

Treatment of Hepatic Adenomatosis

Claire Meyer¹ · Mauricio Lisker-Melman¹

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Abstract Hepatic adenomatosis and hepatocellular adenomas share risk factors and the same pathophysiologic spectrum. The presence in the liver of 10 hepatocellular adenomas defines hepatic adenomatosis. The diagnosis may be established incidentally during a liver radiologic examination in the asymptomatic patient, or after associated right upper quadrant pain, hepatomegaly or liver test abnormalities. Upon the diagnosis of hepatic adenomatosis or either of its life-threatening complications—hemorrhage and progression to hepatocellular carcinoma—consideration should be given to potential medical, radiologic, and surgical interventions including observation (estrogen and androgen withdrawal), resection, transarterial embolization, radiofrequency ablation, and liver transplantation. The management of patients with hepatic adenomatosis can be challenging. These patients should be ideally referred to centers with expertise in the management of liver diseases.

Keywords Hepatic adenomatosis · Liver adenomatosis · Treatment of hepatic adenomatosis · Management of liver adenomatosis

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✉ Mauricio Lisker-Melman
mlisker@dom.wustl.edu
Claire Meyer
cmeyer@dom.wustl.edu

¹ Division of Gastroenterology, Washington University School of Medicine, 660 South Euclid Ave, Box 8124, St. Louis, MO 63110, USA

Introduction

Balancing the real risk of life-threatening complications in hepatic adenomatosis—hemorrhage and progression to hepatocellular carcinoma—with the hazard of invasive interventions on numerous benign liver lesions presents a management challenge. Here, we review the diagnosis and classification of hepatic adenomatosis and the therapeutic options for this unusual liver entity.

Background

Definition

Hepatic adenomatosis is characterized by multiple adenomas in an otherwise-normal liver [1]. The minimum number of adenomas required to for a diagnosis of adenomatosis was originally arbitrarily defined as 10 [1], and this remains the most widely used definition, although in more recent years, a minimum number of 4 to establish the diagnosis has been proposed [2]. While hepatic adenomatosis has historically been regarded as an entity distinct from solitary hepatocellular adenomas, the two conditions are now thought to exist on the same pathophysiologic spectrum, with similar genetic alterations and clinical complications [3, 4].

Clinical History and Presentation

Known risk factors for the development of hepatocellular adenomas include exogenous (or elevated levels of endogenous [5•]) estrogen/progesterone [6] or androgens [7], glycogen storage diseases [8•], maturity-onset diabetes of the young type 3 (MODY3) [9], iron-overload disorders [10], obesity and the metabolic syndrome [11, 12], and vascular

abnormalities [13]. In men, excessive alcohol and tobacco use are also recognized risk factors [14]. Although patients with a history of glycogen storage disease or exogenous estrogen or androgen use were excluded from the original description of hepatic adenomatosis, given the subsequent findings of the same cellular and molecular processes as in cases with fewer adenomas, it is likely that risk factors are the same for both conditions, although perhaps to varying degrees.

Patients with hepatic adenomatosis may present with abdominal pain, hepatomegaly, and/or elevated liver enzymes—in this case, alkaline phosphatase and gamma-glutamyltransferase. In asymptomatic patients, the diagnosis is determined after the incidental finding of multiple adenomas on imaging [13]. While hemorrhage within an adenoma may be asymptomatic, bleeding (either intratumoral or intraperitoneal due to adenoma rupture) may be the initial presentation; it is characterized by abdominal pain, an acute increase in abdominal girth (in the case of intraperitoneal bleeding), decrease in hematocrit, and in some cases, hemodynamic instability [15•]. Hemorrhage is the most common complication of hepatocellular adenomatosis, reported in 42–62.5 % in case series [1, 2]. The risk of progression to malignancy (hepatocellular carcinoma), on the other hand, is estimated to be less than 10 % [16].

Diagnosis and Classification

The diagnosis of hepatic adenomatosis may in some cases be made based on CT or MR imaging or suspected based on ultrasound. If active bleeding is suspected, CT angiography can provide the most timely information for patients who may need urgent intervention [15•]. Otherwise, in the absence of contraindications, contrast-enhanced MR has the advantage of being able to distinguish between some subtypes of adenomas [17].

Based on imaging findings, hepatic adenomatosis can be further classified as massive (in which lesions enlarge and deform the contour of the liver) or multifocal (multiple smaller lesions with a normal liver size and contour); the former is considered more difficult to manage surgically [18]. Imaging findings relevant to whether resection may be indicated include size of the lesions, evidence of bleeding, and/or changes suggestive of malignant transformation. In addition, the location of the lesions and the amount of normal-appearing liver remaining inform whether resection is feasible [19].

Current guidelines from the American College of Gastroenterology recommend that “biopsy should be reserved for cases in which imaging is inconclusive and biopsy is deemed necessary to make treatment decisions [5•].” Biopsy can distinguish between the four subtypes of hepatic adenomas: hepatocyte nuclear factor 1-alpha (HNF1A) inactivated, inflammatory, B-catenin activated, and unclassifiable (those lacking the characteristic findings of the other subtypes) [8•], as

shown in Table 1. Variations of inflammatory adenomas include those with activated B-catenin [20] and those with telangiectatic features (formerly termed telangiectatic focal nodular hyperplasia) [5•]. When molecular testing for mutations in the genes encoding HNF1A and B-catenin is not feasible, these subtypes may be identified based on immunohistochemistry showing absent liver fatty acid binding protein (L-FABP) in the case of inactivated HNF1A or B-catenin accumulation in the nucleus and increased cytoplasmic glutamine synthase in the case of activated B-catenin [20, 21]. Nuclear accumulation of B-catenin may also be seen due to mutation of the APC gene in hepatocellular adenomas in patients with familial adenomatous polyposis (FAP), and hepatic adenomatosis due to inactivated HNF1A has also been reported in an FAP patient [8•]. Notably, activated B-catenin may be present in some but not all adenomas in a given patient [21]. Risk of progression to malignancy is lower in HNF1A-inactivated adenomas and higher in those with activated B-catenin, while telangiectatic adenomas have a high risk of bleeding [5•, 8•].

Management

General Considerations

Once the diagnosis of hepatic adenomatosis is established, estrogens and androgens should be withdrawn or avoided given the increased risk of bleeding associated with their use [5•, 16]. In the absence of evidence of benefit from estrogen deprivation by oophorectomy or tamoxifen administration, these measures are typically not recommended [2]. Guidelines suggest that “pregnancy is not generally contraindicated in cases of hepatocellular adenoma <5 cm [5•].” Regarding the safety of anticoagulation and/or antiplatelet agents in patients with hepatic adenomatosis, there is little to guide clinicians, though one case series of patients with spontaneous liver bleeding found rates of anticoagulant and antiplatelet use similar to that in the general population [15•, 22]. Finally, genetic counseling should be considered in patients with hepatic adenomatosis related to inactivated HNF1A, which is a germline mutation in some cases and can be associated with MODY3 [16].

Observational Management

Asymptomatic patients with hepatic adenomatosis whose largest lesion is ≤ 3 cm, not increasing in size on serial imaging, and without high-risk features on biopsy or imaging (see “Resection,” below) are considered at low risk of complications (bleeding or malignant transformation) and appropriate

Table 1 Hepatic adenomas

Adenoma type	Percentage of all adenomas	Mutation	Clinical association	Radiology	Histochemistry
Hepatocyte nuclear factor 1 alpha	30–40 %	HNF1A gene	Familial adenomatosis Intense steatosis Maturity-onset diabetes of the young type 3	Diffuse signal dropout on T1 weighted sequence	Loss of liver fatty acid binding protein
Beta catenin activated	10–15 %	Beta catenin gene	Males High risk of malignancy Mutation also present in subset of inflammatory adenomas	No specific radiologic characteristics	Glutamine synthase positive Nuclear beta catenin positive
Inflammatory	40–50 %	Genes IL6ST/gp130 GNAS STAT3 Unknown mutation	Inflammatory syndrome with anemia Castleman Disease McCune-Albright Syndrome	Intense signal on T2 weighted sequence and enhancement in portal venous phase	Cytoplasmic overexpression of serum amyloid A and C-reactive protein
Unclassified	10 %	Undetermined	Oral contraception as described for other adenomas	No specific radiologic characteristics	–

References: [20, 33]

for observational management with serial imaging and measurement of alpha fetoprotein (AFP) [2, 23].

Imaging (CT or MR, with intravenous contrast) and AFP should be performed at least yearly; ACG guidelines suggest surveillance every 6 months for 2 years following diagnosis and yearly thereafter [2, 5•, 13]. AFP alone is not sufficient as it may remain normal even in cases of malignancy [8•]. This observation strategy is also applicable to patients who have had a large adenoma resected but have smaller adenomas remaining elsewhere in the liver [2]. Although 5 cm is often cited as the size criteria for more aggressive treatment, some have suggested resection of any lesions >3 cm that are easily amenable to surgery [23]; the most appropriate management of lesions between 3 and 5 cm is not well established [24] and should be individualized based on patient and tumor characteristics.

Resection

Resection can be considered in symptomatic patients, those with lesions 5 cm or larger (given higher risk of bleeding or malignant transformation), and those with lesions with a size increase of 1 cm or more on serial imaging [2, 5•, 24]. In addition to size, the presence of high-risk features on imaging or biopsy should prompt the physician to consider resection. These features include evidence of abnormal B-catenin, telangiectatic or unclassified subtypes, and hypervascularity [5•, 8•, 25]. In addition, males with hepatic adenomatosis are at higher risk of complications, so resection of small lesions (<5 cm) could be considered in this population [8•]. The finding of dysplasia or atypia on biopsy of a hepatocellular adenoma should also prompt consideration of resection, as this does not regress with withdrawal of exogenous

steroids, and may progress to malignancy even if the size of the lesion decreases on subsequent imaging [8•]. The finding of malignant transformation (hepatocellular carcinoma) on biopsy or imaging in the setting of hepatic adenomatosis requires aggressive management, as detailed elsewhere [26].

Transarterial Embolization

For actively hemorrhaging lesions in hepatic adenomatosis, management similar to that recommended for bleeding liver tumors in general is likely applicable, given that hepatic adenomas constitute a substantial proportion of tumors in case series of bleeding (40 % in one series, for example [22]), and recent evidence suggests that management considerations in cases of adenomatosis and solitary or few adenomas are similar [4]. Transarterial embolization (TAE) is considered to be the first-line treatment for active bleeding and is successful in achieving hemostasis in more than 80 % of cases; in cases where embolization cannot be performed, surgical hemostasis (packing for 24–72 h) is an alternative [15•]. Poor outcomes from emergent liver resection make this a treatment choice of last resort, if at all, for persistent bleeding [4, 15•]. For actively hemorrhaging lesions successfully treated with embolization, elective liver resection can be considered after 3–6 months, when hematoma resorption allows for less-extensive resection with fewer complications [4, 15•].

In non-bleeding adenomas, embolization is an option in cases where resection is indicated based on the criteria outlined above but cannot be performed due to patient or tumor factors (i.e., comorbidities, difficult-to-resect locations) [5•]. In addition, TAE can be considered as a less invasive option in pregnant patients for whom resection would otherwise be indicated [27]. In highly vascular tumors, pre-operative embolization

may be performed in an effort to decrease surgical bleeding risk [25]. In case series, embolization has most often been performed for patients with multiple lesions requiring treatment, likely due to the fact that resection of multiple tumors may not be feasible given the need to retain at least 20 % of the functioning liver [19, 25]. Risks of TAE include treatment failure, post-embolization syndrome (fever and abnormal liver function tests), and the possibility of non-absorbable embolization materials making future hepatic surgeries more difficult [15•].

Radiofrequency Ablation

Radiofrequency ablation (RFA) for hepatocellular adenoma has been described and, like TAE, may lead to a decrease in the size of lesions [27]. In general, RFA and TAE can be considered in the same setting—i.e., cases where resection is indicated but not feasible due to characteristics of the patient or the lesions. In one case series of 18 patients, 50 % required more than one session of RFA [28].

Liver Transplantation

Hepatocellular adenomatosis is a rare indication for liver transplantation; a 2005 review found 17 case reports in the literature [29], with at least six cases reported since then [4, 19, 24, 30–32]. It can be considered as one of the treatment options for hepatocellular carcinoma in cases where adenomatosis progresses to malignancy. It has also been reported in cases of bleeding in hepatocellular adenomatosis too extensive to resect and in cases of significant tumor re-growth following resection [13, 19].

Conclusions

The management of hepatic adenomatosis—the presence of multiple adenomas in an otherwise-normal liver—is driven by the assessment of the risk of its primary complications: hemorrhage and progression to hepatocellular carcinoma. Risk assessment requires cross-sectional imaging to determine the size, vascularity, and subtype of lesions. In some cases, biopsy is needed to determine subtype and may also disclose the presence of atypia or dysplasia. Even in those cases deemed to be low risk, the risk of occult or evolving malignancy warrants close observation with CT or MR imaging and AFP measurement at least yearly. Resection is indicated for lesions 5 cm or larger, as well as symptomatic patients and those with lesions with high-risk features on imaging or biopsy. Transarterial embolization and radiofrequency ablation are options in cases where resection is indicated but not practicable due to patient comorbidities or the location of the lesion(s). Liver transplantation is an option in rare cases of significant complications from unresectable adenomas.

Compliance with Ethics Guidelines

Conflict of Interest Claire Meyer reports NIH support under award number T32DK007130. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Mauricio Lisker-Melman is a member of the Speaker Bureau of Gilead, AbbVie, and Simply Speaking.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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