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# Update: Radiologic-pathologic correlation of hepatocellular adenoma

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**H**epatocellular adenoma (HA) is a relatively uncommon benign liver neoplasm that is typically seen in obese women of childbearing age who are on long-term oral contraceptives.<sup>1</sup> It is also reported to occur in men secondary to androgen drug use and in patients with rare metabolic disorders such as glycogen storage disease, maturity onset diabetes of the young and metabolic syndrome.<sup>2-4,5</sup> Accurate identification and characterization of HA is clinically relevant as there is an increased tendency of this distinctive tumor to rupture and cause hemorrhage, to increase in size during pregnancy as well as to undergo malignant transformation.<sup>4</sup> Recent patho-genetic studies have revealed that HA is a heterogeneous entity that may be classified into specific subtypes based on unique molecular signatures, histological features and immunohistochemistry.<sup>1,6-9</sup> Based

on characteristic MRI characteristics, specific HA subtypes may be identified non-invasively.<sup>10,11</sup> Radiologists and pathologists have an equally important role to play in the diagnosis and morpho-molecular subtyping of HAs. This review focuses on the radiological and pathological features of HAs and its morphologic subtypes, and in addition dwells on the differential diagnosis of HAs based on imaging characteristics.

## Epidemiology and etiologic associations

Hepatocellular adenoma has an incidence of 1–1.3 million cases per year in North America and Europe.<sup>12</sup> Several studies have consistently linked the occurrence of HAs to oral contraceptive pill (OCP) use.<sup>13-15</sup> The risk of HA is associated with dose and duration of oral contraceptive use; HAs were particularly associated with use of older generation of OC pills with high-estrogen content. Regression of Hepatocellular adenoma has been reported to occur following cessation of OCPs.<sup>16</sup> HAs have also been reported to occur in men secondary to anabolic steroid/androgen use.<sup>2,3</sup> Other hormonal therapies and risk factors include: clomiphene, danazol,<sup>5</sup> testosterone in patients with Fanconi anemia (FA) and without FA, Klinefelter's syndrome, Glycogen storage disorders I, III and IV, alcohol, and

metabolic syndrome. Hepatocellular adenomatosis, defined as development of >10 HAs in a patient, is usually related to germline mutations of HNF1- $\alpha$  gene and is also seen in patients with type 3 maturity onset diabetes of young (MODY 3).<sup>17</sup>

## Clinical presentation

The majority of HAs are clinically occult and are incidentally detected on imaging. The risk factors for hemorrhage are size >5 cm, a subcapsular location and longstanding OCP use.<sup>10,18,19</sup> HCA associated with hemorrhage may present with acute abdominal pain, elevated liver enzymes, and hypovolemic shock. Inflammatory HCA has the highest risk of hemorrhage and may show elevated levels of acute-phase reactants. The  $\beta$ -catenin activated subtype has the highest predilection for malignant transformation of all HCAs and this may be seen as a rapid increase in the size of a previously known HCA.<sup>10,18,19</sup>

## Classification

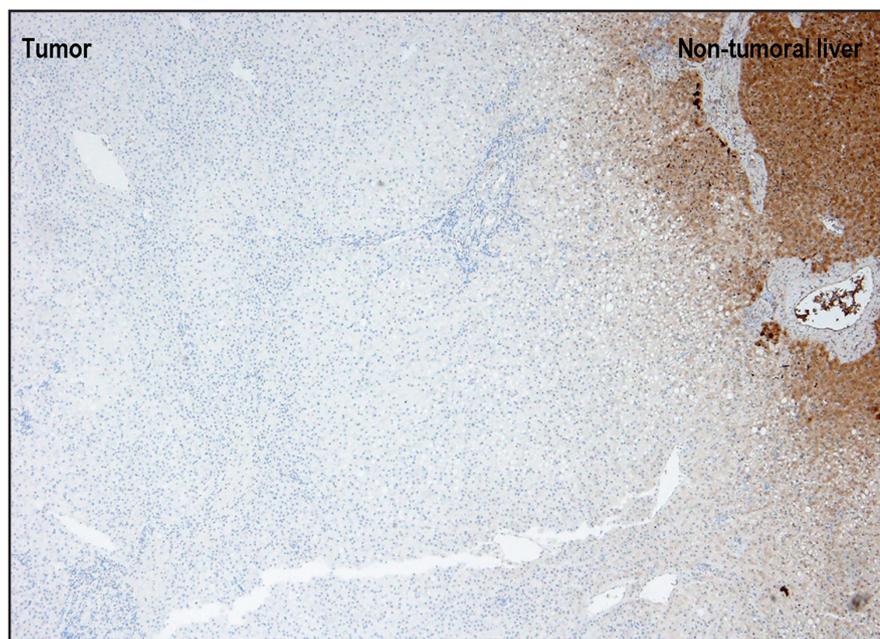
Hepatocellular adenoma (HA) was considered a homogeneous entity until the early 2000s, when a French group of clinical researchers demonstrated somatic bi-allelic mutations of transcription factor 1 (TCF 1) gene encoding hepatocyte nuclear factor 1 (HNF 1) in a subset of HAs.<sup>20</sup> Subsequently, they

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**Table 1. Clinical, Radiologic and Pathologic Features of Subtypes of HCA**

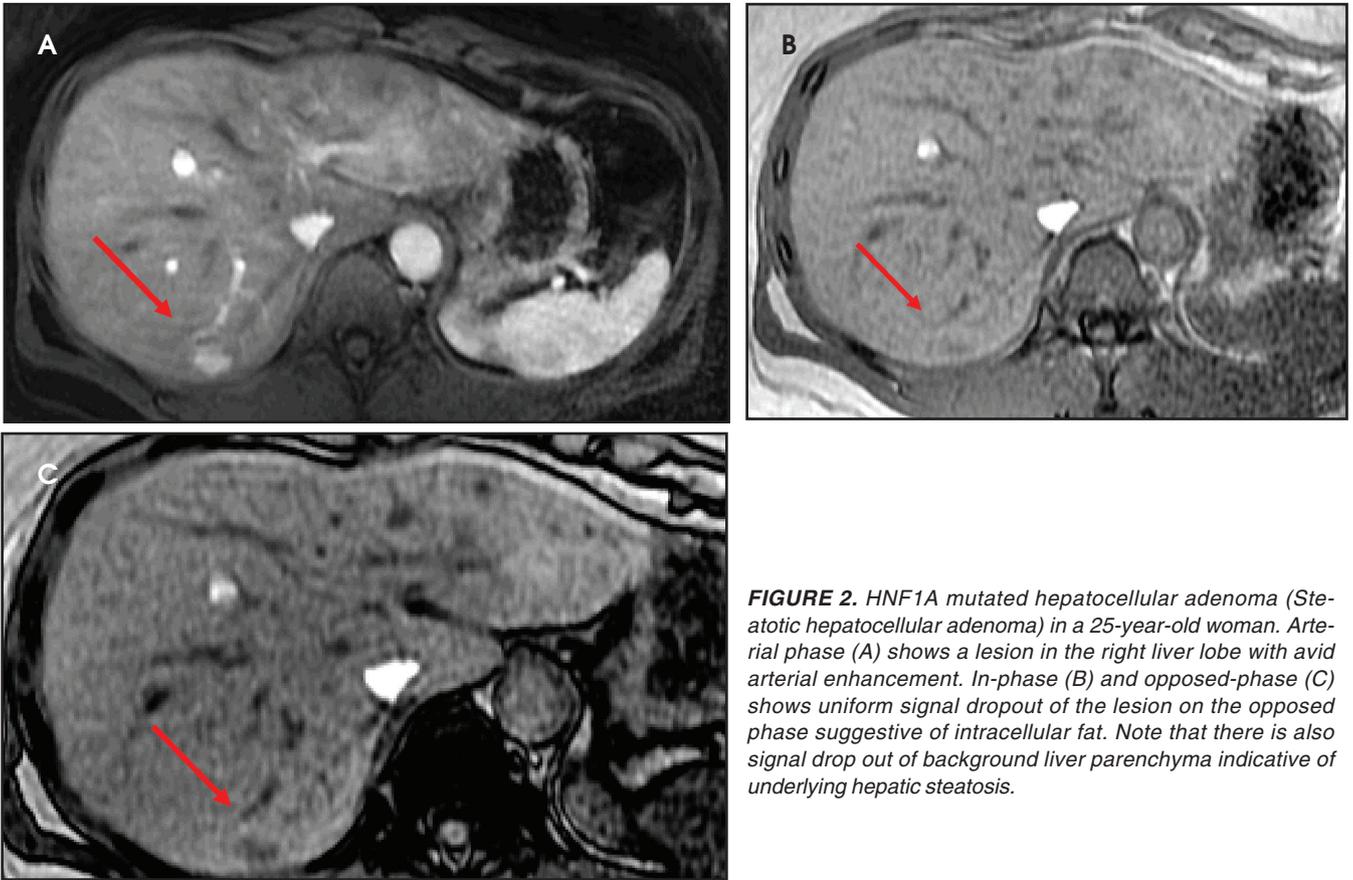
Subtype	Frequency	Clinical features and associations	Imaging features	Pathologic features	Complications
Inflammatory HCA (IL6ST mutations)	Most common: 40%–55%	<ul style="list-style-type: none"> <li>• Obesity</li> <li>• Alcohol use</li> <li>• Hepatic steatosis</li> <li>• Metabolic syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Can mimic FNH</li> <li>• T2 moderate hyperintensity</li> <li>• Intracellular fat seen occasionally</li> <li>• Variable degree of uptake on hepatobiliary phase</li> </ul>	<ul style="list-style-type: none"> <li>• Pseudo-portal tracts with thick arteries, sinusoidal dilatation, and variable steatosis</li> <li>• Increased expression of inflammatory proteins CRP and SAA on immunostaining</li> </ul>	<ul style="list-style-type: none"> <li>• Bleeding is main complication</li> <li>• 10% also express <math>\beta</math>-catenin and hence may show malignant transformation</li> </ul>
HCA with <i>TCF1</i> gene mutation	30%–50%	<ul style="list-style-type: none"> <li>• Hepatic adenomatosis</li> <li>• Maturity-onset diabetes of the young type 3</li> </ul>	<ul style="list-style-type: none"> <li>• Intracellular lipid</li> </ul>	<ul style="list-style-type: none"> <li>• Variable steatosis</li> <li>• Absence of expression of L-fatty acid binding protein on immunostaining</li> </ul>	<ul style="list-style-type: none"> <li>• No significant bleeding risk</li> <li>• No risk for malignant transformation</li> </ul>
$\beta$ -catenin–mutated HCA	10%–18%	<ul style="list-style-type: none"> <li>• Glycogen storage disease</li> <li>• Male hormone administration</li> </ul>	<ul style="list-style-type: none"> <li>• Not usually steatotic</li> <li>• There can be washout during portal venous phase on non-hepatocellular gadolinium contrast agents</li> </ul>	<ul style="list-style-type: none"> <li>• May have cytologic and architectural atypia</li> <li>• Immunostain for <math>\beta</math>-catenin is positive in nuclei</li> <li>• Glutamine synthetase shows diffuse and strong cytoplasm expression</li> </ul>	<ul style="list-style-type: none"> <li>• Malignant transformation</li> </ul>
Unclassified	10%	<ul style="list-style-type: none"> <li>• No specific association</li> </ul>	<ul style="list-style-type: none"> <li>• No specific features</li> </ul>	<ul style="list-style-type: none"> <li>• No specific features</li> </ul>	<ul style="list-style-type: none"> <li>• Increased risk of bleeding in the subset with sonic hedgehog activation</li> </ul>

CRP indicates C-reactive protein; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; SAA, serum amyloid A.

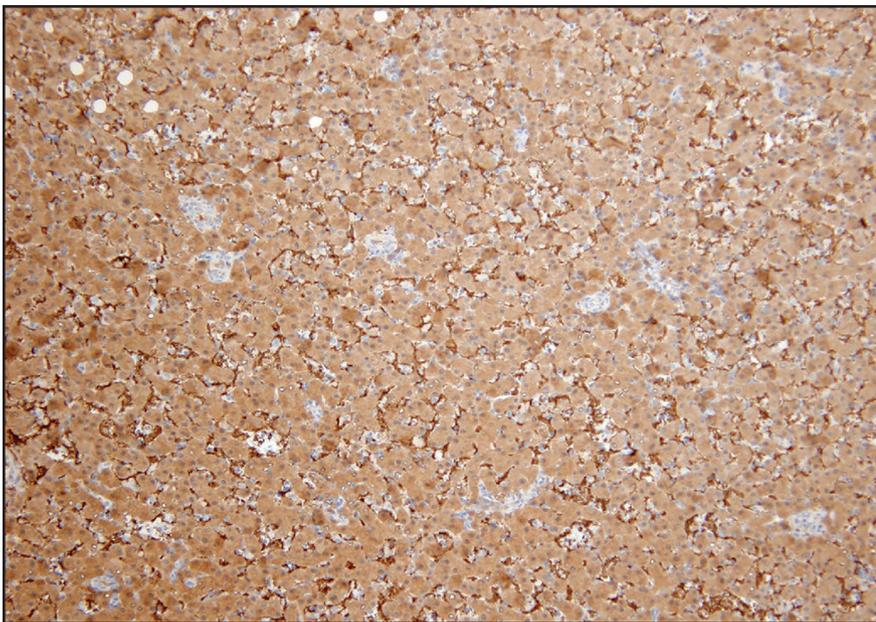


**FIGURE 1.** *HNF1A* mutated hepatocellular adenoma. Immunostain for L-FABP showing loss of expression in tumor, versus retained expression in surrounding non-neoplastic liver.

reported that telangiectatic focal nodular hyperplasias (T-FNHs) are monoclonal lesions and clinically behave similar to HAs without HNF-1- $\alpha$  mutation.<sup>21</sup> These were later classified as inflammatory HAs.<sup>22</sup> Ongoing genomic studies of HAs by the same French group led to the landmark paper in 2006 that introduced the genotype-phenotype taxonomy of HAs.<sup>22</sup> According to this schemata, the HAs are classified into 4 subtypes, of which the first three have unique molecular signatures as well as histological, immunophenotypical and radiological features.<sup>7</sup> These were: 1. HNF-1- $\alpha$  (HNF 1A) mutated HAs; 2.  $\beta$ -catenin mutated HAs; 3. Inflammatory-type HAs. The last group classified as “unclassified” refers to HAs that do not satisfy the diagnostic criterion described in the three other subtypes (Table 1). Using sequencing and gene expression



**FIGURE 2.** *HNF1A* mutated hepatocellular adenoma (Steatotic hepatocellular adenoma) in a 25-year-old woman. Arterial phase (A) shows a lesion in the right liver lobe with avid arterial enhancement. In-phase (B) and opposed-phase (C) shows uniform signal dropout of the lesion on the opposed phase suggestive of intracellular fat. Note that there is also signal drop out of background liver parenchyma indicative of underlying hepatic steatosis.



**FIGURE 3.** *Inflammatory hepatocellular adenoma.* Immunostain for L-fatty acid binding protein with retained cytoplasmic expression in tumor. X100.

profiling, this classification has further been refined recently to include 6 subgroups of HAs.<sup>9, 1, 23</sup> The  $\beta$ -catenin mutated HAs (BHA and IHA with  $\beta$ -catenin mutations) are further split into: (a) BHA

with exon 3 mutations; (b) BHA with exon 7/8 mutations. A subset of unclassified HA has been found to show constitutive activation of sonic hedgehog (shh) pathway due to overexpression of

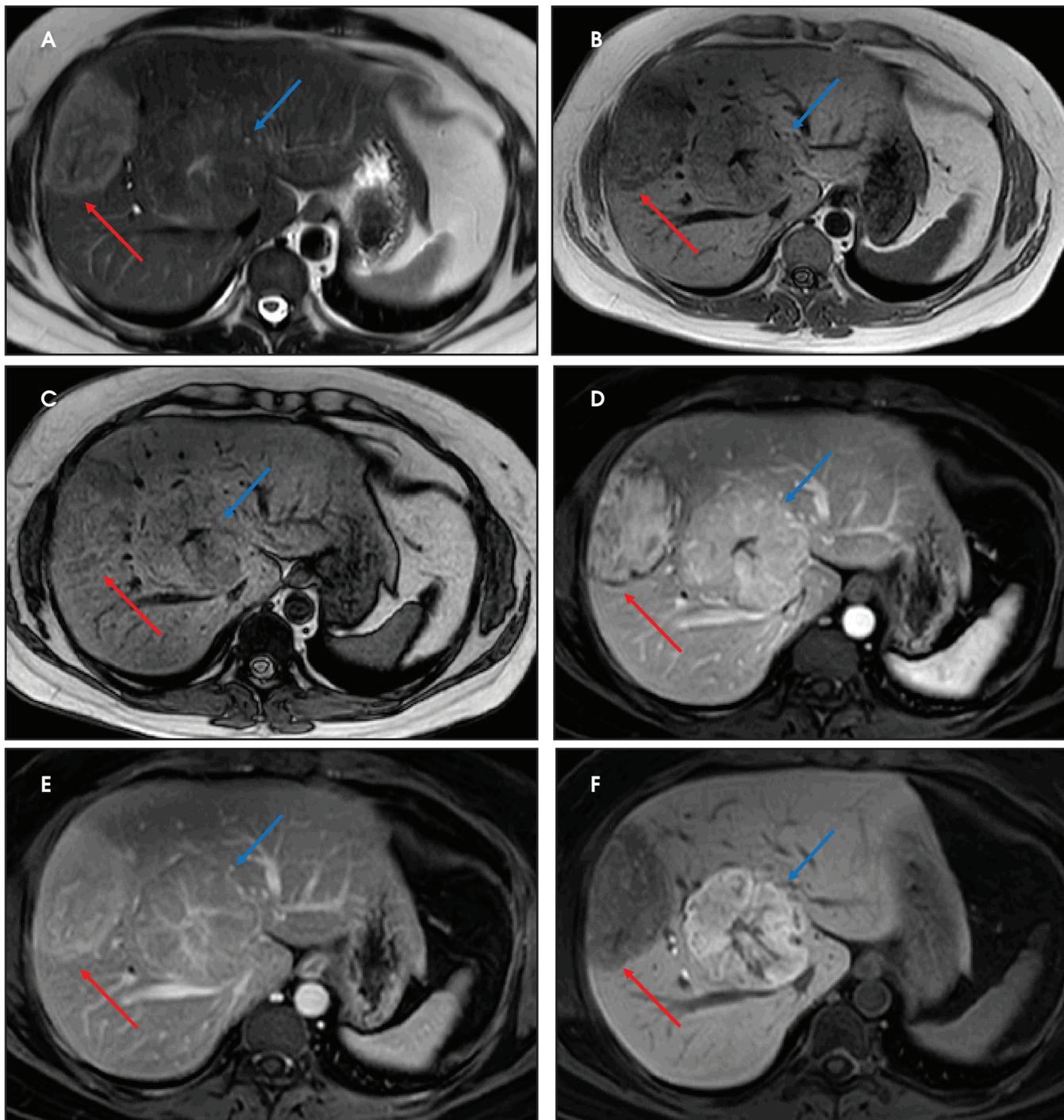
GLI family zinc finger 1 (GLI1). These HAs are associated with a higher risk of bleeding. They do not have specific morphological features or immunoppression profiles.

We will focus on four subtypes of HAs in this review, as radiologic features of the newer subtypes are not well defined. Clinical implementation of this classification in diagnostic medicine has brought about a paradigm shift in the management of HAs, as this helps determine the potential for complications including bleeding and malignant transformation, and thereby guide further management in terms of resection and/or surveillance.

**Pathology**

**Gross evaluation**

Hepatocellular adenomas are well-demarcated lesions that can occasionally be encapsulated and range in size from 1-30 cm.<sup>8</sup> HA may present as a solitary mass or as multifocal, variably sized, soft tissue masses. They typically arise in non-fibrotic liver, however, they may

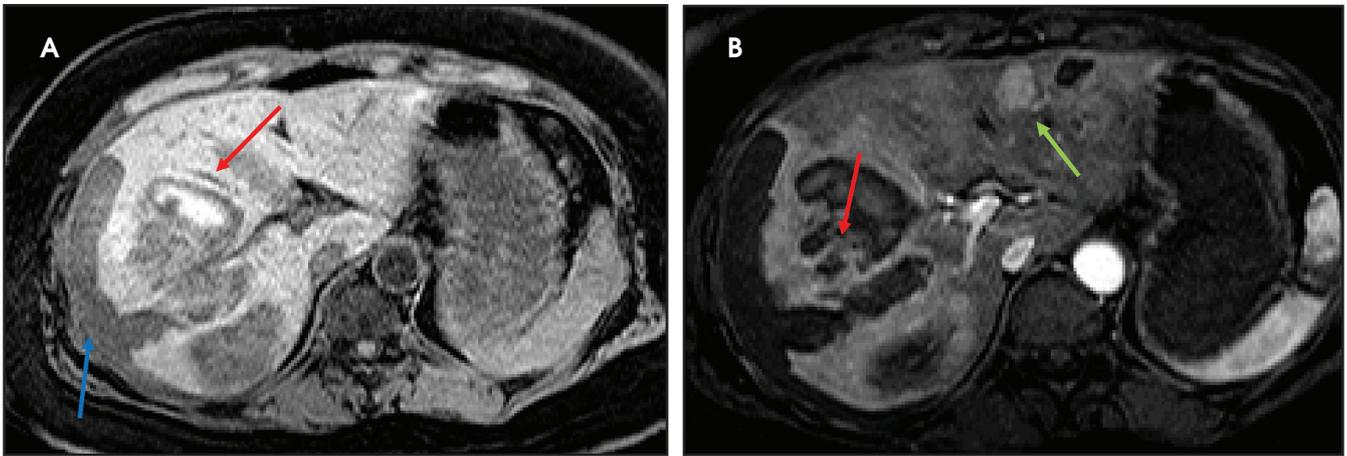


**FIGURE 4.** Large inflammatory hepatocellular adenoma (IHA) in a 30-year-old woman along with associated focal nodular hyperplasia (FNH). (A) Moderately heterogeneous, mildly hyperintense lesion (IHA) is seen in the right lobe on a T2-weighted image (red arrow). Incidental iso-intense lesion (FNH) with a central scar (blue arrow). In-phase (B) and out-of-phase (C) images demonstrate no signal loss within the both lesions. Arterial (D) and portal venous phase (E) post gadoxetic acid images show marked heterogeneous hyperenhancement of the adenoma (IHA) (red arrow) and moderate enhancement of the FNH with a central scar (blue arrow). Hepatobiliary phase image (F) reveals the lateral lesion (IHA) with mild and heterogeneous retention of contrast (red arrow) and intense uptake within the medial lesion (FNH).

occur in the background of cirrhosis. HAs reported in the setting of cirrhosis are usually of the inflammatory subtype.<sup>24-26</sup> Rare cases of multiple HNF-

1- $\alpha$  mutated HAs has been reported to occur in the background of congenital hepatocellular fibrosis.<sup>27</sup> The cut surface of HA may be tan-yellow or red-brown

depending upon the presence of steatosis or peliosis/hemorrhage/old hemorrhage, respectively. Inflammatory HA shows alternating pale red and dark-red surface.<sup>8</sup>



**FIGURE 5.** Ruptured inflammatory hepatocellular adenoma in a 25-year-old woman presenting with acute right upper quadrant pain and hypovolemic shock. Precontrast (A) and arterial phase (B) MR images show a focal lesion involving the right lobe of the liver. On the pre-contrast image, the lesion is heterogeneously hyperintense (red arrow in A), with associated blood products (blue arrow in A) in the perihepatic space, a finding consistent with rupture. The mass shows heterogeneous enhancement during the arterial phase (red arrows in B). In addition, in the arterial phase, the left hepatic lobe has an enhancing focal lesion (green arrow in B), a finding consistent with a second adenoma.

### Microscopic evaluation

Hepatocellular adenoma is classically characterized by sheets of benign-appearing hepatocytes with interspersed thin-walled, unpaired arteries. The hepatocyte trabeculae are 1-3 cells thick and the reticulin framework is preserved. Portal tracts containing portal veins or bile ducts are absent. Few randomly distributed pseudo-portal tract areas with thick walled vessels and ductular reaction can be seen in some HAs. Other variable features include steatosis, inflammatory cell infiltrate, sinusoidal dilatation, myxoid changes<sup>(28)</sup> and presence of pigments such as bile pigment, lipofuscin or Dubin Johnson-like pigment.<sup>29,30</sup>

### Radiologic and pathologic features of subtypes of hepatocellular adenoma

#### *Hepatocyte nuclear factor-1- $\alpha$ (HNF1A) mutated Hepatocellular adenoma*

These comprise 35% to 40% of all HA. Their molecular signature is characterized by bi-allelic inactivating mutations of TCF-1, a tumor suppressor gene, located on long arm of chromosome 12, and encodes for transcription factor HNF-1A, which is involved in hepatocyte differentiation and expression of certain genes encoding for albumin,  $\beta$ -fibrinogen and  $\alpha$ -1-antitrypsin.<sup>20</sup> The mutations are largely somatic,

however, germline mutations of TCF1 (HNF1A) gene are associated with type 3 maturity onset diabetes of the young (MODY 3). This is an autosomal dominant disease, which presents in early adulthood and is associated with development of familial adenomatosis.<sup>17</sup> HNF1A mutation down-regulates liver type-fatty acid binding protein (L-FABP) and causes lipogenesis by promoting fatty acid synthetase.<sup>31</sup>

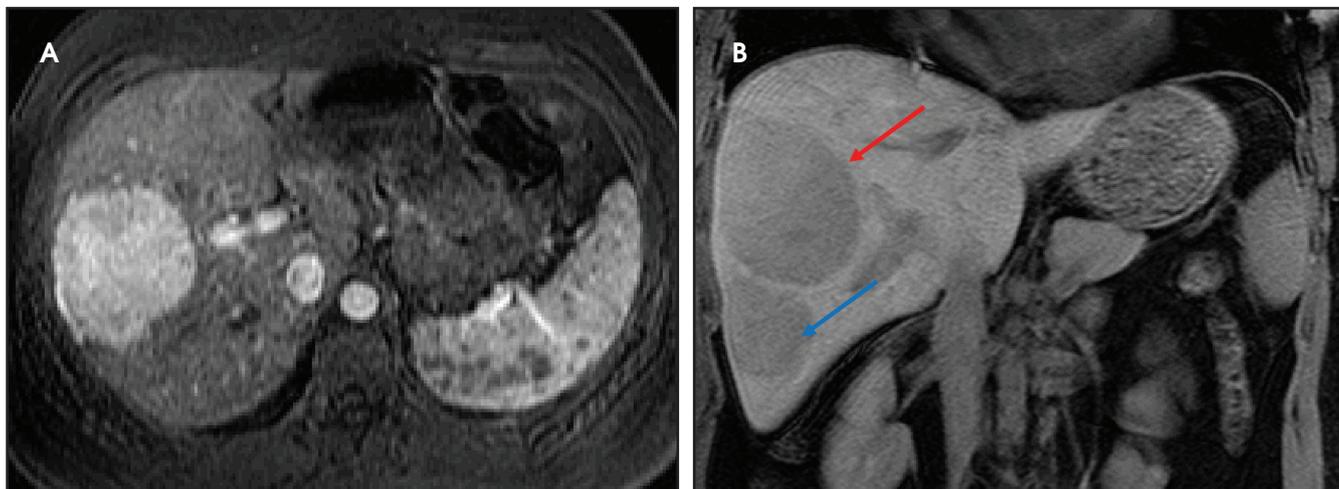
Gross examination of HNF1A mutated HA shows a well-demarcated solid tumor with a tan-yellow soft to firm cut surface. The phenotypic correlate of above-mentioned molecular alterations is presence of moderate to diffuse steatosis in majority of HNF1A mutated HA. No significant inflammation or cellular atypia is seen. Immunostaining with antibodies to L-FABP shows loss of expression in the HA, whereas, the expression is preserved in the surrounding non-neoplastic liver parenchyma (Figure 1).

HNF-1 $\alpha$ -mutated HAs are associated with MODY type 3 and hepatic steatosis. MR imaging findings include isointense signal on T2WI, isointense on T1WI and typically show intracellular lipid as evidenced by diffuse signal drop-off on a chemical shift sequence (Figure 2).<sup>10,18,19,32</sup> HNF-1 $\alpha$ -mutated HAs demonstrate intense enhancement in the arterial phase and become

isointense to the liver parenchyma in the portal venous and delayed phases. These lesions remain hypointense on HBP phase with hepatocyte specific gadolinium agents. Tumors less than 5 cm in maximum dimension show minimal risk of bleeding and carry minimal or no risk for malignancy.<sup>10,18,19</sup>

#### *Inflammatory hepatocellular adenoma (IHCA)*

Historically, IHCA were referred to as telangiectatic FNHs until 2004-2005, when studies showed these to be monoclonal neoplasms, which behave biologically similar to HAs. IHCA comprise about 30-35% of all HAs. This subtype of HA is characterized by activation of signal transducer and activation of transcription 3 (STAT 3) signaling pathway leading to induction of acute phase inflammatory response within the tumoral hepatocytes. About two-thirds of IHCA show mutations of interleukin 6-signal transducer gene (IL6ST gene), which encodes for glycoprotein 130 (gp130), a component of IL-6 receptor. Activation of IL-6 promotes the STAT3 signaling pathway. About one-third of the HAs do not show mutations of IL6ST gene, yet, show evidence of STAT 3 activation and gp130 protein expression through unknown mechanisms. About 10% of IHCA show concomitant  $\beta$ -catenin mutations.



**FIGURE 6.**  $\beta$ -catenin–mutated hepatocellular adenoma in a 35-year-old woman. Arterial phase post-gadobenate dimeglumine image (A) shows heterogeneous hyperenhancement of the lesion. The mass (red arrow) shows uniform hypoenhancement relative to adjacent liver on a hepatobiliary phase image (B) obtained 20 min following gadobenate dimeglumine injection. In addition, in the hepatobiliary phase, the right hepatic lobe has another hypoenhancing focal lesion (blue arrow in B), a finding consistent with a second adenoma.

Gross characteristics of IHCA include a well-demarcated tumor with red-brown variegated cut surface. Histologically, these are characterized by sinusoidal dilatation, peliosis, presence of pseudo-portal tracts like areas with dystrophic blood vessels, ductular reaction and varying degree of inflammatory infiltrates. Focal steatosis may be seen in some cases. Immunohistochemical staining with antibodies to acute phase inflammatory reactants, serum amyloid A (SAA) and C reactive protein (CRP), show diffuse cytoplasmic expression of both SAA and CRP. Immunostain for L-FABP shows retained cytoplasmic expression in tumoral hepatocytes (Figure 3). IHCA with  $\beta$ -catenin mutations show nuclear expression of  $\beta$ -catenin on immunohistochemical staining. Glutamine synthetase is a surrogate marker of  $\beta$ -catenin mutation.<sup>33</sup> Some IHCAs with  $\beta$ -catenin mutations may be positive or negative for nuclear  $\beta$ -catenin expression on immunostaining, but will show strong diffuse/patchy cytoplasmic staining for glutamine synthetase.<sup>34</sup> These  $\beta$ -catenin mutations may occur on exon 3 or exon 7/8.<sup>1,23</sup>

Inflammatory HAs show mild to moderate hyperintense signal on T2WI and are iso-intense or mildly hyperintense on T1WI with no significant signal drop-off with chemical shift

imaging.<sup>32</sup> After administration of extracellular gadolinium-based contrast material, IHAs usually show intense enhancement during the arterial phase, with persistent enhancement in the portal venous and delayed phases. IHAs may show uptake of hepatobiliary specific gadolinium agent and may show peripheral rim like uptake or heterogeneous internal retention of contrast on the hepatobiliary phase.<sup>32,35</sup> (Figure 4). Inflammatory HAs show the highest risk of bleeding due to the presence of sinusoidal dilatation, which can occur in about 30% of these tumors and particularly seen in tumors larger than 5 cm maximum dimension and subcapsular tumors (Figure 5). About 10% of inflammatory HAs show an increased risk of malignancy.<sup>10,18,19</sup>

#### ***$\beta$ -catenin activated hepatocellular adenoma (BHA)***

These adenomas comprise about 20% of all HAs.<sup>8</sup> Wnt/ $\beta$ -catenin pathway is involved in hepatocellular development and zonation. In normal, non-neoplastic hepatocytes, activation of  $\beta$ -catenin protein is transient followed by degradation. Mutations of  $\beta$ -catenin gene (CTNNB1 gene) lead to production of mutant protein that has prolonged half-life and is resistant to degradation.<sup>36</sup> In 10% of cases, there are deletions CTNNB1 exon 3 leading

to decrease in  $\beta$ -catenin degradation.<sup>1,23</sup> In other cases, there are point mutations targeting hotspots in exon 3 or those in exon 7/8.<sup>4,9</sup>

Gross characteristics of  $\beta$ -catenin mutated HA are unremarkable. They may present as well-demarcated tumors with fleshy cut surface. Histologically, they lack a distinctive morphology. They are composed of sheets of hepatocytes with interspersed unpaired arteries. Some may show cytologic and architectural atypia characterized by pseudoacinar formation. Steatosis is not a typical feature. Immunostain for beta-catenin will show nuclear beta-catenin staining, however, this can be very focal in distribution. Glutamine synthetase is a surrogate marker for  $\beta$ -catenin mutation. Immunostain for glutamine synthetase shows strong diffuse cytoplasmic staining, however, the staining can be heterogeneous and variable.<sup>23</sup>

No specific imaging findings have been reported to diagnose  $\beta$ -catenin–mutated hepatocellular adenomas on imaging. T1 and T2 signal of these tumors is variable depending on the presence of hemorrhage and/or necrosis.<sup>10,18,19</sup>  $\beta$ -catenin–mutated HAs commonly demonstrate strong arterial enhancement with portal venous washout and no uptake on hepatobiliary phase (Figure 6). The risk of hepatocellular carcinoma is about 5%–10% in these HAs.  $\beta$ -catenin–

mutated HAs carry the highest risk of malignancy.<sup>10,18,19</sup>

### Hepatocellular adenoma unclassified

Unclassified HA constitutes 10% of all HAs and these tumors do not show any specific genetic abnormalities. No specific MR imaging findings are reported to identify unclassified HAs.<sup>10,18,19</sup>

### Conclusion

Hepatocellular adenomas are a diverse group of benign liver neoplasms with increased propensity to bleed and to undergo malignant transformation. Recent genetic studies have identified several subtypes with distinctive tumor genetics and pathways as well as specific risk factors and risks of complications. MRI plays a key role in the diagnosis and classification of HAs as well as in surveillance. Hepatocellular adenomas with  $\beta$ -catenin mutations frequently undergo malignant change, inflammatory HAs commonly bleed, and steatotic HAs typically portend a favorable prognosis. A knowledge of the clinical and imaging findings and associated complications of the subtypes of hepatocellular adenoma permit optimal patient management.

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