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Hepatic vascular tumors

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ABSTRACT

The most common hepatic vascular tumor in the pediatric population is the infantile hepatic hemangioma. Although these lesions have a spectrum of presentations, there are three main subtypes that have been described—focal, multifocal, and diffuse. An algorithm on the workup, treatment, and follow-up of these lesions can be based on this categorization. Recent shifts in the management of hemangiomas with beta-blockers (propranolol) have also influenced the treatment of hepatic hemangiomas. This article reviews the current understanding of hepatic hemangiomas and protocols in the management of these patients.

Introduction

The liver is the most common extracutaneous site of hemangiomas, and hepatic hemangiomas are the most common benign liver tumors of infancy, followed by mesenchymal hamartomas. Among malignant liver tumors, hepatoblastoma is the most common, although tumors such as rhabdomyosarcoma and angiosarcoma can also occur.[1,2]

As with their cutaneous counterparts, hepatic hemangiomas exhibit multiple patterns of presentation and differing biologic behaviors. The severity of these lesions varies widely, ranging from asymptomatic to life-threatening, with associated clinical manifestations that may include hepatomegaly, high-output congestive heart failure, anemia, thrombocytopenia, respiratory distress, hypothyroidism, and jaundice. Until the past decade, little was understood to predict the natural history of any particular patient or facilitate rational choice of therapy. It is now possible to reliably determine which patients require intervention, allowing the majority to avoid dangerous treatments without fear. Our article presents an overview of the key clinical issues associated with hepatic vascular tumors, focusing on hemangiomas and briefly touching on the risk of malignancy.

Clinical presentation

Multiple cutaneous hemangiomas

The presence of multiple cutaneous hemangiomas has long been recognized to herald the presence of hepatic hemangiomas (Figure 1). In a retrospective study of infants with hepatic hemangiomas who were followed over a 12-year period by the Vascular Anomalies Team at Cincinnati Children's Medical Center, Dickie et al.[3] reported that 18 of 26 patients (69%) had five or more associated cutaneous lesions. More recently, a prospective study conducted by the Hemangioma Investigator Group (HIG) sought to determine whether infants with five or more cutaneous lesions had a greater frequency of hepatic hemangiomas and to also characterize the clinical features of these lesions. As reported by Horii et al.,[4] HIG findings confirm that infants with five or more cutaneous hemangiomas are at risk for hepatic hemangiomas and that this risk is significantly higher than in infants with fewer than five cutaneous lesions. Important for clinicians to note, however, is that authors of the HIG study also reported, despite their findings, the percentage of infants with hepatic hemangiomas requiring treatment for liver disease was low (8%). Recent analysis of the International Liver Hemangioma Registry based at Boston Children's Hospital (www.liverhemangioma.org) demonstrates that hepatic lesions detected by ultrasonographic screening of patients with multiple cutaneous lesions result in less morbidity and mortality than those not screened, even when only lesions requiring treatment are considered (unpublished). As well, Dickie et al.[3] noted that although it is uncommon, hepatic hemangiomas can cause symptomatic liver disease without associated cutaneous lesions. These patients may present with an upper abdominal mass, cardiac failure, and hypothyroidism.[3,5]

Patterns of hepatic involvement

Historically, inconsistencies in the pediatric literature led to confusion and uncertainty among clinicians pertaining to the natural history, treatment approaches, and outcomes of hepatic

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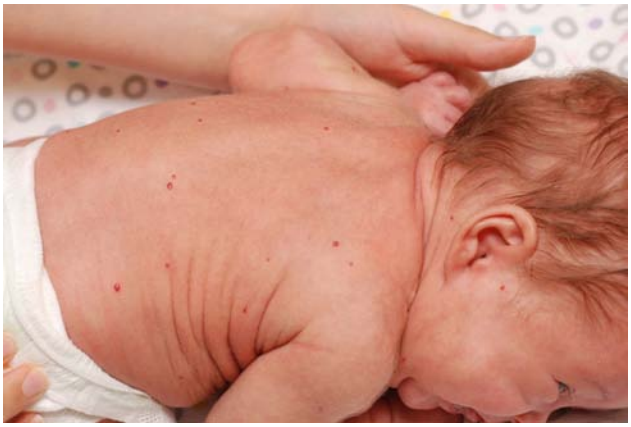

Fig. 1. Multiple cutaneous hemangiomas. A 34-week ex-preemie, now 1 month of age, presenting with multiple cutaneous hemangiomas (greater than 30) that on screening ultrasonography was found to have multiple liver hemangiomas. She was treated with propranolol (2 mg/kg/day), and now at 5 months of age, the liver lesions have almost completely involuted.

hemangiomas. In an effort to shed light on these issues, Christison-Lagay et al.[5] at Boston Children's Hospital examined radiologic analyses and pathologic studies to determine whether hepatic hemangiomas could be categorized, thereby allowing better predictability of their natural history and enabling clinicians to make more judicious choices of therapeutic strategies. This study was the first to propose that hepatic hemangiomas do not represent a single entity but rather comprise three major categories of lesions with distinct presentations: focal, multifocal, and diffuse.

Focal

Focal hepatic hemangiomas are discrete solitary, spherical lesions that exhibit hypoechoic density on ultrasonography (US) and may be detected on prenatal US. These lesions are centrally hypodense on computed tomography (CT) with centripetal enhancement. The periphery is more dense with contrast than the surrounding normal hepatic parenchyma. This can be an important distinguishing factor from hepatoblastoma, which may also enhance peripherally, but generally similar in intensity to surrounding normal liver. On magnetic resonance imaging (MRI), they are hypointense on T1-weighted sequences and hyperintense on T2-weighted sequences (Figure 2). Doppler US, CT, and MRI all reveal high flow.[6,7] On review of the data collected in the Liver Hemangioma Registry at Boston Children's Hospital Vascular Anomaly Center, Kulungowski et al. demonstrated focal tumors are the hepatic form of the cutaneous rapidly involuting congenital hemangioma (RICH), an uncommon subset of vascular tumors. Unlike hemangiomas of infancy, RICH is fully grown at birth (allowing antenatal detection) and generally undergoes an accelerated involutive phase, which is completed by 12–14 months of age.[8–10] As with cutaneous RICH, immunohistochemical staining of focal hepatic lesions is negative for glucose transporter-1 (GLUT-1) protein—a marker for hemangiomas of infancy in all stages of their life cycle.[8,9,11–13] The central hypodensity seen in hepatic RICH likely represents hemorrhage and thrombosis occurring with transition from fetal to postnatal circulation. This explains the typical moderate self-limited anemia and thrombocytopenia seen in the early neonatal period. The thrombocytopenia does not reach the extremely low levels of the Kasabach–Merritt phenomenon, which is not seen with any hepatic lesion. The central thrombus, rather than tumor growth, may also explain temporary enlargement sometimes seen with hepatic RICH. Resorption of the clot may cause a conjugated hyperbilirubinemia. Some hepatic RICH

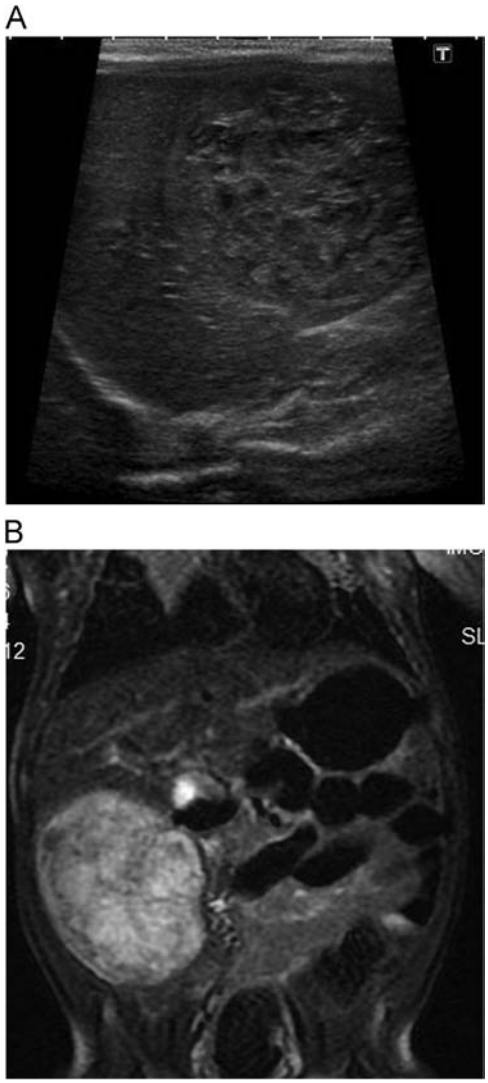

Fig. 2. Focal hepatic hemangioma. Focal hemangioma presenting in a 1 month old infant with an abdominal mass. (A) Initial ultrasound and (B) corresponding MRI demonstrating a focal hemangioma of the right lobe. The lesion continued to involute over time with no treatment.

have large arterial feeding vessels adjacent to the lesions, which may have direct shunts to hepatic veins resulting in a high-output cardiac state and potentially frank symptomatic cardiac failure.

Multifocal

Multifocal hepatic hemangiomas are individual spherical lesions separated by normal intervening liver parenchyma. On CT, these lesions are hypodense with uniform or centripetal enhancement and may show indications of arteriovenous shunting. Unlike focal lesions, multifocal lesions undergo the typical life cycle of hemangiomas of infancy and demonstrate Glut-1 immunoreactivity (Figure 3). A subset of patients with multifocal hepatic hemangiomas will have high-flow shunting vessels resulting in high-output cardiac failure. Hypothyroidism occurs in some patients with multifocal lesions (see below).

Diffuse

Diffuse hepatic hemangiomas differ from multifocal lesions in that they have extensive replacement of the hepatic parenchyma with innumerable centripetal enhancing lesions[3,5] (Figure 4). They exist in a continuum with multifocal lesions and likely result from