczne rozpoznanie? Opis przypadku niemowlęcia z zespołem wieloogniskowych naczyniaków wątroby

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Abstract

Multifocal hepatic haemangiomas are the most common benign vascular tumours of the liver that are detected in children with concomitant multiple infantile haemangiomas. Reported lesions are usually undetectable at birth, which presents a diagnostic problem for general practitioners. Ultrasound should be the imaging examination performed in the first instance in search for vascular anomalies in children. In pharmacotherapy, the first-choice treatment is propranolol, administered orally. In the described case, a boy with multiple hepatic and skin haemangiomas, after treatment with propranolol, achieved a significant improvement in the ultrasound image of the liver. Skin lesions were also reduced. The importance of the physical examination should be emphasised in the context of detecting cutaneous haemangiomas, which usually accompany multifocal hepatic haemangiomas and should prompt the physician to regularly observe and repeat abdominal ultrasound examinations of the diagnosed and/or treated child.

Keywords: liver, infant, haemangioma, propranolol

Streszczenie

Wieloogniskowe naczyniaki wątroby to najczęstsze łagodne guzy naczyniowe wątroby; są powszechnie wykrywane u dzieci, z towarzyszącymi licznymi skórnymi naczyniakami niemowlęcymi. Opisywane zmiany są zwykle niewykrywalne przy urodzeniu, co stanowi problem diagnostyczny dla lekarzy pierwszego kontaktu. Jako pierwsze w kolejności w przypadku anomalii naczyniowych u dzieci wykonuje się badanie ultrasonograficzne. W farmakoterapii lekiem pierwszego wyboru jest propranolol podawany doustnie. W opisywanym przypadku u chłopca z mnogimi naczyniakami wątrobowymi i skórnymi po leczeniu propranololem uzyskano znaczną poprawę w obrazie ultrasonograficznym wątroby. Zmiany skórne również uległy redukcji. Należy podkreślić znaczenie badania przedmiotowego w wykrywaniu naczyniaków skórnych, które zwykle towarzyszą wieloogniskowym naczyniakom wątrobowym. Powinno ono skłonić lekarza do regularnej obserwacji i powtarzania badań ultrasonograficznych jamy brzusznej u diagnozowanego i/lub leczonego dziecka.

Słowa kluczowe: wątroba, niemowlę, naczyniak, propranolol

INTRODUCTION

Vascular tumours of the liver are a significant medical issue, representing an underappreciated chapter of medical and surgical hepatology. There are three main types of vascular lesions diagnosed in the liver: focal, multifocal, and diffuse[1]. Multifocal hepatic haemangiomas (MHHs) are the most common benign vascular tumours of the liver that are detected in children with concomitant multiple infantile haemangiomas[2,3]. Vascular lesions undergo the phases of proliferation and growth, followed by involution, the onset of which occurs in the second half of the child's first year of life[4]. A study by Ji et al. revealed the median age at diagnosis to be 2.5 months[2]. Hepatic haemangioma is a benign vascular tumour caused by uncontrolled proliferation of vascular endothelial cells (ECs)[5]. Genes responsible for the formation of haemangiomas have not been sufficiently identified, however, glycolysis-associated molecules, including glucose transporter-1 (GLUT-1), seem to be implicated[5,6]. The risk factors are not fully known, either[2]. Female infants demonstrate higher incidence rates of the disease, compared to male infants, the ratio being 1.3:1 to 2:1, respectively. No racial predisposition has been found. A familial tendency towards MHH has also been described[4].

MHHs are usually undetectable at birth[7]. With the development of high-resolution prenatal ultrasound (US) technology and routine US follow-up, practised at most teaching and/or tertiary referral hospitals, the detection rate of hepatic haemangiomas in infants has been demonstrating a clear growing tendency in recent years[8]. One should, therefore, emphasise the important role of diagnostic imaging in the identification of hepatic haemangiomas at an early stage.

Patients with MHH, not previously diagnosed, are most commonly identified by some enlargement of the abdominal circumference, congestive heart failure (CHF), anaemia, thrombocytopaenia, hypothyroidism (due to the expression of iodothyronine deiodinase), jaundice, and biliary obstruction or liver failure[2,7].

As a consequence of the above-mentioned complications, some patients may develop a life-threatening condition. The heterogeneity of the lesions and the presence of comorbidities frequently render the management of infantile hepatic haemangiomas a true challenge, also for highly specialised medical professionals[9].

Referring to older publications, the mortality rate ranged between 30% and 80%, but recently published studies show a significant decrease in the incidence rate of the disease. Currently, the mortality rate for untreated hepatic haemangiomas is estimated at 18%[3,10]. Considering such a rate, attention should be paid to the early diagnosis of the disease and the implementation of appropriate treatment, which significantly improves patient prognosis.

CASE REPORT

A boy from pregnancy II, delivery I, was born at the 30th week of gestation. Respiratory distress syndrome was identified in history and the neonate was diagnosed and treated at the Neonatal Intensive Care Unit. Cranial ultrasound scan (CrUSS) revealed status post grade II haemorrhage on the right side. A series of US examinations performed at bedside at the Neonatal Intensive Care Unit demonstrated normal images of the abdominal organs (Fig. 1) – the US examination was performed four times on days 3, 17, 24, and 40 of the baby's life.

At week four, clinical deterioration was observed, including an increased frequency of apnoea, vomiting, gastric retention, and elevated inflammatory markers. *Klebsiella aerogenes* and respiratory syncytial virus infections were diagnosed. The baby was then transferred to the Department of Neonatal Intensive Care and Pathology, where the previous recommendations were carried on. An abdominal US was performed again, revealing normoechoic liver with the midclavicular line of 41 mm.

At four months of age, due to increased posseting and distress, the child was referred to the Department of Paediatrics, where abdominal US revealed multiple hypoechoic focal

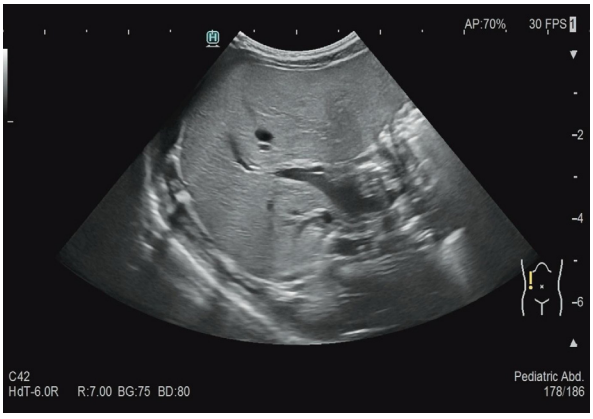

Fig. 1. Normal image of abdominal organs

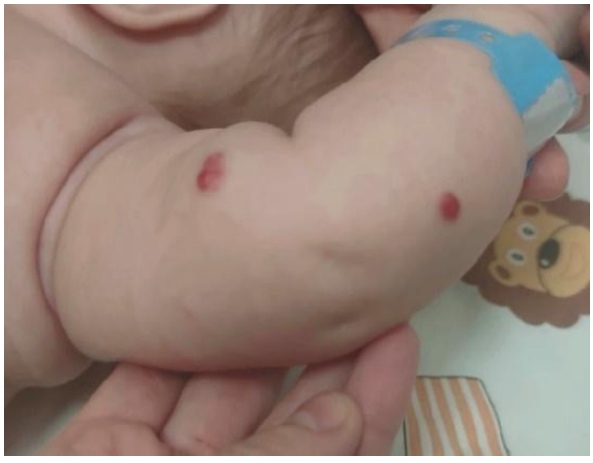

Fig. 2. Multiple haemangiomas on skin

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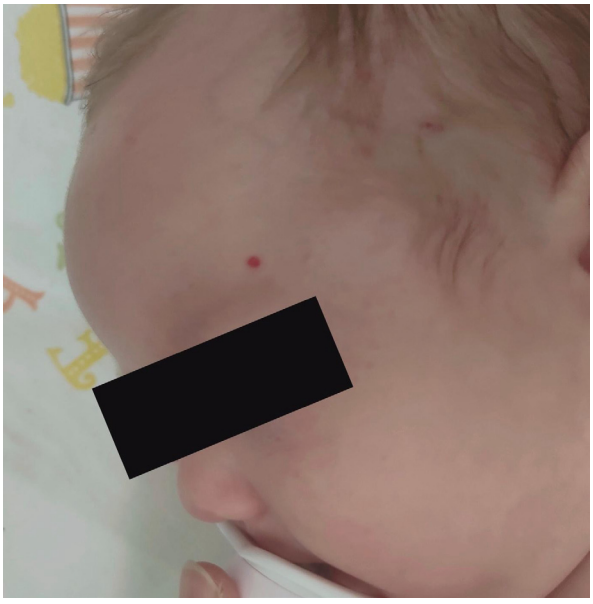

Fig. 3. Multiple haemangiomas on skin

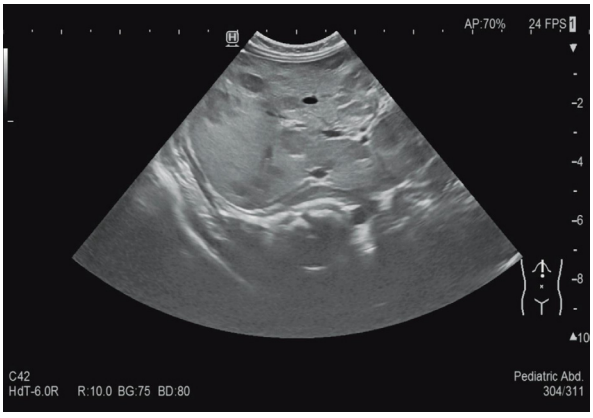

Fig. 4. Multiple hypoechoic liver lesions of up to approximately 12 mm in size

lesions of approximately 13 mm in size. A suspicion of multifocal infantile haemangiomas in the proliferative phase was raised. After a few days, the child was transferred to the Department of Paediatric Gastroenterology and Hepatology for verification of the diagnosis. Laboratory results were as follows: alpha-fetoprotein normal for age, bone alkaline phosphatase (bALP): 234 [U/L] (20–40), alkaline phosphatase (ALP): 313 [U/L] (80–280), alanine aminotransferase (ALT), asparagine aminotransferase (AST) normal, total bilirubin normal, γ-glutamyltranspeptidase (GGTP): 93 [U/L] (10–78). In addition, the child had multiple haemangiomas on the skin (Figs. 2, 3).

As part of the inpatient diagnostic work-up, an abdominal US was performed, confirming the presence of multiple hypoechoic liver lesions of up to approximately 12 mm in size (Fig. 4). Some of the lesions showed sparse peripheral vascularisation (Fig. 5). In order to extend the diagnostic picture of the described focal lesions, dynamic contrast-enhanced abdominal magnetic resonance imaging (MRI) scanning was

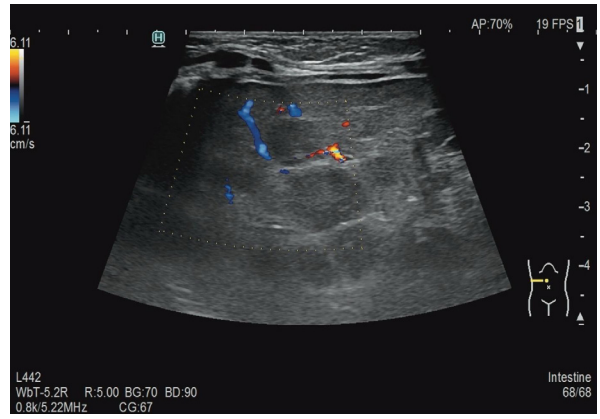

Fig. 5. Sparse peripheral vascularisation of lesions

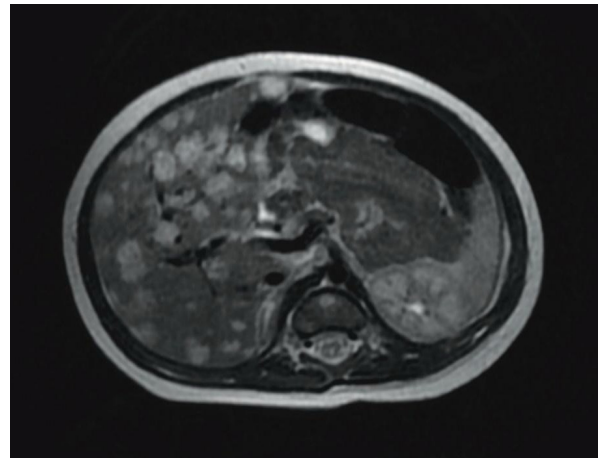

Fig. 6. Multiple hyperintense lesions in T2-weighted sequences, scattered throughout liver

performed, revealing multiple hyperintense lesions in T2-weighted sequences, scattered throughout the liver (Fig. 6). The identified lesions showed characteristic post-contrast enhancement in signal intensity (rising from peripheral to central areas), maintaining a high signal also in delayed phases. The diffusion-weighted imaging (DWI) sequence did not show any features of water molecule diffusion restriction. The image described was characteristic of haemangiomas. The final diagnosis of the MHH syndrome was established.

A cardiological consultation was also carried out, identifying no worrying cardiovascular symptoms or contraindications to propranolol treatment. The patient was discharged from the Department with recommendations of follow-up at the hospital's paediatric surgical outpatient clinic and regular follow-up visits at the district outpatient clinic, as well as of periodic gastrological check-ups.

At five months of age, the child had a follow-up visit at the hospital surgical outpatient clinic, where propranolol was introduced at a dose of 2 mg 3×/day. Due to the ongoing symptoms of posseting, trimebutine, a syrup with anti-reflux effect, was also included and the milk mixture was recommended to be thickened carob powder. In addition, supplementation with vitamins B, D and iron was prescribed. The reflux

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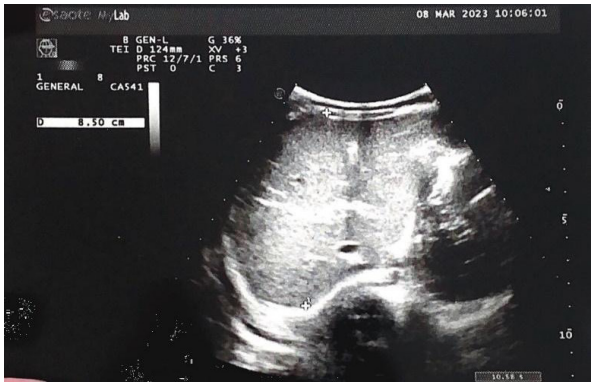

Fig. 7. Almost complete regression of hepatic haemangiomas

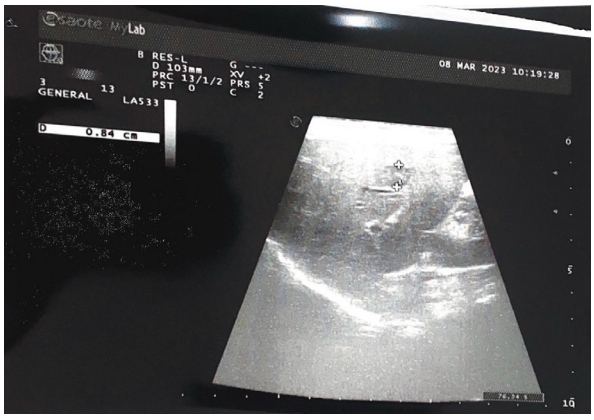

Fig. 8. Circular hypoechoic lesion located in segment VI

(posseting) episodes disappeared after the anti-reflux medication. After one week, the propranolol dose was increased to 4 mg 3×/day. After a period of another two weeks, a decision was taken to increase the dose of the drug to 6 mg 3×/day. A follow-up cardiological consultation was performed, confirming no contraindications to continue the β-blocker therapy. At seven months of life, the dose of propranolol was increased to 7.5 mg 3×/day.

An abdominal US examination performed during a neonatal and surgical consultation at nine months of life showed almost complete regression of the hepatic haemangiomas (Fig. 7). Liver with homogeneous parenchymal echogenicity was observed, with the exception of a circular hypoechoic lesion, located in segment VI, its diameter being 9 mm (Fig. 8). The liver size in the midclavicular line was 77 mm. No fresh skin lesions were found, and the previously described lesions either faded or completely regressed (Figs. 9, 10). The boy's general condition after pharmacotherapy was good. In consideration of the positive effects of the treatment and the literature data, a decision was made to continue propranolol treatment at a dose of 7.5 mg 3×/day until the child was 12 months old.

DISCUSSION

Infants are usually taken to a physician within the first few weeks of life when observed skin lesions become

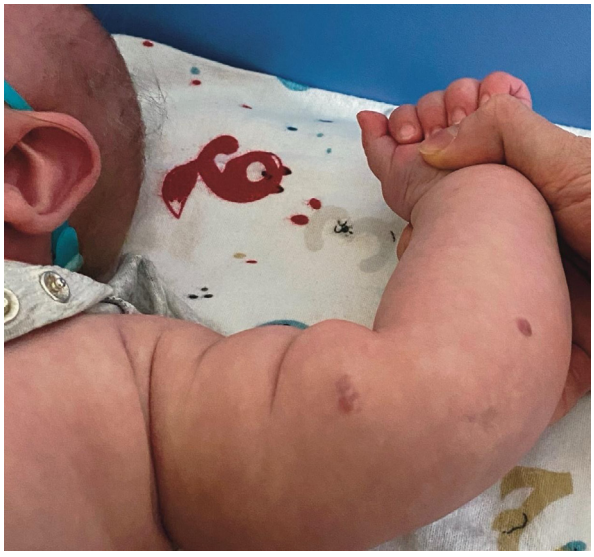

Fig. 9. Previously described lesions either faded or completely regressed

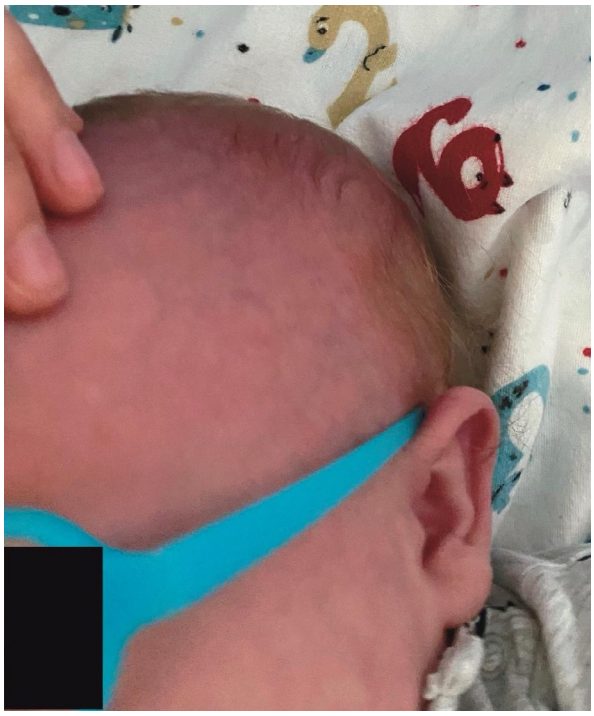

Fig. 10. Previously described lesions either faded or completely regressed

proliferative, as in case of the boy described here. The association of infant haemangiomas (IHs) with their hepatic counterpart has led to indications that abdominal US should be performed in patients with multiple skin lesions[7]. However, no significant link has been found between the number of hepatic haemangiomas and the number of IHs[2]. The vascular skin lesions in the patient described were quite discrete, which was a great disproportion vs. the massive vascular lesions in the liver. The true incidence of MHH remains undetermined, as many small lesions produce no symptoms and

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are impossible to identify. MHHs are sometimes incidentally detected during imaging scans for various unrelated pathologies[4,11]. It follows that screening should be a common practice during the first months of life for infants with the above-mentioned skin lesions[12].

Screening for infantile hepatic haemangiomas is recommended in infants under nine months of age with five or more cutaneous haemangiomas[13].

US should be the imaging examination performed in the first instance in search for vascular anomalies in children. Other examinations which are, however, performed relatively infrequently, include computed tomography (CT) and MRI[1].

Currently, the most common treatment regimen is based on prednisone and propranolol, administered orally[2]. Propranolol, a non-selective blocker of the β-adrenoceptor (AR), is the first-line treatment for haemangiomas. Mast cells participate in the pathophysiology of propranolol-treated haemangioma. β-blocker inhibits the proliferation of HemECs and stimulates their apoptosis and autophagy through acting on both β1 and β2 adrenoceptors in mast cells[14]. The treatment of haemangiomas with non-selective β-blockers, if no contraindications are identified, should be implemented as soon as the diagnosis is established, regardless of the child's age[15].

In order to improve the clinical condition of the presented patient more rapidly, it was decided to introduce propranolol in monotherapy. Some papers recommend propranolol at a dose of 2–3 mg/kg/day. Pharmacotherapy is usually continued for at least 6 months and is often maintained until 12 months of age[5,16].

Propranolol has become a crucial element in MHH management, alongside various other medical, procedural, and surgical options that aim to promote quicker resolution and prevent or alleviate complications[17]. The use of propranolol in therapy definitely had an impact on reducing the number of operations but it did not completely rule out invasive treatment[18]. Despite their benign course, some infantile hepatic haemangiomas, especially in multiple and diffuse forms, may require medical and/or surgical intervention. Therefore, continuous follow-up and observation of the patient are required until the lesions completely resolve[3]. Consequently, the described boy with the diagnosis of MHH is under a constant care of the surgical outpatient clinic. No aggressive treatment should be implemented in asymptomatic patients, in whom observation appears to be a safer choice. Invasive treatment is usually indicated in symptomatic or progressive multiple hepatic haemangiomas only[2]. In the aforementioned patient, the expected results were achieved with pharmacotherapy, without the need of invasive treatment.

Surgical treatment, comprising embolisation, ligation of the hepatic artery or resection of the liver, is necessary for more aggressive clinical courses of the disease. The size of hepatic haemangiomas is also an important issue, affecting intraoperative blood loss and the timing of the operation itself[19].

CONCLUSIONS

It appears from the presented case report that imaging scans, such as US, CT and MRI, play the most important role in the diagnosis and monitoring of MHH. The importance of the physical examination should also be emphasised in the context of detecting cutaneous haemangiomas, which usually accompany MHH and should prompt the physician to regularly observe and repeat abdominal US examinations of the diagnosed and/or treated child. Propranolol is an effective pharmacological option which should be implemented into treatment as soon as MHHs are diagnosed.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations that could adversely affect the content of the publication and claim rights to this publication.

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Institutional review board statement

The study did not require ethical approval. The study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were waived for this study due to the character of the study (case report).

Informed consent statement

Written informed consent has been obtained from the patient(s) to publish this paper.

Author contribution

Original concept of study: JB, WB, AJ, KBD. Collection, recording and/or compilation of data: JB, WB, AJ, EK, AS, KGK, AG, AS. Analysis and interpretation of data: JB, WB, AS. Writing of manuscript: JB, WB. Critical review of manuscript: AJ, JK, AG, AS, KBD. Final approval of manuscript: JB, WB, AJ, JK, KBD.

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