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Cavernous hemangioma of the liver: factors affecting disease progression in general hepatology practice

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Abstract

Background—Although for asymptomatic hepatic hemangiomas, conservative management is generally recommended, factors affecting disease course are still not very well understood.

Aim—To determine disease characteristics of cavernous hemangioma and factors affecting its progression in patients from a general hepatology clinic in Tehran, Iran.

Methods—We reviewed medical records of 198 patients with cavernous hemangioma of the liver visiting a large private hepatology clinic in Tehran from 1997 to 2007. Of a total of 198 cases, 129 could be followed up for a period of 3.2±2.5 years, and 80 of these had 1 to 5 repeat sonographies.

Results—Patients were between 27 and 84 years old (mean age 44.3±10.9), and 131 (66.2%) were female. Thirty-six patients (18.2%) had giant hemangiomas. Abdominal pain was the primary reason for evaluation in 100 (50.5%) patients. Abdominal pain at the beginning of follow-up was significantly associated with having irritable bowel syndrome (OR=8.3; 95%CI: 3.1-28.7) or other GI diseases (OR=3.9; 95%CI: 2.6-10.2), but not with hemangioma size, number or location. During follow-up, having a single giant lesion at the time of diagnosis, adjusted for age, sex and presence of IBS, was a strong predictor of persistent pain during follow-up (OR=11.1; 95%CI: 3.2-38.6). In repeat sonographies, 35% showed increased size, which was significantly associated only with having a single lesion (p=0.04).

Conclusion—Many symptoms in hepatic hemangioma are attributable to accompanying GI diseases. Patients with a single giant lesion are more likely to have persistent pain, and single lesions are more likely to grow in size.

Keywords

liver; hemangioma; ultrasonography

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INTRODUCTION

Cavernous hemangiomas are the most common benign liver tumors, and the liver is the internal organ most affected by hemangioma.[1-2] Many patients are asymptomatic, but in others, symptoms may vary from abdominal discomfort to life-threatening complications.[1] Women are more often affected by hepatic hemangioma,[3] and some studies have found that women exposed to exogenous estrogens, progesterone, contraceptives or hormone replacement therapy show a significant increase in the size of their tumors.[4-5] Ultrasonography is usually the first imaging study and is 70-80% accurate in diagnosing cavernous hemangiomas.[6-7] Since this method is not invasive and is easily repeated, it is an ideal way of following the tumor once the diagnosis is established.[8-9] MRI is the most accurate imaging technique (95% sensitive, and up to 100% specific).[10-11] Carefully-performed needle biopsy can be used in uncertain cases.[12]

Diagnostic and therapeutic challenges in the evaluation of hepatic hemangiomas have been addressed in a number of publications[13-15]. In recent years, many reports have shown very good results after surgical resection or enucleation,[16-18] but for asymptomatic hepatic hemangiomas, conservative management is generally recommended, [16,19-20] even for giant lesions.[21]

In general factors affecting disease course and outcome are still not very well known and since many of the reports on the follow-up results have come from surgical centers, the results may be biased towards larger, more complicated tumors.[22] This is reflected by high rates of resection and symptomatic disease in many published reports.[14,17,22] There are only a few published reports on cavernous hemangioma of the liver and its natural history in the Middle East region. We conducted this study of patients diagnosed with hepatic cavernous hemangioma in a general hepatology clinic in Tehran, Iran to determine disease characteristics and factors affecting its progression and outcomes in patients presenting in this setting.

METHODS

In this retrospective study, we reviewed all medical records of patients who had visited the gastroenterology and hepatology clinic of one of the authors (R.M.) in Tehran, Iran for 10 years, from 1997 to 2007. Located in the northeast of Tehran, this clinic is a very busy center, admitting both new patients and referral cases from all over the country. Among the patients seen at this center, 198 were diagnosed as having cavernous hemangioma of the liver during this period. The diagnosis of cavernous hemangioma was confirmed by ultrasonography, CT scan, MRI and/or FNA.[6] All other possible diagnoses, including other liver tumors, were excluded in patients before a definite diagnosis was made. Data collected included age, sex, time since diagnosis, imaging results, pregnancy or estrogen usage during follow up, presence of accompanying gastrointestinal (GI) diseases, symptoms and signs before and after diagnosis, course of disease, treatment, complications, and recurrence using a structured questionnaire. Patients were followed up every 6-12 months, and a new ultrasonography was performed whenever necessary.

For each patient, all the related files were reviewed, and in cases with incomplete information or loss to follow-up, the patient was contacted. Patients were asked to visit the clinic at a convenient time, with all of the medical records they had, and a new sonography was performed if indicated. Whenever the patient was unable to revisit the clinic, a telephone interview was performed to ensure as much follow-up data as possible. Of the total 198 cases, 129 (65%) could be followed up for a period of 3.2±2.5 years (range: 1- 12 years), and 80 of these (40.5% of all cases) had 1 to 5 repeat sonographies.

Descriptive data are reported as frequencies and means±standard deviations. Lesion size is reported as the greatest dimension of the largest lesion detected by ultrasonography. A giant lesion was defined as one measuring 5 cm or more in greatest size.[21] The association of each risk factor with disease outcome was analyzed using chi-square and Fisher's exact tests for categorical variables and t-test for continuous data. Odds ratios and 95% confidence intervals (95%CI) were used to assess the strength of associations. A multivariate logistic regression model was used to adjust for confounders. All of the analyses were two-tailed, and a p-value of less than 0.05 was considered significant.

RESULTS

Patients were between 27 and 84 years old (mean age 44.3±10.9), and 131 (66.2%) were female. Table 1 shows the baseline characteristics of the patients. While most patients had 1 to 4 lesions; one patient had 9 and another had 15 separate tumors. Thirty-six patients (18.2%) had giant hemangiomas (≥ 5 cm), with the largest lesion measuring 25 cm. 115 patients complained of abdominal pain, and this pain was the reason for evaluation in 100 (50.5%). Presence of abdominal pain at the beginning of follow-up was significantly associated with having irritable bowel syndrome (OR=8.3; 95%CI:3.1-28.7) or other GI diseases (OR=3.9; 95%CI:2.6-10.2), but not with hemangioma size, number or location (Table 2). In 25 patients (21.7% of those with abdominal pain) no reason other than hemangiomatosis was found for this symptom.

Among the 129 patients who could be followed up, none of the 48 previously asymptomatic patients became symptomatic during this period. In 81 who had reported abdominal pain at the beginning of the study, pain persisted in 23 (28.4%) and disappeared in 58 (71.6%) patients due to treatment of underlying diseases, and/or non-specific pain relief methods. As the right panel of Table 2 shows, having greater lesion size, a single lesion or a history of IBS were significantly associated with persistent pain. Having a single giant lesion at the time of diagnosis was a strong predictor of persistent pain during follow-up (OR=10.9; 95%CI: 2.8-42.5). The association even got stronger when adjusted for age, sex and presence of IBS (OR=11.1; 95%CI: 3.2-38.6).

Nine patients (7% of those available for follow-up) underwent surgical resection, after an average duration of 2.0±1.8 years: 4 because of abdominal pain unresponsive to pain relief medication, 4 because of the large size of the lesion, and one due to rupture and bleeding of the hemangioma. In three of these 9 patients, the hemangioma recurred after surgery.

In the 80 patients with repeat sonographies, the average size of the largest lesion did not show a significant change (from 50.0±49.2 mm to 49.2±52.0 mm; p=0.7). Increased size of the largest lesion was observed in 28 (35%) of the follow-up sonographies. Table 3 compares patients with and without increased lesion size. Among those with stable lesion sizes, multiple lesions (p=0.04) and left lobe involvement were more common (p=0.07).

DISCUSSION

In this relatively large series of patients with hepatic cavernous hemangioma, we found that in most cases the disease had a benign course. The pain at presentation seemed to be more common in those with accompanying GI disease, especially IBS, but large tumors were more likely to cause persistent pain later during follow-up.

Among our patients 58% had abdominal pain at baseline, and in 50% of cases this pain was the reason for referral which led to the diagnosis of liver hemangioma. However, in only 12.6% of the cases could the pain be attributed to the hemangioma; in the other patients, other GI diseases, especially IBS and peptic ulcer disease, were also present. IBS was also a

determinant of persistent abdominal pain in our patients. Other studies of hepatic cavernous hemangioma have also reported that the majority of patients have other causes for abdominal pain.[1,9] In a study by Farges and colleagues [14], pain disappeared in 54% of patients after treatment of associated disorders, and in 4 out of 11 patients, pain persisted even after tumor resection. In this series, pain also diminished in many patients even in the absence of any specific treatment. When no other reason is found for symptoms in patients with hepatic hemangiomas, pain is thought to be present as a result of infarct and necrosis of the tumor[22] or the result of the tumor pressing on the liver capsule or adjacent organs.[10] The latter is especially important in large tumors and left-lobe lesions.[14] In our study, although lesion size was not associated with pain at the start of the study, patients who experienced continued pain during follow-up had larger lesions. It is also interesting to notice that the main determinant of continued pain was the baseline size of the tumor, and not an increase in tumor size during follow-up. We think that at baseline most of the abdominal pain in our patients was caused by other GI diseases, and this masked any pain caused by the hemangioma. With the exception of IBS, pain from these other diseases was relieved by appropriate treatment, and then the effect of hemangioma size on pain became more evident.

Similar to previous studies, our patients showed a female predominance. The 2:1 female:male ratio in our study is lower than those reported in most earlier series, which were usually in the range of 5-6:1.[6-7] However, a few other studies have also reported a 2:1 sex ratio.[8-9,22] While some studies show that female sex hormones may play an important role in the pathogenesis of these tumors, the literature is inconclusive in this regard.[3] Gemer et al., in a case-control study of 40 women with liver hemangiomas, reported that the disease was not associated with menstrual or reproductive history or oral contraception use.[23] However, this study may have been underpowered to show such associations. In a larger study by Glinkova and colleagues, 94 women with 181 hemangiomas were followed for an average of 7.3 years.[4] They concluded that both exogenous and endogenous sex hormones may influence hepatic hemangimatosis, although significant enlargement was relatively uncommon even in patients receiving hormone therapy. In our patients, pregnancy history or estrogen use had no significant effect on lesion progression or symptoms during follow-up.

Cavernous hemangiomas of the liver usually follow a benign and non-progressive course.[1] In most studies, these tumors show little change in size during follow–up, and are rarely complicated.[24] In our patients the average size of their lesions did not change significantly during their 3.2 year follow-up period. On the other hand, 35% of the lesions with more than one sonography did show some degrees of size increase which is higher than the 10-13% enlargement rates reported in other series [14]. It is believed that dilatation or ectasia of the vascular channels, and not than proliferation of endothelial cells, is the main reason for the enlargement of these lesions.[25] Glinkova and colleagues[4] reported a 12.7% increase in size. Similar to our study, they found an inverse association between hemangioma number and the likelihood of progression (OR=0.27; p=0.006). We didn’t find any association between size increase and symptoms.

We found a resection rate of 7% in our series. Different studies have reported resection rates from 3.2% to 45% for cavernous hemangioma.[14,17,20,22] Many previous series have come from surgical centers, where patients had been referred because of progressive disease, and this may have led to results biased in favor of more advanced, symptomatic disease and treatment by surgical resection.[14,17] In contrast, our study was conducted in the setting of a general hepatology clinic, thus giving a better insight into the natural history of patients seen in non-surgical settings. It is also important to note that our study was not conducted in

hospital setting, so its findings should be closer to that of the everyday experience of most internists and hepatologists.

One limitation of our study was that many of our patients could not be followed or had incomplete information, due to the retrospective nature of the study. Most of the other studies published about cavernous hemangimatosis of the liver have this same limitation.

The usual approach for cavernous hemangiomatosis of the liver is conservative management, and there are only a few indications for surgery, such as complicated or symptomatic lesions or diagnostic uncertainty.[1,21] Previous series have reported that symptoms persist post-operatively in many of patients, irrespective of the exact surgical methods.[19] Also, in three of our patients, we observed recurrence of the hemangioma following tumor resection. Risk of surgical complications appears to be related to the hemangioma size and not the technique used, and thus the indications for surgery must be carefully weighed for each individual.[16]

In conclusion, our study confirms previous findings about the benign and non-progressive nature of hepatic cavernous hemangiomas. It also shows that many of the symptoms in patients with these tumors, especially abdominal pain, are attributable to accompanying GI diseases, especially IBS, and lesion growth alone does not often cause symptoms. Later during the course of the disease, patients with a single giant hemangioma are more likely to have persistent pain, and single lesions are more likely to grow in size, so they must be followed up for any remarkable change in disease course. Neither abdominal pain nor lesion size alone warrant surgical intervention.

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Table 1

Baseline characteristics of 198 hemangioma patients

Baseline characteristic	Value
Age at diagnosis (years)	44.3±10.9
Sex	
Female	131 (66.2)
Male	67 (33.8)
Reason for evaluation	
Abdominal pain	100 (50.5)
Other GI symptoms	34 (17.2)
Incidental finding	64 (32.3)
Patients with multiple lesions	32 (16.2)
Patients with a giant lesion (>5 cm)	36 (18.2)
Average size of the largest lesion (mm)	50.2±46.5
Location	
Right lobe	176 (89)
Left lobe	13 (6.5)
Both	9 (4.5)
Accompanying GI or liver disease	
Gastroesphageal Reflux disease	57 (28.9)
IBS	45 (22.7)
Hepatitis/liver disease	22 (11.1)
Peptic ulcer	15 (7.6)
Diseases of billiary system	10 (5.1)
Colorectal disease	6 (3.0)

Values shown are mean±standard deviation or number (percent)

GI: gastrointestinal; IBS: irritable bowel syndrome

Table 2

Comparison of patients with and without abdominal pain

	Abdominal pain at baseline†		Abdominal pain during follow-up‡	
	Abdominal pain present (n=115)	**Abdominal pain absent (n=83)**	**Abdominal pain present (n=23)**	**Abdominal pain absent (n=106)**
Lesion size (mm)	47.3±41.3	54.2±52.5	68.4±43.2**	38.4±36.4
History of IBS	40 (34.8)**	5 (6)	11 (47.8)*	17 (16.0)
History of other GI disease	78 (67.8)**	29 (34.9)	14 (60.8)	55 (51.9)
Giant lesion (>5 cm)	17 (14.8)	19 (22.9)	10 (43.5)**	13 (12.3)
Multiple lesions	18 (15.7)	14 (16.9)	0 (0)**	21 (19.8)
Left lobe involvement	11 (9.5)	11 (13.3)	3 (13.0)	16 (15.1)

Values shown are mean±standard deviation or number (percent) GI: gastrointestinal; IBS: irritable bowel syndrome

† among all 198 patients

‡ among 129 available to follow-up

* $p<0.05$ compared to those without abdominal pain

** $p<0.01$ compared to those without abdominal pain

Table 3

Factors associated with increased hemangioma size among 80 patients with repeat sonographies

	Lesion size increased (n=28)	Lesion size decreased or constant (n=52)	p value
Age at diagnosis (years)	43.6±9.6	41.7±9.3	0.4
Disease duration (years)	3.8±2.9	3.3±2.7	0.4
Female patients	23 (82.2)	40 (76.9)	0.6
Giant lesion (>5 cm)	5 (17.9)	15 (38.8)	0.1
Multiple lesions	2 (7.1)	14 (26.9)	0.04
Persistent pain during follow-up	3 (10.7)	6 (11.5)	0.8
Estrogen use*	13 (56.5)	22 (55.0)	0.7
Pregnancy *	14 (60.9)	24 (60.0)	0.7
Left lobe involvement	2 (7.1)	12 (23.1)	0.07

Values shown are mean±standard deviation or number (percent)

* percentages are calculated only in women