Infantile Hepatic Hemangioma/ Hemangioendothelioma

Contents

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Abstract

Infantile hepatic hemangioma (IHE; previously termed infantile hepatic hemangioendothelioma) is a vascular liver tumor presenting as solitary or multiple lesions and diagnosed almost exclusively in infants and children before 6 months of age. Apart from focal involvement of the liver, a diffuse phenotype is also recognized. IHE usually manifests as hepatomegaly, but part of patients show cardiovascular failure due to intratumoral shunting, coagulopathy, jaundice, respiratory distress, and a distinct form of consumptive hypothyroidism. IHE can be associated with angiomatous lesions in other organs, including chorangioma of the placenta. Macroscopically, IHE manifests as solitary or multiple, well-circumscribed, and spherical vascular tumors. Histology is characterized by a network of densely arranged and thin vascular channels with an endothelial lining. Calcifications and other regressive changes can develop. Part of patients show a histology with variable cellular atypias, previously termed type 2 lesions. There is an overlap between such lesions and a distinct form of infantile hepatic angiosarcoma.

Introduction

Infantile hepatic hemangioma (IHE) (synonym: infantile hepatic hemangioendothelioma, IHHE) is a vascular liver tumor that presents with solitary or multiple lesions, presents almost exclusively in children before 6 months of age, and has a slight female preponderance. The term hemangioendothelioma was first coined in 1912, based on a tumor observed in a cirrhotic liver (Kothny 1912). Multiple hepatic hemangioendotheliomas were first reported in 1911 (Bondy 1911) and in 1913 (Veeder and Austin 1913). These authors described a 10-week-old female infant who died with increasing abdominal distention and progressive weakness (heart failure), and autopsy revealed multiple hepatic nodules consisting of vascular spaces with interposed fibrosed hepatic tissue. Foote (1919) reported a further case and reviewed the literature on congenital hemangioendothelioma of the liver. He proposed that these lesions be called hemangioendotheliosarcoma, because they originated from a rapid and seemingly unrestrained proliferation of hepatic vascular endothelia. The ten patients reviewed by Foote (1919) showed a fatal termination of disease before they were 6 months of age. Numerous cases have since been reported, using different terms to denote the lesions.

Selected References Goodale 1930; Kunstadter 1933; Taylor and Moore 1933; Howard 1936; Dodrick 1938; Schumann 1941; Blauel 1942; Andries and Kaump 1944; Schwartz 1945; Videback 1946; Berezin et al. 1948; Hendrick 1948; Sweed and Weinberg 1950; Caussade et al. 1954; Winters et al. 1954; Berman et al. 1955; Packard and Palmer 1955; Siderys et al. 1962; Arcardi and Nezelof 1963; Desbaillets 1963; Christaens et al. 1964; Schneegans et al. 1964; Bellini and Beltrame 1965; Cruveiller et al. 1965; Daudet 1965; Falcone et al. 1965; Robbins and Castle 1965; Stone and Nielsen 1965; Burman et al. 1967; De Lorimier et al. 1967; Graivier et al. 1967; Hurmuzache et al. 1968; Berdon and Baker 1969; Selke and Cornell 1969; Diaz et al. 1970; Touloukian 1970; Dehner and Ishak 1971; Tawes et al. 1971; McLean et al. 1972; Verger et al. 1972; Leonidas et al. 1973; Matolo and Johnson 1973; Chabalko and Fraumeni 1975; Pollice and Pagliarulo 1975; Stovis et al. 1975; Van Acker et al. 1975; Bohm and Jacobi 1976; Sloane et al. 1977; Stanley et al. 1977; Dehner 1978; Othersen and Watanatittan 1978; Pavlenishvili and Nemsadze 1978; Dachman et al. 1983; Weinberg and Finegold 1983; Dehner 1987; Selby et al. 1994.

Hemangioendothelioma Versus Hemangioma: Novel Issues of Definition and Classification of Hepatic Hemangiomas in Infants and Children

The terminology of IHE has gone through an entire spectrum of names, having resulted in some confusion, as in several reports the exact

nature of the vascular tumor can only be reconstructed with difficulty. Terms to denote the lesions comprise hemangioma, capillary hemangioma, cavernous hemangioma, cellular hemangioma, hemangiomatosis, arteriovenous malformation, and hemangioendothelioma. At least part of the tumors have, e.g., been called hemangiomatosis (Braun et al. 1975) or juvenile hemangioendothelioma of the liver (Blumenfeld et al. 1969). It has to be emphasized that the term hemangioendothelioma was not used for hepatic lesions in the same sense as for those located in other organs, e.g., the skin, where the term cellular hemangioma has been proposed to be preferable at a certain time (Gonzales-Crussi and Reyes-Mugica 1991). IHE shared biological and morphologic features with cutaneous infantile or juvenile hemangioma, and frequently cutaneous and hepatic lesions coexist in the same patient. Infantile hemangioma of the skin, which may be associated with hepatic hemangioendotheliomas, is the most common vascular tumor. It is an endothelial cellular proliferation, stimulated after birth (tenth day), and then usually undergoes a slow involution. Congenital hemangioma of the skin is a lesion different from infantile hemangioma, because it develops prenatally and is fully developed at birth. The outcome follows two pathways, i.e., non-involuting congenital hemangioma (NICH), which requires surgery, and rapidly involuting congenital hemangioma (RICH). As also infantile hepatic hemangiomas can undergo involution, it is tempting to assume that the cutaneous and visceral forms of infantile hemangiomas are closely linked entities. To date, the widely used term, IHHE, has therefore been replaced by the term, infantile hepatic hemangioma (IHE; Christison-Lagay et al. 2007), and this new nomenclature will be employed in the present chapter. Recently, other classification schemes have been proposed. IHE was classified as single focus, multiple foci, and diffuse phenotypes (Christison-Lagay et al. 2007; Dickie et al. 2009; Dong et al. 2009; Table 1). According to Christison-Lagay et al. (2007), focal lesions are well-defined, solitary, and spherical tumors that are hypointense relative to the liver on T1-weighted sequences and hyperintense on T2-weighted sequences. The lesions can show central necrosis and hemorrhage. Most focal lesions are asymptomatic and are rarely accompanied by cutaneous hemangiomas. Many focal tumors are detected antenatally on routine prenatal ultrasonography. The lesions variably demonstrate the presence of high-flow shunts, and some of the lesions are associated with minor anemia or thrombocytopenia. Multifocal lesions present as homogeneously enhancing spherical tumors by MRI, and flow voids present in or adjacent to the nodules may indicate the presence of arteriovenous shunts. Multifocal IHE is associated with cutaneous hemangiomas. Some of the lesions are asymptomatic, while others cause high-output heart failure and/or coagulopathy. The lesions may undergo the typical course of involution, as cutaneous hemangiomas. Diffuse lesions are those which exhibit extensive hepatic involvement and near-total replacement of parenchyma with innumerable centripetally enhancing lesions. Most of the infants with the diffuse form have severe clinical manifestations with massive hepatomegaly with compression effects, but the diffuse form is usually not associated with cardiac failure. The patients may develop hypothyroidism (see below). Based on patients studied in a hemangioma registry (cases entering the registry between 1995 and 2010; www.liverhemangioma.org), tumor was studied according to this three-level classification. Of 119 tumors, 33 were focal, 68 were multifocal, and 18 were diffuse lesions. The focal type had a balanced sex distribution, whereas multifocal and diffuse types were more common in women (66.2 % and 70.0 %, respectively) (Kulungowski et al. 2012).

Table 1 Classification of infantile hepatic hemangiomas and related lesions

Christison-Lagay et al. classification (2007)	
	Synonym
Focal	Solitary
Multifocal	Multinodular
Diffuse	Disseminated
Mo et al. classification (2004)	
Hepatic infantile hemangioma (HIH), GLUT1 positive	
Hepatic vascular malformation with capillary proliferation (HVMCP), GLUT1 negative	

IHEs have also been classified according to their angiographic phenotype. Based on angiograms obtained in 15 infants with a diagnosis of hepatic hemangioma, Kassarjian and coworkers (2002) distinguished five types of these vascular tumors. Type 1 was defined as the classic appearance with early filling of abnormal vascular channels, stagnation of contrast medium, and no evidence of a direct shunt; type 2 showed high-flow nodules without direct shunts; type 3 was characterized by direct arteriovenous shunts, type 4 by direct portovenous shunts, and type 5 by both direct arteriovenous and portovenous shunts.

A further classification of these hepatic lesions relates to tumors sensu strictiori versus congenital vascular malformations, an issue that has previously been discussed (Boon et al. 1996; Prokurat et al. 2002). A refined version of this distinction or classification was proposed by Mo et al. (2004). They distinguished multifocal hepatic lesions with features of IHE (termed, by the authors, hepatic infantile hemangioma (HIH)) from solitary angiomatous hepatic lesions (termed hepatic vascular malformation with capillary proliferation (HVMCP)). Apart from the clearly different macroscopic presentation and growth pattern, IHI differed from HVMCP that IHI was GLUT1 positive and HVMCP not, suggesting that the two groups represent two fundamentally different hepatic vascular lesions in infants and young children.

Epidemiology

IHE accounts for about 12–20 % of all childhood hepatic tumors and is the most common symptomatic liver tumor during the first 6 months of life. Altogether, 85 % of patients with IHHE are diagnosed before the age of 2 months, and the tumor is rarely diagnosed beyond the age of 3 years. The tumor may develop during the fetal period and may be manifest as a congenital neoplasm (Schiavon et al. 1982; de Bievre et al. 1994; Sheu et al. 1994; Dreyfus et al. 1996; Morris et al. 1999; Gembruch et al. 2002; Morimura et al. 2003; Pott Bartsch et al. 2003; Ritter et al. 2003; Walsh et al. 2004; Chou et al. 2005; Govender et al. 2006; De Paoli et al. 2007; Schmitz et al. 2009; Franchi-Abella et al. 2012).

In a review of 30 patients, 20 were female (McLean et al. 1972). Prenatal sonographic appearances of (early) lesions (Gonen et al. 1989; Abuhamad et al. 1993; Sepulveda et al. 1993; Chuileannain et al. 1999; Meirowitz et al. 2000; Chou et al. 2005; Schmitz et al. 2009) and features in fetal MRI (Dong et al. 2010) have been reported. Such studies are of particular interest because they have described the dynamic evolution of the complex vascularization of IHE, including feeding arteries with altering flow patterns and characteristics of the continuously changing umbilical-placental circulation (Abuhamad et al. 1993; Meirowitz et al. 2000). IHE can result in fetal hydrops (Skopec and Lakatua 1989; Gonen et al. 1989). In one investigation, hepatic hemangioma was detected prenatally in 30 % of patients with the focal type (Kulungowski et al. 2012). Even though most IHEs occur, as the term implies, in the infantile period, the majority being manifest in the first 6 months, rare instances of such tumors in adolescence (18 years; Selby et al. 1994) and adult patients are known (Diment et al. 2001). The tumor has also been observed in heterotopic intrathoracic liver (Shah et al. 1987).

Clinical Features

General Features

The majority of focal/solitary IHEs are asymptomatic, most symptoms and signs therefore being associated with multifocal or diffuse lesions (Christon-Lagay et al. 2007). The dominant clinical features of multifocal IHE comprise hepatomegaly (83 %); an enlarging upper abdominal mass (66 %); sequelae of the shunting vascular mass, such as cardiovascular failure and coagulopathy; and jaundice. In case of multiple or diffuse lesions, hepatomegaly can be massive (Cohen and Myers 1986; De Paoli et al. 2007). In a study of 19 patients surveyed by the Japanese Infantile Hepatic Hemangioma Study Group, abdominal distention (47.4 %), high-output

cardiac failure (47.4 %), coagulopathy (42.1 %), and respiratory distress (31.6 %) were the major presentations (Kuroda et al. 2011). Solitary lesions exert symptoms and signs in relation to their size and the shunting volume (McGahon et al. 1964; Mortele et al. 2002). In regard to frequency, mass effects and shunt effects are followed by less common manifestations such as vomiting (Bay et al. 2005), splenomegaly, jaundice, ascites, gastrointestinal bleeding, anemia, feeding difficulties, and hepatic bruit (Pellerin et al. 1971; Smith et al. 1978). Vomiting, in particular projectile vomiting, is a rather uncommon sign of IHE (Bay et al. 2005). Obstructive jaundice has been observed in IHE located to the hepatic hilar region (Hase et al. 1995).

Selected References Fox and Cella 1951; Crocker and Cleland 1957; Sommacal 1957; Dachman et al. 1983; Hanchard et al. 1983; Holcomb et al. 1988; Becker and Heitler 1989; Cornelius et al. 1989; Samuel and Spitz 1995; Woltering et al. 1997; Amonkar et al. 1999; Daller et al. 1999; Robben et al. 1999; Lu et al. 2002; Kasahara et al. 2003; Walsh et al. 2004; Riley et al. 2006; Dickie et al. 2009; Moon et al. 2009; Van der Meijs et al. 2009; Zenzen et al. 2009; Marsciani et al. 2010

Cardiac and Circulatory Complications

Multifocal, but usually not focal or diffuse, IHE can result in congestive heart failure (due to arteriovenous shunting), and cardiac failure may even be the initial manifestation, suggesting congenital heart disease (38.5–58 % of the patients) (Levick and Rubic 1953; Cleland 1959; Bredon and Baker 1969; Leonidas et al. 1973; Braun et al. 1975; Slovis et al. 1975; Rocchini et al.1976; Prabhu and Purandare 1977; Rotman et al. 1980; Vorse et al. 1983; Zavota et al. 1984; Burrows et al. 1985; Becker and Heitler 1989; Stanley et al. 1989; Davenport et al. 1995; Pethe et al. 1995; Iyer et al. 1996; Lu et al. 2002; Chen et al. 2003; Sidwell et al. 2004; Jothilakshmi et al. 2006). The relative incidences of these manifestations vary considerably among different reports. In the series reported by Chen et al. (2003), 50 % had abdominal distention, 38.8 % congestive heart failure, 38.8 % abdominal mass, 30 % jaundice, and 23 % skin hemangiomas. In another report, the most common presenting features among 16 patients were high-output cardiac failure (69 %), consumptive coagulopathy (75 %), and anemia (75 %) (Samuel and Spitz 1995). In a recent study on 13 patients (median age, 14 days), congestive heart failure and abdominal mass were predictive of 5-month mortality rates, and patients who underwent resection surgery, with or without OLT, had a lower 5-month mortality rate and a greater 2-year survival rate than those who underwent hepatic artery ligation or embolization (Daller et al. 1999). The severe cardiac complications of IHE can clinically present as acute asystole (Malvy et al. 1978) and may cause sudden unexpected death (Dempers et al. 2011). The arteriovenous shunting depends on the formation of feeding vessels that are perfused by blood from the hepatic artery. High-output failure of infants with IHE can dramatically be controlled by hepatic artery ligation (de Lorimier et al. 1967; Rake et al. 1970; Mattioli et al. 1974; Laird et al. 1976; Malvy et al. 1978; Moazam et al. 1983). Cardiac decompensation and circulatory failure can already occur in patients with fetal IHE. Among 16 fetuses with focal IHE, four had associated cardiomegaly and five had cardiac failure. Eight of the nine fetuses with cardiac disorders were symptomatic at birth. Prenatal cardiac abnormality, enlargement of more than one hepatic vein, and large volume of the hepatic lesion were associated with symptomatic disease (Franchi-Abella et al. 2012).

Coagulopathy

Coagulopathy is a complication of multifocal IHE and is caused by consumption mechanisms and activation of the coagulation cascade within the large vascular network (Nöller and Freundt 1958; Haferland 1961; Linderkamp et al. 1976; Hase et al. 1995; Jayanthi et al. 2000). This complication may already develop in fetal hepatic hemangioendothelioma (Gembruch et al. 2002). Similar to

other highly vascularized tumors, IHE may, therefore, induce the Kasabach-Merritt phenomenon or syndrome (Kasabach and Merritt 1940; Sevinir and Özkan 2007). Skopec and Lakatua 1989). Large tumors may cause obstructive jaundice (Linderkamp et al. 1976). IHE may undergo a rapid course ending up with coagulopathy, liver insufficiency, and cardiac failure (Grabhorn et al. 2009; van der Meijs et al. 2009).

Other Complications

Further complications mainly include tumor rupture and/or hepatic rupture, followed by hematoperitoneum and hemorrhagic shock. Sudden death may ensue (Caussade et al. 1954; Karbel' et al. 1990; Lunetta et al. 2004).

Consumptive Hypothyroidism

Interestingly, IHE can cause disorders of thyroid hormone function, specifically hypothyroidism caused by iodothyronine deiodinases, a disorder termed consumptive hypothyroidism. This complication almost exclusively occurs in the diffuse form of IHE. Hypothyroidism occurring in patients with IHE is caused by increased thyroxine catabolism by the tumor and was first reported in 2000 (Huang et al. 2000). To normalize the serum TSH levels in IHE patients, unusually high doses of intravenous liothyronine and LT4 are required. In the autopsy case of Huang et al. (2000), samples revealed that the IHE tissue had high D3 iodothyronine deiodinase, showing that IHE can produce type 3 iodothyronine deiodinase which converts T4 and T3 to inactive metabolites, i.e., reverse T3 and 3,3′-diiodothyronine, respectively (review: Huang 2005). Several other cases of IHE-induced consumptive hypothyroidism have been reported (Mason et al. 2001; Konrad et al. 2003; Güven et al. 2005; Ho et al. 2005; Kalpatthi et al. 2006; Cho et al. 2008; Mouat et al. 2008; Cetinkaya et al. 2010; Peters et al. 2010; Jassam et al. 2011; Imteyaz et al. 2012). In patients with regression of hepatic IHE associated with consumptive hypothyroidism, the hormonal disorder also regresses (Konrad et al. 2003), as it does following liver transplantation for IHE (Lee et al. 2006; Balazs et al. 2007). Consumptive hypothyroidism can occur in recurrent IHE after steroid therapy, caused by increased type 3 iodothyronine deiodinase activity (Bessho et al. 2010). There is a relationship between the incidence of hypothyroidism and the growth pattern of IHE. In a study of 121 patients, hypothyroidism was documented in all patients with diffuse hepatic hemangioma and 21.4 % in patients with multifocal hepatic hemangioma, but not in patients with focal hepatic hemangioma (Kulungowski et al. 2012). Consumptive hypothyroidism caused by increased deiodinase activity has also been found in adults with hepatic vascular tumors (Huang et al. 2002; Howard et al. 2011). The disorder has also been noted in non-angiomatous tumors, e.g., malignant solitary fibrous tumor, as a manifestation of a paraneoplastic syndrome (Ruppe et al. 2005). In one infant, both increased activity of the tumor for type 3 iodothyronine deiodinase and an increased production of a TSH-like hormone were detected (Ho et al. 2005).

Production of Thyrotropin

Ayling et al. (2001) reported on seven with IHE showing increased thyrotropin levels. The serum thyroxine level was decreased in 4 and increased in 2. Immunohistochemistry of the tumors exhibited positive staining of tumor tissue, but of normal liver tissue, for thyrotropin, suggesting the synthesis and secretion of a thyrotropin-like factor by some IHE.

Elevation of Serum AFP Levels

IHE can be associated with elevated serum AFP (sometimes several thousand ng/ml) leading to the suspicion of hepatoblastoma, but probably not related to the tumor as such (Urbach et al. 1987; Han et al. 1998; Herman and Siegel 2001; Lu et al. 2002; Zenge et al. 2002; Sari et al. 2006;

Moon et al. 2009; Kim et al. 2010; Seok and Kim 2010). Among 16 patients with IHE, two patients with bilobar disease showed elevated levels of serum AFP at presentation (Moon et al. 2009). In an immunohistochemical study, it was demonstrated that, in two cases of IHE, hepatocytes near or entrapped within the tumors were the source of AFP (Kim et al. 2010). An elevated serum AFP has also been reported to occur in the mother in case of a fetal IHE (Meirowitz et al. 2000; Mhanni et al. 2000), and maternal AFP may be the first manifestation of the developing tumor (Meirowitz et al. 2000).

Associations

Extrahepatic Hemangioendotheliomas

Hepatic IHE can occur in conjunction with splenic IHE (hepatosplenic IHE; Kumar et al. 2000; Ng et al. 2003; Wang et al. 2009). Association of IHE with a paraspinal hemangioendothelioma was described (Wood et al. 1977).

Skin Angiomas

IHE is known to come together with other angiomatous lesions, particularly hemangiomas of the skin, the latter apparently being detectable in up to 50 % of the patients (Sween and Weinberg 1950; Prabhu and Purandare 1977; Robinson and Hambleton 1977; Berman and Lim 1978; Dehner 1987; Douri 2005; Mendiratta et al. 2008; Dickie et al. 2009; Horii et al. 2010; Tan et al. 2011; Yeh et al. 2011). In a series of 91 patients, skin hemangiomas were noted in 11 % (Selby et al. 1994). The incidence of accompanying cutaneous hemangiomas is correlated with the type of growth pattern of IHE. Of 121 patients studied within a hemangioma registry, cutaneous hemangiomas accompanied 77.4 % of multifocal hepatic hemangioma, 53.3 % of diffuse hepatic hemangioma, and 15.3 % of focal hepatic hemangioma (Kulungowski et al. 2012). There is a relationship between the number of cutaneous hemangiomas and the probability of associated hepatic hemangiomas. A multicenter prospective study of children with cutaneous infantile hemangiomas conducted at pediatric dermatology clinics at Hemangioma Investigator Group sites in the United States, Canada, and Spain between 2005 and 2008 revealed that 24 of 151 infants (16 %) with five or more cutaneous infantile hemangiomas had hepatic hemangiomas identified by abdominal ultrasound, versus none of the infants with fewer than five (Horii et al. 2011).

Placental Lesions

The tumor has been observed together with chorangioma (Meirowitz et al. 2000), with placental tumor manifestations (Marton et al. 1997), or with anomalous dilated and tortuous vessels on the placental surface (Kanai et al. 1998), suggesting a generalized anomaly of vascular morphogenesis. IHE was found in association with congenital circumscribed choroidal hemangioma/chorangioma (Shturman-Ellstein et al. 1978; Shaikh et al. 2001). IHE is also commonly associated with non-tumoral placental pathologies. In a group of 13 infants who developed IHE, gross lesions with disturbance of the uteroplacental circulation were found in all placentas from children who developed IHE, including retroplacental hematoma in two infants, extensive ischemic infarction in seven, and large dilated vascular communications, severe vasculitis, chorioamnionitis, and funiculitis in four. It was suggested that such abnormalities may cause fetal hypoxic stress followed by release of vascular endothelial growth factors and placental growth factor, potentially playing a role in hepatic vasoproliferation (Lopez Gutiérrez et al. 2007).

Non-angiomatous Tumors

A very rare association is IHE combined with hepatic mesenchymal hamartoma (Bejarano et al. 2003; Hsiao et al. 2007; Behr et al. 2012), sometimes causing elevated serum AFP levels (Hsiao et al. 2007). In a 6-month-old child, continuously shrinking IHE after interventional

therapy was followed by focal nodular hyperplasia (FNH) at the site of the former IHE (Turowski et al. 2009). Similar to other situations, FNH may have been induced by the focal circulatory disorder connected with the shunting vascular tumor. Multicentric IHE was found in association with a large brain hemangioma (Bar-Sever et al. 1994).

Other Associations

A vertical association of IHE with biliary atresia has been suggested (Sharp et al. 2008). In one patient, IHE was associated with congenital hemihypertrophy (Wood et al. 1977). IHE has been found in association with congenital absence of the pericardium and congenital diaphragmatic hernia (Terbruegge et al. 2005) and with agenesis of the corpus callosum with interhemispheric cyst and trisomy 21 (Murphy et al. 2006).

Imaging Features

IHE has characteristic sonographic features, characterized by complex heterogeneous masses that usually reveal hypoechoic components. Calcifications may be seen, and Doppler evaluation may uncover shunting (Abuhamad et al. 1993; Kardorff et al. 2001; Zenge et al. 2002; Ng et al. 2003; Kassarjian et al. 2004; Breysem et al. 2008). Sonographically, the lesions may initially present as a roundish solitary lesion predominantly consisting of markedly perfused and tortuous cavities, whereas multifocal type 2 lesions may present as solid tumors. Fetal IHE can be suspected and monitored by sonography (Meirowitz et al. 2000). Sonography is also useful for the monitoring of the treatment response (Warmann et al. 2003). Non-contrast CT images show several or multiple hypoattenuating masses or nodules of lower density than the surrounding liver, while postcontrast images reveal intense enhancement of the lesions. Many IHEs show a characteristic dense peripheral nodular enhancement. The typical enhancement patterns are similar to those seen in adult hemangiomas (Presedo et al. 1996; Robben et al. 1999; Herman and Siegel 2000; Parmar et al. 2001; Kaniklides et al. 2000; Ng et al. 2003; Kassarjian et al. 2004; Singh et al. 2008; Feng et al. 2010). In a large series of patients, contrast-enhanced CT showed a peripheral rim (51.6 %), uniform (48.4 %), fibrillary (33.3 %), and nodular (28.8 %) contrast enhancement in the hepatic arterial phase. Homogeneous (100 %), rim (98.2 %), and mixed enhancement patterns were noted in tumors <1.0 cm, >2.0 cm, and 1.0–2.0 cm in diameter, respectively, in the hepatic arterial phase (Feng et al. 2010). Rarely, ringlike calcifications on CT and MRI have been found (Mavili et al. 2006). MRI with or without gadolinium enhancement reveals mostly hypointense masses in T1-weighted images, with an isointense and sometimes irregular border, and hyperintense masses in T2-weighted images. In case of tumor necrosis, contrast material is absent in the tumor center (Chung et al. 1996; Presedo et al. 1996; Mortele et al. 2002; Kassarjian et al. 2004; Halefoglu 2007; Feng et al. 2010). Angiography findings of IHE are rather complex and characterized by early filling of abnormal vascular channels with or without extensive shunts (Jackson et al. 1977; Mortensson and Pettersson 1979; Burke et al. 1986; Kassarjian et al. 2002). As complex and heterogeneous tumors, IHEs show considerable variations in the vascular supply (Burrows 1991; Park et al. 1996). In particular, part of the tumors reveal portal vein-hepatic vein fistulas and extensive systemic arterial supply with formation of a complex collateral circulation (Burrows 1991; McHugh and Burrows 1992). The diagnosis and evolution of IHE can be confirmed and followed by technetium-99 m-labeled red blood cell scans (Kristidis et al. 1991; Hertleb et al. 1994), and dynamic and static hepatic scintigraphy will demonstrate the vascularity and size of the liver masses and provide distinction from other tumors (Cruveiller et al. 1965; review: Stanley et al. 1977).

Regression/Involution of IHE

Part of infantile hemangiomas, particularly those in the skin, show a distinct sequence of

developmental stages, characterized as a proliferation or growth phase, followed by an involuting phase, and complete involution itself. Early growth of infantile hemangiomas seems to be influenced by endothelial progenitor cells (Yu et al. 2004). Involution depends on finely tuned apoptosis of endothelial cells (Razon et al. 1998). As their cutaneous counterpart, IHE can undergo involution, but this phenomenon is mainly seen in the multifocal form of IHE. Similar to its cutaneous counterpart, IHE may undergo rapid involution (RICH; Sakamoto et al. 2011; Roebuck et al. 2012), sometimes associated with hepatic failure (Zenzen et al. 2009). It is not yet known whether involuting IHE displays the same or similar features in the involution pattern in comparison with hemangiomas of the skin. The histologic appearance of RICH differs from that of non-involuting tumors (NICH) and common hemangiomas, but there are important overlaps. RICH was composed of small to large lobules of capillaries with moderately plump endothelial cells, the lobules being surrounded by fibrous tissue. Involuting zones are visualized as centrolobular atrophy, fibrosis, and draining channels, associated with hemosiderosis and/or calcifications. The endothelia in RICH were not GLUT1 positive (Berenguer et al. 2003). Involuting lesions differ from hepatic vascular malformations in that they express GLUT1 and, by activation of apoptotic pathways, are associated with expression of the Wilms tumor 1 gene/WT1 (Lawley et al. 2005).

Pathology

Macroscopy

Macroscopically, three growth patterns can be distinguished, i.e., solitary (focal; single focus), multifocal (multinodular), and diffuse phenotypes (Figs. 1 and 2). In multifocal tumors, the lesions may be scattered throughout the liver or may be clustered within one lobe (Dehner and Ishak 1971), resulting in a gross pattern resembling metastatic liver disease. In most cases, the tumor nodules are lighter in color than the surrounding liver tissue, and in cut sections the lesions usually

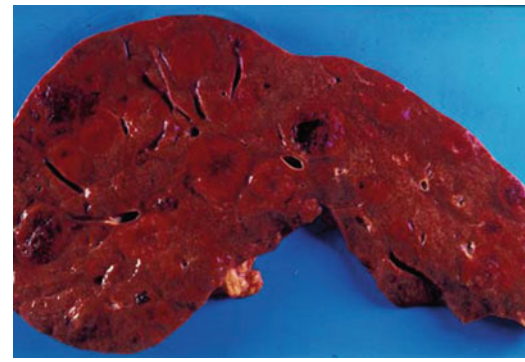

Fig. 1 Infantile hepatic hemangioma. The liver exhibits numerous tumor nodules with central hemorrhage (unfixed necropsy specimen)

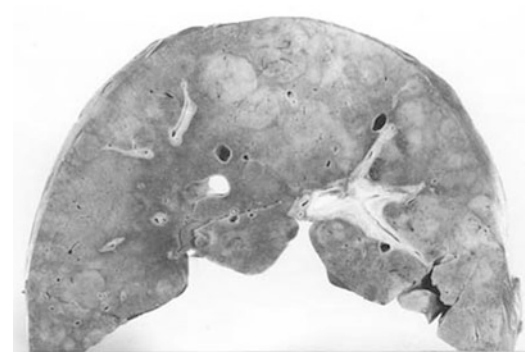

Fig. 2 Infantile hepatic hemangioma. Numerous, in part confluent tumor nodules in both liver lobes (fixed necropsy specimen)

reveal a dark-red center surrounded by a lighter-colored ring (Foote 1919; McLean et al. 1972). In cases with a high content of blood in the lesions, the liver surface is covered with purple to bluish-red nodules varying in size from a marble to a ping-pong ball. When the remaining liver shows fatty change, these nodules stand on a dull yellow background of liver substance (Goodale 1930). The subcapsular nodules are flat or umbilicated and are usually soft on palpation. In the diffuse form of IHE, almost the entire liver is densely occupied by nodules of IHE which may touch each other and which leave only a small amount of functioning parenchyma. The nodules are usually well circumscribed, not encapsulated, relatively soft and spongy, or discretely firm, with a reddish-brown or gray to white cut surface

(Dachman et al. 1983; Lunetta et al. 2004). Solitary (focal) lesions tend to be more solid and gray, whereas multifocal lesions tend to be soft and yellowish red, with small hemorrhages. In one study, the tumor nodules ranged from 0.2 to 15 cm in diameter, and there was no significant difference in size between solitary and multifocal forms (Dehner and Ishak 1971). The tumors tend to grow by compression rather than invasion. Pedunculated lesions are uncommon. Central parts of large masses may show evidence of infarction, hemorrhage, necrosis, fibrosis, and/or focal dystrophic calcification.

There is evidence that the gross growth pattern is related to a specific cell lineage or differentiation pathway involved. GLUT1-positive tumors were shown to form multiple white-tan nodules showing central regressive changes in some cases (Mo et al. 2004). These were the tumors representing the classical IHEs or, as proposed by the authors, infantile hepatic hemangiomas (IHIs). Patients with GLUT1-negative lesions usually had a single large mass with a mean diameter of 8 cm, typically with a central infarcted and hemorrhagic area. These lesions were termed hepatic vascular malformation with capillary proliferation/HVMCP (Mo et al. 2004).

Histopathology

As already specified above, Dehner and Ishak (1971) subdivided this tumor histologically into types 1 and 2. The histopathology of the former type I lesions has been described in detail (Figs. 3, 4, 5, and 6; Touloukian 1970; Dehner and Ishak 1971; Dehner 1978). These nodules show irregularly dilated and usually rather small, compressed vascular channels lined by a single layer or, less commonly, several layers of flat endothelial cells with only minor structural anomalies. The channels are outlined by a reticulin fiber sheath. In highly vascular areas, the extracellular space is not well developed and contains only few fibroblastoid cells and very few lymphoid cells. Part of the tumors contain areas with more stromal elements, sometimes with myxoid features resembling mesenchymal hamartoma (Dehner and Ishak 1971). Areas of central fibrosis are seen in part of the tumors, mainly in solitary/focal lesions. Some cases show a cavernous differentiation or arteriovenous structures, probably representing shunts. In the study of Dehner and Ishak (1971), ten out of 17 type I lesions had cavernous hemangiomatous foci. Rarely, extramedullary hemopoiesis was detected (Orzechowski 1928; Sigameni et al. 2010). Solitary IHE can undergo extensive cystic necrosis (Herman and Siegel 2001). The tumors often contain clusters of biliary ductules and may contain entrapped, cytokeratin 7-positive small bile ducts (Bhattacharyya et al. 2007).

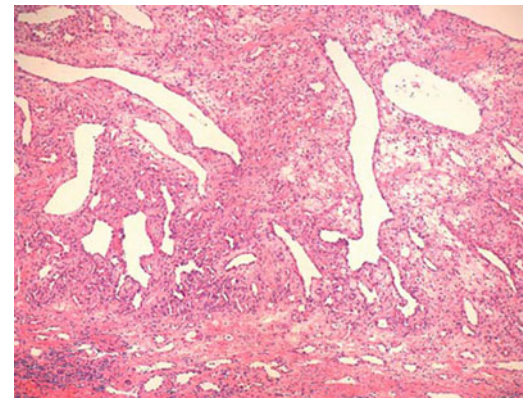

Fig. 3 Infantile hepatic hemangioma, type 1. *Solid* areas with small vascular spaces alternate with cavernous spaces. The interface to the adjacent liver is at the bottom of the figure (hematoxylin and eosin stain)

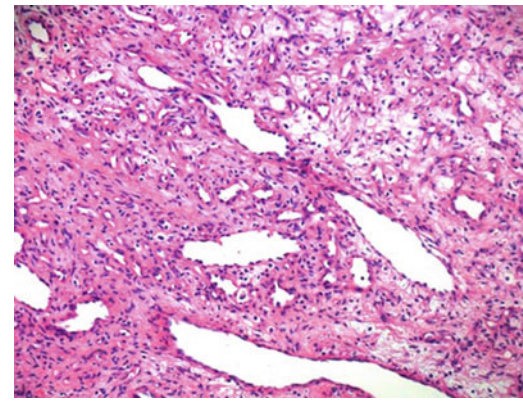

Fig. 4 Infantile hepatic hemangioma. The small and also the larger vascular channels are lined with flat endothelial cells. The intervascular tissue has a fibrous or myxoid aspect (hematoxylin and eosin stain)

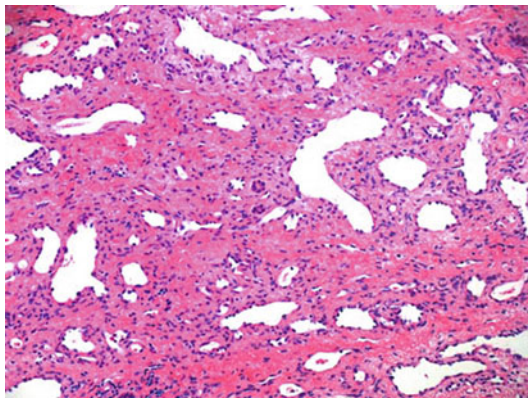

Fig. 5 Infantile hepatic hemangioma, type 1. Older lesions may undergo fibrosclerotic change. Note the portal tract with small bile ducts in the center. Infantile hepatic hemangiomas can integrate preexisting structures of the liver (hematoxylin and eosin stain)

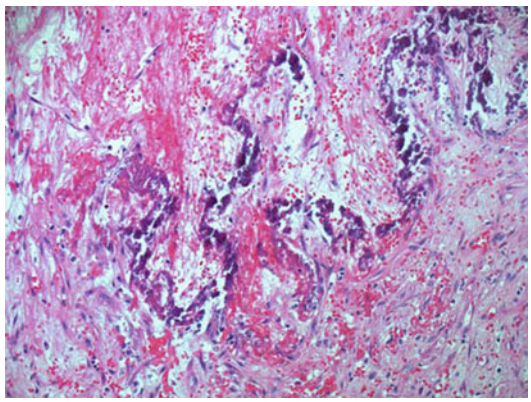

Fig. 6 Infantile hepatic hemangioma, type 1. In this tumor, regressive changes are associated with calcifications (hematoxylin and eosin stain)

Hepatic infantile hemangiomas (IHIs) as defined by Mo et al. (2004) and being GLUT1-positive multiple lesions are histologically characterized by closely packed small capillary-sized vessels with interspersed pericytes and collagen fibers, resembling cutaneous infantile hemangioma and corresponding to type 1 IHE according to Dehner and Ishak's classification. The second group of lesions defined by Mo et al. (2004) is the solitary large masses that are GLUT1 negative and called hepatic vascular malformation with capillary proliferation (HVMCP). These lesions show a central zone of hemorrhage and necrosis/infarction and a peripheral zone with congested and dilated thin-walled vessels lined by flattened epithelium, associated with vascular thrombi and calcifications. This zone is surrounded by a rim of myxoid stroma containing numerous capillary-type blood vessels, with an indistinct demarcation between the lesion and adjacent liver (Mo et al. 2004).

The former type 2 lesions show a very vascular and in part hypercellular neoplasm composed of atypical, anastomosing vascular channels admixed with necrosis and hemorrhage (Andries and Kaump 1944; Dehner and Ishak 1971). That such lesions differ in biology and histology from the more common type 1 lesions was first worked out by Andries and Kaump in 1944. These authors underlined the absence of encapsulation and an infiltrative growth with whorls of spindle-shaped cells. The irregularly shaped lumina are lined by atypical, flattened polygonal endothelial cells, sometimes with hobnail-like formations, similar to those noted in angiosarcomas. Polygonal cells may form multilayered structures and show cytoplasmic microlumina. Part of the vascular spaces display papillary intraluminal projections covered with one of the several layers of enlarged endothelial cells. Mainly in areas with necrosis, structures resembling Schiller-Duval bodies of yolk sac tumors may be observed (Ganguly and Mukherjee 2010). Mitotic activity is brisk, sometimes with atypical and tetrapolar mitotic figures. The vascular spaces contain erythrocytes, at some places with pooling of blood in cavernous or peliosis-like spaces. Erythrophagocytosis by the abnormal endothelial cells is found. The same or a similar histology was found in lymph node metastases or remote metastases of the hepatic tumors (Ganguly and Mukherjee 2010). The nodules may contain foci of extramedullary erythropoiesis. Ductular biliary profiles and hepatocytes are intermingled with vascular channels in the majority of cases.

Cytology

Fine needle aspiration cytology smears revealed clusters of and isolated cuboidal, round cells with benign-looking features (Kumar et al. 2010).

Spindle-shaped cells with scant cytoplasm and wavy, kinked, and indented nuclear outlines were also found (Sigamani et al. 2010).

Ultrastructure

Electron microscopically, type 1 IHE showed large numbers of vascular channels of varying sizes lined by abnormal endothelial cells. An incomplete basement membrane separated endothelial cells from extracellular matrix, in the absence of pericytes. The interstitium contained fibroblastoid cells, microfibrils, and collagen fibers (Feldman et al. 1978). No pericytes were observed in another study (Selby et al. 1994). However, another EM investigation of type 1 IHE had uncovered a high density of pericytes in the walls of vascular channels, and these cells may play a role in vessel contractility and the establishment of shunting (Zerbini et al. 1991). In type 2 I.E. electron microscopy revealed that tumor endothelial cells appeared less differentiated and more disorganized than in type 1 tumors. Marked thickening and duplication of basement membranes were noted (Chan et al. 1986).

Immunohistochemistry

Immunohistochemically, endothelial cells of the abnormal vascular channels are reactive to von Willebrand factor, CD31, CD34 (Fig. 7), Ulex europaeus I lectin, an endothelial cell marker (EC), and vimentin and are lined by a continuous basement membrane (Yasunaga et al. 1989; Selby et al. 1994; Cerar et al. 1996; Amonkar et al. 1999; Lunetta et al. 2004; Riley et al. 2006; Ganguly and Mukherjee 2010; Zhang et al. 2010). Subendothelial cells, enveloped with basement membrane, express smooth muscle actin, but not desmin, and appear to represent a pericyte phenotype (Cerar et al. 1996), also detectable by use of EM (Zerbini et al. 1991). Focal IHEs are not reactive for GLUT1, an erythrocyte-type glucose transporter protein (North et al. 2000), whereas the endothelial cells of multifocal lesions and diffuse lesions are typically GLUT1 positive, like typical cutaneous hemangiomas of this age group (Drut and Drut 2004; Hernandez et al. 2005; Christison-Lagay et al. 2007). Reactivity for GLUT1 distinguishes IHE from other types of hepatic angiomatous tumors, in particular congenital hepatic vascular malformations (Mo et al. 2004). In contrast to cutaneous hemangiomas, nuclei of IHE are not reactive for p57KIP2 (Drut and Drut 2005). D2-40-reactive lymph vessels are not present within the tumors (Fig. 8).

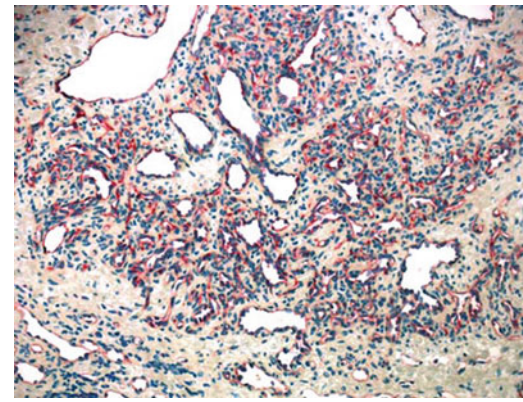

Fig. 7 Infantile hepatic hemangioma, type 1. The endothelial lining is CD34 positive (CD34 immunostain)

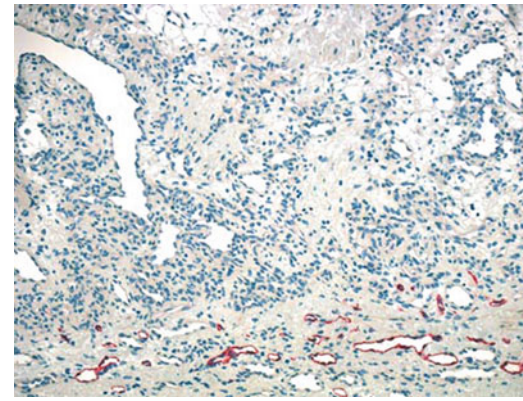

Fig. 8 Infantile hepatic hemangioma, type 1. Lymph vessels are detectable in liver tissue adjacent to the tumor (*bottom*), while the neoplasm itself does not contain lymphatics (D2-40 immunostain)

Differential Diagnosis

IHE must be distinguished from other hepatic vascular tumors occurring in the pediatric age group, in particular angiosarcoma, cavernous hemangioma, capillary hemangioma, and epithelioid hemangioendothelioma. Angiosarcoma of the adult type occurs in the pediatric liver and shows the characteristic histology of highly atypical and sometimes large or pleomorphic endothelial cells that often reveal the hobnail phenomenon and line markedly abnormal and often slit-like spaces. Bizarre and giant cells with massively abnormal mitotic figures are a typical feature, as are solid sarcomatous foci with spindle cells. Cavernous hemangioma of the liver is much less common in infants and children than IHE and is histologically characterized by widely dilated, thin-walled vascular channels lined with flat endothelial cells and by an intervening stroma that may contain lymphoid cells. Capillary hepatic hemangioma is a very rare tumor in infants and children, but its histology may be very close to that of type 1 I.E. However, in contrast to IHE, capillary hemangioma of the liver is usually a small and solitary tumor. Epithelioid hemangioendothelioma is an intermediate-grade invasively growing vascular tumor with medium-sized to large cells forming strands and clusters within a stroma and displaying vacuole-like intracellular lumina. In case mutlifocal IHE is associated with splenic or retroperitoneal hemangioma, neuroblastoma with liver metastases may be suspected on clinical and radiological grounds (Wang et al. 2009).

Biology of Disease: Type 2 IHE as a Low-Grade Angiosarcoma

Two histologic types (type 1 and type 2; Dehner and Ishak 1971; see below) have been recognized, their identification possibly being of importance insofar as IHE1 eventually regresses, and type 2 IHE has been proposed to show a more aggressive phenotype and has been reported to undergo malignant change, i.e., to angiosarcoma or related lesions (Orzechowski 1928; Andries and Kaump 1944; Schwartz 1945; Kauffman and Stout 1961; Kirchner et al. 1981; Noronha and Gonzales-Crussi 1984; Strate et al. 1984; Dehner 1987; Selby et al. 1992; Nazir and Pervez 2006; Ganguly and Mukherjee 2010). One of the first reported cases referred to a 2.5-month-old girl, who was markedly icteric and had a hepatic hemangioendothelioma which had metastasized to the lung and the skin (Orzewchowski 1928). Type 2 IHE may show a fulminant course with extrahepatic extension affecting intestine, lung, skin, and soft tissues, hence being clinically confounded with neuroblastoma (Garcia-Rodriguez et al. 2010). However, the histologic distinction between these two lesions may be difficult, and the prediction of the ultimate course is not easy and often not possible (Dehner an Ishak 1971; Awan et al. 1996; Prokurat et al. 2002), all the more so because the patterns may coexist in the same lesion (Noronha and Gonzalez-Crussi 1984). Even in the case of a benign-looking histology (type 1), multifocality, rapid growth, poor treatment response, and of course metastatic disease indicate malignancy characteristic for at least part of the tumors classified as type 2 (Zurcher et al. 1982). On the other hand, part of the cases, and probably those with a type 1 histology, may show spontaneous regression within 12–18 months (Araujo et al. 2008). Although type 2 IHE thus appears to be associated with a poorer outcome in part of cases, some series have not substantiated this observation (Selby et al. 1994; Cerar et al. 1996). In the large series (91 patients) of Selby et al. (1994), 87 % were first seen before the age of 6 months; the 6-month-survival rate, based on 71 patients, was 70 %, all deaths occurring during the initial presentation/hospitalization of infants, with the exception of two patients who died 3 months and 7 months after diagnosis. Significant factors predicting death 6 months after diagnosis included the presence of congestive heart failure, jaundice, multiple tumor nodules, and absence of cavernous differentiation (Selby et al. 1994). The issue of type 2 lesions as angiosarcoma is further discussed in the chapter of pediatric hepatic angiosarcoma.

References

Abuhamad AZ, Lewis D, Inati MN, Johnson DR, Copel JA (1993) The use of color flow Doppler in the diagnosis of fetal hepatic hemangioma. J Ultrasound Med 12:223–226

Amonkar P, Desai S, Deb R, Kane S, Kurkure P, Deshpande RK, Chinoy R (1999) Infantile hemangioendothelioma of the liver. Med Pediatr Oncol 32:392–394

Andries GH, Kaump DH (1944) Multiple malignant hemangiomas of the liver. Am J Clin Pathol 14(suppl):489

Araujo AR, Maciel I, Costa JC, Vieira A, Enes C, Santos Silva E (2008) Infantile hepatic hemangioendothelioma. A multifocal, bilobular and asymptomatic case with spontaneous regression (in Spanish). An Pediatr (Barc) 68:507–510

Arcardi J, Nezelof C (1963) L'hémangiomatose multinodulaire du foie du nourrisson. Commentaires anatomocliniques à propos de quatre observations. Arch Fr Pédiatr 20:933

Awan S, Davenport M, Portmann B, Howard ER (1996) Angiosarcoma of liver in children. J Pediatr Surg 31:1729–1732

Ayling RM, Davenport M, Hadzic N, Metcalfe R, Buchanan CR, Howard ER, Mieli-Vergani G (2001) Hepatic hemangioendothelioma associated with production of humoral thyrotropin-like factor. J Pediatr 138:932–935

Balazs AE, Athanassaki I, Gunn SK, Tatevian N, Huang SA, Haymond MW, Karaviti LP (2007) Rapid resolution of consumptive hypothyroidism in a child with hepatic hemangioendothelioma following liver transplantation. Ann Clin Lab Sci 37:280–284

Bar-Sever Z, Horev G, Lubin E, Kornreich L, Naor N, Ziv N, Shimoni A, Grunebaum M (1994) A rare coexistence of a multicentric hepatic hemangioendothelioma with a large brain hemangioma in a preterm infant. Pediatr Radiol 24:141–142

Bay A, Oner AF, Etlik O, Koseoglu B, Kaya A (2005) Unusual presentation of infantile hemangioendothelioma. Pediatr Blood Cancer 44:267–269

Becker JM, Heitler MS (1989) Hepatic hemangioendothelioma in infancy. Surg Gynecol Obstet 168:189–200

Behr GG, Fishman SJ, Caty MG, Kulungowski AM, Paltiel HJ, Alomari AI (2012) Hepatic mesenchymal hamartoma and infantile hemangioma: a rare association. J Pediatr Surg 47:448–452

Bejarano PA, Serrano MF, Casillas J, Dehner LP, Kato T, Mitral N, Rodriguez MM, Tzakis A (2003) Concurrent infantile hemangioendothelioma and mesenchymal hamartoma in a developmentally arrested liver of an infant requiring hepatic transplantation. Pediatr Dev Pathol 6:552–557

Bellini F, Beltrame A (1965) On a case of hepatic hemangioendothelioma in an infant (in Italian). Arch Ital Chir 91:594–602

Berdon WE, Baker DH (1969) Giant hepatic hemangioma with cardiac failure in the newborn infant. Value of high-dosage intravenous urography and umbilical angiography. Radiology 92:1523–1528

Berenguer B, Mulliken JB, Enjolras O, Boon LM, Wassef M, Josset P, Burrows PE et al (2003) Rapidly involuting congenital hemangioma: clinical and histopathologic features. Pediatr Dev Pathol 6:495–510

Berezin SW, Sharnoff JG, Stein JD (1948) Primary hemangioendothelioma of the liver in infancy. N Engl J Med 238:906

Berman B, Lim HWP (1978) Concurrent cutaneous and hepatic hemangiomata in infancy: report of a case and a review of the literature. J Dermatol Surg Oncol 4:869–873

Berman JK, Kirkhoff P, Levene N (1955) Hepatic lobectomy for hemangioma of the liver in a five-day-old infant. AMA Arch Surg 71:249–253

Bessho K, Etani Y, Ichimori H, Miyoshi Y, Namba N, Yoneda A, Ooue T, Chihara T et al (2010) Increased type 3 iodothyronine deiodinase activity in a regrown hepatic hemangioma with consumptive hypothyroidism. Eur J Pediatr 169:215–221

Bhattacharyya NK, Chatterjee U, Sen S, Sarkar S (2007) Infantile hemangio-endothelioma of liver: report of two cases. Indian J Pathol Microbiol 50:340–342

Blauel I (1942) Ueber das Hämangioendotheliom der Leber bei Kindern. Monatsschr F Kinderheilkde 91:345

Blumenfeld TA, Fleming ID, Johnson WW (1969) Juvenile hemangioendothelioma of the liver. Report of a case and review of the literature. Cancer 24:853–857

Bohm N, Jacobi H (1976) Infantile hemangiomatosis of liver (in German). Med Welt 27:1887–1891

Bondy J (1911) Angiosarcoma of the liver in an infant. JAMA 56:873

Boon LM, Burrows PE, Paltiel HJ, Lund DP, Ezekowitz RA, Folkman J, Mulliken JB (1996) Hepatic vascular anomalies in infancy: a twenty-seven-year experience. J Pediatr 129:346–354

Braun P, Ducharme JC, Riopelle JL, Davignon A (1975) Hemangiomatosis of the liver in infants. J Pediatr Surg 10:121–126

Breysem L, Allewaet S, Claus F, De Beer A, Van Geet C, Rayyan M, Smet MH (2008) The use of duplex doppler ultrasound in a case of multifocal hepatic hemangioma. JBR-BTR 91:145–148

Burke DR, Verstandig A, Edwards O, Meranze SG, McLean GK, Stein EJ (1986) Infantile hemangioendothelioma: angiographic features and factors determining efficacy of hepatic artery embolization. Cardiovasc Intervent Radiol 9:154–157

Burman D, Mansell PWA, Warin R (1967) Miliary hemangiomata in the newborn. Arch Dis Child 42:193

Burrows PE (1991) Variations in the vascular supply to infantile hepatic hemangio-endothelioma. Radiology 181:631–632

Burrows PE, Rosenberg HC, Chuang HS (1985) Diffuse hepatic hemangiomas: percutaneous transcatheter

embolization with detachable silicone balloons. Radiology 156:85–88
Caussade L, Neimann N, Tridon P (1954) Hémangioendothéliome du foie chez un nouveau-né mort par rupture du foie. Arch Fr Pédiatr 11:514
Cerar A, Dolenc-Strazar ZD, Bartenjev D (1996) Infantile hemangioendothelioma of the liver in a neonate. Immunohistochemical observations. Am J Surg Pathol 20:871–876
Cetinkaya S, Peltek Kendirici HN, Yilmaz Agladioglu S, Bas VN, Ozdemir S, Bozkurt C et al (2010) Hypothyroidism due to hepatic hemangioendothelioma: a case report. J Clin Res Pediatr Endocrinol 2:126–130
Chabalko JJ, Fraumeni JF (1975) Blood-vessel neoplasms in children: epidemiological aspects. Med Pediatr Oncol 1:135–141
Chan YF, Choi AC, Ma L, Leung MP (1986) Infantile hemangioendothelioma of the liver: ultrastructural study of a type II case. Pathology 18:463–468
Chen CC, Kong MS, Yang CP, Hung IJ (2003) Hepatic hemangioendothelioma in children: analysis of thirteen cases. Acta Paediatr Taiwan 44:8–13
Cho YH, Taplin C, Mansour A, Howman-Giles R, Hardwick R, Lord D, Howard NJ (2008) Case report: consumptive hypothyroidism consequent to multiple infantile hepatic haemangiomas. Curr Opin Pediatr 20:213–215
Chou SY, Chiang HK, Chow PK, Wu CF, Liang SJ, Hsu CS (2005) Fetal hepatic hemangioma diagnosed prenatally with ultrasonography. Acta Obstet Gynecol Scand 84:301–302
Christiaens L, Demaille A, Clay A, Farriaux JP (1964) Multinodular hemangiomatosis of the liver in an infant (in French). Lille Med 35:484–487
Christison-Lagay, Burrwos PE, Alomari A, Dubois J, Kozakewich HP, Lane TS, Paltiel HJ et al (2007) Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. J Pediatr Surg 42:62–67
Chuileannain FN, Rowlands S, Sampson A (1999) Ultrasonographic appearances of fetal hepatic hemangioma. J Ultrasound Med 18:379–381
Chung T, Hoffer FA, Burrows PE, Paltiel HJ (1996) MR imaging of hepatic hemangiomas of infancy and changes seen with interferon alpha-2a treatment. Pediatr Radiol 26:341–348
Cleland RS (1959) Benign and malignant tumors of the liver. Pediatr Clin North Am 6:427–447
Cohen RC, Myers NA (1986) Diagnosis and management of massive hepatic hemangiomas in childhood. J Pediatr Surg 21:6–9
Cornelius AS, Womer RB, Jakacki R (1989) Multiple hemangioendotheliomas of the liver. Med Pediatr Oncol 17:501–504
Crocker DW, Cleland RS (1957) Infantile hemangioendothelioma of the liver; report of three cases. Pediatrics 19:596–606
Cruveiller J, Lafourcade J, Vallée G, Bocquet L, Laurent M, Turpin R (1965) Congenital hepatic hemangiomatosis. Clinical and scintigraphic study of a case with a favorable outcome (in French). Sem Hop 41:3049–3063
Dachman AH, Lichtenstein JE, Friedman AC, Hartman D (1983) Infantile hemangioendothelioma of the liver: a radiologic-pathologic-clinical correlation. AJR Am J Roentgenol 140:1093–1096
Daller JA, Bueno J, Gutierrez J, Dvorchik I, Towbin RB, Dickman PS, Mazariegos G, Reyes J (1999) Hepatic hemangioendothelioma: clinical experience and management strategy. J Pediatr Surg 34:98–105
Daudet M (1965) Reflections apropos of a case of hepatic hemolymphangioma of the infant. Operation recovery (in French). Pediatrie 20:445–451
Davenport M, Hansen L, Heaton ND, Howard ER (1995) Hemangioendothelioma of the liver in infants. J Pediatr Surg 30:44–48
de Bièvre P, Dufour P, Lefèbvre C, Vinatier D, Bernardi C, Depret S, Monnier JC (1994) Prenatal diagnosis of hepatic hemangioendothelioma. Apropos of a case (in French). J Gynécol Obstet Biol Reprod (Paris) 23:435–439
de Lorimier AA, Simpson EB, Baum RS, Carlsson E (1967) Hepatic-artery ligation for hepatic hemangiomatosis. N Engl J Med 277:33–337
De Paoli AG, Williams M, Parsons SJ, Long E, Brothers L, Dargaville PA (2007) Massive hepatic congenital haemangioma: clinical dilemmas. J Paediatr Child Health 43:321–314
Dehner LP (1978) Hepatic tumors in the pediatric age group: a distinctive clinicopathologic spectrum. Perspect Pediatr Pathol 4:217–268
Dehner LP (1987) Liver, gallbladder and extrahepatic biliary tract. In: Dehner LP (ed) Pediatric surgical pathology, 2nd edn. Williams and Wilkins, Baltimore, pp 483–523
Dehner LP, Ishak KG (1971) Vascular tumors of the liver in infants and children. Arch Pathol 92:101–111
Dempers J, Wadee SA, Boyd T, Wright C, Odendaal HJ, Sens MA, Prenatal Alcohol and SIDS and Stillbirth (PASS) network (2011) Hepatic hemangioendothelioma presenting as sudden unexpected death in infancy: a case report. Pediatr Dev Pathol 14:71–74
Desbaillets P (1963) Hémangioendothéliome du foie à symptomatologie avant tout cardiaque. Radiol Clin 32:301
Diaz P, Ferrada C, Gonzales G, Espinoza J, Lopez I (1970) Hepatic diffuse hemangiomatosis (in Spanish). Rev Chil Pediatr 41:130–136
Dickie B, Dasgupta R, Nair R, Alonso MH, Ryckman FC, Tiao GM, Adams DM, Azizkhan RG (2009) Spectrum of hepatic hemangiomas: management and outcome. J Pediatr Surg 44:125–133
Diment J, Yurim O, Pappo O (2001) Infantile hemangioendothelioma of the liver in an adult. Arch Pathol Lab Med 125:931–932
Dodrick JR (1938) Multiple malignant hemangioendotheliomas in an infant. Am J Dis Child 55:559

Dong KR, Zheng S, Xiao X (2009) Conservative management of neonatal hepatic hemangioma: a report from one institute. Pediatr Surg Int 25:493–498

Dong SZ, Zhu M, Zhong YM, Yin MZ (2010) Use of foetal MRI in diagnosing hepatic hemangioendotheliomas: a report of four cases. Eur J Radiol 75:301–305

Douri T (2005) Multiple cutaneous hemangiomas accompanied by hepatic hemangiomas. Dermatol Online 11:21

Dreyfus M, Baldauf JJ, Dadoun K, Becmeur F, Berrut F, Ritter J (1996) Prenatal diagnosis of hepatic hemangioma. Fetal Diagn Ther 11:57–60

Drut RM, Drut R (2004) Extracutaneous infantile haemangioma is also Glut1 positive. J Clin Pathol 57:1197–1200

Drut R, Drut RM (2005) Expression of p57KIP2 in infantile hemangioma. J Mol Hist 36:195–197

Falcone DM, Friedman S, Peker H (1965) Precordial murmurs in high cardiac output states: differentiation from murmurs of congenital heart disease in infancy. J Pediatr 66:729

Feldman PS, Shneidman D, Kaplan C (1978) Ultrastructure of infantile hemangioendothelioma of the liver. Cancer 42:521–527

Feng ST, Chan T, Ching AS, Sun CH, Guo HY, Fan M, Meng QF, Li ZP (2010) CT and MR imaging characteristics of infantile hepatic hemangioendothelioma. Eur J Radiol 76:e24–e29

Foote J (1919) Hemangio-endothelioma of liver. JAMA 73:1042

Fox PF, Cella LE (1951) Hemangioendothelioma of the liver. Ann Surg 134:1042–1047

Franchi-Abella S, Gorincour G, Avni F, Guibaud L, Chevret L, Pariente D, SFIPP-GRRIF (2012) Hepatic haemangioma – prenatal imaging findings, complications and perinatal outcome in a case series. Pediatr Radiol 42:298–307

Ganguly R, Mukherjee A (2010) Infantile hemangioendothelioma: a case report and discussion. Pathol Res Pract 206:53–58

Garcia-Rodriguez E, Calderon-Lopez G, Salinas-Martin V, Ferrari-Cortes A, Pavon-Delgado A et al (2010) Neonatal fulminant type 2 infantile hepatic hemangioendothelioma involving skin, viscera and soft tissue. Fetal Pediatr Pathol 29:338–343

Gembruch U, Baschat AA, Gloeckner-Hoffmann K, Gortner L, Germer U (2002) Prenatal diagnosis and management of fetuses with liver hemangiomata. Ultrasound Obstet Gynecol 19:454–460

Gonen R, Fong K, Chiasson DA (1989) Prenatal sonographic diagnosis of hepatic hemangioendothelioma with secondary nonimmune hydrops fetalis. Obstet Gynecol 73:485

Gonzales-Crussi F, Reyes-Mugica M (1991) Cellular hemangiomas ("hemangioendotheliomas") in infants. Light microscopic, immunohistochemical, and ultrastructural observations. Am J Surg Pathol 15:769–778

Goodale RH (1930) Hemangio-endothelioma of the liver. Arch Pathol 9:528–533

Govender L, Panday S, Moodley J (2006) Prenatal diagnosis of congenital hepatic haemangioma. J Obstet Gynaecol 26:69–70

Grabhorn E, Richter A, Fischer L, Krebs-Schmitt D, Ganschow R (2009) Neonates with severe infantile hepatic hemangioendothelioma: limitations of liver transplantation. Pediatr Transplant 13:560–564

Graivier L, Votteler TP, Dorman GW (1967) Hepatic hemangiomas in newborn infants. J Pediatr Surg 2:299–307

Güven A, Aygun C, Ince H, Aydin M, Pinarli FG, Baysal K, Küçüködük S (2005) Severe hypothyroidism caused by hepatic hemangioendothelioma in an infant of a diabetic mother. Horm Res 63:86–89

Haferland W (1961) Hämangiomatose im Pfortadergebiet als Kasabach-Merrittsches Syndrome. Z Kinderheilkde 85:125–140

Halefoglu AM (2007) Magnetic resonance imaging of infantile hemangioendothelioma. Turk J Pediatr 49:77–81

Han SJ, Tsai CC, Tsai HM, Chen YJ (1998) Infantile hemangioendothelioma with a highly elevated serum alpha-fetoprotein level. Hepatogastroenterology 45:459–461

Hanchard B, Persuad V, Kerr G, Baum P (1983) Primary infantile haemangioendothelioma of the liver. West Indian Med J 32:44–47

Hase T, Kodama M, Kishida A, Matsushita M, Kurumi Y, Mizukuro T, Okabe H, Uno M, Ohta S (1995) Successful management of infantile hepatic hilar hemangioendothelioma with obstructive jaundice and consumption coagulopathy. J Pediatr Surg 30:1485–1487

Hendrick JG (1948) Hemangioma of the liver causing death in a newborn infant. J Pediatr 32:309–310

Herman TE, Siegel MJ (2000) Special imaging casebook. Infantile hepatic hemangioendothelioma. J Perinatol 20:447–449

Herman TE, Siegel MJ (2001) Solitary hepatic hemangioendothelioma with extensive cystic necrosis and markedly elevated alpha-fetoprotein. J Perinatol 21:568–570

Hernandez F, Navarro M, Encinas JL, Lopez Gutierrez JC, Lopez Santamaria M, Leal N et al (2005) The role of GLUT1 immunostaining in the diagnosis and classification of liver vascular tumors in children. J Pediatr Surg 40:801–804

Hertleb M, Sliwinski Z, Boldys H, Kloc T, Baron J (1994) Angiomatosis of the liver (in Polish). Wiad Lek 47:138–141

Ho J, Kendrick V, Dewey D, Pacaud D (2005) New insight into the pathophysiology of severe hypothyroidism in an infant with multiple hepatic hemangiomas. J Pediatr Endocrinol Metab 18:511–514

Holcomb GW, O'Neill JA, Mahboubi JR, Bishop HC (1988) Experience with hepatic hemangioendothelioma in infancy and childhood. J Pediatr Surg 23:661–666

Horii KA, Drolet BA, Baselga E, Frieden IJ, Metry DW, Morel KD, Newell BD, Nopper AJ et al (2010) Risk of

hepatic hemangiomas in infants with large hemangiomas. Arch Dermatol 146:201–203
Horii KA, Drolet BA, Frieden IJ, Baselga E, Chamlin SL, Haggstrom AN, Holland KE et al (2011) Prospective study of the frequency of hepatic hemangiomas in infants with multiple cutaneous infantile hemangiomas. Pediatr Dermatol 28:245–253
Howard WA (1936) Multiple hemangio-endotheliomas of the liver. J Pediatr 8:588
Howard D, La Rosa FG, Huang S, Salvatore D, Mulcahey M, Sang-Lee J, Wachs M et al (2011) Consumptive hypothyroidism resulting from hepatic vascular tumors in an athyreotic adult. J Clin Endocrinol Metab 96:1966–1970
Hsiao KH, Lin LH, Chen DF, Huang SH (2007) Hepatic mesenchymal hamartoma combined with infantile hepatic hemangioendothelioma in an infant. J Formos Med Assoc 106(suppl):S1–S4
Huang SA (2005) Physiology and pathophysiology of type 3 deiodinase in humans. Thyroid 15:875–881
Huang SA, Tu HM, Harney JW et al (2000) Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. N Engl J Med 343:185–189
Huang SA, Fish SA, Dorfman DM, Salvatore D, Kozakewich HP, Mandel SJ, Larsen PR (2002) A 21-year-old woman with consumptive hypothyroidism due to a vascular tumor expressing type 3 iodothyronine deiodinase. J Clin Endocrinol Metab 87:4457–4461
Hurmuzache E, Barbuta R, Haimovici M, Bogdan A (1968) Congenital multiple hepatic hemangioma in an infant, with favorable evolution (in Romanian). Pediatr (Bucur) 17:41–44
Imteyaz H, Karnsakul W, Levine MA, Burrwos PE, Benson J, Hsu S, Schwarz KB (2012) Unusual case of hypothyroidism in an infant with hepatic hemangioma. J Pediatr Gastroenterol Nutr 54:692–695
Iyer CP, Stanley P, Mahour GH (1996) Hepatic hemangiomas in infants and children: a review of 30 cases. Am Surg 62:356–360
Jackson C, Greene HL, O'Neill J, Kirchner S (1977) Hepatic hemangioendothelioma. Angiographic appearance and apparent prednisone responsiveness. Am J Dis Child 131:74–77
Jassam N, Visser TJ, Brisco T, Bathia D, McClean P, Barth JH (2011) Consumptive hypothyroidism: a case report and review of the literature. Ann Clin Biochem 48:186–189
Jayanthi V, Shankar TR, Ravindarn C, Sudalaimuthu S, Chandrasekar TS (2000) Diffuse hepatic hemangiomatosis: case report. Trop Gastroenterol 21:188–189
Jothilakshmi K, Matthai J, Paul S, Singal AK (2006) Symptomatic hepatic hemangioendothelioma in a newborn. Indian Pediatr 43:908–910
Kalpatthi R, Germak J, Mizelle K, Yeager N (2006) Thyroid abnormalities in infantile hepatic hemangioendothelioma. Pediatr Blood Cancer 49:1021–1024
Kanai N, Saito K, Homma Y, Makino S (1998) Infantile hemangioendothelioma of the liver associated with anomalous dilated and tortuous vessels on the placental surface. Pediatr Surg Int 13:175–176
Kaniklides C, Dimopoulos PA, Bajic D (2000) Infantile hemangioendothelioma. A case report. Acta Radiol 41:161–164
Karbel' GG, Lebedev DV, Iastrebov II (1990) Hemangioendothelioma of the liver as the cause of sudden death (in Russian). Sud Med Ekspert 33:57–58
Kardorff R, Fuchs J, Peuster M, Rodeck B (2001) Infantile hemangioendothelioma of the liver – sonographic diagnosis and follow-up (in German). Ultraschall Med 22:258–264
Kasabach HA, Merritt KK (1940) Capillary hemangioma with extensive purpura: report of case. Am J Dis Child 59:1063–1070
Kasahara M, Kiuchi T, Haga H, Uemoto S, Uryuhara K, Fujimoto Y, Ogura Y, Oike F et al (2003) Monosegmental living-donor liver transplantation for infantile hepatic hemangioendothelioma. J Pediatr Surg 38:1108–1111
Kassarjian A, Dubois J, Burrows PE (2002) Angiographic classification of hepatic hemangiomas in infants. Radiology 222:693–698
Kassarjian A, Zurakowski D, Dubois J (2004) Infantile hepatic hemangiomas: clinical and imaging findings and their correlation with therapy. AJR Am J Roentgenol 182:785–795
Kauffman SL, Stout AP (1961) Malignant hemangioendothelioma in infants and children. Cancer 14:1186–1196
Kim TJ, Lee YS, Song YS, Park CK, Shim SI, Kang CS, Lee KY (2010) Infantile hemangioendothelioma with elevated serum alpha fetoprotein: report of two cases with immunohistochemical analysis. Hum Pathol 41:763–767
Kirchner SG, Heller RM, Kasselberg AG, Greene HL (1981) Infantile hepatic hemangioendothelioma with subsequent malignant degeneration. Pediatr Radiol 11:42–45
Konrad D, Ellis G, Perlman K (2003) Spontaneous regression of severe acquired infantile hypothyroidism associated with multiple liver hemangiomas. Pediatrics 112:1424–1426
Kothny K (1912) Über ein Hämangioendotheliom in zirrhotischer Leber. Frankfurt Z Pathol 10:20–40
Kristidis P, de Silva M, Howman-Giles R, Gaskin KJ (1991) Infantile hepatic haemangioma: investigation and treatment. J Paediatr Child Health 27:57–61
Kulungowski AM, Alomari AI, Chawla A, Christison-Lagay ER, Fishman SJ (2012) Lessons from a liver hemangioma registry: subtype classification. J Pediatr Surg 47:165–170
Kumar R, Gupta R, dasan BJ, Khullar S, Marwah A (2000) Infantile hemangioendothelioma of the liver, spleen and anterior abdominal wall. Clin Nucl Med 25:938
Kumar PV, Salimi A, Ahmadi J (2010) Infantile hepatic hemangioendothelioma: report of a case with fine needle aspiration findings. Acta Cytol 54(suppl):807–810

Kunstadter RH (1933) Hemangioendothelioma of the liver in infancy. Am J Dis Child 46:803

Kuroda T, Kumagai M, Nosaka S, Nakazawa A, Takimoto T, Hoshino K, Infantile Hepatic Hemangioma Study Group, Japan (2011) Critical infantile hepatic hemangioma: results of a nationwide survey by the Japanese Infantile Hepatic Hemangioma Study Group. J Pediatr Surg 46:2239–2243

Laird WP, Friedman S, Koop CE, Schwartz GJ (1976) Hepatic hemangiomatosis. Successful management by hepatic artery ligation. Am J Dis Child 130:657–659

Lawley LP, Cerimele F, Weiss SW, North P, Cogen C, Kozakewich HP, Mulliken JB et al (2005) Expression of Wilms tumor 1 gene distinguishes vascular malformations from proliferative endothelial lesions. Arch Dermatol 141:1297–1300

Lee TC, Barshes NR, Agee EE, O'Mahoney CA, Karpen SJ, Carter BA, Bristow JD et al (2006) Resolution of medically resistant hypothyroidism after liver transplantation for hepatic hemangioendothelioma. J Pediatr Surg 41:1783–1785

Leonidas JC, Strauss L, Beck AR (1973) Vascular tumors of the liver in newborns. Am J Dis Child 125:507–510

Levick CB, Rubic J (1953) Hemangioendothelioma of the liver simulating congenital heart disease in an infant. Arch Dis Child 28:49–51

Linderkamp O, Hopner F, Klose H, Riegel K, Hecker WC (1976) Solitary hepatic hemangioma in a newborn infant complicated by cardiac failure, consumption coagulopathy, microangiopathic hemolytic anemia, and obstructive jaundice. Case report and review of the literature. Eur J Pediatr 124:23–29

Lopez Gutiérrez JC, Avila LF, Sosa G, Patron M (2007) Placental anomalies in children with infantile hemangioma. Pediatr Dermatol 24:353–355

Lu CC, Ko SF, Liang CD, Kuo HW, Tiao MM (2002) Infantile hepatic hemangioendothelioma presenting as early heart failure: report of two cases. Chang Gung Med J 25:405–410

Lunetta P, Karikoski R, Penttila A, Sajantila A (2004) Sudden death associated with a multifocal type II hemangioendothelioma of the liver in a 3-month-old infant. Am J Forensic Med Pathol 25:56–59

Malvy P, Leborgne J, Le Neel JC, Bouhour JB, Petitier H, Lefèvre M (1978) Diffuse multinodular haemangioma of the liver in the infant presenting as acute asystole and treated by ligation of the hepatic artery (in French). Chirurgie 104:506–511

Marsciani A, Pericoli R, Alaggio R, Brisigotti M, Vergine G (2010) Massive response of severe infantile hepatic hemangioma to propranolol. Pediatr Blood Cancer 54:176

Marton T, Silhavy M, Csapo Z, Szende B, Papp Z (1997) Multifocal hemangioendothelioma of the fetus and placenta. Hum Pathol 28:866–869

Mason KP, Koka BV, Eldredge EA, Fishman SJ, Burrows PE (2001) Perioperative considerations in a hypothyroid infant with hepatic haemangioma. Pediatr Anaesth 11:228–232

Matolo NM, Johnson DG (1973) Surgical treatment of hepatic hemangioma in the newborn. Arch Surg 106:725–727

Mattioli L, Lee KR, Holder TM (1974) Hepatic artery ligation for cardiac failure due to hepatic hemangioma in the newborn. J Pediatr Surg 9:859–862

Mavili E, Kahriman G, Tuna IS, Coskun A (2006) Atypical imaging findings of infantile hemangioendothelioma: a case report. Acta Radiol 47:1091–1093

McGahon JJ, Crellin PR, Whittinghill JA, Swenson OA (1964) Solitary infantile hemangioendothelioma of the liver: report of one case. Rocky Mt Med J 61:38–39

McHugh K, Burrows PE (1992) Infantile hepatic hemangioendotheliomas: significance of portal venous and systemic collateral arterial supply. J Vasc Interv Radiol 3:337–344

McLean RH, Moller JH, Warwick WJ, Satran L, Lucas RV (1972) Multinodular hemangiomatosis of the liver in infancy. Pediatrics 49:563–573

Meirowitz NB, Guzman ER, Underberg-Davis SJ, Pellegrino JE, Vintzileos AM (2000) Hepatic hemangioendothelioma: prenatal sonographic findings and evolution of the lesion. J Clin Ultrasound 28:258–263

Mendiratta V, Anand R, Chander R, Harjai B, Gupta T (2008) Multiple neonatal haemangiomatosis with liver haemangiomas and anaemia. Australas J Dermatol 49:42–43

Mhanni AA, Chodirker BN, Evans JA, Menticouglou S, Wiseman N, MacDonald N, Chudley AE (2000) Fetal hepatic haemangioendothelioma: a new association with elevated maternal serum alpha-fetoprotein. Prenat Diagn 20:432–435

Mo JQ, Dimashkieh HH, Bove KE (2004) GLUT1 endothelial reactivity distinguishes hepatic infantile hemangioma from congenital hepatic vascular malformation with associated capillary proliferation. Hum Pathol 35:200–209

Moazam F, Rodgers BM, Talbert JL (1983) Hepatic artery ligation for hepatic hemangiomatosis of infancy. J Pediatr Surg 18:120–123

Moon SB, Kwon HJ, Park KW, Yun WJ, Jung SE (2009) Clinical experience with infantile hepatic hemangioendothelioma. World J Surg 33:597–602

Morimura Y, Fujimori K, Ishida T, Ito A, Nomura Y, Sato A (2003) Fetal hepatic hemangioma representing non-reassuring pattern in fetal heart rate monitoring. J Obstet Gynaecol Res 29:347–350

Morris J, Abbott J, Burrwos P, Levine D (1999) Antenatal diagnosis of fetal hepatic hemangioma treated with maternal corticosteroids. Obstet Gynecol 94:813–815

Mortele KJ, Vanzieleghem B, Mortele B, Benoit Y, Ros PR (2002) Solitary hepatic infantile hemangioendothelioma: dynamic gadolinium-enhanced MR imaging findings. Eur Radiol 12:862–865

Mortensson W, Pettersson H (1979) Infantile hepatic haemangioendothelioma. Angiographic considerations. Acta Radiol Diagn (Stockh) 20:161–169

Mouat F, Evans HM, Cutfield WS, Hofman PL, Jefferies C (2008) Massive hepatic hemangioendothelioma and consumptive hypothyroidism. J Pediatr Endocrinol Metab 21:701–703

Murphy AM, Brenner C, Ann Lynch S (2006) Agenesis of the corpus callosum with interhemispheric cyst, hepatic hemangioma and trisomy 21. Clin Dysmorphol 15:149–151

Nazir and Pervez (2006) Pub Med PMID 16410090

Ng WH, Ching AS, Chan KF, Fung WT (2003) Clinics and diagnostic imaging (89). Infantile hepatosplenic haemangioendotheliomas. Singapore Med J 44:491–495

Nöller HG, Freundt KJ (1958) A case of thrombopenia-hemangioma syndrome in a young infant, Kasabach-Merritt disease (in German). Arch Kinderheilkd 157:258–270

Noronha R, Gonzales-Crussi F (1984) Hepatic angiosarcoma in childhood: a case report and review of the literature. Am J Surg Pathol 8:863–871

North PE, Waner M, Miteracki A, Mihm MC (2000) GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 31:11–22

Orzechowski G (1928) Hämangioendothelioma der Leber. Virchows Arch 267:63

Othersen HB, Watanatittan S (1978) Giant hemangiomatosis of the liver in infancy. Am Surg 44:20–25

Packard GB, Palmer HD (1955) Primary neoplasms of the liver in infants and children. Ann Surg 142:214

Park CH, Hwang HS, Hong J, Pak MS (1996) Giant infantile hemangioendothelioma of the liver. Scintigraphic diagnosis. Clin Nucl Med 21:293–295

Parmar RC, Bavdekar SB, Borwankar SS, Muranjan MN, Shenoy A (2001) Infantile hemangioendothelioma. Indian J Pediatr 68:459–461

Pavlenishvili IV, Nemsadze KP (1978) Disseminated hemangiomatosis of the liver in a newborn infant (in - Russian). Vopr Okhr Materin Det 23:85–87

Pellerin D, Alagille D, Bertin P (1971) Retentional jaundice and hepatic angiomatosis in a newborn (in French). Arch Fr Pediatr 28:1093–1100

Peters C, Langham S, Mullis PE, Dattani MT (2010) Use of combined liothyronine and thyroxine therapy for consumptive hypothyroidism associated with hepatic haemangiomas in infancy. Horm Res Paediatr 74:149–152

Pethe VV, Kalgutkar AD, Mondkar J, Oak SN, Deodhar KP, Deshmukh SS (1995) Hepatic hemangioendothelioma of infancy with congestive heart failure – report of a case. Indian J Cancer 32:186–188

Pollice L, Pagliarulo G (1975) Primary hepatic infantile hemangioendothelioma (in Italian). Tumori 61:565–574

Pott Bartsch EM, Peak BW, Yoshizawa J, Goldstein RB, Ferrell LD, Coakley FV et al (2003) Giant fetal hepatic hemangioma. Case report and literature review. Fetal Diagn Ther 18:59–64

Prabhu SR, Purandare SM (1977) Infantile hemangioendothelioma of the liver with congestive cardiac failure. Indian J Cancer 14:370–373

Presedo A, Martinez-Ibanez V, Castellote A, Lucaya X, Sanchez de Toledo J, Marques A, Boix-Ochoa J (1996) Infantile hepatic hemangioendothelioma of the liver: report of 11 cases (in Spanish). Cir Pediatr 9:51–54

Prokurat A, Kluge P, Chrupek M et al (2002) Hemangioma of the liver in children: proliferating vascular tumor or congenital vascular malformation? Med Pediatr Oncol 39:524–529

Rake MO, Liberman MM, Dawson JL, Evans R, Raftery EB, Laws J, Williams R (1970) Ligation of the hepatic artery in the treatment of heart failure due to hepatic haemangiomatosis. Gut 11:512–515

Razon MJ, Kraling BM, Mulliken JB, Bischoff J (1998) Increased apoptosis coincides with onset of involution in infantile hemangioma. Microcirculation 5:189–195

Riley MR, Garcia MG, Cox KL, Berquist WE, Kerner JA (2006) Hepatic infantile hemangioendothelioma with unusual manifestations. J Pediatr Gastroenterol Nutr 42:109–113

Ritter S, Jorn H, Ahaus M, Rath W (2003) Prenatal diagnosis of hepatic hemangioendothelioma and peripartual management 8 in German). Z Geburtshilfe Neonatol 207:29–32

Robben SG, Meradji M, Woltering MC, Egeler RM (1999) Infantile hepatic hemangioendothelioma. JBR-BTR 82:123

Robbins BH, Castle RF (1965) Hemangiomas, hepatic involvement, congestive failure. Letter to the editor. Pediatrics 35:868

Robinson D, Hambleton G (1977) Cutaneous and hepatic haemangiomata. Arch Dis Child 52:155–157

Rocchini AP, Rosenthal A, Issenberg HJ, Nadas AS (1976) Hepatic hemangioendothelioma: hemodynamic observations and treatment. Pediatrics 57:131–135

Roebuck D, Sebire N, Lehmann E, Barnacle A (2012) Rapidly involuting congenital haemangioma (RICH) of the liver. Pediatr Radiol 42:308–314

Rotman M, John M, Stowe S, Inamdar S (1980) Radiation treatment of pediatric hepatic hemangiomatosis and coexisting cardiac failure. N Engl J Med 302:852

Ruppe MD, Huang SA, Jan de Beur SM (2005) Consumptive hypothyroidism caused by paraneoplastic production of type 3 iodothyronine deiodinase. Thyroid 15:1369–1372

Sakamoto S, Kasahara M, Shigeta T, Fukuda A, Kakiuchi T, Miyasaka M, Nosaka S et al (2011) Living donor liver transplantation for multiple intrahepatic portosystemic shunts after involution of infantile hepatic hemangiomas. J Pediatr Surg 46:1288–1291

Samuel M, Spitz L (1995) Infantile hepatic hemangioendothelioma: the role of surgery. J Pediatr Surg 30:1425–1429

Sari N, Yalcin B, Akyüz C, Haliloglu M, Büyükpamukçu M (2006) Infantile hepatic hemangioendothelioma with elevated serum alpha-fetoprotein. Pediatr Hematol Oncol 23:639–647

Schiavon G, Dal Pozzo A, Alessandrini H (1982) Hepatic hemangioma in the neonate: description of a case treated surgically with favorable outcome (in Italian). Pediatr Med Chir 4:571–573

Schmitz R, Heinig J, Klockenbusch W, Kiesel L, Steinhard J (2009) Antenatal diagnosis of a giant fetal hemangioma and treatment with maternal corticosteroid. Ultraschall Med 30:223–226

Schneegans E, Korn R, Haarscher A, Alt J (1964) Multinodular hemangiomatosis of the liver (in French). Pediatrie 19:799–805

Schumann HD (1941) Beitrag zur Kasuistik des primären Hämangioendotheliomas der Leber. Frankfurt Z Pathol 55:1

Schwartz AR (1945) Multiple malignant hemangioendothelioma in infant: report of a case. Arch Pediatr 62:1

Selby DM, Stocker JT, Ishak KG (1992) Angiosarcoma of the liver in childhood: a clinicopathologic and follow-up study of 10 cases. Pediatr Pathol 12:485–498

Selby DM, Stocker JT, Waclawiw MA, Hitchcock CL, Ishak KG (1994) Infantile hemangioendothelioma of the liver. Hepatology 20:39–45

Selke AC, Cornell SH (1969) Infantile hepatic hemangioendothelioma. Am J Roentgenol Radium Ther Nucl Med 106:200–203

Seok JY, Kim YB (2010) Infantile hemangioendothelioma with increased serum alpha-fetoprotein (in Korean). Korean J Hepatol 16:192–196

Sepulveda WH, Donetch G, Giuliano A (1993) Prenatal sonographic diagnosis of hepatic hemangioma. Eur J Obstet Gynecol Reprod Biol 48:73–76

Sevinir B, Özkan TB (2007) Infantile hepatic hemangioendothelioma: clinical presentation and treatment. Turk J Gastroenterol 18:182–187

Shah KD, Beck R, Jhaveri MK, Keohane M, Weinberg B, Gerber MA (1987) Infantile hemangioendothelioma of heterotopic intrathoracic liver associated with diaphragmatic hernia. Hum Pathol 18:754–765

Shaik S, Sanislo S, O'Brien JM, Alcorn D (2001) Congenital circumscribed choroidal haemangioma associated with infantile hepatic haemangioendothelioma. Br J Ophthalmol 85:626

Sharp L, Makin E, Davenport M (2008) Hepatic haemangioendothelioma: a vertical association with biliary atresia? Eur J Pediatr Surg 18:277–279

Sheu BC, Shyu MK, Lin YF, Lee CN, Hsieh FJ, Chou YH, Yau KI, Huang SF (1994) Prenatal diagnosis and corticosteroid treatment of diffuse neonatal hemangiomatosis: case report. J Ultrasound Med 13:495–499

Shturman-Ellstein R, Greco MA, Myrie C, Goldman EK (1978) Hydrops fetalis, hydramnios and hepatic vascular malformation associated with cutaneous hemangioma and chorangioma. Acta Paediatr Scand 67:239–243

Siderys H, Moore TC, Shumacker HB (1962) Left hepatic lobectomy for hemangioma of the liver in the newborn. Surgery 52:502–504

Sidwell RU, Daubeney PE, Porter W, Roberts NM (2004) Neonatal hemangiomatosis and atrial septal defect: a rare cause of right heart failure in infancy. Pediatr Dermatol 21:66–69

Sigamani E, Iyer VK, Agarwala S (2010) Fine needle aspiration cytology of infantile haemangioendothelioma of the liver: a report of two cases. Cytopathology 21:398–402

Singh S, Chowdhury V, Prakash A, Aggarwal A (2008) Infantile haemangio-endothelioma of liver: a case report. J Indian Med Assoc 106:120

Skopec LL, Lakatua DJ (1989) Non-immune fetal hydrops with hepatic hemangioendothelioma and Kasabach-Merritt syndrome: a case report. Pediatr Pathol 9:87–93

Sloane CE, Baek SM, Beck AR (1977) Solitary neonatal hepatic hemangioendothelioma: case report and discussion. Mt Sinai J Med 44:234–240

Slovis TL, Berdon WE, Holler JO, Casarella WJ, Baker DH (1975) Hemangiomas of the liver in infants. AJR Am J Roentgenol 123:791–801

Smith GG, Lohr JA, Malcolm BS, Kelser RW (1978) Hepatic hemangioendothelioma and hyperbilirubinemia. South Med J 71:1439–1441

Sommacal D (1957) A case of multiple hemangiomatosis in infants (in German). Helv Paediatr Acta 12:666–678

Stanley P, Gates GF, Eto RT, Miller SW (1977) Hepatic cavernous hemangiomas and hemangioendotheliomas in infancy. AJR Am J Roentgenol 129:317–321

Stanley P, Geer GD, Miller JH, Gilsanz V, Landing BH, Boechat IM (1989) Infantile hepatic hemangiomas. Clinical features, radiologic investigations, and treatment of 20 patients. Cancer 64:936–949

Stone HH, Nielson IC (1965) Hemangioma of the liver in the newborn. Report of a successful outcome following hepatic lobectomy. Arch Surg 90:319–322

Stovis TL, Berdon WE, Holler JO et al (1975) Hemangiomas of the liver in infants. AJR Am J Roentgenol 123:791

Strate SM, Rutlddge JC, Weinberg AG (1984) Delayed development of angiosarcoma in multinodular infantile hepatic hemangioendothelioma. Arch Pathol Lab Med 108:943–944

Sweed A, Weinberg T (1950) Hemangioendothelioma of the liver in infancy. Am J Dis Child 80:436–441

Tan ST, Itinteang T, Leadbitter P (2011) Low-dose propranolol for multiple hepatic and cutaneous hemangiomas with deranged liver function. Pediatrics 127: e772–e776

Tawes RL, Nelson JA, Hyde GA (1971) Hepatic hemangioma: successful resection in a neonate. Surgery 70:782–785

Taylor AC, Moore E (1933) Multiple hemangiomas showing certain malignant characteristics in an infant. Am J Cancer 19:31

Terbruegge MO, Rennie JM, Haugen SE (2005) Congenital absence of the pericardium associated with congenital diaphragmatic hernia and hepatic hemangioendothelioma: case report and review of the literature. Pediatr Surg Int 21:557–559

Touloukian RJ (1970) Hepatic hemangioendothelioma during infancy: pathology, diagnosis and treatment with prednisone. Pediatrics 45:1–6

Turowski C, Feist H, Alzen G, Glüer S, Petersen C (2009) Conversion of a neonatal hepatic hemangioma to focal nodular hyperplasia. Pathol Int 59:251–254

Urbach AH, Zitelli BJ, Blatt J et al (1987) Elevated alpha-fetoprotein in a neonate with a benign hemangioendothelioma of the liver. Pediatrics 80:596–597

Van Acker P, Derom F, De Gendt G, Berzsenyi G (1975) Haemangioma of the liver in newborn infant (in Dutch). Acta Chir Belg 74:545–550

Van der Meijs BB, Merks JH, de Haan TR, Tabbers MM, van Rijn RR (2009) Neonatal hepatic haemangioendothelioma: treatment options and dilemmas. Pediatr Radiol 39:277–281

Veeder BS, Austin JH (1913) Multiple congenital hemangio-endotheliomas of the liver. Am J Med Sci 143:102–107

Verger P, Guillard JM, Cixous P, Laigle JL (1972) Case of multinodular hemangiomatosis of the liver with favorable outcome (in French). Arch Fr Pédiatr 29:1115–1116

Videback A (1946) Haemangio-endothelioma of the liver. Acta Paediatr 33:129–143

Vorse HB, Smith EI, Luckstead EF, Fraser JJ (1983) Hepatic hemangiomatosis of infancy. Am J Dis Child 137:672–673

Walsh R, Harrington J, Beneck D, Ozkaynak MF (2004) Congenital infantile hemangioendothelioma type II treated with orthotopic liver transplantation. J Pediatr Hematol Oncol 26:121–123

Wang J, Pei G, Yan J, Zhang G (2009) Coexistence of a giant splenic hemangioma and multiple hepatic hemangiomas mimicking a left adrenal neuroblastoma accompanied with multifocal hepatic metastases: pyrite answer. J Pediatr Hematol Oncol 31:983–984

Warmann S, Bertram H, Kardorff R, Sasse M, Hausdorf G, Fuchs J (2003) Interventional treatment of infantile hepatic hemangioendothelioma. J Pediatr Surg 38:1177–1181

Weinberg AG, Finegold MJ (1983) Primary hepatic tumors of childhood. Hum Pathol 14:512–537

Winters RW, Robinson SJ, Bates G (1954) Hemangioma of the liver with heart failure. A case report. Pediatrics 14:117

Woltering MC, Robben S, Egeler RM (1997) Hepatic hemangioendothelioma of infancy: treatment with interferon alpha. J Pediatr Gastroenterol Nutr 24:348–351

Wood BP, Putnam TC, Chacko AK (1977) Infantile hepatic hemangioendotheliomas associated with hemihypertrophy. Pediatr Radiol 5:242–245

Yasunaga C, Sueishi K, Ohgami H, Suita S, Kawanami T (1989) Heterogeneous expression of endothelial cell markers in infantile hemangioendothelioma. Immunohistochemical study of two solitary cases and one multiple one. Am J Clin Pathol 91:673–681, Curr. Opin. Pediatr. 14, 99-102

Yeh I, Bruckner AL, Sanchez R, Jeng MR, Newell BD, Frieden IJ (2011) Diffuse infantile hepatic hemangiomas: a report of four cases successfully managed with medical therapy. Pediatr Dermatol 28:267–275

Yu Y, Flint AF, Mulliken JB, Wu JK, Bischoff J (2004) Endothelial progenitor cells in infantile hemangioma. Blood 103:1373–1375

Zavota L, Bini F, Carano N, Agnetti A, Squarcia U (1984) Hepatic hemangiomatosis with congestive cardiac failure and development into a cholestatic hepatopathy (in Italian). Pediatr Med Chir 6:621–624

Zenge JP, Fenton L, Lovell MA, Grover TR (2002) Case report: infantile hemangioendothelioma. Curr Opin Pediatr 14:99–102

Zenzen W, Perez-Atayde AR, Elisofon SA, Kim HB, Alomari AI (2009) Hepatic failure in a rapidly involuting congenital hemangioma of the liver: failure of embolotherapy. Pediatr Radiol 39:1118–1123

Zerbini et al. (1991) Pub Med PMID 2036623

Zhang Z, Chen HJ, Yang WJ, Bu H, Wei B, Long XY, Fu J, Zhang R, Ni YB, Zhang HY (2010) Infantile hepatic hemangioendothelioma: a clinicopathologic study in a Chinese population. World J Gastroenterol 16:4549–4557

Zürcher B, Caflisch U, Hofer B, Schärli A, Laissue J (1982) Hemangio-endothelioma of the liver (case report). Z Kinderchir 35:26–31