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Genetics and Imaging of Hepatocellular Adenomas: 2011 Update[1]

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CME FEATURE

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LEARNING OBJECTIVES FOR TEST 2

After completing this journal-based CME activity, participants will be able to:

■ Describe a current update of genotype-phenotype classification of hepatocellular adenomas.

■ Explain the correlation of MR imaging findings with genotype-phenotype tumor features.

■ Discuss management implications of the current classification of the subtypes of hepatocellular adenomas.

INVITED COMMENTARY

See discussion on this article by Ros and Goodman (pp 1543–1545).

TEACHING POINTS
See last page

Hepatocellular adenomas are benign liver neoplasms with specific but varied histopathologic findings and tumor biology. The results from recent studies of the pathologic and genetic basis of hepatocellular adenomas provide important insights into the pathogenesis and molecular changes, as well as the putative oncologic pathways used by diverse adenoma subtypes. On the basis of the genetic and pathologic features, hepatocellular adenomas are categorized into three distinct subtypes: *(a)* inflammatory hepatocellular adenomas, *(b)* hepatocyte nuclear factor 1 α–mutated hepatocellular adenomas, and *(c)* β-catenin–mutated hepatocellular adenomas. Different subtypes show variable clinical behavior, imaging findings, and natural history, and thus the options for treatment and surveillance may vary. Cross-sectional imaging plays an important role in the diagnosis, subtype characterization, identification of complications, and surveillance of hepatocellular adenomas. New schemas for genotype-phenotype classification of hepatic adenomas, as well as management triage of patients with specific subtypes of adenomas, are being proposed in an attempt to improve clinical outcomes.

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Teaching Point

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Introduction

Hepatocellular adenomas are rare benign hepatic tumors that commonly occur in women who have been receiving oral contraceptives for more than 2 years (1). The results of recent studies indicate that hepatocellular adenoma is not a single disease but a heterogeneous group of tumors characterized by specific genetic and pathologic abnormalities and tumor biology. Accordingly, hepatocellular adenomas are currently categorized into three distinct genetic and pathologic subtypes: *(a)* inflammatory hepatocellular adenomas, *(b)* hepatocyte nuclear factor 1 alpha (HNF-1α)–mutated hepatocellular adenomas, and *(c)* β-catenin–mutated hepatocellular adenomas (2). Hepatocellular adenomas without any known genetic abnormalities are categorized in the "unclassified" subtype. Genotype-phenotype classification of hepatocellular adenomas was proposed after the completion of a large multicenter study of the molecular markers of hepatocellular adenoma and their correlation with pathologic findings (3,4). Although this classification is new and is not widely accepted, it has definitive diagnostic and management implications. Recently, Bioulac-Sage et al (5) also concluded that hepatocellular adenoma is a complex entity and that management needs to be adapted to the phenotype classification. It is important to understand the different subtypes of hepatocellular adenoma as separate entities because of the noticeable differences in the imaging findings and the management strategies. Although image-guided biopsy or surgical resection with histopathologic and immunohistochemical analysis is necessary for complete characterization of hepatocellular adenomas, imaging plays an important role in diagnosis, subtype characterization, identification of complications, and surveillance.

The purpose of this article is to present the genetic abnormalities, oncogenesis, and imaging characteristics of specific subtypes of hepatocellular adenoma and to discuss their management implications. First, the characterization of the subtypes of hepatic adenoma is discussed, along with the role of magnetic resonance (MR) imaging. Then the following categories are presented:

inflammatory hepatocellular adenoma, HNF-1α–mutated hepatocellular adenoma, β-catenin–mutated hepatocellular adenoma, unclassified hepatocellular adenoma, and hepatic adenomatosis. Finally, the genotype-phenotype classification and management implications are discussed.

Characterization of Subtypes: Role of MR Imaging

Ultrasonography (US), multidetector computed tomography (CT), and MR imaging constitute commonly used imaging modalities for the evaluation of hepatocellular adenomas. Among these modalities, MR imaging is the imaging modality of choice for subtype characterization of hepatocellular adenomas. Currently, to our knowledge, no large studies have been performed to evaluate the role of multidetector CT and nonenhanced US for this purpose. Contrast material–enhanced US may show certain imaging findings that can help in subtype categorization of hepatocellular adenomas (6).

At MR imaging, the imaging features of hepatocellular adenomas vary on the basis of the histopathologic findings and associated complications. Lewin et al (7) concluded that three MR imaging patterns in patients with hepatic adenomatosis are associated with three pathologic forms, which include steatotic, peliotic, and mixed types. In a study with results that support the genotype-phenotype classification of hepatocellular adenomas proposed by Bioulac-Sage et al (2), Laumonier et al (8) analyzed the MR imaging findings of different subtypes of hepatocellular adenomas for correlation between the MR imaging features and pathologic findings. In the findings from this study, Laumonier et al (8) concluded that HNF-1α–mutated hepatocellular adenomas and inflammatory hepatocellular adenomas were associated with specific MR imaging patterns that were related to diffuse fat distribution and to sinusoidal dilatation, respectively. Although biopsy with histopathologic confirmation is needed to establish the specific subtype, certain imaging findings may be able to help in the subtype characterization of hepatocellular adenomas, the prediction of complications, and the guidance of patient management (5). In the results of a recent study, Ronot

MR Imaging Characteristics of Different Subtypes of Hepatocellular Adenoma

Subtype	T1-weighted Gradient-Echo MR Images	T2-weighted MR Images	Gadolinium-enhanced T1-weighted MR Images
Inflammatory hepatocellular adenoma	Isointense or mildly hyperintense, without signal drop-off with use of chemical shift sequence	Diffusely hyperintense	Intense enhancement during arterial phase that persists in the portal venous and delayed phases
HNF-1α–mutated hepatocellular adenoma	Hyper- or isointense, with diffuse signal drop-off with use of chemical shift sequence	Isointense to slightly hyperintense	Moderate enhancement in the arterial phase, with no persistent enhancement in the portal venous and delayed phases
β-Catenin–mutated hepatocellular adenoma*	…	…	…

*No specific MR imaging patterns; may mimic hepatocellular carcinoma on MR images (strong enhancement during arterial phase, with portal venous washout).

et al (9) concluded that MR imaging and biopsy analysis are two efficient methods for subtyping hepatocellular adenomas, and the association of these two methods increases the diagnostic confidence. The MR imaging appearances of different subtypes of hepatocellular adenoma are summarized in the Table.

Inflammatory Hepatocellular Adenoma

Inflammatory hepatocellular adenoma is the most common subtype and accounts for about 40%–50% of all hepatocellular adenomas. Inflammatory hepatocellular adenomas include liver tumors previously referred to as "telangiectatic focal nodular hyperplasia" or "telangiectatic adenomas" (5,10). Inflammatory hepatocellular adenomas occur most frequently in young women with a history of oral contraceptive usage and in obese patients (10). Patients with inflammatory hepatocellular adenomas may present with signs of chronic anemia and/or "systemic inflammatory syndrome," characterized by fever, leukocytosis, and elevated serum levels of C-reactive protein (11). Abnormal results of liver function tests, including increases in the serum levels of transaminases, alkaline phosphatase, and γ-glutamyl transferase, may be found, especially in patients with intratumoral bleeding or multiple adenomas (12).

Sustained activation of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway (JAK-STAT pathway), with resultant hepatocellular proliferation, is the proposed pathogenesis in the development of inflammatory hepatocellular adenomas (13). About 60% of inflammatory hepatocellular adenomas result from somatic gain-of-function mutations of the interleukin-6 signal transducer gene *(IL6ST)* (13). The *IL6ST* gene is located at chromosome 5q11 and encodes for glycoprotein 130 (13,14). Gain-of-function mutations in glycoprotein 130 constitutively trigger glycoprotein 130 dimerization and JAK–STAT-3 activation without interleukin-6 binding, which leads to the development of inflammatory hepatocellular adenomas. The remaining 40% of inflammatory hepatocellular adenomas show overexpression of wild-type glycoprotein 130, which results in STAT-3 activation by an unidentified mechanism (Fig 1) (15). In addition, the chemokine CCL20 (C-C motif ligand 20) is also overexpressed in these tumors, which results in the recruitment of polymorphous inflammatory cells within the tumors (15,16). Although the exact pathogenesis of marked tumoral peliosis is unknown, the condition has been attributed to suppression of the transthyretin gene *(TTR)*, the

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Figure 1. Flowchart illustrates the pathogenesis of inflammatory hepatocellular adenomas *(IHCAs)*. *ALB* = albumin, *CCL20* = C-C motif ligand 20, *gp-130* = glycoprotein 130, *HCA* = hepatocellular adenoma, *IGF1* = insulinlike growth factor, *IL-6* = interleukin-6, *IL6ST* = interleukin-6 signal transducer, *JAK* = Janus kinase, *STAT* = signal transducer and activator of transcription, *TTR* = transthyretin.
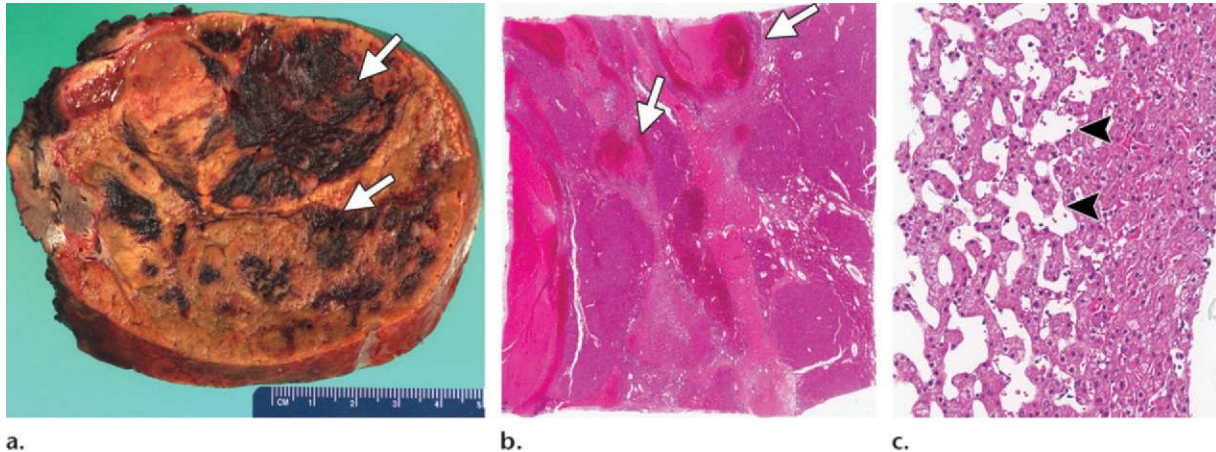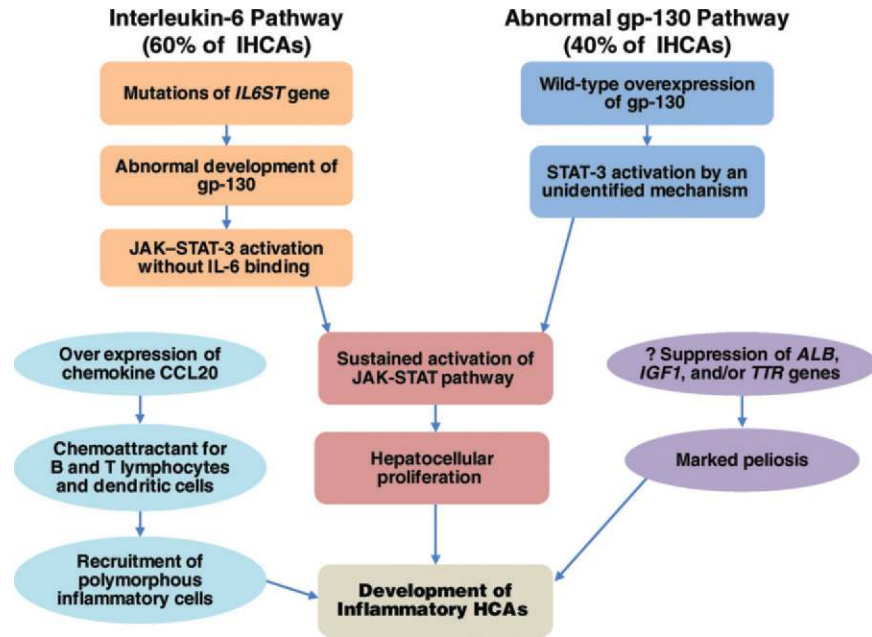

Figure 2. Histopathologic findings of an inflammatory hepatocellular adenoma in a 27-year-old woman. **(a)** Cut section of the gross specimen shows scattered areas of frank hemorrhage (arrows). **(b)** Low-power photomicrograph (hematoxylin-eosin [H-E] stain; original magnification, ×20) shows multiple hemorrhagic areas (arrows). **(c)** High-power photomicrograph (H-E stain; original magnification, ×100) shows dilated sinusoidal spaces (arrowheads).

insulinlike growth factor gene *(IGF1)*, and the human albumin gene *(ALB)* in some inflammatory hepatocellular adenomas (15).

At gross pathologic examination, inflammatory hepatocellular adenomas are heterogeneous in appearance, with areas of congestion and frank hemorrhage (Fig 2a) (3). At histopathologic examination, inflammatory hepatocellular adenomas show intense polymorphous inflammatory infiltrates, marked sinusoidal dilatation or congestion, and thick-walled arteries (Fig 2b,

2c) (17). Tumor cells show immunoreactivity to acute phase inflammatory markers such as serum amyloid A and C-reactive protein (3).

At MR imaging, inflammatory hepatocellular adenomas are diffusely hyperintense on T2-weighted images, with a higher signal intensity in the periphery of the lesion, correlating with dilated sinusoids. On T1-weighted images, inflammatory hepatocellular adenomas are iso-intense or mildly hyperintense, with minimal or no signal drop-off with chemical shift sequences (7,8). After administration of gadolinium-based contrast material, inflammatory hepatocellular adenomas usually show intense enhancement during the arterial phase, which persists in the portal venous and delayed phases (Fig 3) (7,8).

Teaching Point
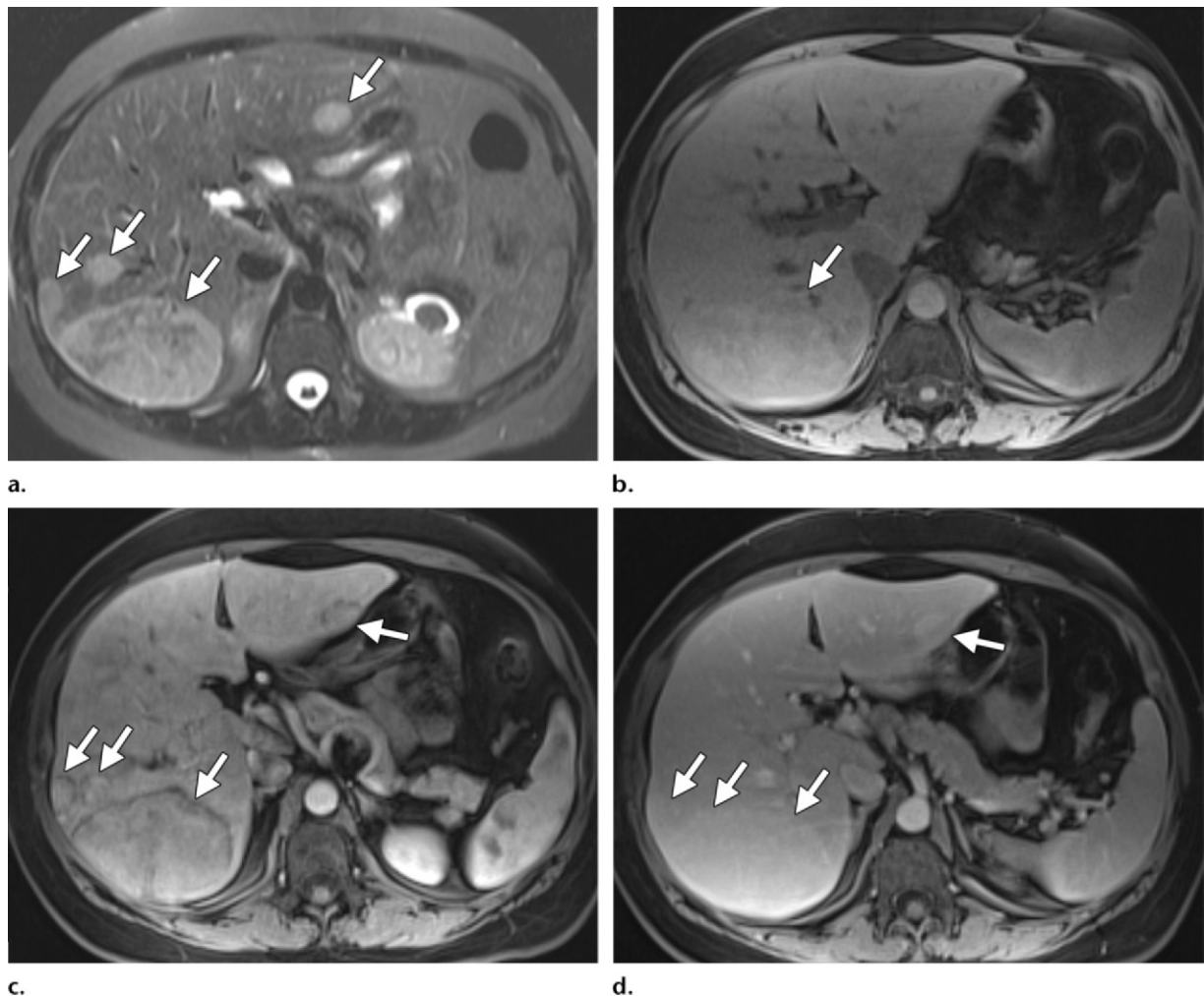
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Figure 3.   Multiple inflammatory hepatocellular adenomas in a 45-year-old woman with long-term use of oral contraceptive pills. **(a, b)** Axial T2-weighted **(a)** and T1-weighted **(b)** MR images depict multiple focal hepatic lesions that are hyperintense on the T2-weighted image (arrows in **a**) and isointense to slightly hyperintense on the T1-weighted image (arrow in **b**). **(c, d)** Contrast-enhanced T1-weighted MR images obtained in the arterial **(c)** and portal venous **(d)** phases show the lesions with intense arterial phase enhancement (arrows in **c**), which persists into the portal venous phase (arrows in **d**). The findings from histopathologic examination of the specimen from percutaneous core biopsy helped confirm the diagnosis of inflammatory hepatocellular adenoma.

Marked T2 hyperintensity associated with delayed persistent enhancement had a sensitivity of as much as 85% and a specificity of 87% for the diagnosis of inflammatory hepatocellular adenomas (8). At multidetector CT, inflammatory hepatocellular adenomas may be depicted as heterogeneously hyperattenuating masses on nonenhanced CT images and show enhancement characteristics similar to those demonstrated at MR imaging. At contrast-enhanced US, inflammatory hepatocellular adenomas show arterial vascularity with centripetal filling, a peripheral rim of sustained enhancement, and central washout in the late venous phase (6). The discrepancy between the delayed washout that is depicted on

contrast-enhanced US images and is not depicted on contrast-enhanced MR images may be related to the diffusion of the gadolinium-based contrast material, but not the microbubbles, into the interstitial spaces (6).

The two most common complications of hepatocellular adenomas are *(a)* intratumoral bleeding with associated rupture and *(b)* the development of hepatocellular carcinoma. Different subtypes of hepatocellular adenoma show variable complication rates. Intratumoral bleed-
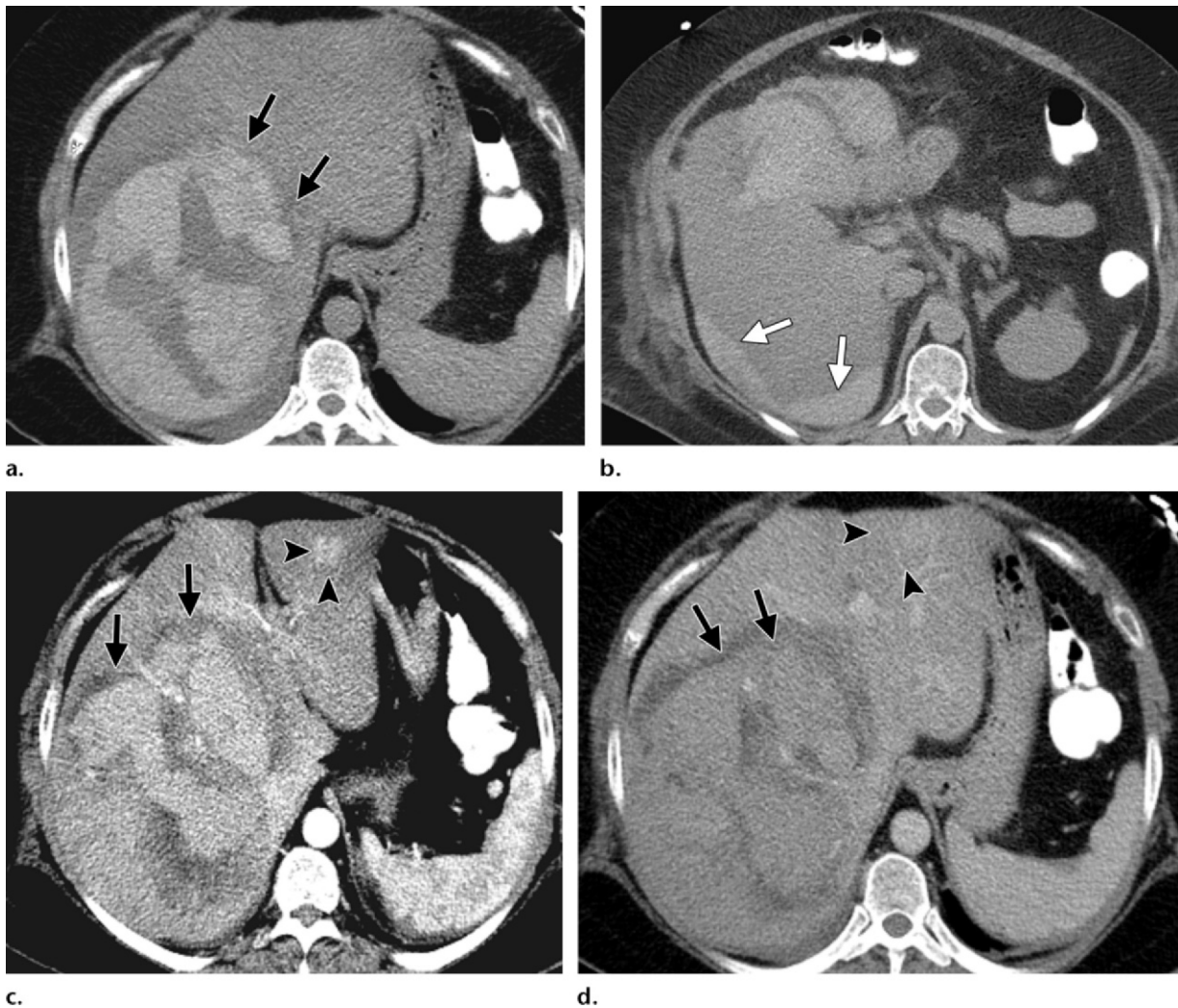
Teaching Point

Figure 4.   Ruptured inflammatory hepatocellular adenoma in a 30-year-old woman presenting with acute right upper quadrant pain. Axial CT images obtained at the level of the liver in the nonenhanced phase **(a, b)** and the hepatic arterial **(c)** and portal venous **(d)** phases show a focal lesion involving the right lobe of the liver. On the nonenhanced images, the lesion is heterogeneously hyperattenuating (arrows in **a**) compared to the liver, with associated hemorrhage (arrows in **b**) in the perihepatic space, a finding consistent with rupture. The mass shows heterogeneous enhancement during the arterial phase (arrows in **c**) and is iso- to hypoattenuating compared to the hepatic parenchyma in the portal venous phase (arrows in **d**). In addition, in the arterial phase, the left hepatic lobe has an enhancing focal lesion (arrowheads in **c**), which is isoattenuating to mildly hyperattenuating in the portal venous phase (arrowheads in **d**), a finding consistent with a second hepatocellular adenoma. The findings from surgical resection with histologic examination helped confirm the diagnosis of inflammatory hepatocellular adenoma.

ing can occur in 20%–25% of hepatocellular adenomas; tumors larger than 5 cm in maximum dimension and subcapsular tumors show more tendency for bleeding and rupture (3,12). Of all subtypes, inflammatory hepatocellular adenomas show the highest risk of bleeding, which can occur in about 30% of these tumors (Fig 4). Inflammatory hepatocellular adenomas are more prone to bleeding, given the presence of sinusoidal dilatation, peliotic areas, and abnormal arteries (3,4). About 10% of inflammatory hepatocellular adenomas show an increased risk of malignancy (3,4).
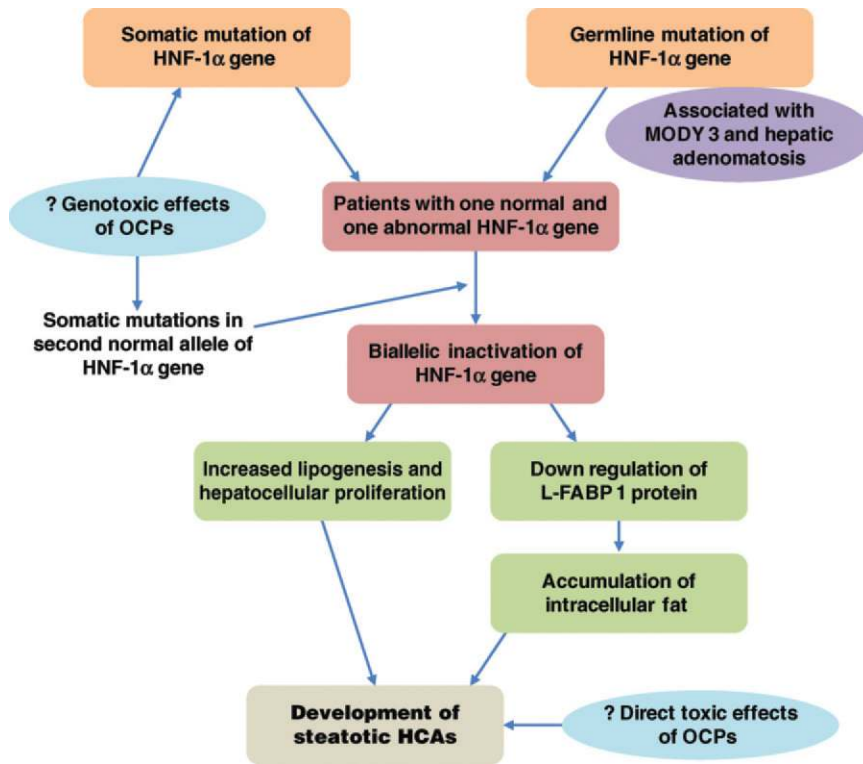
Figure 5. Flowchart shows pathogenesis of HNF-1α–mutated hepatocellular adenomas. *HCA* = hepatocellular adenoma, *L-FABP* = liver fatty acid–binding protein, *OCP* = oral contraceptive pill.

HNF-1α–mutated Hepatocellular Adenoma

HNF-1α–mutated hepatocellular adenomas are the second most common type of hepatocellular adenoma and constitute about 30%–35% of all hepatocellular adenomas. Biallelic inactivating mutations of the HNF-1α gene *(HNF1A)* are responsible for the development of HNF-1α–mutated hepatocellular adenomas, and some cases have an association with *(a)* maturity-onset diabetes of the young (MODY), type 3, and *(b)* familial hepatic adenomatosis (4,5,18). HNF-1α–mutated hepatocellular adenomas develop exclusively in female patients, with more than 90% of patients having a history of oral contraceptive use, and the tumors are multiple in about 50% of patients. Many HNF-1α–mutated hepatocellular adenomas are asymptomatic and are depicted incidentally during imaging studies performed for other reasons, such as trauma or nonspecific abdominal pain.

HNF-1α–mutated hepatocellular adenomas result from biallelic inactivating mutations of the *HNF1A* gene (also known as transcription factor-1 gene) (19). The *HNF1A* gene is a tumor suppressor gene located at chromosome 12q24, and the gene encodes the HNF-1α protein, a transcription factor involved in hepatocyte differentiation (10). In about 90% of cases, both mutations are of somatic origin; in the remaining 10% of cases, HNF-1α–mutated hepatocellular adenomas show one germline mutation and one somatic mutation (3,19). Patients with germline mutations have a predisposition to MODY type 3 and to familial hepatic adenomatosis (20,21). Estrogens in oral contraceptives may act as endogenous genotoxic agents, and it has been proposed that estrogens are responsible for somatic mutations in HNF-1α–mutated hepatocellular adenomas (19,22). The final outcome of all of these mutations is the production of nonfunctioning HNF-1α protein, which promotes lipogenesis and hepatocellular proliferation (Fig 5) (23). In addition, abnormal HNF-1α protein causes silencing of liver fatty acid–binding protein, resulting in impaired fatty acid trafficking in hepatocytes, which leads to intracellular fat deposition (23).

Finally, all of these changes lead to the development of hepatocellular adenomas with diffuse intratumoral steatosis. At histologic examination, HNF-1α–mutated hepatocellular adenomas are characterized by excessive lipid accumulation in the tumor hepatocytes (Fig 6) (18). No portal tract elements or cytologic and/or nuclear abnormalities are identified within the tumor cells. Lack of liver fatty acid–binding protein is a characteristic feature of HNF-1α–mutated hepatocellular adenomas at immunochemical analysis (18).

At MR imaging, HNF-1α–mutated hepatocellular adenomas are predominantly hyper- or isointense on T1-weighted images, with diffuse signal drop-off with use of a chemical shift sequence because of intracellular steatosis (7,8). In addition, the background liver also shows diffuse fatty infiltration because HNF-1α–mutated hepatocellular adenomas are associated with MODY type 3 and hepatic steatosis (24). HNF-1α–mutated hepatocellular adenomas are isointense to slightly hyperintense on T2-weighted images. Moderate enhancement in the arterial phase is identified after administration of gadolinium-based contrast material, with no persistent enhancement in the portal venous and delayed phases (Fig 7) (8). The sensitivity and specificity of homogeneous signal drop-off on chemical shift images for the diagnosis of HNF-1α–mutated hepatocellular adenomas were as high as 86% and 100%, respectively (8). The intra- and intercellular lipid of the hepatocellular adenomas may uncommonly manifest as macroscopic fat deposits that can be identified at multidetector CT, and such lipid is diagnostic of HNF-1α–mutated hepatocellular adenomas (25). MR imaging is more sensitive and specific for the identification of intratumoral fat. Approximately 7% of hepatocellular adenomas may show fat when imaged with CT, whereas about 35%–77% of hepatocellular adenomas demonstrate fat at chemical shift MR imaging (26,27). At contrast-enhanced US, HNF-1α–mutated hepatocellular adenomas show isovascularity to moderately increased vascularity, with mixed filling in the arterial phase after contrast material administration, and are isoechoic in the portal venous and delayed phases (6).
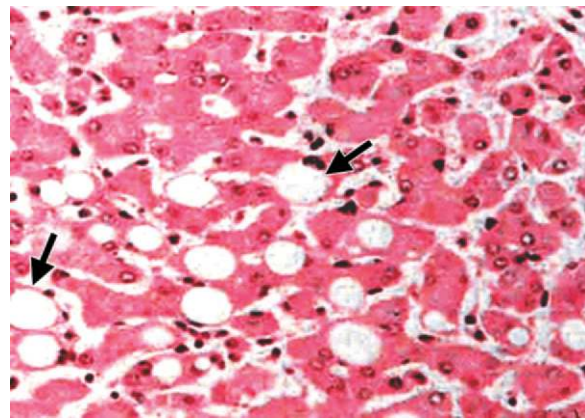

Figure 6. Photomicrograph (H-E stain; original magnification, ×40) of an HNF-1α–mutated hepatocellular adenoma in a 39-year-old woman shows fat deposition (arrows) within the hepatocytes.

Among all hepatocellular adenomas, the HNF-1α–mutated hepatocellular adenomas are the least aggressive subtype: Tumors less than 5 cm in maximum dimension show minimal risk of bleeding and subsequent rupture and carry minimal or no risk for the development of malignancy.

β-Catenin–mutated Hepatocellular Adenoma

β-Catenin–mutated hepatocellular adenomas constitute about 10%–15% of all hepatocellular adenomas and are due to activating mutations of the β-catenin gene (18). β-Catenin–mutated hepatocellular adenomas occur more frequently in men and are associated with male hormone administration, glycogen storage disease, and familial adenomatosis polyposis (10).

β-Catenin–mutated hepatocellular adenomas develop because of sustained activation of β-catenin protein, resulting in uncontrolled hepatocyte proliferation (28). β-Catenin is encoded by the catenin β 1 gene *(CTNNB1)*, which is located at chromosome 3p21. β-Catenin is an important downstream effector of the Wnt/β-catenin pathway, which has a major role in liver embryogenesis, cell adhesion, growth, zonation, and regeneration. In the steady state, in the absence of a Wnt signal, β-catenin is phosphorylated and degraded by a cytoplasmic destruction complex formed by the adenomatous polyposis coli gene *(APC)* and the Axin family of genes in associa-
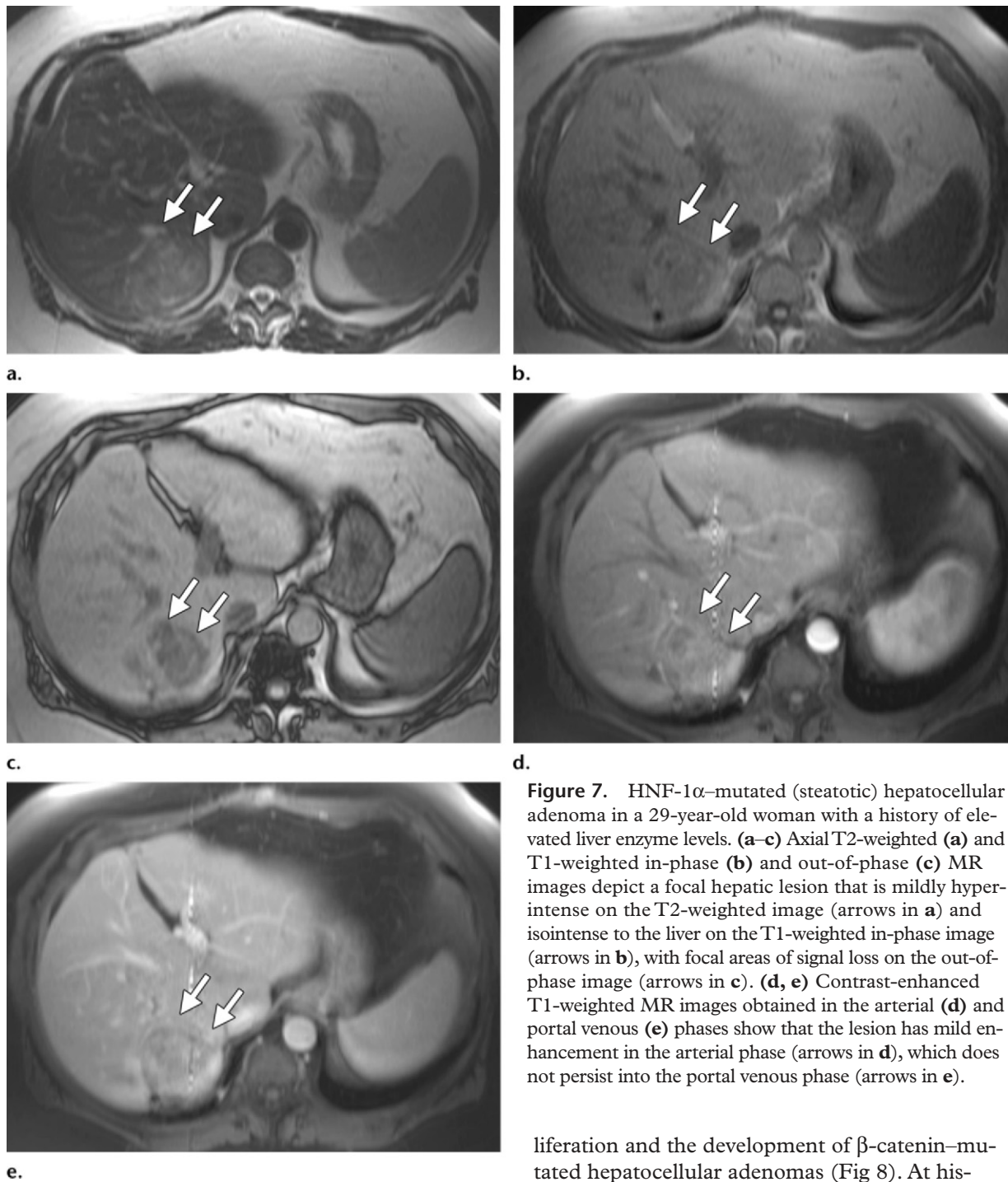
a.

b.

c.

d.

e.

Figure 7. HNF-1α–mutated (steatotic) hepatocellular adenoma in a 29-year-old woman with a history of elevated liver enzyme levels. **(a–c)** Axial T2-weighted **(a)** and T1-weighted in-phase **(b)** and out-of-phase **(c)** MR images depict a focal hepatic lesion that is mildly hyperintense on the T2-weighted image (arrows in **a**) and isointense to the liver on the T1-weighted in-phase image (arrows in **b**), with focal areas of signal loss on the out-of-phase image (arrows in **c**). **(d, e)** Contrast-enhanced T1-weighted MR images obtained in the arterial **(d)** and portal venous **(e)** phases show that the lesion has mild enhancement in the arterial phase (arrows in **d**), which does not persist into the portal venous phase (arrows in **e**).

tion with glycogen synthase kinase (29). Mutated β-catenin protein, abnormal activation of Wnt protein, or mutations of the *APC* gene cause increased cytoplasmic availability of β-catenin, which causes sustained activation of its targeted genes, resulting in uncontrolled hepatocyte pro-liferation and the development of β-catenin–mutated hepatocellular adenomas (Fig 8). At histopathologic examination, the hepatocytes of β-catenin–mutated hepatocellular adenomas show cytologic abnormalities, such as a high nuclear-cytoplasmic ratio, nuclear atypia, and formation
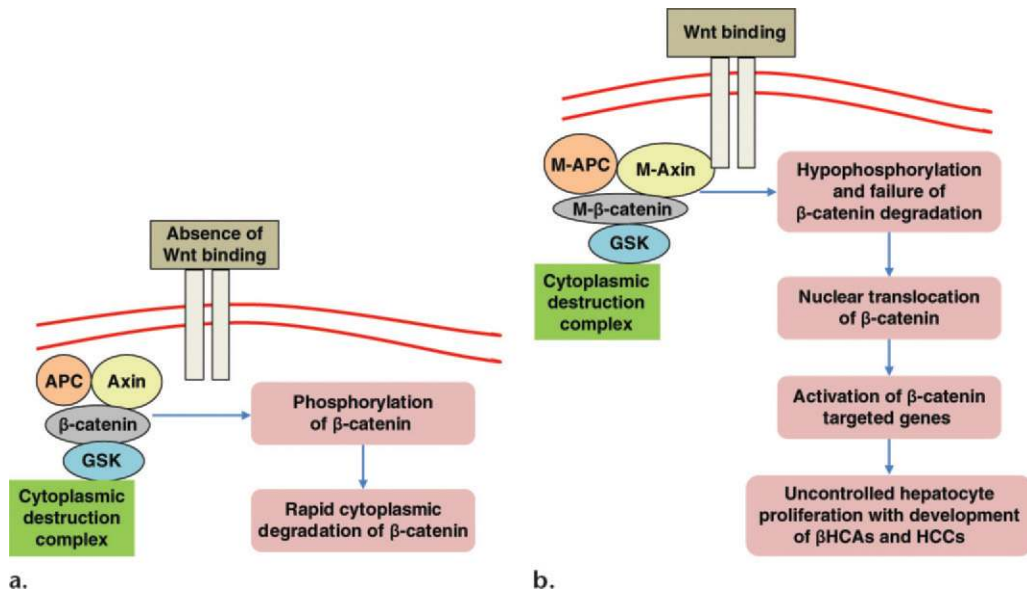
Figure 8. Flowcharts relating to β-catenin–mutated hepatocellular adenoma *(βHCA)*. **(a)** Cytoplasmic destruction of β-catenin in the steady state with absence of Wnt binding and with normal *APC,* β-catenin, and Axin genes. **(b)** Pathogenesis of β-catenin–mutated hepatocellular adenomas and hepatocellular carcinomas *(HCCs)* via the Wnt/β-catenin pathway, secondary to mutations of the *APC,* β-catenin, and Axin genes and abnormal binding of Wnt protein. *APC* = adenomatous polyposis coli, *GSK* = glycogen synthase kinase, *M-* = mutated gene.

of acini, and are difficult to distinguish from the hepatocytes of well-differentiated hepatocellular carcinomas (10). The glutamate-ammonia ligase gene *(GLUL)*, a β-catenin–targeted gene that encodes glutamine synthase, is overexpressed in β-catenin–mutated hepatocellular adenomas, resulting in strong and diffuse positivity to glutamine synthase at immunohistochemical analysis (2). In addition, heterogeneous aberrant nuclear and cytoplasmic staining of β-catenin is also identified (2,10).

No specific MR imaging patterns have yet been proposed to identify β-catenin–mutated hepatocellular adenomas, and on T1- and T2-weighted images, these tumors may show homogeneous or heterogeneous hyperintense signal intensity, depending on the presence of hemorrhage and/ or necrosis. β-Catenin–mutated hepatocellular adenomas commonly demonstrate strong arterial enhancement that may or may not persist on the portal venous and delayed phases, and these tumors may mimic hepatocellular carcinomas at imaging (8). No specific US or multidetector CT findings for β-catenin–mutated hepatocellular adenomas have been reported in the literature.

Overall, the risk of hepatocellular carcinoma development in hepatocellular adenomas is about 5%–10% (30). The important risk factors for malignant transformation of hepatocellular adenomas are male sex, concomitant glycogen storage disease, anabolic steroid usage, the β-catenin–mutated subtype, and tumors larger than 5 cm in maximum dimension (24,30,31). Of all hepatocellular adenomas, β-catenin–mutated hepatocellular adenomas carry the highest risk of malignancy and are interpreted as borderline lesions between hepatocellular adenoma and hepatocellular carcinoma (Fig 9) (10). The Wnt/β-catenin pathway involved in the pathogenesis of β-catenin–mutated hepatocellular adenomas is also a major player in the development of hepatocellular carcinoma, with about 35% of hepatocellular carcinomas showing β-catenin mutations (32,33). This finding explains the high incidence of cancer in β-catenin–mutated hepatocellular adenomas compared with the incidence in other subtypes. In a recent study, Farges et al (31) concluded that metabolic syndrome is an emerging condition associated with malignant transformation of hepatocellular adenoma in men. In the study, these investigators also showed that the presence of malignancy with hepatocellular adenoma is
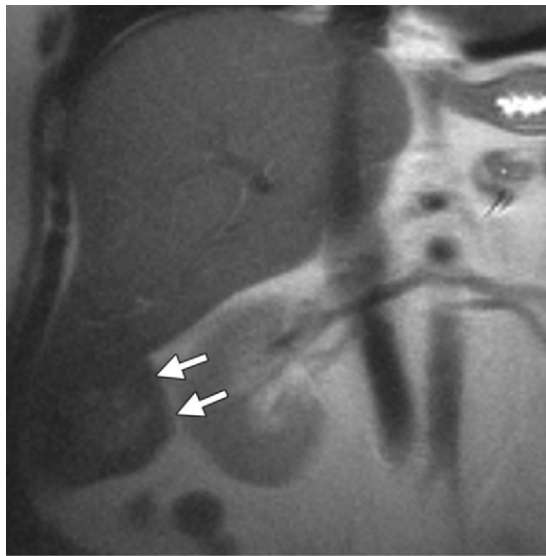
Figure 9. Hepatocellular adenoma with malignant change in a 40-year-old man. **(a)** Coronal T2-weighted MR image shows an isointense exophytic focal lesion (arrows), 7 cm in maximum dimension, arising from hepatic segment VI, with focal hyperintense areas within the lesion. **(b, c)** Axial T1-weighted contrast-enhanced MR images obtained in the arterial **(b)** and portal venous **(c)** phases show intense arterial enhancement in the arterial phase (arrow in **b**), with washout in the portal venous phase (arrow in **c**). The findings from surgical resection and histopathologic examination showed a well-differentiated hepatocellular carcinoma arising from a hepatocellular adenoma with β-catenin mutations.

a.

b.   c.

10 times more frequent in men than in women, and management should primarily be based on the sex of the patient (31). Hepatocellular carcinomas may develop either as a macroscopic nodule larger than 1 cm in maximum dimension or as multiple microscopic foci. Although β-catenin–mutated hepatocellular adenomas also have a risk of bleeding, the exact incidence of this complication is not known.

Unclassified Hepatocellular Adenoma
Approximately 10% of all hepatocellular adenomas are without specific genetic and/or pathologic abnormalities. This subset of tumors is grouped under the rubric of the unclassified subtype (10).

No specific MR imaging patterns have yet been proposed to identify unclassified hepatocellular adenomas. These hepatocellular adenomas are poorly understood; detailed studies will be required to evaluate the oncogenesis, clinical features, and pathologic and radiologic findings of this rare subtype of hepatocellular adenoma.
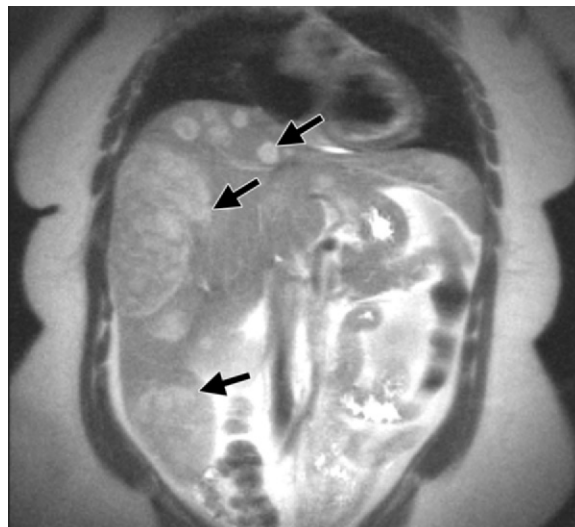
Hepatic Adenomatosis
To our knowledge, hepatic adenomatosis was first described by Flejou et al (34) in 1985 and is defined as the presence of multiple adenomas (arbitrarily >10) involving both lobes of the liver, without any history of steroid therapy or glycogen

storage disease (35). Hepatic adenomatosis commonly occurs in women during the 4th and 5th decades of life (35,36). Although the exact etiology of hepatic adenomatosis is still unclear, congenital or acquired hepatic vascular abnormalities, mutations of the *HNF1A* gene, and nonalcoholic fatty liver disease have been proposed as potential causes for the development of hepatic adenomatosis (35,37,38). In addition, patients with familial hepatic adenomatosis who have germline mutations of the *HNF1A* gene tend to develop MODY type 3. Hepatocellular adenomas in patients with hepatic adenomatosis may be of the inflammatory, HNF-1α–mutated, or β-catenin–mutated subtypes, and their imaging appearances may vary accordingly (Fig 10) (7). In contradistinction to previous beliefs, hepatic adenomatosis per se does not have any increased risk of complications; tumor size and subtype determine the risks of malignancy and bleeding (36). Management of hepatocellular adenomas in patients with hepatic adenomatosis is similar to management of other hepatocellular adenomas. In addition, diabetes mellitus and mutations of the *HNF1A* gene should be sought in patients with hepatic adenomatosis, and liver imaging is recommended in their relatives (20).

Genotype-Phenotype Classification: Management Implications

The classification of hepatocellular adenomas into different subtypes on the basis of genetic and pathologic characteristics allows a better understanding of the natural history and prognoses of these rare tumors, so that management and follow-up options may be modified accordingly. On the basis of the recommendations by Bioulac-Sage et al (5), the management strategies for different hepatocellular adenoma subtypes in asymptomatic and symptomatic patients have been summarized in a chart (Fig 11).

Incidental depiction in an asymptomatic patient is one of the common clinical presentations of hepatocellular adenoma. For this group of patients, the first step in management is subtype classification, on the basis of the cross-sectional imaging findings, into one of two groups: *(a)* hepatocellular adenomas with diffuse steatosis or *(b)* heterogeneous hepatocellular adenomas without steatosis (5). As discussed previously, MR imaging is preferred to CT for identification of intracellular microscopic fat and for better characterization of the hepatocellular adenoma. A thorough clinical examination with determination of the medication history is recommended to help identify any

a.
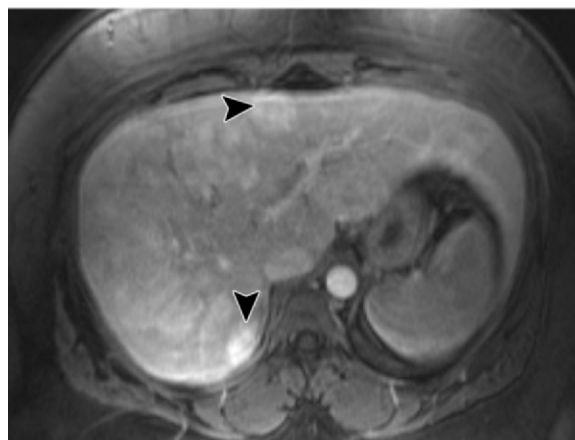
b.

Figure 10. Hepatic adenomatosis in a 38-year-old woman. Coronal T2-weighted **(a)** and axial contrast-enhanced T1-weighted **(b)** MR images depict multiple T2 hyperintense lesions (arrows in **a**) throughout the liver, which show intense enhancement in the arterial phase (arrowheads in **b**), a finding consistent with multiple inflammatory hepatocellular adenomas.

known cause, such as usage of oral contraceptives, barbiturates, or steroids. If such usage is found, withholding the medication and repeating the imaging studies in 3–6 months are suggested.

Stable and regressing hepatocellular adenomas may be monitored with imaging studies without any therapeutic interventions. Hepatocellular adenomas that are growing despite discontinuation of the usage of potentially causative medications need further evaluation on the basis of the sex of the patient and the size of the tumor (3). Genetic counseling with regard to a family history of hepatocellular adenomas, hepatic adenomatosis, and MODY type 3 may be performed in patients with suspected steatotic hepatocellular adenomas measuring less than 5 cm in maximum dimension (5).
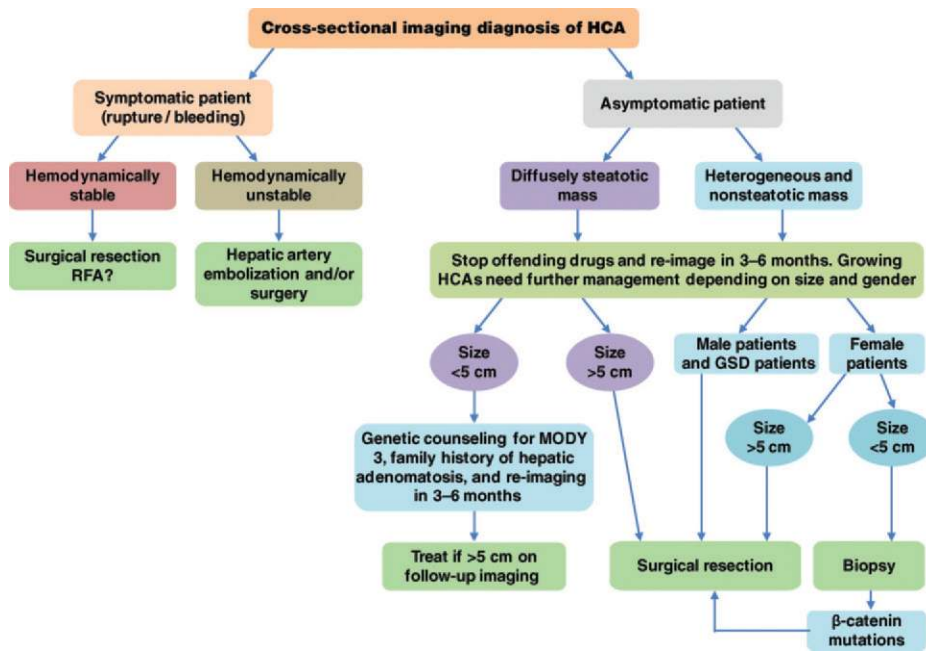
Figure 11. Flowchart illustrates management strategies for different subtypes of hepatocellular adenoma *(HCA)*. *GSD* = glycogen storage disease, *RFA* = radiofrequency ablation.

In patients with heterogeneous small (<5-cm) hepatocellular adenomas, percutaneous biopsy and histopathologic review are warranted to identify β-catenin mutations. Hepatocellular adenomas larger than 5 cm in maximum dimension, in male patients, and in patients with glycogen storage disease should be surgically resected (5,12,39,40). Surgically resected hepatocellular adenomas and those subjected to biopsy should undergo detailed histopathologic review to characterize them on the basis of the genotype-phenotype classification. Hepatocellular adenomas with β-catenin mutations, inflammatory features with β-catenin mutations, and hepatocellular adenomas mimicking hepatocellular carcinomas at histopathologic evaluation are to be considered as hepatocellular carcinomas that require treatment and surveillance accordingly (5). Female patients with inflammatory hepatocellular adenomas, HNF-1α–mutated hepatocellular adenomas, and unclassified tumors require treatment of diabetes mellitus and clinical and MR imaging follow-up until menopause (5). To our knowledge, there are no definite guidelines to recommend an optimal interval for follow-up examinations; annual imaging follow-up has been recommended by some investigators for both solitary hepatocellular adenoma and hepatic adenomatosis (41). In addition to surgery, other definitive treatment options include radiofrequency ablation and hepatic artery embolization. Radiofrequency ablation is indicated for *(a)* tumors smaller than 4 cm in maximum dimension, *(b)* patients who are not surgical candidates, and *(c)* those who prefer to avoid surgery after discussion and full understanding of available treatment options (40,42). Tumors

that grow to larger than 5 cm in maximum dimension during follow-up need definitive treatment.

The management of patients with symptomatic hepatocellular adenomas depends on the duration and type of symptoms. Patients with ruptured hepatocellular adenomas who present in hemodynamically unstable condition and patients with hepatocellular adenomas larger than 5 cm in maximum dimension require immediate treatment with either hepatic artery embolization or surgery (43,44). Conservative treatment may be considered in hemodynamically stable patients, even though they present with rupture (44). Patients with continued symptoms, with growing hepatocellular adenomas, or with tumors larger than 5 cm in maximum dimension need definitive treatment. Further management is guided by the specific subtype of hepatocellular adenoma on the basis of the genotype-phenotype classification, as discussed for asymptomatic patients (5).

Conclusions

Hepatocellular adenomas are a diverse group of benign neoplasms that are characterized by specific genetic mutations, molecular abnormalities, histopathologic features, imaging findings, tumor biology, and natural history. The current genotype-phenotype classification of hepatocellular adenomas identifies three distinct subtypes (inflammatory, HNF-1α–mutated, and β-catenin–mutated hepatocellular adenomas). Novel insights into the pathogenesis of adenomas permit

better understanding of the tumor subtypes and their biologic behaviors. Hepatocellular adenomas with β-catenin mutations frequently undergo malignant change, inflammatory hepatocellular adenomas commonly bleed, and steatotic hepatocellular adenomas typically portend a favorable prognosis.

Contrast-enhanced MR imaging is the imaging modality of choice for the differentiation of the subtypes of hepatocellular adenoma. Inflammatory hepatocellular adenomas are diffusely hyperintense on T2-weighted images and have isointense or mildly hyperintense signal intensity on T1-weighted images, with minimal or no signal drop-off with the use of chemical shift sequences. After contrast material administration, inflammatory hepatocellular adenomas show intense enhancement during the arterial phase that persists in the portal venous and delayed phases. HNF-1α–mutated hepatocellular adenomas are hyper- or isointense on T1-weighted images, with diffuse signal drop-off with use of the chemical shift sequence, and are isointense to slightly hyperintense on T2-weighted images. Moderate enhancement is depicted in the arterial phase, with an absence of persistent enhancement in the portal venous and delayed phases. No specific MR imaging patterns have been proposed to identify β-catenin–mutated and unclassified hepatocellular adenomas. A knowledge of the biologic diversity of hepatocellular adenomas and a familiarity with the clinical and imaging findings of the subtypes of hepatocellular adenoma and their associated complications permit optimal patient management.

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Genetics and Imaging of Hepatocellular Adenomas: 2011 Update

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Accordingly, hepatocellular adenomas are currently categorized into three distinct genetic and pathologic subtypes: *(a)* inflammatory hepatocellular adenomas, *(b)* hepatocyte nuclear factor 1 alpha (HNF-1α)–mutated hepatocellular adenomas, and *(c)* β-catenin–mutated hepatocellular adenomas (2).

Page 1532 (Figure on page 1533)

At MR imaging, inflammatory hepatocellular adenomas are diffusely hyperintense on T2-weighted images, with a higher signal intensity in the periphery of the lesion, correlating with dilated sinusoids. On T1-weighted images, inflammatory hepatocellular adenomas are iso-intense or mildly hyperintense, with minimal or no signal drop-off with chemical shift sequences (7,8). After administration of gadolinium-based contrast material, inflammatory hepatocellular adenomas usually show intense enhancement during the arterial phase, which persists in the portal venous and delayed phases (Fig 3) (7,8).

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The two most common complications of hepatocellular adenomas are *(a)* intratumoral bleeding with associated rupture and *(b)* the development of hepatocellular carcinoma. Different subtypes of hepatocellular adenoma show variable complication rates.

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At MR imaging, HNF-1α–mutated hepatocellular adenomas are predominantly hyper- or isointense on T1-weighted images, with diffuse signal drop-off with use of a chemical shift sequence because of intracellular steatosis (7,8).

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Hepatocellular adenomas larger than 5 cm in maximum dimension, in male patients, and in patients with glycogen storage disease should be surgically resected (5,12,39,40). Surgically resected hepatocellular adenomas and those subjected to biopsy should undergo detailed histopathologic review to characterize them on the basis of the genotype-phenotype classification.