Review Article

INDICATION AND TREATMENT OF BENIGN HEPATIC TUMORS

Indicação e tratamento dos tumores benignos do fígado

Júlio Cezar Uili **COELHO**, Christiano M.P. **CLAUS**, Priscilla **BALBINOT**,
Rodrigo **NITISCHE**, Victor Mamoru **HAIDA**

From the Digestive Tract Surgery Department, Division of Health Sciences and Liver Transplantation Service, Hospital de Clínicas, Federal University of Parana, Curitiba, PR, Brazil.

ABSTRACT - ***Background*** – Benign hepatic tumors occur in 9% of the population. The majority is diagnosed in asymptomatic patients during routine imaging exams. ***Aim*** – To present the main aspects of indications and treatment of benign hepatic tumors. ***Methods*** - A review was conducted based on literature search in PubMed, Scielo and Bireme crossing the headings liver cancer, hemangioma, adenoma and focal nodular hyperplasia. Was selected studies of surgical techniques and added the experience of the authors. Hemangioma is the most common hepatic tumor. It is identified in 5% to 7% of the autopsies. It is more common between the 3rd and 5th decades of the life and in female. This tumor may increase in size during pregnancy and with administration of sexual hormones. Although the etiology is not known, it is related with sexual hormones. Complications include inflammation, coagulopathy, bleeding and compression of neighboring organs. Spontaneous rupture is exceptional, with only 35 cases described in the literature. Adenoma and focal nodular hyperplasia are more common in young women, aged 20 to 40 years. Adenomas are treated by hepatic resection due to the risk of malignant transformation and bleeding. Focal nodular hyperplasia does not require treatment. ***Conclusions*** – The most common benign hepatic tumors are hemangioma, focal nodular hyperplasia, and adenoma. The differentiation between benign and malign tumors is usually based on clinical data and imaging exams. Hemangioma and focal nodular hyperplasia usually do not need treatment, while adenoma requires hepatic resection due to the risk of malignant transformation and bleeding.

Correspondence:
Júlio Cezar Uili Coelho,
e-mail: coelhojcu@yahoo.com.br

RESUMO - ***Introdução*** – Os tumores hepáticos benignos ocorrem em 9% da população. A grande maioria dessas neoplasias é diagnosticada em pacientes assintomáticos durante a realização de exames de imagem de rotina. ***Objetivo*** - Apresentar os principais aspectos das indicações e tratamento dos tumores hepáticos benignos. ***Métodos*** - Foi realizada revisão de literatura baseada em pesquisa no PubMed, Bireme e Scielo cruzando os descritores neoplasia hepática, hemangioma, adenoma e hiperplasia nodular focal. Foram selecionados, estudos de técnicas cirúrgicas e acrescentada a experiência dos autores. O hemangioma é o tumor hepático mais comum, sendo identificado entre 5% e 7% das necropsias. É mais comum nas mulheres entre as 3ª e 5ª décadas da vida e pode aumentar de tamanho na gravidez e com a administração de estrogênios. Apesar de não estabelecida, a sua causa está relacionada com os hormônios sexuais. As complicações incluem inflamação, coagulopatia, sangramento e compressão de estruturas vizinhas. Rotura espontânea é excepcional, com somente 35 casos descritos na literatura internacional. O adenoma e a hiperplasia nodular focal predominam no sexo feminino e na faixa etária de 20 a 40 anos. Enquanto o primeiro requer ressecção hepática pelo risco de sangramento e malignização, o segundo deve ter conduta expectante. ***Conclusões*** - Os tumores hepáticos benignos mais comuns são em ordem decrescente de frequência o hemangioma, hiperplasia nodular focal e o adenoma. A diferenciação entre tumores benignos e malignos é geralmente realizada com segurança com base nos dados clínicos e nos exames de imagem. O hemangioma e a hiperplasia nodular focal geralmente tem conduta expectante, enquanto que o adenoma requer ressecção pelo risco de hemorragia e de transformação em carcinoma.

INTRODUCTION

The liver tumors are very common occurring in 9% of the population, but, fortunately, most are benign, asymptomatic and found accidentally on imaging[1,2,3,4,5]. However, malignant tumors are serious and are increasing in incidence. Despite its high mortality rate for the delayed diagnosis, the cure rate is high when the diagnosis is established early.

Liver tumors are divided into benign and malignant. The most common benign tumors are hemangioma, adenoma and focal nodular hyperplasia[6,7,8,9,10,11,12]. The most common malignancy is hepatocellular carcinoma, followed by cholangiocarcinoma. Table 1 shows the classification of benign liver tumors[13,14,15,16,17].

TABLE 1 - Histological classification of benign liver tumors

EPITHELIAL ORIGIN	Tumor
Hepatocyte	Hepatocellular adenoma
	Multiple adenomatosis
	Focal nodular hyperplasia
	Nodular regenerative hyperplasia
Bile Cells	Bile duct adenoma
	Biliary hamartomas (von Meyenburg complex)
NON-EPITHELIAL	
Mesenchymal	Hemangioma
	Angiomyolipoma
	Lipoma, myelolipoma
Other	Inflammatory pseudotumor

With the routine use of abdominal imaging, benign liver tumors are being identified more frequently[18,19,20,21,22,23]. The differentiation between benign and malignant tumors is essential and can usually be safely based on clinical data and imaging studies[24,25,26,27]. Liver biopsy is rarely necessary to differentiate benign from malignant. The objective of this paper is to present the main aspects of the indications and treatment of benign liver tumors.

Hemangioma

Hemangioma is the most common liver tumor, identified from 5% to 7% of autopsies. More frequent between the 3rd and 5th decades of life and women and can increase in size during pregnancy and the administration of estrogens.

The cause of this neoplasm is still unclear. It is speculated the role of sex hormones, due to the following observations: 1) presence of estrogen receptors in some hemangiomas; 2) higher prevalence in women by a ratio of 4:1 to 6:1; 3) increase in size occurs more often at puberty, pregnancy, oral contraceptives or sex hormones (estrogens and androgens).

Most hemangiomas are unique and measuring <4 cm in diameter. Only 10% are multiple and can reach dimensions of up to 27 cm in diameter. Giant hemangioma is defined when has ≥ 4 cm in diameter. The size of the vast majority remains unchanged over time.

Most hemangiomas are asymptomatic, but large lesions may cause abdominal discomfort or pain. Complications occur rarely and include: 1) inflammation[24], 2) coagulopathy, 3) bleeding, 4) compression of neighboring structures.

Rupture of hepatic hemangioma with subsequent bleeding is exceptional. By 2009, in PubMed/Medline there were only 35 cases of spontaneous rupture of hepatic hemangioma[5,12,23,26]. Considering the high prevalence of this tumor, the possibility of rare spontaneous rupture, even in giant lesions, should not be considered as indications for treatment. The liver tumors with a greater chance of bleeding are the adenoma and hepatocellular carcinoma.

Tumor growth or thrombosis can cause more severe clinical manifestations. Rarely is the Kasabach-Merritt syndrome, characterized by thrombocytopenia and consumption coagulopathy.

The diagnosis is usually established with certainty with the imaging. Computed tomography and magnetic resonance imaging usually establish the diagnosis, the typical pattern of impregnation nodular peripheral and discontinuous with gradual increase in the impregnation, and the homogenization trend is observed in later stages. In addition, magnetic resonance imaging, hemangiomas typically have a high signal, ie, is bright in T2-weighted sequences. Scintigraphy with labeled red blood cells shows high accuracy for hemangiomas > 2 cm, but is rarely necessary.

Most hemangiomas do not need treatment, even large ones. There is no scientific support to stop the use of hormonal contraceptives or avoid pregnancy in patients with hepatic hemangioma, including the giants. Once the diagnosis of hemangioma is done, there is no indication of periodic monitoring exams.

Complications related to hepatic hemangioma are much more frequent after surgery than expectant management. Although the rates of complications of hepatectomy have been reduced sharply in recent decades, especially in specialized centers, bile leaks, bleeding, abdominal collections, systemic complications (thromboembolism, pneumonia) and mortality from 0.5% to 1% are reported in large series. These complications make surgical routine indication of hepatectomy unacceptable in patients with hemangioma (benign disease with minimal symptoms or complications), except in special cases.

The hemangioma resection is indicated in rare cases when it is impossible to exclude malignancy and in the presence of important clinical manifestations,

significant growth or Kasabach-Merritt syndrome. Resection can usually be done by enucleation of the hemangioma, but occasionally anatomical liver resections may be indicated. Comparative studies of anatomical resection and enucleation suggest that enucleation is associated with a lower rate of abdominal complications, especially biliary fistula. One possible explanation for this difference is that the hemangioma compress the adjacent liver tissue and enucleation inside the fibrous tumor tissue prevents injury to the bile ducts and vessels.

Although exceptional, the spontaneous rupture of hepatic hemangioma is associated with high mortality, ranging from 60% to 75%. In a recent review of the literature, Corigliano et al reported a mortality rate of 36.4% of patients undergoing surgical treatment. Surgical excision is the treatment most often used 5. Arterial embolization of the ruptured vessel has also been successfully used[12,26].

Adenoma

It is uncommon benign tumor of the liver, which is predominant in females (90% of cases) between the ages of 20 and 40 years. Its size ranges from millimeters to mass occupying almost the entire liver. The adenoma has a high propensity for bleeding, which can be intratumoral or to the abdominal cavity. Some adenomas can transform into hepatocellular carcinoma (<10%).

This cancer is very rare, but after the introduction of oral contraceptives in the 1960s, several cases have to be described. Currently, it is accepted that the cause is related to the ingestion of hormones, especially hormonal contraceptives. The annual incidence of hepatic adenomas is about 1 per 1 million women who never used oral contraceptives, compared to 30 to 40 per million in women using these drugs for a long time[22]. It can also occur in men receiving androgen. Some cases are associated with conditions of abnormal metabolism of carbohydrates, such as familial diabetes mellitus, glycogen storage disease type I and III and galactosemia. The incidence of hepatic adenomas is 50% in patients with glycogen accumulation type I and type III in 25%. These adenomas are more common in males before the 3rd decade of life[14].

Most hepatic adenomas are found incidentally during the course of routine imaging. Clinical manifestations are common and include abdominal pain and hypotension secondary to intrabdominal hemorrhage (hypovolemic shock) caused by rupture of the adenoma. The risk of bleeding is higher during pregnancy, history of prolonged use of oral contraceptives, multiple adenomas and large lesions and subcapsular location. On physical examination, can be palpate the enlarged liver or tumor.

Laboratory tests are usually normal, but can rise in patients with lesions that had very large or bleeding. Alpha-fetoprotein is normal, but can rise in cases of malignancy.

CT and MRI show rapid uptake of contrast material by the tumor in the arterial phase, followed by rapid washing of contrast material into the portal and equilibrium phases. These findings are similar to focal nodular hyperplasia. However, the adenoma may present increased signal on MRI of fat, compared with focal nodular hyperplasia. Moreover, a quarter of focal nodular hyperplasia has a characteristic central scar on CT and MRI.

Treatment consists of withdrawal of hormonal contraceptives and resection of tumors ≥ 4 cm by the possibility of bleeding and malignant transformation. Lesions <4 cm can be observed initially due to the low rate of bleeding and malignancy. These patients should not use more sex hormones, especially contraception and should avoid pregnancy. Although some studies have shown regression of a few adenomas, the majority does not show regression of the lesion after discontinuation of oral contraceptives. These patients should undergo imaging control periodically.

The surgical procedure should be performed as the location and size of the tumor and may be: enucleation or anatomical segmental liver resection. In most patients, is the best option or anatomical segmental resection, which can be performed via open or when available, laparoscopic technique. Although malignant transformation occurs in up to 10% of adenomas, there is no need for extensive resection margin due to the fact that malignant cells are confined to the tumor in most cases. However, the evidence of more extensive malignancy, treatment should be similar to that of hepatocellular carcinoma.

Liver transplantation may be indicated in rare cases of glycogen storage disease and liver adenomatosis.

Liver adenomatosis

It was first described by Flege et al.[8] in 1985 as a distinct entity, characterized by the presence of 10 or more adenomas spread in the liver parenchyma[8,11]. Except for the presence of adenomas, the hepatic parenchyma is normal, including absence of disease accumulation of glycogen.

Some authors suggest that the diagnosis of liver adenomatosis should be established when the number of adenomas is ≥ 4 or ≥ 5, since rarely patients with liver adenoma have more than four nodes[11].

The vast majority of cases occur in young women (90%) in the 3rd and 4th decades of life. However, sporadic cases have been reported in adolescents aged 13 years and seniors over 60 years of age[25]. Half of the 24 women with this condition use oral contraceptives[25].

The etiology remains unclear and several predisposing factors have been described. Although several authors have observed association of liver adenomatosis with abnormal hepatic circulation, this hypothesis lacks scientific proof. Some authors have suggested that an increase or decrease in portal or hepatic blood flow could cause hepatocyte hyperplasia and subsequent formation of liver nodules.

Although estrogen receptors have been identified in normal hepatocytes and adenomas, the exact role of sex hormones in tumorigenesis and progression of these lesions remains unknown. Ribeiro et al.[21] performed immunohistochemical analysis of estrogen and progesterone receptors in eight cases of liver adenomatosis. Six of them had adenomas with both negative and positive receptors for estrogen and progesterone. However, tamoxifen therapy (antiestrogen) and oforectomy were not effective in the treatment of adenomas.

Several more recent studies show an association of liver adenomatosis with diabetes, suggesting a genetic cause, at least in some patients.

Patients may be completely asymptomatic and the diagnosis confirmed incidentally by imaging. However, most patients have complications described as acute or chronic abdominal pain due to hepatomegaly, intratumoral hemorrhage or necrosis. Some patients may present with intraperitoneal hemorrhage due to rupture of an adenoma, causing hypovolemic shock associated with abdominal pain. In the literature, the rate of intratumoral and intraperitoneal bleeding ranges from 46% to 63% of the cases described[25]. Intraperitoneal bleeding was reported in 24% of patients in symptomatic patients. However, the true prevalence of bleeding is difficult to determine, because symptomatic patients are more likely to seek medical attention, may cause a statistical bias.

Transformation to carcinoma may occur in up to 10% of patients. The diagnosis may be suspected by elevated alpha-fetoprotein or an increase in tumor imaging. There are no established factors that predispose to malignant transformation.

The diagnosis is established by imaging, usually CT or MRI. Histologic examination is usually necessary to confirm the diagnosis. Laboratory tests are usually normal or alkaline phosphatase and glutamyl are mildly or moderately high due to the presence of multiple lesions in liver parenchyma.

There is still no consensus on treatment. The therapeutic options are indicated by the likelihood of developing complications. Although this condition is usually benign, fatal complications with hypovolemic shock and transformation to carcinoma may occur. Bleeding occurs in half to 2/3 of the cases described in the literature. Malignant transformation occurs in less than 10% of cases.

Although the role of sex hormones in the evolution of liver adenomatosis be controversial, it is prudent to suspend the administration of these substances. Antiestrogen therapy (tamoxifen and oforectomy) seems to be ineffective and should not be indicated.

Hepatic resection in patients with adenomatosis may present high risk of complications due to the large number of diffuse lesions that require resection. In general, resection is indicated in patients with severe symptoms, complications and those with lesions ≥ 5 cm, regardless of the presence of symptoms or complications.

Due to the risk of complications, including bleeding and malignancy be directly related to adenoma size, all with ≥ 5 cm should be resected. Ribeiro et al. reported that the risk of re-bleeding is lower in patients with adenomas ≥ 5 cm who underwent resection of the tumor[21]. Thus, these authors recommended that tumors ≥ 5 cm are resected even in asymptomatic patients to reduce the possibility of bleeding and development of symptoms or other complications.

In patients with bilateral tumors ≥ 5 cm, resection should be performed in two steps. Initially, resected tumors ≥ 5 cm of a lobe, after a few weeks followed by resection of tumors ≥ 5 cm of the remaining lobe. No need for resection of smaller tumors. After resection, patients should be evaluated periodically with serum alpha-fetoprotein and imaging exam to make sure that small adenomas do not show significant growth or turn into cancer.

In patients with intraperitoneal hemorrhage is indicated selective arteriography of the hepatic artery embolization with the resection of the bleeding vessel or hemorrhagic nodules, depending on the patient's age, experience, service and availability of angiography.

Living donor liver transplantation or death is indicated in rare cases where the patient has a complication, which can not be treated with hepatic resection. Another indication is the patient with extensive bilateral disease that has significant limitations in their quality of life, especially in young women who desire pregnancy[4]. The transplant is not indicated to prevent bleeding and development of carcinoma. Tumor recurrence in the transplanted liver can occur. In Brazil, patients with liver adenomatosis may also be submitted to liver transplantation. When indicated the transplant, these patients receive the MELD score (Model for End-stage Liver Disease) 20. If they are not transplanted in three months, the score will automatically switch to 24 and after six months to 29.

Focal nodular hyperplasia
As the name suggests, this condition is not

cancer but focal nodular hyperplasia of the liver. It is the 2nd most common benign tumor of the liver and, despite being more common in women of reproductive age, the cause is not related to the use of hormonal contraceptives. The vast majority of lesions are asymptomatic.

The importance of this lesion is its differentiation from adenomas or, more rarely, malignant tumors. Most injuries can be diagnosed by MRI or CT. The presence of central scar with the characteristics of present high signal intensity on T2 MRI does not show enhancement in the arterial phase and show enhancement in the equilibrium phase or delayed after the intravenous administration of contrast is suggestive, but not present in most lesions. Occasionally, scintigraphy with sulfur or tin colloid can be useful because this tumor contains Kupffer cells, which can capture (50% of lesions) the radiomarker. The benign tumors do not contain Kupffer cells and therefore do not capture sulfur or colloid tin.

Due to not cause bleeding and having no risk of malignancy, the indication of resection is limited to symptomatic masses, which are growing or in doubt.

Hepatic angiomyolipoma

It is a rare benign mesenchymal neoplasm, first described by Ishak in 1976[19]. This tumor is composed of variable portions of three components: fat tissue, smooth muscle cells and blood vessels. This cancer often occurs in the kidney and rarely in the liver and has no malignant potential.

It occurs predominantly in women of any age between 26 and 86 years old. Most lesions are diagnosed with >5 cm in diameter; is well circumscribed and is identified incidentally on imaging. Although the vast majority of lesions are asymptomatic, large tumors can cause symptoms due to mass effect with compression of neighboring structures. Rupture of the tumor is very rare.

When the diagnosis is established with certainty, treatment is usually expectant. Liver resection is indicated in cases of significant clinical manifestations, growth of the lesion and diagnosis doubts.

CONCLUSIONS

Most liver tumors are benign, and occur in 9% of the population. The most common benign liver tumors, in decreasing order of frequency are hemangioma, focal nodular hyperplasia and adenoma. The differentiation between benign and malignant tumors is usually performed with security based on clinical data and imaging studies. However, in some cases, the diagnosis is established only after resection of hepatic mass. Hemangioma and focal nodular hyperplasia are usually watchful waiting, whereas the adenoma usually requires resection of bleeding and the risk of transformation into carcinoma.

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