Management of Hepatocellular Adenoma: Recent Advances

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Hepatocellular adenoma (HCA) is a rare benign liver cell neoplasm that occurs more frequently in young women with a history of prolonged use of oral contraceptives. Surgical resection is considered because of the risk of hemorrhage in 25% and of malignant transformation in 5% of patients with HCA. HCA is a heterogeneous disease comprising 3 subtypes with distinct molecular and complication profiles. The inflammatory or telangiectatic subtype is at increased risk for hemorrhage, the β-catenin-activated subtype is at increased risk for malignant transformation, and the hepatocyte nuclear factor-1α-inactivated or steatotic subtype is at the least risk for complications. One-third of the patients with HCA have multiple tumors on imaging with no increased risk of complications. Magnetic resonance imaging is the modality of choice for the diagnosis and subtype characterization of HCA. Systematic resection of HCA is recommended in male patients owing to the higher incidence of malignant transformation, and surgical excision in women should be reserved for tumors 5 cm or larger associated with an increased risk of complications. Cessation of hormonal therapy and radiologic surveillance in women with HCA tumors smaller than 5 cm shows that the vast majority of HCA remain stable or undergo spontaneous regression. Percutaneous core needle biopsy is of limited value because the therapeutic strategy is based primarily on patient sex and tumor size. Transarterial embolization is the initial treatment for HCA complicated by hemorrhage. Pregnancy should not be discouraged in the presence of HCA, however; frequent sonographic surveillance is recommended.

Keywords: Hepatocellular Adenoma; Malignant Transformation; Hemorrhage; Liver Resection; Conservative Management; Pregnancy.

Pathogenesis

Although identification of genetic mutations has provided novel insight into the pathogenesis of HCA, hormonal therapy remains the dominant predisposing factor in the development of HCA. Other drugs implicated in its development include anabolic androgenic steroids for aplastic or Fanconi’anemia, hereditary angioedema, and athletic performance enhancement is a risk factor for the development of HCA and potentially the imbalance in endogenous sex hormones in Klinefelter’s and polycystic ovarian syndromes. Other drugs implicated in its development include barbiturates, clomiphene, and recombinant human growth hormone.

Genetic syndromes including familial adenomatous polyposis and glycogen storage diseases (GSDs) are associated with HCA tumors, which occur in 75% of patients with GSD type Ia, and more than half of the patients have multiple tumors. Other underlying metabolic diseases include maturity-onset diabetes of the young type 3 and McCune–Albright syndrome. In patients without an identifiable etiology for HCA, an association with environmental factors such as obesity and alcohol consumption has been reported, with multiple tumors being frequent in the presence of hepatic steatosis. In a review of 27 patients with inflammatory HCA, 61% were overweight, of whom more than half were obese. In an

Abbreviations used in this paper: CT, computed tomography; FHN, focal nodular hyperplasia; GSD, glycogen storage disease; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; HNF, hepatocyte nuclear factor; MRI, magnetic resonance imaging; OC, oral contraceptive; TAE, transarterial embolization.
evolving epidemiologic environment for the development of HCA, obesity and metabolic syndrome are emerging as important risk factors with a diminishing impact of OCs. Abnormalities of the hepatic vasculature including the absence or occlusion of the portal vein and intrahepatic portosystemic venous shunt also are considered predisposing factors in the pathogenesis of HCA.\textsuperscript{37–39}

**Pathology**

HCCs usually are solitary, well-delineated, and, occasionally, pedunculated tumors with parenchyma composed of plates of hepatocytes separated by sinusoids without portal tract elements or bile ductules, a key feature in the histologic distinction of HCA from focal nodular hyperplasia (FNH).\textsuperscript{40} Inflammatory HCA is an exception because it shows ductular structures unlike other HCA subtypes, which previously led to its classification as telangiectatic FNH.\textsuperscript{41} HCA may be complicated by necrosis or hemorrhage because the thin-walled sinusoids are supplied by the high-pressure arterial system and the absence of a capsule with prominent subcapsular vessels predisposes to tumor rupture and free intraperitoneal hemorrhage. Distinguishing HCA from a well-differentiated hepatocellular carcinoma

<table>
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<th>Table 1. Genotype–Phenotype Classification of HCA</th>
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<td><strong>Inflammatory HCA</strong></td>
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<td><strong>Epidemiology</strong></td>
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<td>Predominantly seen in women</td>
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<td>Associated with a high BMI, alcohol consumption, and systemic inflammatory syndrome</td>
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BMI, body mass index; MODY, maturity-onset diabetes of the young.
(HCC) may be difficult in some cases and the loss of normal reticulin stain in HCA may suggest a HCC.\textsuperscript{10,42} Malignant transformation of HCA is based on the demonstration of a transition zone with dysplastic changes within HCC or a pattern of a nodule within a nodule or 2 adjacent tumors without a transition zone.\textsuperscript{11,43}

**Genotype–Phenotype Classification**

Identification of genetic heterogeneity in HCA tumors was the basis of the molecular classification,\textsuperscript{44–47} with distinct epidemiologic and clinical features of each subtype. HCA tumors were classified into 3 subtypes, namely, inflammatory, hepatocyte nuclear factor (HNF)-1\(\alpha\)–inactivated, and \(\beta\)-catenin–activated based on specific genetic mutations. Approximately 10\% of HCAs remain poorly characterized with no identifiable clinical or molecular markers and are designated as unclassified.\textsuperscript{3} The clinicopathologic and immunohistochemical characteristics of each subtype are shown in Table 1 and Figure 1.\textsuperscript{48–53} The specific phenotypic and complication profile of each HCA subtype may have an important role in the establishment of an individualized management strategy.

**Needle Biopsy**

In the vast majority of hepatic tumors, high-quality imaging permits accurate characterization and diagnosis, rendering a percutaneous core needle biopsy unnecessary.\textsuperscript{54} An image-guided percutaneous biopsy of the liver tumor may be useful when radiologic findings are nondiagnostic, and specific patterns of immunostains analyzed by an expert pathologist may be helpful in the distinction of HCA from FNH, well-differentiated HCC, or steatotic nontumoral liver.\textsuperscript{55–58} In a review of 239 needle biopsies, a diagnosis of HCA was established with routine staining of core needle biopsy specimens in 58.6\% of patients, which increased to 74.3\% after the use of
specific immunostains including identification of HCA subtypes with a similar distribution in surgical specimens.57

**Radiologic Diagnosis**

Most HCAs are diagnosed on contrast-enhanced, multiphase computed tomography (CT) or magnetic resonance imaging (MRI).59 Multiphase dynamic contrast-enhanced MRI is considered the modality of choice in the diagnosis of HCA and its subtypes.4,5,60–63 HCAs typically are hypoattenuating on noncontrast CT, hypervascular and heterogeneous on the arterial phase, and isoattenuating or hypoattenuating on the portal venous phase of contrast-enhanced CT scan.61 The accurate diagnosis of HCA and its differentiation from other benign hepatic tumors, particularly FNH, is important. Arterial enhancement is a common feature of HCA and FNH, and hepatocyte-specific contrast agents allow differentiation between the 2 lesions when standard imaging is indeterminate, as shown in Figure 2.64,65

Laumonier et al4 and Ronot et al5 described MRI as a useful tool for the identification of the 2 major HCA subtypes: HNF-1α–inactivated and inflammatory HCA with specific features related to intratumoral steatosis and sinusoidal dilatation, respectively. The typical MR findings of the HCA subtypes are summarized in Table 1. Heterogeneity of signal intensity on T2-weighted images owing to the presence of fat, hemorrhage, or necrosis is one the most consistent features of HCA.63 Findings of marked hyperintensity on T2-weighted images with delayed persistent enhancement in inflammatory HCA and diffuse signal drop-out on chemical shift imaging as a result of diffuse intratumoral steatosis in HNF-1α–inactivated HCA are highly sensitive and specific as shown in Figures 3 and 4.4,66 On contrast-enhanced ultrasound, homogeneous hyperechogenicity correlated with fat content in HNF-1α–inactivated HCA and arterial hypervascularity with centripetal filling was predictive of inflammatory HCA.5,67 Unclassified and β-catenin–activated HCA were not characterized by any specific MR features and the latter subtype may mimic HCC.

Inflammation may be seen in the β-catenin–activated tumors showing a MR pattern typical of inflammatory HCA tumors.

**Clinical Features and Treatment Outcome**

The increased use of diagnostic abdominal imaging has led to an increase in the incidental diagnosis of HCA.1,16 More than half of the patients are asymptomatic and abdominal pain is the most common symptom in the other patients, usually related to tumoral hemorrhage.8,68,69 Abnormal liver function tests may occur in patients with large HCA tumors including increased γ-glutamyl transferase levels, alkaline phosphatase secondary to cholestasis, or an increase in transaminase levels as a result of hepatic steatosis.9 Serum biomarkers of inflammation including fibrinogen and C-reactive protein were increased in 90% of patients with inflammatory HCA and returned to normal after surgical resection of the tumor.35

**Hemorrhage**

Hemorrhage occurs in 21% to 40% HCAs.8–10,70–74 Bleeding is intratumoral in most cases, however, it may cause rupture of the tumor, leading to subcapsular or intraperitoneal hemorrhage. Hemorrhage occurs predominantly in HCA tumors greater than 5 cm and other risk factors include inflammatory subtype, increasing tumor size, hormone use within the past 6 months, and pregnancy.3,8,10,68,69 Rupture of HCA may present with severe abdominal pain and free intraperitoneal hemorrhage, however, hemodynamic instability is uncommon, permitting conservative management in most cases.3,71,74 Initial stabilization and selective transarterial embolization (TAE) is preferred because emergent surgery for ruptured HCA has a mortality rate of 5% to 10% and delayed resection is associated with lower surgical risk, blood loss, postoperative complications, and a shorter length of stay.9,16,69,74,75
Malignant Transformation

The risk of malignant transformation in HCA is 5% and its predictors are patient sex, tumor size, and subtype. A 6- to 10-fold higher incidence of malignant transformation has been reported in men, and systematic resection of HCA regardless of the tumor size is recommended in men.9,11 As systematic review of the literature showed only 3 cases of HCC in tumors measuring smaller than 5 cm, with the smallest measuring 4 cm.9,10,76 Patients with Fanconi’s anemia are at increased risk for developing HCC, which may result from the malignant transformation of HCA tumors developing secondary to androgen treatment.77 β-catenin mutations are associated with an increased risk of malignant transformation and up to 46% of β-catenin-activated HCA may show the presence of HCC (Table 1).9,10 Approximately 10% of inflammatory HCA show a mutated β-catenin gene and malignant transformation.3,16,46 Hepatocellular dysplasia, a premalignant condition, may be present in HCA with malignant degeneration, however, some investigators have questioned the progression of HCA to HCC.9,43,78,79 HCC within HCA usually is identified on the surgical specimen because the preoperative serum α-fetoprotein level typically is normal, with no vascular involvement or satellite nodules, and the tumor is well differentiated, rendering diagnosis on biopsy difficult.9,10,77 The prognosis after complete resection of HCA with malignant degeneration is favorable and recurrence is uncommon.9,43 These cases should be distinguished from the exceptional cases of multiple degenerated HCC occurring in young severely asthenic women with symptomatic hepatomegaly and high α-fetoprotein levels.

Multiple Hepatocellular Adenomas

A third of patients with HCA may be diagnosed with multiple tumors on imaging and radiographically undetected microadenomas have been reported on resected specimens of a single HCA.9,10,16 Conditions of obesity, hepatic steatosis, and metabolic syndrome are associated with multiple HCAs.15,32-36 The development of complications including hemorrhage or malignant transformation is unrelated to the number of HCA tumors.9,10,60,81 HCA tumors in liver adenomatosis are predominantly of the low-risk HNF-1α-inactivated subtype.15,82 Long-term follow-up evaluation of small residual HCAs after surgical resection showed that 90% of tumors remained stable, regressed, or completely disappeared.9 Because of several obstacles to liver transplantation for GSD 1a, resection of enlarging HCA tumors may be an effective intermediate step in the prevention of HCC.83,84 Genetic counseling is recommended for patients with liver adenomatosis, particularly for the familial variant, and screening of their relatives with HCA and maturity-onset diabetes of the young type 3.15,49

Pregnancy

HCA in pregnancy requires special consideration because of the potential for hormone-induced growth and rupture, however, the majority of HCAs remain stable during pregnancy.9,85,86 Most tertiary care centers
with hepatobiliary surgeons do not discourage pregnancy in women with HCAs smaller than 5 cm provided the patients are accompanied and likely to be compliant with sonographic monitoring every 3 months and in the postpartum period.9,10,59,86–89

**Therapeutic Strategy**

The diagnosis of HCA, particularly in a young woman, has significant implications considering potential tumor-related complications, impact on future pregnancies, use of OCs, and major surgical intervention.9,16 Systematic resection of newly diagnosed HCA owing to the risk of tumor-related complications is no longer acceptable and the initial management is conservative with a selective policy of intervention in tumors at increased risk of complications.9–11,59 Considerations for invasive treatment for HCA include patient sex, tumor size, and subtype (Figure 5). The application of percutaneous biopsy in the decision making for subtyping of HCA tumors is variable, with some investigators advocating a

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**Figure 4.** Gadolinium-enhanced MRI of HNF-1α-mutated HCA. (A) A T1 in-phase image shows a lesion (arrow) that is iso-intense in comparison with the surrounding liver and (B) an out-of-phase image shows a signal decrease within the lesion (arrow) compatible with intra-tumoral fat.

**Figure 5.** Management of HCA. Current diagnostic accuracy of MRI for the subtyping of HCA now limits the impact of biopsy on decision making to a restricted number of situations. These include doubtful cases after complete imaging work-up and the remaining cases in which pathologic results will have an impact on the management of the lesions. One situation that may require percutaneous liver biopsy is the MRI suspicion of a steatotic lesion greater than 5 cm in a female patient. In such context, obtaining clear pathologic confirmation of the HNF-1α subtype is mandatory to support a nonsurgical management.
Intraoperative ultrasound is useful because HCA tumors often are soft and nonpalpable with ill-defined margins between the tumor and the adjacent steatotic hepatic parenchyma. In patients with a large HCA, a 2-step surgical approach with portal vein occlusion may be required. Resection is not indicated for multiple tumors smaller than 5 cm because the vast majority of residual HCAs remain stable or undergo spontaneous regression.9 Intrahepatic portosystemic venous shunt is a predisposing factor in the pathogenesis of HCA and its treatment requires closure by transcatheter embolization or surgical resection.37,93,94 Failure to close the shunt may result in progression of the residual HCAs.38 Seyama et al17 recommend simultaneous resection of the HCAs and closure of the shunt, which resolves the disturbance in the hepatic vascularity and may reduce the multicentric occurrence of HCA.

TAE is recommended for HCA complicated by hemorrhage. Patients with tumor hemorrhage rarely present with hemodynamic instability, permitting initial TAE followed by delayed surgery. TAE is indicated within 2 to 3 days after tumoral hemorrhage and is best performed using a selective approach. During the first week after the procedure, there may be abdominal pain, fever, right pleural effusion, and increased transaminase levels, which generally return to normal in the second week. The patient may be discharged with advice to discontinue hormonal therapy and undergo a CT scan after a month and every 3 months thereafter. Liver resection is considered only after resorption of the peritumoral hematoma, usually 6 months after the initial hospitalization. TAE may result in regression or complete involution of the tumor, and the absence of residual tissue on MRI may justify a nonsurgical approach with surveillance whereas radiographic persistence of HCA tissue remains an indication for surgical resection.9,10,95–98 Tumor regression after TAE for hemorrhagic HCA has led to utilization of this approach for the elective reduction of tumor mass in unruptured HCA.13,69 TAE is minimally invasive, safely repeated, and 80% of tumors may show stability, regression, or complete involution.13,14,99 Although these results are reported in small tumors, TAE may be used in the management of large multiple or bilateral tumors or preoperative reduction in tumor size.14,95

Radiofrequency ablation may be appropriate for patients who are not surgical candidates, express an active desire for pregnancy with hormone-sensitive tumors, have a centrally located tumor, underlying liver disease, or show progression of residual tumors after resection.9,10,12,100–103 The size of the HCA should be smaller than 4 cm for effective ablation and initial experience suggests it is safe and well tolerated.104

Liver transplantation is no longer indicated for multiple unresectable HCA tumors and a favorable long-term outcome does not justify the use of limited grafts.9,15,82

In exceptional cases, liver transplantation may be
considered for multiple unresectable HCA tumors in men or those associated with an intrahepatic portosystemic venous shunt. Despite the tendency for HCA progression in GSD Ia, there is no increased risk of hemorrhage or malignant transformation. Although liver transplantation provides definitive treatment for GSD Ia by correcting the underlying enzymatic defect, it should be considered only based on the condition of the underlying liver parenchyma.

In conclusion, the inability to differentiate HCA from other benign tumors or to identify patients at increased risk for tumor-related complications may result in unnecessary liver resections. With the increasing incidence of metabolic syndrome, association of HCA with obesity and hepatic steatosis, and recognition of low-risk HCA subtypes, a selective approach to intervention may be considered. Although advances in immunohistochemical techniques have enhanced the ability to identify high-risk HCA subtypes, tumor size and patient sex are the primary criteria in the selection of patients for invasive treatment and the choice of the optimal therapeutic modality. Furthermore, the long-term outcome of a selective approach to HCA management requires systematic evaluation and, given the rarity of the disease, it may require a multicenter study.

References


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Conflicts of interest
The authors disclose no conflicts.