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Risk factors for mortality in patients with multifocal and diffuse hepatic hemangiomas

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ABSTRACT

Purpose: Multifocal and diffuse hepatic hemangiomas are true infantile hemangiomas, which likely exist in a continuum. We reviewed our hepatic hemangioma registry to identify prognostic indicators for mortality.
Methods: Registry records entered between 1995 and 2012 were reviewed. Clinical characteristics were evaluated for prognostic significance using the multivariable Cox proportional hazards model. Survival data were analyzed using the Kaplan–Meier product–limit method.
Results: We identified 123 patients with multifocal (n = 91) and diffuse (n = 32) hepatic hemangiomas. Mortality was 16% (n = 20); 40% (n = 8) had multifocal and 60% (n = 12) had diffuse lesions. A diagnosis of diffuse disease (hazard ratio: 9.9, 95% CI: 2.0–50.8, $P = .002$) and congestive heart failure (CHF) (hazard ratio: 3.9, 95% CI: 1.3–14.2, $P = .031$) were significant risk factors for mortality across the continuum; age at presentation, cardiomegaly, presence of shunts, and hypothyroidism were not statistically significant independent risk factors. Among patients with diffuse lesions, eight (67%) who died had abdominal compartment syndrome, which was also associated with mortality ($P = .002$).
Conclusions: Hepatic hemangioma patients with CHF or diffuse disease are at higher risk for mortality. Patients with multifocal lesions without CHF may go undetected until lesions become diffuse. Aggressive treatment of symptomatic patients and close follow-up of asymptomatic patients may improve mortality.

Hepatic hemangioma (HH) is the most common tumor of the liver during infancy. Until the last decade, there had been little characterization of the variability in clinical course seen in patients harboring hemangiomas in their liver. Because most clinicians had seen devastating outcomes with some patients, there was a general attitude of fear and trepidation whenever an infant presented with an HH. However, some patients were known to experience lesion involution without sequelae. In order to study and characterize these benign vascular tumors, we established a registry www.liverhemangioma.org [1]. Lesions have been categorized morphologically into three types: focal, multifocal, and diffuse [1,2]. Evaluation of registry patients allowed us to determine that focal HH is the hepatic form of the cutaneous rapidly involuting congenital hemangioma (RICH) [3]. RICH is fully grown at birth and biologically distinct from multifocal and diffuse HH, which are true infantile hemangiomas [3].

Like their cutaneous counterparts, true infantile hepatic hemangiomas undergo a phase of proliferation and growth, followed by involution. Most lesions resolve without complication. However, in a subset of patients, serious symptoms can develop, including abdominal distention, congestive heart failure (CHF), anemia, thrombocytopenia, hypothyroidism, jaundice secondary to biliary obstruction, and liver failure [4–7]. Both macroscopic and microscopic intralesional arteriovenous shunts can occur, which may lead to congestive heart failure [8]. Historically, mortality rates have been as high as 30% to 80%, but more recently published studies have reported rates of 11% to 18% for both treated and untreated HH [9–12]. The purpose of this study was to evaluate the hepatic hemangioma registry to identify which factors place patients with multifocal and diffuse HH at increased risk for mortality.

1. Materials and methods

1.1. Study population

With approval of the Committee on Clinical Investigation, our Vascular Anomalies Center database and online registry (www.liverhemangioma.org) were reviewed for all patients with HH entered from 1995 to 2012. All patients with clinical history and radiographic imaging consistent with multifocal and diffuse HH were

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included. Multifocal HH were characterized as multiple lesions with intervening segments of normal hepatic parenchyma, while diffuse HH were characterized as extensive hepatic involvement with near-total replacement of hepatic parenchyma. Focal lesions (RICH) were excluded. Records were reviewed for gender, age, symptoms, imaging, treatment, and outcome. Age at presentation was defined as date hepatic lesions were first confirmed by imaging or exam. Survival time was defined as time between presentation and death.

1.2. Statistical analysis

Descriptive statistics were used for all patient characteristics. Several variables had missing data points. Univariate analyses were performed using Fisher's exact test for comparing proportions. Clinical variables were evaluated for prognostic significance using the multivariable Cox proportional hazards regression model. The threshold for age at presentation was determined using the Youden J-index in conjunction with receiver operating characteristic (ROC) curve analysis. Survival data were analyzed using the Kaplan–Meier product–limit method with significance determined by the log-rank test and 95% confidence intervals constructed using Greenwood's formula. Statistical significance was defined as P values less than or equal to .05. Data analysis was conducted with IBM SPSS Statistics (version 21.0, IBM, Armonk, NY).

2. Results

A total of 205 patients with hepatic hemangioma were identified. Of these, 123 patients had multifocal (n = 91) or diffuse (n = 32) hepatic hemangiomas. Fifty-two patients (42%) were evaluated at our institution. The majority (65%) were female. The median age of presentation was 49 days (interquartile range (IQR) 14–98 days). Cutaneous lesions were present in 74% of patients for which these data were available (n = 90/121). Anemia and thrombocytopenia were present in 40% (n = 34/86) and 18% (n = 15/84), respectively. Thirty-three percent (n = 35/107) had hypothyroidism. Cardiomegaly was present in 32 of 117 patients (27%), while 29 of 122 patients (24%) had heart failure. Arteriovenous shunts were detected in 24% (n = 28/115) of patients. The median length of follow-up was eight months (IQR 3–30 months). Thirty-six (29%) had adequate imaging data to determine time to resolution, which occurred at a median of 14 months (IQR 8–26 months) and a median age of 17 months (IQR 12–29 months).

Data regarding treatment were available for 116 patients. Seventy-three (63%) received some form of treatment, including all of the diffuse HH patients. The most common type of treatment was corticosteroids (n = 58, 50%), followed by propranolol (n = 22, 19%). Other forms of medical therapy included interferon (n = 12, 10%), vincristine (n = 11, 9%), and bevacizumab (n = 1, 1%). Twenty-seven patients (23%) were treated with more than one medical therapy. There was no difference in survival amongst patients who received propranolol compared to those that did not (log rank test = 3.39, P = .066). Eleven patients (9%) underwent embolization of arteriovenous shunts causing CHF; five died following the procedure.

The overall mortality rate was 16% (n = 20). Eight of these patients were multifocal and 12 were diffuse HH. Median age at death was 115 days (IQR 43–179 days). Seven multifocal (88%) and seven diffuse (58%) patients who died had CHF. Eight (67%) diffuse non-survivors had abdominal compartment syndrome (ACS). Causes of death are listed in Table 1. Three patients died of CHF or complications thereof. Complications from ACS, leading to sepsis and multisystem organ failure (MSOF), were the most common causes of death among diffuse patients. Three patients died from pulmonary complications. Two patients died of liver failure while awaiting hepatic transplantation. Hemoperitoneum was a cause of death in two patients. Other patients died from subarachnoid hemorrhage and/or complications of gastroenteritis. The cause of death was unknown in one diffuse patient.

Table 1
List of non-survivors with causes of and age at death.

Patient ID	IHH Type	Age at Death (days)	Cause of Death	CHF	ACS
1	M	11	CHF, coagulopathy	Y	N
2	M	105	CHF	Y	N
3	M	39	Subarachnoid hemorrhage	Y	N
4	M	154	Pulmonary hemorrhage	Y	N
5	M	210	Pulmonary hypoplasia and pneumonia	N	N
6	M	154	Hemoperitoneum	Y	N
7	M	264	Sepsis	Y	N
8	M	94	CHF, DIC	Y	N
9	D	152	ACS, Sepsis	Y	Y
10	D	20	ACS, Sepsis	N	Y
11	D	101	ACS, MSOF	Y	Y
12	D	765	Complications of gastroenteritis	Y	N
13	D	20	ACS, DIC	Y	Y
14	D	44	Liver failure	N	Y
15	D	124	Liver failure	Y	N
16	D	169	ACS, MSOF	N	Y
17	D	397	Pulmonary hypertension	N	N
18	D	710	Unknown	Y	N
19	D	21	ACS, Hemoperitoneum	N	Y
20	D	90	CHF, ACS, MSOF	Y	Y

Legend: Presence of congestive heart failure (CHF) or abdominal compartment syndrome (ACS) indicated in two right-hand columns. IHH = infantile hepatic hemangioma, M = multifocal, D = diffuse, DIC = diffuse intravascular coagulation, MSOF = multisystem organ failure, SAH = subarachnoid hemorrhage, Y = yes, N = no.

Hepatic pathology was available for five of the 32 infants with diffuse hemangioma derived at the time of autopsy. The livers at autopsy examination were markedly enlarged, weighing four to seven times greater than expected, causing abdominal distention and elevated diaphragms (Fig. 1A). Most of the parenchyma was occupied by variably-sized nodules up to 8 cm in diameter in one infant; these were generally soft and reddish with some showing hemorrhage or necrosis (Fig. 1B). Histopathologic examination showed expanded hepatic lobules and variably dilated hepatic sinusoids lined by endothelial cells with slightly enlarged and irregular nuclei with coarsened chromatin (Fig. 1C). Focal endothelial redundancy was present in all cases (Fig. 1D). Occasional mitoses were seen in 2 of the 5 tumors. Immunochemistry for a proliferation marker (MIB-1) performed in two tumors (1 with and 1 without mitoses) revealed positivity in less than 10% of endothelial cells. Lesional endothelial cells were immunopositive for glucose transporter-1 protein in all 4 tumors in which it was performed. Many cords were devoid of hepatocytes and contained only spindled stromal-like cells and collagen. Wide fibrotic cords and obliterated sinusoids were seen in small foci but were particularly prominent in one infant who had received multiple chemotherapeutic agents and external radiotherapy. Other findings present in all instances were dilated hepatic arteries and veins, intracellular, canalicular, and ductal cholestasis, fatty metamorphosis of hepatocytes, extramedullary hematopoiesis, and focal necrosis of tumor and hepatic parenchyma. Geographic necrosis within the tumor nodules or hepatic parenchyma seemed most consistent with a low flow state from causes such as abdominal compartment syndrome or sepsis.

Variables associated with mortality on univariate analysis (Table 2) included younger age at presentation (P = .03), diagnosis of diffuse HH (P < .001), hypothyroidism (P < .001), anemia (P = .032), thrombocytopenia (P = .011), cardiomegaly (P < .001), CHF (P < .001), and shunts (P < .001). Gender (P = .62) and the presence of cutaneous lesions (P = .40) were not statistically significant. Patients with diffuse lesions who had abdominal compartment syndrome were at a significantly higher risk of dying than those who did not have ACS (P = .002). ROC curve analysis determined that an age of 38 days at presentation was predictive of survival outcomes; patients who presented before 38 days of age had a mortality rate of 28%, whereas the mortality rate for those over 38 days of age was 10%.