Adult hepatic hemangioma: An Updated Review with focus on the natural course and treatment options

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Hemangiomas account for the vast majority of benign tumors affecting the liver; females are affected more than males. Mostly, hepatic hemangiomas are asymptomatic and incidentally diagnosed. In this review, we provide an updated discussion on the clinical presentation of hepatic hemangiomas as well as on the natural history and available treatment options. Overall the natural history of hepatic hemangiomas is benign, although a caution should be taken for the catastrophic complication. For most cases, a conservative treatment is recommended unless there is an absolute indication for surgical intervention. Until now, there is no approved effective oral treatment and given the low rate of adverse effects coupled with the effectiveness of propranolol treatment in infantile hepatic and cutaneous hemangiomas. The use propranolol should be encouraged in adult patients with giant hepatic hemangiomas.

Keywords: hepatic hemangiomas; natural history; treatment; propranolol

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Introduction

Hemangiomas (HA) are benign vascular neoplasms; within the liver, benign tumors are mostly HA's and their prevalence might reach 20% [1]. Those tumors mostly affect adult female in their fourth and fifth decade of life, specifically women with high parity (female to male ratio, 3:1), however they can occur at any age in life [2, 3]. Although there is no proven association with the use of oral contraceptive, this association remains controversial. Usually, hepatic HA are asymptomatic without adverse effect on liver enzymes, thus their detection in most instances is incidentally on abdominal imaging studies performed while screening for other causes [4]. Embryologically, they are originating from the mesodermal layer and they consist of non-malignant proliferation of the endothelial cells lining the vascular bed [5]. Macroscopically, HA are well-defined, hypervascular lesion [6]. Microscopically, HA consist of ectatic, enlarged and dis-organized blood vessels, separated by fibrous connective tissue with a variable sclerotic component. Approximately 80% of hepatic HA are of the cavernous type. The less common capillary type, which are multiple, smaller in size and do not generally cause local symptoms, the cavernous type can cause local symptoms given the high growth potential. Hepatic HA more than 4 cm in size are considered giant HA [7, 8] and symptoms seldom appear unless the tumor exceed the size of 4 cm. Most of them show no change on follow up by imaging modality [9].

Clinical presentations

Hepatic HA can cause wide range of symptoms ranging from abdominal pain, fullness or palpable upper abdominal mass to more life threatening conditions such as, bleeding onto the HA, local pressure on the proximal structures, thrombosis, congestive heart failure from massive arterial
venous shunting, consumptive coagulopathy (Kassabach-Merritt syndrome) and even hemo-peritoneum due to tumor rupture [10,11,12,13]. Until now, no known cases of malignant transduction were reported [14, 15]. However, spontaneous regression rarely occur [15,16]. The most frequent indication for surgical procedure is abdominal pain but other causes of abdominal pain should be excluded such as peptic ulcer disease and gallstones. In some patients spontaneous symptomatic improvement might occur [17,18]. Patients with a giant hepatic HA may have inflammatory features. Bornman et al. described a triad in several patients, consisting of elevated erythrocyte sedimentation rate (ESR), thrombocytosis and hyperfibrinogenemia reflecting acute inflammatory process which can be reversed by resection [19]. Moreover, it was shown that giant cavernous hepatic HA was associated with clinical features of polymyalgia rheumatica and These features also resolved following resection [20].

**Diagnosis modalities**

Hepatic HA tend to be hypo-dense on non-contrast computerized tomography (CT). On contrast CT, initially show peripheral followed by central enhancement. Typical sign is Iso-enhancement with the adjacent arteries. Delayed scans show persistent contrast enhancement which reflect the abnormal vessels within the lesion. Iso-dense with the aorta, has been shown to be 100% specific in differentiating HA from metastases [21]. The diagnosis of hepatic HA can be confirmed by magnetic resonance imaging (MRI). Typical features include high signal intensity on T 2-weighted series and discontinuous nodular peripheral enhancement [22].

**Presentation and Natural History**

Most of the hepatic HA's are characterized by benign uncomplicated course [7,16] and most lesions are asymptomatic. However symptoms attributed to hepatic HA should be interpreted carefully. A study included 163 patients with hepatic HA, reported 47 patients had other identifiable causes or their gastrointestinal complaints, also in this study, the patients were followed for 92 months, 9 patients had an increase in the hepatic HA size while decreased in 7 patients. Furthermore, 5 patients developed complications, included 2 cases of Kasabach-Merritt syndrome, 1 intra-hepatic bleed, and 2 cases of Budd-Chiari syndrome. Overall 16 patients underwent variable surgical interventions [23]. hepatic HA mostly known to be stable in size, however, Weimann et al. reported size increases in 11 (10.6%) of 104 patients [8]. Kasabach-Merritt syndrome usually associated with large HA [24] and it is characterized by consumptive coagulopathy and thrombocytopenia that result from platelets trapping in the HA with the consequent activation of both platelets and clotting pathways. The mortality rate of Kasabach-Merritt syndrome reach 30% that might necessitate an urgent surgical intervention [25].

A recent study examining the natural course of hepatic HA found that almost 40% exhibit growth overtime and the growth rates reach 2 mm/year [26].

**Pathogenesis**

The pathogenesis of hepatic HA is still unclear. Previously, it was referred to be congenital vascular malformation that enlarges secondary to progressive ectasia or growth. There were some theories that their growth is hormonally mediated as occurred in pregnancy or due to the effect of estrogen and progesterone therapy [27, 28, 14]. In the other hand, HA growth occurred in postmenopausal women, suggesting the limited role of sex hormones [29]. Recently, the role of abnormal and unopposed angiogenesis mediated by specific growth factors such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) have been described as the main underlying mechanism involving in the hepatic HA development [30, 31]. Furthermore, it has been reported shrinkage of hepatic HA using VEGF inhibitor bevacizumab which exert an anti-tumor effect on hepatic hemangiomatous tissue [32].

**Treatment option**

There are several treatment options that can be offered for the treatment of hepatic HA, include, ligation of the hepatic artery, resection of the hepatic HA, radiation therapy and finally in selected cases liver transplantation is performed [7,12,13]. However, those above mentioned procedure have limited beneficial effects and also they are associated with high rate of complications [33, 34, 35, 36, 37] and the long term results were poor [12]. Trans-arterial chemoembolization was reported to be effective in the treatment of giant hepatic HA [38]. However, the beneficial effect of trans-arterial chemoembolization on hepatic HA still not well established and in some cases it might cause an increase in tumor mass [39]. Several studies reported high morbidity of 10-27% and mortality of 2% after resection or enucleation of the hepatic HA [40, 41].

Definitive surgical procedure remains the only effective curative treatment for giant hepatic HA and should be considered for patients with established complications such as HA rupture with secondary hemo-peritoneum, hemorrhage into the tumor, the development of Kasabach-Merritt syndrome [10, 42, 43], in non-resolving abdominal symptoms and when the diagnosis remains uncertain despite extensive investigation [44]. In the other hand, conservative management is preferred for most of the patients. Most
hepatic HA remain stable over time and surgical treatment is not recommended unless there is signs of rapidly growing hepatic HA or when the size at the presentation is more than 15 cm [23]. Furthermore, factors such as widespread lesion, proximity to the vasculature and the presence of co-morbidities favor the use of conservative treatment or minimally invasive radiological procedures (transcatheter arterial embolization, radiofrequency ablation), although those methods are considered efficient but they have considerable limitations [45, 46]. Despite the fact that hepatic HA are stable, but they may be associated with mortality and morbidity [47]. It is widely accepted that even giant, asymptomatic hepatic HA are managed by observation and no clinical intervention is taken unless symptoms occur and the conclusion from several reports [44, 12, 48] addressed that in asymptomatic patients even in the presence of a giant HA conservative management is reasonable.

Propranolol, which is an oral non-selective beta blocker, was shown to be effective treatment for proliferative HA in 2008 [49]. Propranolol exert its effects on the growing infantile HA by three mechanisms: vasoconstriction, induction of apoptosis and down-regulation of angiogenic factors such as vascular endothelial growth factor and basic fibroblast growth factor which suppress the angiogenesis [49, 50]. Furthermore, propranolol exert an inhibitory effect on matrix metalloproteinase 9, which is involved in the up-regulation of angiogenesis process [51]. It has been used widely in the treatment of infantile HA with beneficial effects ranged from significant improvement to complete resolution of the hepatic HA [52], in this study, the dose of propranolol ranged between 2-3.5 mg per kg per day without reported side effects. Mhanna et al. reported regression of skin and hepatic HA in three patients, two of them had cardiovascular instability from high cardiac output failure and one had extensive liver involvement [53]. The safety of propranolol was good without cardiovascular adverse effects when examined on 25 patients with cutaneous infantile HA [54]. Several other reports addressed successful medical management with propranolol [55, 56].

Due to its significant efficacy and safety profile as been reported by multiple open label trials, placebo-controlled trials and single case reports [49, 57, 58, 59], an oral propranolol was approved by the Federal Drug Administration in the USA as first line treatment of infantile HA.

Conclusion

The benign uncomplicated course of hepatic hemangiomas favors the conservative management including giant hepatic HA in the majority of cases. However, the risk of potential fatal complications must guide the clinician in the daily clinical practice to consider an oral treatment vs. prophylactic operative procedure for the prevention of future complication of giant hepatic HA taking into account that the application of prophylactic surgical intervention is more difficult to justify due to the high rates of procedure related complications. While those patients with hepatic HA, specifically giant hepatic HA are managed by follow up without oral treatment, it is reasonably and even recommended in the era of propranolol with the highly effective and safety profile to be used in adult patients with giant hepatic. Further prospective randomized controlled trials should be carried out to prove the efficacy of propranolol in adult hepatic hemangiomas.

Conflict of interest

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