



Clinical features of infantile hepatic hemangioendothelioma

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Purpose: Infantile hepatic hemangioendothelioma (IHHE) is the most common type of hepatic vascular tumor in infancy. We conducted this study to review our clinical experience of patients with IHHE and to suggest management strategies.

Methods: We retrospectively analyzed the medical records of 23 IHHE patients (10 males, 13 females) treated at the Asan Medical Center between 1996 and 2009.

Results: Median age at diagnosis was 38 days (range, 1 to 381 days). Seven patients (30%) were diagnosed with IHHE based on sonographically detected fetal liver masses, 5 (22%) were diagnosed incidentally in the absence of symptoms, 5 (22%) had congestive heart failure, 3 (13%) had skin hemangiomas, 2 (9%) had abnormal liver function tests, and 1 (4%) had hepatomegaly. All diagnoses were based on imaging results, and were confirmed in three patients by histopathology analysis. Six patients were observed without receiving any treatment, whereas 12 received corticosteroids and/or interferon-alpha. One patient with congestive heart failure and a resectable unilobar tumor underwent surgical resection. Three patients with congestive heart failure and unresectable tumors were managed by hepatic artery embolization with/without medical treatment. At a median follow-up of 29 months (range, 1 to 156 months), 21 (91%) patients showed complete tumor disappearance or >50% decrease in tumor size. One patient died due to tumor-related causes.

Conclusion: IHHE generally has a benign clinical course with low morbidity and mortality rates. Clinical course and treatment outcome did not differ significantly between medically treated and non-treated groups. Surgically unresectable patients with significant symptoms may be treated medically or with hepatic artery embolization.

Key words: Infant, Liver, Hemangioendothelioma, Corticosteroid, Interferon-alpha, Therapeutic embolization

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Introduction

Hepatic tumors in children are relatively rare, accounting for 1 to 4% of all pediatric solid tumors. Infantile hepatic hemangioendothelioma (IHHE) is the most common vascular tumor of the liver in children, accounting for 12% of all childhood hepatic tumors. Almost 85% of patients with IHHE are diagnosed during the first 6 months of life, and IHHE is the most common symptomatic tumor occurring during this time period. Tumors show a female predominance, with a female to male ratio of 1.3 to 2:1¹⁻⁶.

The most common chief complaint in patients with IHHE is abdominal mass. Other symptoms and signs include hepatomegaly, high-output cardiac failure, skin hemangioma, thrombocytopenia, hemolytic anemia and peritoneal bleeding. The natural history of IHHE varies, but up to two-thirds of symptomatic patients, especially those with heart failure and/or jaundice, may die^{3,7}.

Although children with asymptomatic lesions may experience spontaneous regression within a year, those with symptomatic lesions require aggressive management due to the risk of death once symptoms commence. The therapeutic options available for these patients include both medical and interventional modalities. Medical therapy includes treatment with corticosteroids and interferon-alpha (INF- α), whereas interventional modalities include embolization and ligation of the hepatic artery, resectional surgery, and liver transplantation^{1,2,8,9}.

Because most previous studies of IHHE are small case series it has been difficult to formulate guidelines for the clinical assessment and therapeutic approach in patients with IHHE. This study describes the clinical features and outcomes of patients with IHHE diagnosed and treated over a 14-year period at a tertiary health center and to suggest strategies to manage such patients.

Materials and methods

The medical records of 23 patients diagnosed with IHHE at the Asan Medical Center between April 1996 and April 2009 were analyzed retrospectively. Factors evaluated included gender and age at presentation, presenting symptoms, diagnostic procedures, tumor location (solitary or multiple), laboratory findings (complete blood count, liver function tests [LFTs], thyroid function tests, coagulation parameters and alpha-fetoprotein [AFP] concentrations), therapeutic modality and treatment outcomes.

Most patients were initially diagnosed by abdominal sonography and later evaluated by computed tomography (CT) and/or magnetic resonance imaging (MRI), based on the results of sonography. Tumors that could not be diagnosed radiologically were examined

histopathologically. When required, patients with congestive heart failure were assessed by echocardiography.

Treatment was based on tumor size and symptom severity, and was at the discretion of the treating physician. Patients who were asymptomatic and had relatively small tumors were observed or treated with corticosteroids and/or interferon- α (INF- α). Patients with clinical symptoms and unilobar disease were treated by surgical resection, whereas symptomatic patients with inoperable tumors were treated medically, with or without preceding hepatic artery embolization.

Treatment outcomes were classified as complete resolution, $\geq 90\%$ decrease in tumor size, regression (50 to 90% decrease), no change and progression, with complete resolution and decreasing by 90% defined as a major response to therapy.

Results

Twenty-three patients (13 girls, 10 boys) were enrolled; their demographic and clinical characteristics at the time of diagnosis are summarized in Table 1. Median age at diagnosis was 38 days (range, 1 to 381 days), with 18 (78%) patients diagnosed during their first 3 months of life, including 7 who were diagnosed by prenatal sonography. Median follow-up duration after diagnosis was 29 months (range, 1 to 156 months). Excluding the seven prenatally diagnosed patients and the five asymptomatic patients diagnosed incidentally, the main symptoms at presentation were congestive heart failure and skin hemangioma. Clinical features on physical examination and laboratory findings included hepatomegaly (43%), heart failure (30%), abnormal LFTs (22%), increased thyroid-stimulating hormone (TSH) concentration (22%), coagulopathy (11%), and thrombocytopenia (4%).

Of the 23 patients, 22 were diagnosed by abdominal sonography, followed by CT and MRI in 11 patients each; 5 underwent both CT and MRI. In three patients, in whom hepatoblastoma could not be determined radiologically, the tumors were examined histopathologically. Two patients underwent percutaneous biopsy of the mass, with findings consistent with IHHE. The other patient with heart failure symptoms underwent right partial lobectomy and the resected specimen was confirmed as IHHE.

Imaging showed that all 13 patients with single lobe disease had solitary lesions (10 in the right and 3 in the left hepatic lobe), whereas all 10 patients with bilobar disease had multinodular lesions.

Serum concentrations of AFP were measured in 21 patients and shown to be increased for his/her age in 3 (14%). All three patients had multiple tumors and were treated by different modalities, but all showed complete resolution (Table 2).

Table 1. Patient Demographic and Clinical Characteristics at Diagnosis (n=23)

Characteristic	Value
Age at diagnosis (mo)	1.3 (0-12.7)
0-3	18 (78)
>3	5 (22)
Gender	
Male	10 (43)
Female	13 (57)
Median follow-up (mo)	29 (1-156)
Presenting symptom	
Fetal sonography	7
Heart failure	5
Incidental	5
Skin hemangioma	3
Abnormal HFT	2
Hepatomegaly	1
Clinical features	
Hepatomegaly	10/23 (43)
Heart failure	7/23 (30)
Abnormal HFT	5/23 (22)
Thrombocytopenia	1/23 (4)
Coagulopathy	2/19 (11)
Increased TSH	2/9 (22)
Diagnostic methods	
Sonography	22
CT	11
MRI	11
Biopsy	3
Extent	
Solitary (Rt:Lt)	13 (10:3)
Multiple	10

Values are presented as median (range), number (%), or number. HFT, hepatic function tests; TSH, thyroid-stimulating hormone; CT, computed tomography; MRI, magnetic resonance imaging; Rt, right; Lt, left.

Six of our 23 patients were observed, with 2 showing major response ($\geq 90\%$ decrease in tumor size) after 29 months, and 3 showing spontaneous regression. One patient showed no change in tumor size, but was not treated due to decreased vascularity on follow-up imaging. Six patients received systemic corticosteroid therapy, consisting of a mean dose of 1.9 mg/kg/day of oral prednisolone for a median 43 days (range, 15 to 90 days); 3 (50%) successfully responded to treatment. All four patients treated with INF- α showed major responses to medical treatment. Two patients were treated with a combination of corticosteroids and INF- α .

Interventional modalities included embolization (n=4) and conventional resectional surgery (n=1). One patient with Kasabach-Merritt syndrome (KMS) showed tumor progression despite

Table 2. Tumor Extent and Other Clinical Factors in Three Patients Who Had Increased Concentration of Alpha-Fetoprotein (AFP)

Age (mo)	Extent	AFP (ng/mL)	Diagnosis	Tx	F/U (mo)	Outcome
5.4	Multiple	11,600	US, CT, MRI, Bx	PD	42	Resolution
3.2	Multiple	503	CT, US, Bx	IFN	126	Resolution
2.4	Multiple	37,700	US, CT	No	29	Resolution

Tx, treatment; F/U, follow-up; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; Bx, biopsy; PD, prednisolone; IFN, interferon.

embolization, eventually dying due to coagulopathy, liver failure, and sepsis. The other three patients who underwent embolization showed partial responses to subsequent corticosteroid or INF- α (Table 3). One patient with unilobar disease underwent surgical resection due to the persistence of heart failure symptoms; this patient was successfully cured without complications associated with surgery.

Discussion

Though IHHE is the most common hepatic vascular tumor in children, it is rarely seen in clinical practice. Over a 14-year period, we encountered only 23 patients with this lesion.

IHHE showed a female predominance, with 13 of the 23 patients being girls. Previous studies have reported that the most common presenting signs of IHHE are asymptomatic hepatomegaly and abdominal mass (50%), followed by cutaneous hemangiomas (10 to 40%). Extensive arteriovenous shunting may be detected within these lesions, resulting in decreased peripheral vascular resistance. The maintenance of vascular bed perfusion may require increases in blood volume and cardiac output, which may lead to high cardiac output and congestive heart failure, observed in up to 50 to 60% of patients with IHHE¹⁰⁻¹³.

Hematologic abnormalities may also be present; these include including anemia and especially thrombocytopenia caused by trapping of thrombocytes within the hemangioendothelioma with consumptive coagulopathy (KMS). Less common presentations include splenomegaly, jaundice, ascites, gastrointestinal bleeding, anemia, feeding difficulties, respiratory compromise, and rarely, spontaneous rupture and malignant transformation to angiosarcoma. IHHE has also been reported to be associated with fulminant hepatic failure and associated biliary atresia¹¹, deletion of chromosome 6q¹⁴, heterotopic liver with diaphragmatic hernia¹⁵, trisomy 21, transposition of the great arteries, and extranumerary digits¹¹.

Of our 23 patients, 14 presented with asymptomatic abdominal masses at the time of diagnosis, whereas 5 (22%) were diagnosed incidentally without suspicious symptoms. The main complaints at

Table 3. Clinical Characteristics and Treatment Results of Patients with Infantile Hepatic Hemangioendothelioma

Case	Sex	Age (mo)	Lesions	Presenting Sx	Indication	Tx modality	Tx duration (mo)*	F/U duration (mo)	Outcome
1	F	9	Solitary (Rt)	Abnormal HFT		No		4	In regression
2	F	9	Solitary (Rt)	Incidental		No		15	In regression
3	M	0	Solitary (Rt)	Prenatal		No		6	No change
4	F	3	Multiple	Skin hemangioma		No		29	>90%
5	F	2	Multiple	Abnormal HFT		No		29	Resolution
6	F	1	Solitary (Rt)	Incidental		No		10	In regression
7	F	13	Multiple	Incidental	Multiple	PD 1.6 mg/kg/day	1.8 / 3.9	12.5	In regression
8	F	5	Multiple	Hepatomegaly	Multiple	PD 1.6 mg/kg/day	1.9 / 4.2	41.8	>90%
9	M	1	Solitary (Rt)	Incidental	Huge mass	PD 2.4 mg/kg/day	0.5 / 3.5	30.4	In regression
10	F	0	Solitary (Rt)	Prenatal	Huge mass	PD 1.7 mg/kg/day	1.0 / 2.4	22.9	Resolution
11	M	3	Multiple	Skin hemangioma	Multiple	PD 1.4 mg/kg/day	3.0 / 4.0	37.7	Resolution
12	M	0	Solitary (Lt)	Prenatal	Early CHF	PD 1.9 mg/kg/day	0.5 / 1.4	6.1	In regression
13	M	1	Multiple	Skin hemangioma	Huge mass	IFN- α	5.9	20	>90%
14	F	3	Multiple	CHF	CHF	IFN- α	6.7	126	Resolution
15	F	9	Solitary (Rt)	Incidental	CHF	IFN- α	5.2	35	Resolution
16	M	0	Solitary (Rt)	Prenatal	Huge mass	IFN- α	5.6	49	>90%
17	M	1	Solitary (Rt)	CHF	CHF	IFN- α + PD	4.2	46	In regression
18	F	1	Multiple	CHF	CHF	IFN- α + PD	5.5	48	>90%
19	F	0	Multiple	Prenatal	CHF, KMS	Embolization	NA	1	Progression [†]
20	F	0	Solitary (Lt)	Prenatal	CHF	PD \rightarrow Emb	6.3	156	In regression
21	M	0	Solitary (Lt)	Prenatal	Huge mass, early CHF	Emb \rightarrow PD	2.7	5	In regression
22	M	1	Multiple	CHF	CHF	Emb \rightarrow IFN- α	5.6	57	In regression
23	M	3	Solitary (Rt)	CHF	CHF	Lobectomy	NA	56	Resolution

Sx, symptoms; Tx, treatment; F/U, follow-up; Rt, right; Lt, left; HFT, hepatic function test; CHF, congestive heart failure; KMS, Kasabach Merritt syndrome; PD, prednisolone; IFN- α , interferon-alpha; Emb, embolization; NA, not available.

*Tx duration: full dose / tapering. [†]Progression to coagulopathy, liver failure and sepsis despite embolization in 1 patient.

presentation were heart failure, skin hemangioma, hepatomegaly, and abnormal LFT results. Physical examination revealed hepatomegaly in 10 (43%) patients. Detailed physical examination is usually needed for accurate assessment. About half of our patients with IHHE had high output heart failure, considered a leading cause of death, along with consumptive coagulopathy. In addition, increased serum TSH concentrations were observed in two of the nine patients tested. Clinically significant hypothyroidism may be due to thyroid hormone catabolism by the tumor¹⁶⁾, indicating the need for thyroid function tests in patients suspected of having IHHE. We found, however, that the incidences of hepatosplenomegaly and abdominal mass, previously reported to be the most common presenting signs in patients with IHHE, were lower than previously reported. In contrast to previous reports however, tumors in many of our patients were detected by fetal sonography and few had clinically severe conditions. Thus, high proportion of the patients with incidentally detected IHHE may explain the reduced incidence of patients with clinically severe IHHE.

In addition, because more patients may be diagnosed prenatally,

further studies may be needed to assess the natural history and treatment strategy of IHHE during the neonatal period.

Radiological evaluation is useful for patient diagnosis, with sonography often being the initial diagnostic modality. On sonography, IHHE is characterized by discrete, hypoechoic lesions (either solitary or multiple) within the liver that may have calcifications or shunting on Doppler evaluation.

Of our 23 patients, 22 were diagnosed by sonography including 7 who were diagnosed by fetal sonography. Compared with sonography, CT shows a more variable enhancement pattern, although it offers several advantages, including more precise anatomical localization, tissue enhancement and characterization¹⁷⁾. MRI generally shows well-defined spherical lesions, hypointense to the liver on T1 sequences and hyperintense on T2, with flow-voids and centripetal enhancement after the administration of gadolinium^{17,19)}. However, it may be difficult to establish a definite diagnosis based on imaging modalities alone. Histopathologically, IHHEs are usually composed of vascular channels lined by a single continuous layer of plump endothelial cells in a supporting fibrous

stroma that may contain well-preserved bile ducts. Hematopoietic activity is a specific characteristic of these tumors. Thrombosis with infarction, followed by fibrosis and even calcification, can occur in the centers of large tumors^{8,20}.

Serum AFP is an important tumor marker for the evaluation of pediatric hepatic masses. Serum AFP concentrations decrease rapidly after birth and reach adult levels by 8 months of age. Increased serum AFP concentrations are rarely observed in patients with IHHE, with one study reporting that clinical symptoms, age at presentation, tumor size and AFP concentration were not significantly related to time required for complete tumor regression²¹⁻²³. Similarly, only three of our patients had increased concentrations of AFP, with all three having multiple tumors; despite receiving different treatment modalities, all three showed nearly complete tumor resolution. We found, however, that increased AFP was not directly related to treatment outcome. The etiology of increased serum AFP in IHHE is unclear, but it may be secreted by morphologically normal hepatic cells in response to the tumor^{5,22}. AFP was shown to be expressed by hepatocytes near or trapped within the tumor, but not by tumor cells²³.

The most important prognostic factors are the presence of a symptomatic mass, congestive heart failure, jaundice, and multiple

tumor nodules, and the absence of cavernous differentiation^{3-5,7}.

Not all patients with IHHE require treatment. These tumors tend to grow during the first year of life then spontaneously regress without treatment, probably due to thrombosis and scar formation. The decision not to treat asymptomatic patients is not a strict rule. Each patient should be evaluated individually. Indications for therapy may include cardiac insufficiency, respiratory distress, coagulopathy, abdominal compartment syndrome and deterioration in hepatic function tests. If therapy is needed, first-line medical treatment is recommended, followed in some patients by invasive or surgical procedures^{3,5,7,9}.

Among the medical treatments for these tumors are corticosteroids, cytotoxic agents, INF- α , and irradiation. Patients who do not respond to medical treatment may undergo radical interventions, such as hepatic artery ligation, transcatheter hepatic artery embolization, surgical resection, and even liver transplantation²⁴. Surgical resection is recommended to remove huge masses with a low potential for spontaneous regression and masses for which a diagnosis of malignancy cannot be excluded clinically and/or radiologically²⁵⁻²⁷.

Spontaneous resolution occurred in 2 of 6 asymptomatic patients without specific therapy (33%), and 8 (67%) of 12 patients were successfully treated with corticosteroids and/or INF- α . Of patients

Table 4. Outcomes Relative to Management in Patients with Infantile Hepatic Hemangioendothelioma (n=23)

	Observation (n=6)	Steroid (n=6)	IFN (n=4)	Steroid/IFN (n=2)	Embolization (n=4)	Op (n=1)	No. (%)
Progression	0	0	0	0	1	0	1 (4)
No change	1	0	0	0	0	0	1 (4)
Regression	3	3	0	1	3	0	10 (43)
≥90% Decrease	1	1	2	1	0	0	5 (22)
Resolution	1	2	2	0	0	1	6 (26)

IFN, interferon; Op, operation.

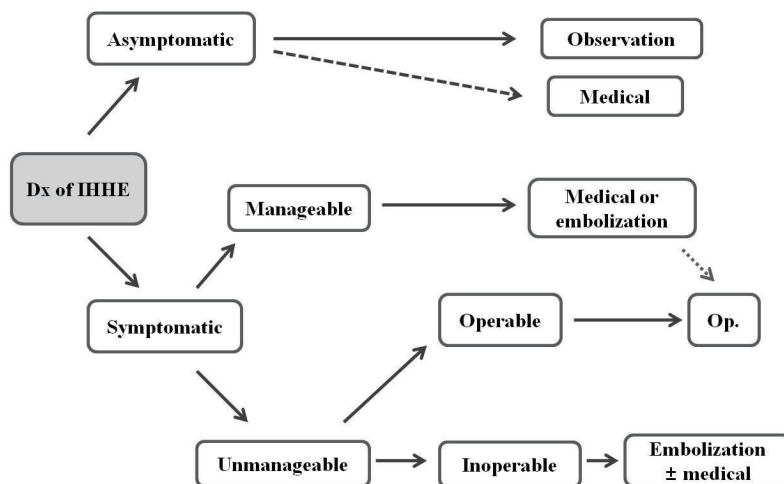


Fig. 1. Management strategy for patients with infantile hepatic hemangioendothelioma (IHHE). Dx, diagnosis; Op, operation.

treated with corticosteroids alone, 50% achieved resolution of the lesion, similar to previously reported response rates as high as 45% in symptomatic patients⁸⁾. Responses often occurred within 1 or 2 weeks and a median time to complete resolution by medical treatment was approximately 30 months (range, 0 to 43 months). Although the precise mechanism of action is unclear, corticosteroids may cause vasoconstriction of the rapidly proliferating immature endothelial cells that line the vascular channels of the lesion³⁾. Moreover, the antiangiogenic agent INF- α , which inhibits endothelial cell migration and proliferation, may also be helpful in causing early regression of hemangioendotheliomas resistant to corticosteroids²⁸⁾. We also found that INF- α yielded satisfactory results, either alone or in combination with steroids. Embolization was effective in three patients who had inoperable, symptomatic, and solitary lesions, but was not successful in one patient despite additional therapy (corticosteroids, INF- α) (Table 4). We found that 48% of patients with IHHE could be managed successfully with or without treatment, with tumor regression observed in an additional 43%.

Based on our experience and the current literature, we propose the following algorithm for the treatment of children with IHHE (Fig. 1). Once the diagnosis is suggested, either by patient symptomatology or as an incidental finding, prompt diagnostic evaluation is mandatory. Asymptomatic unilobar lesions may be observed for regression. However, both asymptomatic, but progressive lesion and symptomatic lesions should be treated with corticosteroids and/or INF- α . If, despite medical treatment, symptoms progress over several weeks or develop in patients with asymptomatic lesions, interventional modalities should be used immediately. If the lesion is accessible to surgical resection, partial hepatectomy should be performed as definitive therapy. Patients with inoperable tumors should undergo embolization followed by medical therapy, either to attempt a definitive cure or as a temporary measure while the patient is evaluated and listed for cadaveric orthotopic liver transplantation or until a suitable living, related donor is identified.

Given the malignant potential of IHHEs, we recommend long-term monitoring of patients with presumed or confirmed IHHE, at least until complete resolution of the hepatic lesion. Monitoring is probably best accomplished by serial clinical examinations and imaging with sonography or CT. Serum AFP concentration should also be monitored if it was increased at the time of diagnosis.

Patients with IHHE usually have an excellent prognosis, especially because the rates of spontaneous regression after the first year of life and long-term survival are about 70%. A multidisciplinary approach that involves pediatric oncologists, radiologists and surgeons is the best treatment option for these patients, increasing their survival.

References

- Emre S, McKenna GJ. Liver tumors in children. *Pediatr Transplant* 2004;8:632-8.
- Shafford EA, Pritchard J. Liver tumors. In: Pinkerton CR, Plowman PN, Pieters R, editors. *Paediatric oncology*. 3rd ed. London: Arnold Publishers, 2004:448-68.
- Daller JA, Bueno J, Gutierrez J, Dvorchik I, Towbin RB, Dickman PS, et al. Hepatic hemangioendothelioma: clinical experience and management strategy. *J Pediatr Surg* 1999;34:98-105.
- Chen CC, Kong MS, Yang CP, Hung IJ. Hepatic hemangioendothelioma in children: analysis of thirteen cases. *Acta Paediatr Taiwan* 2003;44:8-13.
- Moon SB, Kwon HJ, Park KW, Yun WJ, Jung SE. Clinical experience with infantile hepatic hemangioendothelioma. *World J Surg* 2009;33:597-602.
- Ganguly R, Mukherjee A. Infantile hemangioendothelioma: a case report and discussion. *Pathol Res Pract* 2010;206:53-8.
- Sevinir B, Ozkan TB. Infantile hepatic hemangioendothelioma: clinical presentation and treatment. *Turk J Gastroenterol* 2007;18:182-7.
- Davenport M, Hansen L, Heaton ND, Howard ER. Hemangioendothelioma of the liver in infants. *J Pediatr Surg* 1995;30:44-8.
- Amonkar P, Desai S, Deb R, Kane S, Kurkure P, Deshpande RK, et al. Infantile hemangioendothelioma of the liver. *Med Pediatr Oncol* 1999;32:392-4.
- Lu CC, Ko SF, Liang CD, Kuo HW, Tiao MM. Infantile hepatic hemangioendothelioma presenting as early heart failure: report of two cases. *Chang Gung Med J* 2002;25:405-10.
- Riley MR, Garcia MG, Cox KL, Berquist WE, Kerner JA Jr. Hepatic infantile hemangioendothelioma with unusual manifestations. *J Pediatr Gastroenterol Nutr* 2006;42:109-13.
- Selby DM, Stocker JT, Waclawiw MA, Hitchcock CL, Ishak KG. Infantile hemangioendothelioma of the liver. *Hepatology* 1994;20(1 Pt 1):39-45.
- Robbins RC, Chin C, Yun KL, Berry GJ, Bernstein D, Reitz BA. Arterial switch and resection of hepatic hemangioendothelioma. *Ann Thorac Surg* 1995;59:1575-7.
- Ito H, Yamasaki T, Okamoto O, Tahara E. Infantile hemangioendothelioma of the liver in patient with interstitial deletion of chromosome 6q: report of an autopsy case. *Am J Med Genet* 1989;34:325-9.
- Shah KD, Beck AR, Jhaveri MK, Keohane M, Weinberg B, Gerber MA. Infantile hemangioendothelioma of heterotopic intrathoracic liver associated with diaphragmatic hernia. *Hum Pathol* 1987;18:754-6.
- Kalpatthi R, Germak J, Mizelle K, Yeager N. Thyroid abnormalities in infantile hepatic hemangioendothelioma. *Pediatr Blood Cancer* 2007;49:1021-4.
- Ng WH, Ching AS, Chan KF, Fung WT. Clinics in diagnostic imaging (89). Infantile hepatosplenic haemangioendotheliomas. *Singapore Med J* 2003;44:491-5.
- Lucaya J, Enriquez G, Amat L, Gonzalez-Rivero MA. Computed tomography of infantile hepatic hemangioendothelioma. *AJR Am J Roentgenol* 1985;144:821-6.
- Halefoğlu AM. Magnetic resonance imaging of infantile hemangioendothelioma. *Turk J Pediatr* 2007;49:77-81.

20. Konez O, Burrows PE. An appropriate diagnostic workup for suspected vascular birthmarks. *Cleve Clin J Med* 2004;71:505-10.
21. Sari N, Yalçın B, Akyüz C, Haliloglu M, Büyükpamukçu M. Infantile hepatic hemangioendothelioma with elevated serum alpha-fetoprotein. *Pediatr Hematol Oncol* 2006;23:639-47.
22. Seo IS, Min KW, Mirkin LD. Hepatic hemangioendothelioma of infancy associated with elevated alpha fetoprotein and catecholamine by-products. *Pediatr Pathol* 1988;8:625-31.
23. Kim TJ, Lee YS, Song YS, Park CK, Shim SI, Kang CS, et al. Infantile hemangioendothelioma with elevated serum alpha fetoprotein: report of 2 cases with immunohistochemical analysis. *Hum Pathol* 2010;41:763-7.
24. Bachmann R, Genin B, Bugmann P, Belli D, Hanquinet S, Liniger P, et al. Selective hepatic artery ligation for hepatic haemangioendothelioma: case report and review of the literature. *Eur J Pediatr Surg* 2003;13:280-4.
25. Park EA, Seo JW, Lee SW, Choi HY, Lee SJ. Infantile hemangioendothelioma treated with high dose methylprednisolone pulse therapy. *J Korean Med Sci* 2001;16:127-9.
26. Samuel M, Spitz L. Infantile hepatic hemangioendothelioma: the role of surgery. *J Pediatr Surg* 1995;30:1425-9.
27. Shamaly H, Abu-Nassar Z, Groisman GM, Shamir R. Hepatic hemangioendothelioma: the need for early diagnosis and resection. *Isr Med Assoc J* 2006;8:585-6.
28. Woltering MC, Robben S, Egeler RM. Hepatic hemangioendothelioma of infancy: treatment with interferon alpha. *J Pediatr Gastroenterol Nutr* 1997;24:348-51.