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STATE OF THE ART

Biologic and Clinical Features of Benign Solid and Cystic Lesions of the Liver

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This article has an accompanying continuing medical education activity on page e71. Learning Objectives—At the end of this activity, the learner will know the different types, the clinical features, and the diagnosis and treatment options for patients with benign solid and cystic lesions of the liver.

The widespread use of imaging analyses, either routinely or to evaluate symptomatic patients, has increased the detection of liver lesions (tumors and cysts) in otherwise healthy individuals. Although some of these incidentally discovered masses are malignant, most are benign and must be included in the differential diagnosis. The management of benign hepatic tumors ranges from conservative to aggressive, depending on the nature of the lesions. New imaging modalities, increased experience of radiologists, improved definition of radiologic characteristics, and a better understanding of the clinical features of these lesions have increased the accuracy of diagnoses and reduced the need for invasive diagnostic tests. These advances have led to constant adjustments in management approaches to benign hepatic lesions. We review the biologic and clinical features of some common hepatic lesions, to guide diagnosis and management strategies.

Keywords: Adenoma; Hepatocellular; Hyperplasia; Hemangioma; Polycystic Liver Disease; Cystadenoma.

Solid Lesions

The clinical features of several solid hepatic lesions are summarized in Table 1. The pathology and histology of the major lesions are discussed in the Supplementary Material.

Hepatocellular Adenoma

Hepatocellular adenoma (HCA) is a benign neoplasm that tends to develop in individuals with a hormonal or metabolic abnormality that can stimulate hepatocyte proliferation. A consecutive autopsy study found a frequency of these lesions at 12 per 100,000[1] while an ultrasound (US) study found the incidence to be 7 per 100,000[2]; however, there was a marked increase in the incidence of these lesions after the introduction of oral contraceptive (OCP) therapy such that the estimated incidence in women not taking OCPs was 1 to 1.3 per million with an increase to 3.4 per 100,000 in women taking estrogen therapy[3] suggesting a causal relationship between OCPs and hepatic adenomas.

HCAs are found predominantly in women in their third and fourth decades and are most often solitary and located in the right hepatic lobe (Table 1).[3,4] Liver adenomatosis has been variably defined as having anywhere from >3 to ≥10 adenomas, and is generally considered a separate entity from a solitary HCA.[5,6] In addition to a higher prevalence, cases of HCA in women taking OCPs tend to be more symptomatic.[7] HCA has a tendency to regress after discontinuation of OCP therapy, making the connection between the 2 even more definitive.[8,9] While a more recent study concluded that women taking later generation OCPs were not at an increased risk for developing HCA,[10] another study found that estrogen and androgen receptors were present on up to 1 third of HCAs,[11] and HCAs have been known to enlarge during pregnancy,[12] lending additional support to the notion that female sex hormones play a role in tumor development.

Along with OCP use, several metabolic conditions and therapeutic drugs have been associated with HCA tumorigenesis. The use of anabolic androgen steroids (AAS) can lead to the development of HCA.[13,14] Androgens do not only increase the likelihood of developing HCA in males; individuals, male or female, with high levels of endogenous androgens or estrogens are also at risk for developing HCA.[15] Another major risk factor

Abbreviations used in this paper: AAS, anabolic androgenic steroids; ADPKD, autosomal dominant polycystic kidney disease; AP, alkaline phosphatase; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CEUS, contrast enhanced ultrasound; CK, cytokeratin; CRP, C-reactive protein; CT, computed tomography; FNH, focal nodular hyperplasia; GS, glutamine synthetase; GSD, glycogen storage disease; HBCA, hepatobiliary cystadenoma; HBCAC, hepatobiliary cystadenocarcinoma; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; HNF1α, hepatocyte nuclear factor-1α; IHCA, inflammatory hepatocellular adenoma; IPCLD, isolated polycystic liver disease; KMS, Kasabach-Merritt Syndrome; LA, liver adenomatosis; L-FABP, liver fatty acid binding protein; MRI, magnetic resonance imaging; NCAM, neuronal cell adhesion molecule; NRH, nodular regenerative hyperplasia; OCP, oral contraceptive; PCLD, polycystic liver disease; RFA, radiofrequency ablation; RUQ, right upper quadrant; SAA, serum amyloid A; SHC, simple hepatic cyst; THCA, telangiectatic hepatocellular adenoma; US, ultrasound.

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Table 1. Clinical Features of Solid Hepatic Lesions

	HCA	LA	THCA	FNH	Hemangioma
Incidence (%)	1×10^{-6} to 1.2×10^{-4}	$<1 \times 10^{-6}$	$<1 \times 10^{-6}$ to 1.2×10^{-4}	0.3–3	0.4–20
Sex ratio (M:F)	1:8–15	1:8–15	1:9 – or more	1:5–17	1:2–6
Mean age range (*y*)	30–40	30–40	30–40	30–40	30–50
Size range (*cm*)	1–22	1–22	0.1–15	0.1–19	<1 to >30
Percent single (%)	60–80	60–80	20–40	76–81	71–93
Estrogen sensitive	Yes (causally related)	Yes (causally related)	Yes	Possibly	Possibly
Presenting symptoms	Chronic RUQ or epigastric pain; palpable mass; sudden acute pain; circulatory collapse; malaise; chronic iron anemia	Chronic RUQ or epigastric pain; palpable mass; sudden acute pain; circulatory collapse; malaise	Chronic RUQ or epigastric pain; palpable mass; sudden acute pain; circulatory collapse; malaise	Epigastric or abdominal pain; palpable mass; hepatomegaly; weight loss; asthenia; fever	RUQ pain; tumor mass in epigastrium; severe pain, nausea, dyspepsia, early satiety; vomiting; weight gain; hepatomegaly
Hepatic biochemical tests	Elevated transaminase levels and AP	Elevated transaminase levels and AP	Generally normal	Generally normal	Generally normal

F, female; M, male.

for HCA is glycogen storage disease (GSD) types Ia and III.[16] Interestingly, the female-to-male ratio is reversed in patients with GSD who develop HCA from a female predominance to a 1:2 male predominance, and the incidence of adenomas increases dramatically for patients with GSD over 25 years of age. Management of HCA in patients with GSD differs from conventional therapy. Continuous nocturnal feeding has been shown to result in a decrease in tumor size in some patients with GSD.[17] Despite this, hepatocellular carcinoma (HCC) has been known to develop in the background of HCA,[18,19] and while surgical resection is associated with higher morbidity in GSD patients, surgical intervention, whether resection or liver transplantation, appears to be the prudent course.[20] Antiepileptic drugs[21] and hepatic hemosiderosis have also been connected to HCA development.[22] Notwithstanding these myriad risk factors for HCA, otherwise healthy patients—both male and female—with no history of OCP, anabolic androgenic steroids (AAS), or antiepileptic drug use, and no underlying metabolic conditions have been known to develop these lesions.

HCA are often symptomatic, being discovered incidentally in just 12 to 25 percent of cases,[3,23] although this may be changing given the increasing frequency of imaging studies and the greater likelihood of discovering them incidentally. Common presentations are summarized in Table 1.

Imaging studies of HCA are difficult to analyze because of the heterogeneous nature of these lesions (Table 2). Within the past decade, HCAs have been broadly categorized into 4 subtypes based on genetic and pathological criteria: 36%–46% of patients have hepatocyte nuclear factor-1α (HNF1α) inactivating mutations; 18%–44% have the inflammatory subtype (IHCA); 5% present with a β-catenin activating mutation, and an additional 7% have a β-catenin mutation with IHCA features, making the prevalence of β-catenin mutations 13%–14% overall. Currently 9%–23% cannot be phenotypically or genetically categorized.[24–26] A more recent study found that when characterized pathologically, the various HCA subtypes are associated with specific magnetic resonance imaging (MRI) patterns;[27] these typical MRI findings may make it possible to noninvasively determine the subtype of HCA without resorting to biopsy. Enhancement with gadobenate dimeglumine on MRI has also been helpful to differentiate HCA from focal nodular hyperplasia (FNH).[28] Triple phase computed tomography (CT) can be used to image these lesions,[29] and—although not yet clinically used in the United States while awaiting Food and Drug Administration (FDA) approval—European studies in contrast-enhanced ultrasound (CEUS) demonstrate promising results for diagnosing HCA.[30] A definitive diagnosis, however, is difficult to establish by imaging alone (Figure 1).

Biopsy can be of risk in HCA because of the vascular nature of these lesions and their propensity to hemorrhage. Nevertheless, new genetic and molecular criteria have been established that can establish a definitive diagnosis, which can be beneficial in the management of these tumors. While there is some benefit in obtaining a biopsy, at this stage it should be reserved for select cases where genetic and molecular diagnostic tools are available and are deemed necessary in making treatment decisions. Table 3 summarizes pertinent information that can be obtained from a biopsy to assess a differential diagnosis.[31–35]

The recommended management of HCA is more aggressive than most other benign lesions because of the tendency for these lesions to hemorrhage and the slim but real possibility of