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Infantile hepatic hemangioendothelioma: Clinical presentation and treatment

İnfantil karaciğer hemanjioendotelyoması: Klinik ve tedavi

Betül SEVİNİR[1], Tanju B. ÖZKAN[2]

Departments of [1]Pediatric Oncology, and [2]Pediatric Gastroenterology-Hepatology, Uludağ University, School of Medicine, Bursa

Background/aims: *Hepatic hemangioendotheliomas are rare tumors in childhood. We report our 10-years' experience in a tertiary health center.* ***Methods:*** *This retrospective analysis included eight patients with infantile hepatic hemangioendothelioma.* ***Results:*** *The median age at diagnosis was 24 days (age range: 1 to 70 days) and the female/male ratio was 5/3. The main symptoms were abdominal distention and respiratory distress. Cutaneous hemangiomas were present in four cases. Three infants had Kasabach-Merritt syndrome. Four cases had single hepatic tumors while the others had multiple. The tumor size ranged from 2 cm to 10 cm in diameter. These lesions were located equally in the right and left hepatic lobes, and three babies had bilobar involvement. Most of the multifocal hepatic tumors were associated with skin hemangiomas. Treatment options were assessed individually. Systemic prednisolone therapy (2 mg/kg/d) was commenced in six patients. Five patients responded to corticosteroids. One boy with Kasabach-Merritt syndrome did not respond to this therapy. Interferon–alpha (1 million units (MU)/m^2/day) was started, and the daily dose of the drug was increased up to 10 MU/m^2, administered 3 times per week, until clinical improvement was achieved. The response was very good and we observed only constitutional adverse symptoms. Two cases were operated; one died from intraoperative bleeding. Other patients were alive and well for 11 to 66 months. Overall survival was 87% in our series.* ***Conclusions:*** *The treatment approaches depend on the center's experience. A multidisciplinary approach is required for the best treatment option.*

Key words: Infantile hepatic hemangioendothelioma, Kasabach-Merritt syndrome, high dose interferon-alpha treatment

Amaç: *Karaciğer hemanjioendotelyoması çocukluk çağının nadir tümörlerindendir.Bu çalışmada üçüncü basamak sağlık hizmeti veren merkezimizde 10 yıllık deneyimimiz sunuldu.* ***Yöntem:*** *Çalışmada infantil karaciğer endotelyoması olan sekiz hastanın retrospektif analizi yapıldı.* ***Bulgular:*** *Tanıda median yaş 24 gün (yaş sınırları: 1-70gün) ve kız/erkek oranı 5/3 bulundu. Ana yakınma karın şişliği ve solunum sıkıntısı idi. Cilt hemanjiomları dört hastada mevcuttu. Üç olguda Kasabach-Merritt sendromu saptandı. Dört hastada tek, diğerlerinde birden fazla karaciğer lezyonu vardı. Tümor çapı 2 cm ile 10 cm arasında değişiyordu. Lezyonlar sağ ve sol karaciğer lobunda eşit dağılmış olup, üç bebekte her iki lobda tutulum vardı. Multifokal karaciğer tümörlü olguların çoğunda cilt hemanjiomları saptandı. Tedavi seçenekleri bireysel olarak değerlendirildi. Sistemik prednizolon (2 mg/kg/gün) altı hastaya verildi. Beş hastada kortikosteroidlere yanıt alındı. Kasabach-Merritt sendromlu bir erkek bebekte tedaviye yanıt yoktu. İnterferon–alfa (1 milyon ünite/m^2/gün) başlanıp klinik düzelme olana kadar doz arttırımı ile 10 MU/ m^2 /gün , haftada 3 kez uygulandı. İyi yanıt alındı, önemli yan etki gözlenmedi. İki hasta ameliyat oldu. Biri ameliyatta kanama ile öldü. Diğer hastalar 11-66 aylık izlem süresinde iyi olup, serimizde sağkalım oranı % 87 bulundu.* ***Sonuç:*** *Tedavi yaklaşımı merkezlerin deneyimine bağlıdır. En iyi tedavi seçeneği multidispliner yaklaşımla belirlenmelidir.*

Anahtar kelimeler: İnfantil karaciğer hemanjioendotelyoması, Kasabach-Merritt sendromu, yüksek doz interferon-alfa tedavisi

INTRODUCTION

Representing 1 to 5% of all neoplasms of childhood, primary liver tumors are seen very rarely in pediatric practice. Among hepatic neoplasms, malignant tumors are more frequent than their benign counterparts (1, 2). The distribution of hepatic tumors varies in different age groups. Infantile hepatic hemangioendothelioma (IHH), a type of primary mesenchymal hepatic neoplasm, comprises 1-2% of all pediatric hepatic tumors and is seen particularly during the first year of life (3, 4). There are two different histopathologic subtypes, according to cell size and vascularity: Type 1 has benign histopathologic characteristics, although rarely may display malignant clinical behavior,

Address for correspondence: Betül SEVİNİR
Department of Pediatric Oncology, Uludağ University Medical Faculty
16059 Görükle, Bursa, Turkey
Phone: +90 224 442 840 0/1053 • Fax: +90 224 442 81 43
E-mail: bsevinir@yahoo.com

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while Type 2 has more atypical cellular properties. Thrombocytopenia and consumption coagulopathy due to hemangioma or large vascular lesion, called "Kasabach Merritt syndrome" (KMS), may develop in some cases (5-7). In the current literature, data about IHH are usually represented as single cases (7-11). Therefore, there is difficulty in clinical assessment and therapeutic approach in IHH. We report our 10- years' experience in a tertiary health center. The purpose of this study was to determine the clinical problems of the children with IHH, and to discuss treatment choices and results. We also point out our experience with high-dose interferon (IFN)-alpha therapy in a corticosteroid-resistant case.

MATERIALS AND METHODS

The hospital records of patients in the Department of Pediatric Oncology between January 1996 and December 2005 were analyzed retrospectively. During this period, the ratio of hepatic tumors was 2.9% (n:19), and overall incidence of IHH was 1.2% (n:8) among 645 patients with the diagnosis of neoplasia. The data of these eight patients were evaluated. Epidemiologic and clinical features, laboratory studies [complete blood count, renal and hepatic function tests, coagulation parameters, and serum fibrinogen and alpha-fetoprotein (AFP) levels] and response to therapy were recorded for each case. Initial and follow-up imaging records of abdominal ultrasound (US), Doppler sonography and abdominal magnetic resonance imaging (MRI) were obtained. Histopathological examination of tumor was performed in four patients. Urinary catecholamine metabolite vanillylmandelic acid (VMA) levels were determined in all patients by quantitative analysis method in order to rule out neuroblastoma with hepatic metastasis. Treatment options were assessed individually for each patient.

Six cases diagnosed as IHH according to clinical, laboratory and histopathologic examination were treated with prednisolone 2 mg/kg/d. The lesions, which showed no regression in the first month's sonographic evaluation, were defined as "unresponsive". IFN-alpha was considered as an agent of second-line therapy for unresponsive cases. We decided to try "active non-intervention" approach with close observation of those patients with mild clinical symptoms and in good general condition (Case 6). Curative surgery could be achieved in the baby with a large tumor and no medical treatment was given to him subsequently (Case 7). Thyroid functions were screened in neonates, and in the child who was treated with IFN. The follow-up periods for all patients were determined. Because of the limited number of the patients, we could not perform statistical comparison of subgroups. Numeric parameters were given as ratio or mean value with standard deviations.

RESULTS

Among the 645 children with the diagnosis of neoplasia, eight cases were diagnosed as IHH (1.2%). Median age at diagnosis was 24 days (range: 1-70 days). Female / male ratio was 5/3. All of the patients were term babies. One had a gestational history of polyhydramnios. The epidemiologic and clinical features of the cases at the time of diagnosis are summarized in Table 1. The main complaint at admission was abdominal distention as a symptom of hepatomegaly. Three of these children had respiratory distress due to large intrahepatic masses. Four babies presented cutaneous lesions and three had petechiae on physical examination: two cases were admitted with multiple hemangiomas on the lips, face, oral cavity and trunk as having disseminated hemangiomatosis, while the other two had single hemangiomas on lower extremities. Two babies admitted with jaundice. We observed pallor in 5 out of 8 children. Body weight percentiles were less than 5% in Cases 1 and 5.

The mean hemoglobin level was 10.17±1.34 g/dl (range: 8.3-12 g/dl) and mean platelet count was 259,000±294,000 mm^3 (Range: 34,800-762,000/mm^3). The mean values for prothrombin time (PT) and activated partial thromboplastin time (aPTT) were 22.5±19 and 44.5±31.15 seconds, respectively. Five cases revealed increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The mean ALT level was 129.4±135.5 U/L, and the mean AST level was 55.7±32.2 U/L. Renal function tests, thyroid functions, serum AFP levels and 24-hour quantitative urinary VMA excretion were within normal ranges for age in all cases (Table 2).

Three cases were diagnosed as KMS (Cases 1, 2, 5). These patients had platelet counts less than 50,000/mm^3, and all had petechiae in physical examination. All were suffering from anemia resulting from hemolysis due to large vascular lesion. PT and aPTT were prolonged and serum fibrinogen levels were low.

Table 1. Clinical features of patients with infantile hepatic hemangioendothelioma

No	Sex	Age at diagnosis	Gestational status	Symptoms/ signs	Physical examination	Tumor location	Tumor size (Maximum)	Number
1	F	53 days	39 wk, 3500 g	Skin lesions, abdominal distention	Multiple skin hemangiomas (lips, cheek, trunk), petechiae, KMS, tachypnea	Bilobar	2.8 x 2.5 cm	Multiple (n: 12)
2	F	19 days	40 wk, 3500 g	Skin lesions, (limb), petechiae,	Skin hemangioma (left, leg), petechiae, hepatomegaly, KMS	Left hepatic lobe	2 x 2 cm	Single
3	F	29 days	38 wk, 4000 g (polyhydramnios) C/S	Abdominal distention	Hepatic mass, tachypnea	Left hepatic lobe	8 x 4 cm	Single
4	M	Newborn (1st day)	37 wk, 3200 g	Jaundice	Hyperbilirubinemia, hepatomegaly	Right hepatic lobe	2.5 x 1.8 cm	Multiple (n: 6)
5	M	Newborn (1st day)	39 wk, 3750 g	Abdominal distention, respiratory difficulty	Abdominal mass, petechiae KMS, dyspnea, tachypnea, CHF	Right hepatic lobe	10 x 9 cm	Single
6	F	70 days	39 wk, 3175 g C/S	Skin lesion	Hepatomegaly, hemangioma (right thigh)	Bilobar	2.5 x 2 cm	Multiple (n: 11)
7	M	31 days	40 wk, 3800 g	Abdominal distention,	Hepatomegaly, abdominal mass	Right hepatic lobe	7 x 8 cm	Single
8	F	13 days	37 wk, 2400 g	Jaundice, skin lesion	Hyperbilirubinemia, hepatomegaly, multiple skin hemangiomas	Bilobar	2.5 x 2 cm	Multiple (n: 4)

F: Female, M: Male, KMS: Kasabach-Merritt syndrome, C/S: Cesarian section, CHF: Congestive heart failure

Abdominal US revealed hepatomegaly and hypoechoic hepatic nodules in all cases. Hepatic nodules were multiple in four children, three of whom had bilobar involvement (Table 1). These lesions were located in the right hepatic lobe in three cases, and in the left hepatic lobe in two. Skin hemangiomas were found particularly in the cases with bilobar multiple lesions. Single nodules were replacing most of the normal liver parenchyma in Cases 3 and 5.

Written informed consent for liver biopsy could be obtained in four cases. In these cases, histopathologic examination affirmed the diagnosis of IHH-type 1 (Cases 2, 3, 4, 7). One patient was in poor general condition, with a large liver mass causing abdominal distention, cardiac failure, respiratory distress and KMS; hence liver biopsy was desisted in an effort not to compromise the baby's health (Case 5).

Table 2. Laboratory findings*, treatment and outcome of patients with hepatic hemangioendothelioma

No	Hb (g/dl)	Platelets mm³	ALT/AST (U/L)	PT/aPTT (Seconds)	Fibrinogen‡	AFP (ng/ml)	Treatment	Response	Complication	Outcome/ Follow-up
1	8.5	50,000	56/24	18/40	Low-normal	280	CS- 9 months	Partial response (50%)	Cushingoid face, failure to thrive	Alive with fibrotic residual mass, 66 mos.
2	8.3	40,000	83/68	20/39	Low	368	CS- 4 months	Complete response	Cushingoid face	Alive without lesion, 63 mos.
3	9.8	177,000	32/41	14/33	Normal	185	CS- 3 months	Good response (75%)	Cushingoid face	Died at operation, 4 mos.
4	12	215,000	126/115	13/25	Normal	382	CS- 4 months	Complete response	Cushingoid face	Alive without lesion, 34 mos.
5	10	34,800	324/69	18.3/42	Low	2630	CS- 2 months IFN-α	Good response (>50%)	Cushing syndrome, hypertension	Alive with fibrotic residual mass, 33 mos.
6	11.5	684,000	36/17	12.7/31	Normal	450	No treatment	Complete regression	None	Alive without lesion, 23 mos.
7	11.2	762,000	19/37	14/26	Normal	248	Surgery	-	None	Alive without lesion, 17 mos.
8	10.1	110,000	75/359	70/120	Normal	230	CS-3 months	Good response	Cushing syndrome	Alive with shrinkage of lesions, 11 mos.

*At the time of diagnosis, ‡Normal range: 2-4 g/L. CS: Corticosteroids

Systemic corticosteroid therapy with 2 mg/kg/d single dose of prednisolone orally was commenced in six patients, and five of the six patients responded. Hepatic hemangioendothelioma lesions decreased in size in two cases and completely regressed in the other three patients. The skin hemangiomas decreased in size as well. Hemorrhagic diathesis resolved after two weeks of prednisolone therapy. Cushing's syndrome and failure to thrive were the main adverse effects. One of the cases with partial response to corticosteroid died of intraoperative massive bleeding (Case 3). Three cases with KMS required hospitalization at the pediatric intensive care unit due to high output congestive heart failure, severe anemia, thrombocytopenia and respiratory distress (Cases 1, 2, 5). Fresh frozen plasma transfusions, vitamin K, furosemide and digoxin were administered when needed. One patient with KMS did not respond to this first-line therapy (Case 5). Clinical condition deteriorated with respiratory difficulty and tachypnea. Prolonged PT and aPTT levels persisted despite daily fresh frozen plasma transfusions. At the end of the first week, prednisolone dosage was increased to 5 mg/kg/d. After the second week of the systemic corticosteroid therapy, he remained in a life-threatening condition. Interventional treatment modalities were discussed. Embolization or surgery was not suitable because of the large hepatic tumor and inadequate normal liver parenchyma. On the 16th day of prednisolone treatment, we observed sudden pallor and enlargement of abdominal distention. The abdominal US showed a large hematoma in addition to the hemangioendothelioma lesion occupying almost the whole liver parenchyma. The therapy was immediately changed to IFN-alpha with his parents' written consent. Subcutaneous IFN-alpha 1 million units (MU)/m^2/d was started. The dose was increased to 2 and then 3 MU/m^2/d gradually per week. At the end of the fourth week of IFN therapy, there was only minor response and IFN dose was increased to 10 MU/m^2/d, five times a week. Prednisolone was reduced and stopped in a five-weeks' course. Full dose IFN was continued for two months, and then the dosage was lowered to 3 MU/m^2/three times a week, during the following nine months. We observed constitutional adverse reactions as subfebrile fever and fatigue. IFN therapy was continued for 12 months.

In one of eight patients, a "wait-and-see" strategy was applied. Six of the patients were treated with corticosteroids. Two patients underwent surgery. Left lobectomy was performed for the patient with a large hemangioma (Case 3) who had partially responded to corticosteroid therapy, and who had a high risk of hemorrhage. The other patient (Case 7), who had diffuse right lobar involvement with inadequate liver parenchyma, was considered eligible for surgery, and curative right hepatic lobectomy was performed. The first case expired, but the latter is healthy on follow-up.

Except for the patient who died of massive bleeding during surgical operation, all other patients were well during the follow-up period. The median follow-up time was 33 months (range: 11 to 66 months), and overall survival was 87% in our series.

DISCUSSION

Though IHH is the most common vascular-originated hepatic tumor in children, it is rarely seen in clinical practice. Due to inadequate experience, management of IHH is a problem for physicians. Only case reports and a few series about IHH are found in the current literature (3, 4, 7-15).

Regarding our 10-years' experience, primary liver neoplasms account for 2.9% and IHHs comprise 1.2% of all childhood tumors in the southern Marmara region. All of our patients were under three months of age at the time of diagnosis and six of them were admitted during the newborn period. In the literature, 85% of patients were diagnosed before six months (14).

In one study, history of polyhydramnios was reported in 29% of patients (5 of 17 cases) (3). In the present study, polyhydramnios was detected in only one patient (12.5%). Moreover, antenatal diagnosis of IHH cases was reported by US during routine pregnancy examinations (15). Hence, obstetricians should remember to carefully examine the fetal liver for hemangioendothelioma in polyhydramniotic pregnancies.

In our study, patients presented a female predominance (F/M: 5/3). None had accompanying systemic disease. In the literature, frequencies of the main findings were reported as 38-83% for abdominal distention, 51% for congestive heart failure, and 11-66% for cutaneous hemangiomas (3,4,12-15). Rarely, cases may present with hepatic insufficiency, diaphragmatic hernia or intractable vomiting as major symptoms (9,10). In our patient group, the main complaints at admission were abdominal distention and respiratory dist-

ress. Physical examination revealed hepatomegaly in all cases, pallor in 62%, and cutaneous hemangiomas in 50%. These signs were mild in our cases. A detailed physical examination is usually needed for accurate assessment of the patient.

According to the current approach, children with five or more cutaneous hemangiomas should be evaluated for hepatic vascular lesions; however, we found multiple hepatic hemangioendotheliomas in a baby with a single skin hemangioma (16). Moreover, since children with hepatic hemangiomas may have abnormalities of thyroid function (e.g. hypothyroidea), we mention the necessity of noninvasive abdominal US for any baby with skin hemangioma (16).

Kasabach Merritt syndrome occurred in 37% of our patients as a consequence of large vascular lesion. Thrombocytopenia and hypofibrinogenemia usually indicate KMS in a patient with hemangioma, and high output congestive heart failure may develop due to severe anemia.

Elevated aminotransferase levels were reported in 32% of IHH cases (14, 17); similarly, 37% of our patients had high aminotransferase levels (>100 IU/L). AFP is usually considered as a reliable marker for hepatoblastoma and germ cell tumors, but high AFP levels may rarely be associated with IHH (2, 18).

There is no specific laboratory test for the diagnosis of IHH, therefore differential diagnosis is important; particularly, urine VMA levels should be measured in order to exclude neuroblastoma.

Radiological evaluation seems to be useful for diagnosis. Non-invasive procedures like US, computerized tomography (CT) and MRI performed by an experienced radiologist are required for both diagnosis and follow-up.

Treatment of IHH is not needed in all cases. Follow up of asymptomatic cases and those who can be mutually followed by clinical and radiological findings is preferred. On the other hand, Nord et al. (19) reported a case with multiple cutaneous hemangiomas associated with a vascular lesion of the liver in an infant, which was proven to be an angiosarcoma after surgical excision. Decision to not treat asymptomatic patients is not a strict rule. Each patient should be evaluated individually. Indications of therapy in IHH are cardiac insufficiency, respiratory distress, coagulopathy, abdominal compartment syndrome and deterioration of hepatic function tests. If therapy is needed, medical treatment is recommended as a first-line therapy, and afterwards invasive or surgical procedures may be considered individually. Surgical therapy is recommended for huge masses with a low potential for spontaneous regression, or masses for which a diagnosis of malignancy cannot be ruled out clinically and/or radiologically (4, 12-17, 20). Systemic corticosteroids such as prednisolone or high dose methylprednisolone are usually the therapy of choice initially (4, 12-17, 21, 22). Other therapeutic agents which could be used for antiangiogenic effect are cyclophosphamide, vincristine and IFN-alpha (6, 11, 21, 23-26).

Treatment response is expected to occur in one or two weeks, and therapy success with corticosteroids is approximately 30%. In our patient group, six patients received oral corticosteroid, and five patients responded to the therapy. Partial response was seen in three patients. The median duration of treatment was four months (3-9 months). Therapy schedule for IHH has not been established yet, but in our opinion, shorter courses would be inadequate for suppression of angiogenesis. We had to apply IFN therapy to one of the KMS cases who was unresponsive to corticosteroid therapy and had massive abdominal hemorrhage due to hepatic hemangioendothelioma. This was our first experience with IFN for the treatment of IHH, and we managed to administer IFN without any complication at even higher doses than seen in previously reported cases (27). Recently, serum vascular endothelial growth factor levels were used as a reliable indicator of efficacy in patients treated with IFN for IHH (28).

Surgical treatment is currently preferred for intrahepatic shunts and single uni-lobe lesions (2, 4, 13, 15). Before a surgical attempt, probable risks and benefits should be assessed properly. Surgical intervention in IHH carries life-threatening hemorrhage risk, so it must be the last choice of treatment.

In the present study, we could obtain biopsy specimens in four patients (50%) and affirmed the diagnosis of infantile hemangioendothelioma type 1. Due to high hemorrhage risk after biopsy, histopathologic examination could not be performed in every case. This is a limitation for the clinician, knowing that accurate diagnosis of the lesion can be established only by histopathology. Moreover, management of the patients with residual lesions who were treated without histopathologic diagnosis remains unclear. One point to be kept in mind is the importance of residual lesions and their

eventually malignant potential, depending on the nature of lesion (29, 19).

Survival is approximately 12-40% in symptomatic cases without treatment, and treated patients' survival rate increases up to 70% (12-14). In our patient group, overall survival was 87%. Multifocal lesions, intrahepatic shunts and complications like congestive heart failure and hemorrhage are the major prognostic factors (4, 13, 14, 17). Not only pediatricians but also pediatric surgeons, dermatologists, and radiologists should remember IHH, particularly in patients with cutaneous hemangiomas.

In conclusion, IHH is a rare childhood tumor. In this study, we reported the clinical, laboratory and radiological evaluations, and also discussed therapy results and prognosis of our IHH cases. The diagnosis and general treatment strategies are well defined in IHH. However, treatment approach is related to a center's experience. A multidisciplinary approach including pediatric oncologists, radiologists and surgeons is required for the best treatment option for each case. We strongly believe that this approach will increase survival in these patients.

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