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Review Article

Benign tumors of the liver

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Abstract: Benign liver tumors are common in general population, can be seen in 9% to 20% of individuals. Some of these tumors have a completely benign natural history and do not need to be resected, while others carry a risk of growth, hemorrhage, or malignant transformation and should be operatively removed. Obtaining a preoperative diagnosis is therefore critical, and this single factor remains the primary challenge in managing patients with benign tumors of the liver. This article gives basic information about hemangioma, liver cell adenoma, focal nodular hyperplasia, and less common lesions that arise from the hepatic epithelial or mesenchymal tissues.

Keywords: Benign liver tumors, hemangioma, focal nodular hyperplasia, hepatocellular adenoma, nodular regenerative hyperplasia

Introduction

The liver is an organ that is commonly involved either primarily or secondarily with vascular, metabolic, infectious, and malignant processes. Many classification schemes are used to help narrow the differential diagnosis of liver lesions: solid or cystic, single or multiple, cell of origin (hepatocellular, cholangiocellular, or mesenchymal), and benign or malignant [1].

Benign liver tumors are common in general population, can be seen in 9% to 20% of individuals [2, 3]. Although most patients never have symptoms related to these tumors, this lession is now regularly discovered owing to the increased use of radiologic imaging such as USG, CT and MRI [2].

Benign tumors of the liver include hepatic hemangioma, liver cell adenoma, focal nodular hyperplasia (FNH), and less common lesions that arise from the hepatic epithelial or mesenchymal tissue (**Table 1**). Some of these lesions have a completely benign natural history and do not need to be resected, while others carry a risk of growth, hemorrhage, or malignant transformation and should be operatively removed. Obtaining a preoperative diagnosis is therefore critical, and this single factor remains the primary challenge in managing patients with benign tumors of the liver [3].

Hemangioma

Hepatic hemangiomas (cavernous hemangioma) are the most common benign tumors of the liver, with an incidence in autopsy series ranging from 0.4% to 7.3% [4]. They can affect people of all ages, although they manifest most often in the third, fourth, and fifth decades of life. Women are predominantly affected (4:1 to 6:1) and often present at a younger age and with larger tumors in comparison with men [5].

The great majority of hemangiomas are small and asymptomatic and are discovered incidentally during imaging of the liver for another reason, at autopsy, or at laparotomy [5]. They generally becomes symptomatic when they reach diameters of over 4 to 6 cm. Symptoms include non-specific abdominal pain (probably due to thromboses or stretching of Glisson's capsule), pressure symptoms, and fever [6]. Spontaneous or traumatic rupture of a large hemongioma and acute thrombosis are very rare, except the patients who have the severe Kasabach Merritt syndrome-characterized by disseminated intravascular coagulopathy, thrombocythemia, and hypofibrinogenemia [7].

Table 1. Benign tumors of the liver

Epithelial tumors
Hepatocellular
Focal nodular hyperplasia
Hepatocellular adenoma
Nodular regenerative hyperplasia
Bile duct
Bile duct adenoma
Bile duct cystadenoma
Mesenchymal tumors
Blood vessel
Hemangioma
Hemangioendothelioma

The lesion is thought to be a congenital malformation or hamartoma that increases in size, initially with growth of the liver and thereafter by ectasia [5]. Hemangiomas of the liver may be associated with hemangiomas of other organs, and in only 10% patients may be multiple within the liver [7, 8]. Other associated conditions, for example, liver cysts, gallbladder disease, gastroduodenal ulcers, or hiatus hernia are reported in 42% of the patients whom have hepatic hemangioma [9].

Hemangioma occurs anywhere in the liver parenchyma, sometimes directly under the Glisson's capsule. The gross appearance is spongy-reddish or bluish (**Figure 1**) Microscopically, the lesion is clearly demarcated from normal liver tissue. Haemangiomas consist of anastomosing vascular channels of varying size which are lined by a single layer of endothelial cells. Thrombosis might be present. Local fibrosis and calcifications are the results of organized thrombosis.

In most of the benign liver tumours, physical examination and liver function tests have very limited use in the diagnosis of hemangioma [10]. The only physical finding may be an enlarged liver. Serum liver function tests are generaly evaluated at normal level. In certain cases measurement of alpha feto protein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 may help differantiate benign from malign tumors. Benign liver tumors rarely have elevations in these tumor markers, whereas patients with hepatocelluler carcinoma, colorectal cancer with liver metastasis and cholongiocarcinoma will often have elevations in one or more of these serum markers [2].

Radiologic evaluation plays an important role in the diagnosis of hemangiomas. Ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy are the main instruments of the diagnosis.

Most hemangiomas are discovered incidentally with sonography. The typical sonographic appearance of hemangioma is an echogenic mass of uniform echodensity that lies in the posterior segment of the right lobe of the liver, and that is <3 cm in diameter [11]. Non-contrast CT images will reveal a well-defined hypodense mass that may contain areas of calcification or central scarring. Contrast-enhanced images, both on arterial and portal venous phase series will usually demonstrate typical peripheral nodular enhancement [12, 13].

When hemangioma is suspected, and CT fails to confirm the diagnosis, an MRI should be performed. Hemangiomas typically have hypointense signal intensity compared to the surrounding liver tissue on T1-weighted imaging, and hyperintense signal intensity on T2-weighted imaging. The pattern of enhancement on gadolinium images is similar to that seen on contrast enhanced CT imaging. MRI may be more sensitive than CT in detecting subtle enhancement, and recent studies have demonstrated that MRI has a diagnostic accuracy as high as 96% for hepatic hemangioma [13, 14]. Therefore MRI is the best, though most expansive for diagnosis of the hemangioma (**Diagram 1**) [6].

The great majority of cavernous hemangiomas can safely be left untreated. The natural history of these lesions is usually one of stability. The three criteria we use as indications for surgical treatment include severe symptoms, inability to exclude malignancy, and the development of complications from the hemangioma [3]. Surgical resection, enucleation, hepatic artery embolisation and liver transplantation remains the principal effective therapies [15]. Enucleation offers greater preservation of normal hepatic parenchyma and fewer complications and is the preferred technique for suitable lesions. In a study by Hamaloglu et al. patients treated surgically were compared with those treated with enucleation. 10 of 22 patients were treated with enucleation. Operative time was significantly longer in the resection group ($P = 0.048$). Blood transfusion and blood loss rates

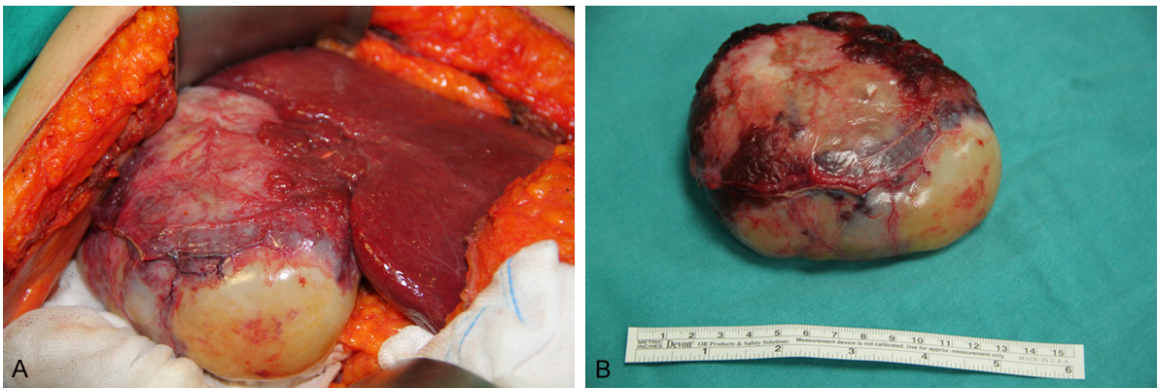

Figure 1. Macrospic view of a giant hemangioma occupying the right lobe of the liver. A. Before resection, B. The specimen.

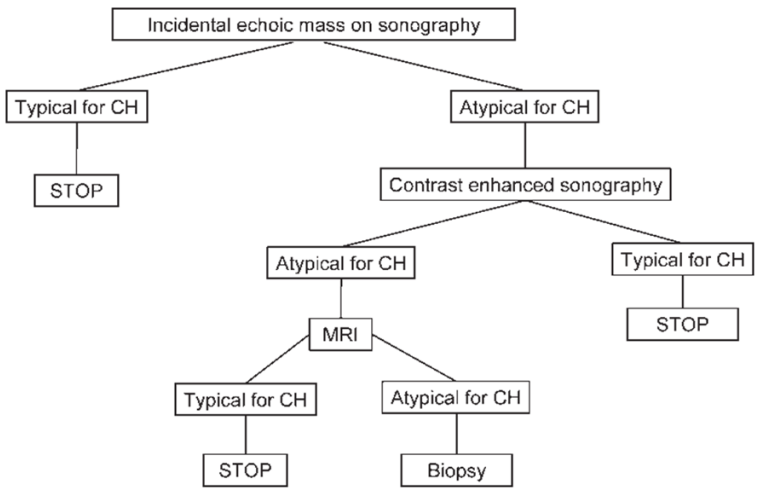

Diagram 1. Suggested imaging strategy for incidentally discovered echoic mass on sonography. CH, cavernous hemangioma [6].

were higher in the resection group during intraoperative period (P = 0.025, P = 0.01, respectively). The study concluded that when the location and the number of hemangiomas are appropriate, enucleation might be good choice of the surgical therapy. Also according to that study if the lesion is located in the inner phase and located near by the hilus of the liver resection may be the choice for the treatment [16].

Size alone should no longer be used as a criterion for resection as recent reports have demonstrated that even large lesions may be safely managed nonoperatively [17, 18]. Liver transplantation has been performed for patients with giant hemangioma and life-threatening coagulopathy secondary to Kasabach-Merritt syndrome, with successful results [19].

Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) occurs in up to 3% of the population and is the second most common solid benign liver lesion after hemangioma and makes up approximately 8% of all primary hepatic tumors [20, 21]. Ninety percent of patients are females in their second and third decades, although cases have been reported in males. Less than 10% of FNH is symptomatic and, in contrast to hepatocellular adenoma, hemorrhage and rupture are rare [20].

In the past, FNH was thought to be either a hamartoma or a neoplasm that forms in response to ischemia. However, more recently, it is considered a nonneoplastic, hyperplastic response to a congenital vascular malformation [22]. Female hormones and oral cantraceptives have been implicated in the development and growth of FNH, but the association is weak and difficult to prove [23]. Most investigators agree that the use of oral contraceptive does not induce the formation of FNH, but it acts only to accelerate the growth of already formed tumors [24].

Focal nodular hyperplasia is usually a small (<5 cm) nodular mass arising in a normal liver. The right lobe of the liver in cured is more than the left side. Lesions are typically well circumscri-

bed but lack a definite capsule. Differentiating FNH from other focal liver lesions, particularly hepatocellular adenoma, remains a challenge. The classical finding of a "central scar" may be absent in approximately 40% of FNH cases [25]. It is unusual for FNH to undergo rapid changes in size and this should call the diagnosis into question. Calcification is a less common finding, occurring in approximately 1.4% of cases [26], and should alert the clinician to the possibility of fibrolamellar hepatocellular carcinoma.

In most patients, FNH presents as an incidental finding at laparotomy or more commonly on imaging studies. If symptoms are noted, they are most often vague abdominal pain, but a variety of nonspecific symptoms have been described. It is often difficult to ascribe these reported symptoms to the presence of FNH, and therefore, other possible causes must be sought [27].

A good-quality three phasic CT scan usually is diagnostic of FNH, on which such lesions appear well circumscribed with a typical central scar [1]. Because of its prominent arterial vascular supply, FNH undergoes marked enhancement during the arterial phase of contrast-enhanced CT, becoming appreciably hyperattenuating relative to the hepatic parenchyma [28].

The management of FNH patients resembles that of hepatic hemangiomas. In asymptomatic patients with FNH, treatment generally includes clinical follow-up to observe for the development of symptoms and radiologic follow-up with US to detect enlarging tumors [29]. Asymptomatic patients mostly remain so over long periods of time. Rupture, bleeding, and infarction are exceedingly rare, and malignant degeneration of FNH has never been reported. Symptomatic patients are thoroughly investigated to look for other pathology to explain the symptoms. Careful observation of symptomatic FNH with serial imaging is reasonable because symptoms may resolve in a significant number of cases. Patients with persistent symptomatic FNH or an enlarging mass need to be considered for resection. Because FNH is a benign diagnosis, resection must be performed with minimal morbidity and mortality [30].

Hepatocellular adenoma

Hepatocellular adenoma [HA] is a rare hepatic tumor that is pathologically characterized by the benign proliferation of hepatocytes. As seen with FNH, HA also occurs predominantly in young women (aged 20-40 years) with a female-to-male ratio of 4:1. Hepatocellular adenomas are usually single, but multiple lesions have been reported in 12% to 30% of cases. The presence of 10 or more adenomas is termed *adenomatosis* which is a condition that is associated with the presence of maturity-onset diabetes of the young (MODY) [31].

Hepatocellular adenoma has significant etiological association with oral contraceptive use in young women [1, 2]. The estimated incidence for longterm contraceptive users is three to four per 100000/year, as opposed to only one per million for non-users or women with less than 2 years of exposure [32].

Hepatocellular adenoma's pathologic features are characterized by a benign proliferation of hepatocytes of unknown origin that may be related to hormone changes. Recent studies have revealed an association between HA and mutations in the hepatocyte nuclear factor-1 (HNF1A) gene [33].

Most of the adenomas are found incidentally. Clinically, up to 50% of patients with HAs may present with a wide variety of symptoms of which right upper quadrant discomfort is the most common (up to 43%) [34]. Palpable mass and severe abdominal pain secondary to rupture or hemorrhage are uncommonly encountered. Rarely, the first presentation of HA can be rather dramatic and life threatening as it is the case in rupture and intraabdominal bleeding. Bleeding and rupture as initial presentation of HA have been reported to be as frequent as 30% [35]. Rare cases of malignant transformation have also been reported (less than 10%), particularly in patients with large or multiple tumors [36].

It has been shown that HAs more than 5 cm tend to bleed, and tumors more than 8 cm tend to undergo malignant change [37]. Hepatocellular adenomas less than 5 cm in size are rarely associated with risk of hemorrhage or malignant transformation and hence can safely be managed conservatively with

serial imaging follow-up [38, 39]. Stopping the offending drugs [OC pills, androgens, barbiturates] and dietary modification as in glycogen storage disease are the recommended initial steps that may help by halting HCA growth and reducing the tendency to bleed. Most small HAs remain stable during surveillance, and a small number of them may disappear [40]. Currently, there are no clear-cut guidelines for the optimal interval and duration of imaging surveillance in HAs. Yearly surveillance with multiphase CT or MRI seems to be the most appropriate strategy, which should probably be continued until menopause [40].

Hemodynamic instability is rarely associated with ruptured HAs, and selective hepatic artery embolization is sufficient to restore hemodynamic stability and to reduce tumor size as well as operative risk during surgery. Embolization may also obviate the need for aggressive surgical resection, which is associated with an increased morbidity [41-43]. Also radiofrequency ablation has been found to be safe and effective in achieving complete tumor ablation in a recently published series of 10 patients with HAs [44]. Behavior of HA during pregnancy has been unpredictable, and resection before a planned pregnancy is usually recommended. Overall, the surgeon must compare the risks of expectant management with serial imaging studies and AFP measurements against those of resection. Most authorities recommend resection because of a very low mortality in experienced hands and the previously mentioned risks of observation. Margin status is not important in these resections, and limited resections can be performed [30].

Nodular regenerative hyperplasia

Nodular regenerative hyperplasia (NRH) (has been referred to by many names in the literature including nodular transformation, noncirrhotic nodulation, and partial nodular transformation) was first defined by Steiner in 1959. It is a rare liver condition characterized by a widespread benign transformation of the hepatic parenchyma into small regenerative nodules [45].

The majority of patients were between 25 and 60 years old at diagnosis, with rare cases in children and even fetuses [46]. According to autopsy studies, the risk of development of NRH and its potential complications increases with age. Sex and ethnicity seem to play no role in development of NRH.

Wide spectrum of systemic diseases and drugs are also associated with NRH such as myeloproliferative disorders, lymphoproliferative disorders, chronic vascular disorders, rheumatologic and collagen vascular diseases [rheumatoid arthritis, Felty's syndrome, polyarteritis nodosa, amyloidosis, and primary biliary cirrhosis], solid organ transplantation [renal and liver transplantation], and use of steroids or chemotherapeutic agents [47].

NRH is a benign disease but it may lead to the development of non-cirrhotic portal hypertension. It comprises 27% of all cases of non-cirrhotic portal hypertension in Europe and about 14% in Japan [48, 49].

Clinically, NRH usually cause no symptoms and are discovered incidentally during imaging studies or surgery. Some patients present mainly with symptoms of portal hypertension such as hepatomegaly, splenomegaly, ascites, or esophageal varices due to the compression of the main portal vein at the hepatic hilum [50]. There are mildly increased liver enzymes, usually alkaline phosphatase, in 11%-25% of patients [51].

Imaging methods have poor sensitivity and specificity for NRH. A diffusely heterogeneous hepatic parenchyma may be the only imaging abnormality. On ultrasound, regenerative nodules are usually not visible due to a small size or isoechogenicity [52]. On computed tomography [CT], regenerative nodules remain isodense or hypodense in both arterial and portal venous phases, distinguishing NRH from focal nodular hyperplasia and adenomas [49]. The significance of magnetic resonance imaging in the diagnosis of NRH is still controversial, although because of its inherent propensity to resolve soft tissue details it may be superior to CT in visualization of regenerative nodules [53].

Macroscopically, NRH is characterized by multiple bulging regenerative nodules in clusters with ranging sizes from 0.1 to 4 cm [54]. Granularity of the hepatic surface may resemble micronodular cirrhosis. However, microscopic features are very characteristic and readily distinguishable from cirrhosis. On the

other hand, NRH and HA share similar benign process and histologic elements and are difficult to be distinguished from each other based on a single-needle biopsy. Multiple biopsies are often helpful as NRH is a diffuse or multinodular process, whereas HA is a solitary process in which the remainder of the liver is normal [47].

Treatment of NRH is directed towards elimination of the causative factor. Concomitant diseases should be treated appropriately and with attention to minimizing drug toxicity. In patients with NRH, the mainstay of management is directed primarily to prevention and treatment of complications related to portal hypertension, i.e. variceal bleeding, the main source of mortality. A portosystemic surgical shunt or transjugular intrahepatic portosystemic shunt may offer a significant therapeutic benefit, especially in the case of severe recurrent esophageal variceal hemorrhage [55]. Rarely, patients may progress to liver failure and finally require liver transplantation [56].

Hepatic epithelioid hemangioendothelioma

Hepatic epithelioid haemangioendothelioma (HEHE) is a rare multifocal vascular tumour that can develop at any age, with a female preponderance. Although vinyl chloride, liver trauma and exogenous hormones have come under suspicion, the aetiology is unclear [57].

Patients with HEHE are usually asymptomatic or have nonspecific symptoms of weight loss and right upperquadrant pain. In rare cases, jaundice and hepatic dysfunction may be noted due to replacement of liver parenchyma by the tumor [58].

The appearance of BHE on conventional US, CT and MRI is that of an inhomogenous mass that might reveal cystic areas [59]. Hepatic angiography provides a good diagnostic accuracy but it is replaced widely by colour Doppler US and angio-MRI. Percutaneous biopsy is contraindicated because of the associated bleeding risk.

There are few treatment options. Chemotherapy and radiotherapy yield no improvement in survival [58]. And surgical excision is usually impossible because of the multifocal nature of the disease; indeed, attempted resection may provoke aggressive regrowth. Orthotopic liver transplantation offers a possibility of long-term cure [60] although some patients do well without any treatment. Out of nearly 40000 liver transplants undertaken in Europe up to 2001, only 11% were for cancers and 66 of these were for epithelioid haemangioendothelioma. 5-year survival is estimated at 55-71% [61].

Bile duct adenoma

Extrahepatic biliary tree benign masses account for only 6% of all tumors of the bile ducts. Of these, the 2 most commonly found are papillomas and adenomas. Adenomas arise from the epithelial lining of duct, may be either tubular, papillary, or tubulopapillary. Their location can vary from the distal common bile duct to the intrahepatic bile ducts. They are not considered premalignant lesions, however, the natural history of the tumor progression and their rate of malignant transformation remains unknown [62-64].

Because of their tendency to remain dormant for long periods, these tumors should be attended by a favorable prognosis. There are no specific symptoms or imaging findings, and the diagnosis of a papillary adenoma, especially differentiating between this condition and a malignant neoplasm is difficult [65].

Bile duct adenoma have no malignant potential but may require excisional biopsy to allow differentiation from the bile duct proliferations found in FNH as well as from some poorly differentiated adenocarcinoma of the biliary tract type. Once diagnosed no treatment is required [recommendation strength: D] [66].

Oral contraceptives & benign hepatic tumors

The liver is morphologically and biochemically altered by sex hormones, including estrogens and androgenic steroids. In vitro and in vivo data indicate estrogens stimulate hepatocyte proliferation; whereas antiestrogens, such as tamoxifen, inhibit hepatocyte proliferation.

Hepatic adenoma and focal noduler hiperplasia have relation with the useage of oral contraceptives where as hemangiomas have no relationship. Severel experiments done about this relation in the literature.

With reference to Hepatic adenomas, in a case-control study from the USA, 82% of 34 cases

had ever used OC versus 56% of 34 controls [67]. In another USA study, 91% of 74 cases of HA and 45% of 220 controls had used OC for >12 months [68]. Like Hepatic adenomas, focal noduler hiperplasia patients also have been searched about the usage of oral contraceptives. A study from Italy concluded that there was a clear trend between oral contraception usage and the incidence of focal nodular hyperplasia [69]. However, this data was controverted by a study by Mathieu and colleagues who examined five separate forms of oral contraceptives varying from high-dose estrogens to pure progesterone therapy. This study found no correlation between extrinsic estrogens and focal nodular hyperplasia [70].

In 2008, the WHO expert working group reviewed this evidence to evaluate current medical eligibility criteria for hormonal contraceptive use in women with liver tumors. The expert working group recommended that women with FNH can generally use hormonal contraception, as the advantages to use outweigh potential risks. For women with HA or carcinoma, ethinylestradiol-containing regimens present an unacceptable risk to health (WHO Category), while all other formulations, including progestogen-only contraception, generally should not be used (WHO Category 3) [71].

Disclosure of conflict of interest

None.

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