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Review

Hepatocellular adenoma: imaging review of the various molecular subtypes

H. Dharmana [a,*], S. Saravana-Bawan [a], S. Girgis [b], G. Low [a]

[a] Department of Radiology & Diagnostic Imaging, University of Alberta Hospital, 2A2.41 WMC, 8440-112 Street, Edmonton, AB T6G 2B7, Canada

[b] Department of Laboratory Medicine & Pathology, University of Alberta Hospital, 5B2.36 WMC, 8440-112 Street, Edmonton, AB T6G 2B7, Canada

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This educational review focuses on the epidemiology and radiological evaluation of the various subtypes of hepatic adenomas (HCAs). It includes detailed discussion of the imaging appearances of each HCA subtype and the clinical relevance of the new classification system. Each HCA subtype has a unique biological behaviour. Imaging plays a central role in diagnosis, subtype characterisation, identification of complications, and follow-up assessment. Management of patients should vary according to the specific HCA subtype.

Introduction

Hepatic adenoma (HCA) is a rare benign monoclonal neoplasm, most commonly encountered in women with a history of oral contraceptive use. Although benign, adenomas may be complicated by haemorrhage or malignant transformation into hepatocellular carcinomas (HCCs).[1–3] Recently, HCA has been categorised into three distinct subtypes based on genetic and histopathological features: (1) inflammatory (I-HCA), (2) hepatocyte nuclear factor-1 alpha inactivated (HNF-1α) HCA, and (3) β-catenin-activated HCA.[4] "Unclassified" HCAs are a small group that lacks specific genetic abnormalities.[4] Although the classification system is new, knowledge of the different subtypes is important because each entity has a different biological behaviour.[4] Furthermore, recent studies have shown that certain subtypes have characteristic imaging features that may permit a confident non-invasive diagnosis.[1,5] In this article, we discuss the epidemiology, pathology, imaging features, differential diagnoses, and management options of HCA and the clinical relevance of the new classification system.

Epidemiology

HCAs are extremely rare. In North America and Europe, the annual incidence is 1–1.3 million cases per year with approximately 86% of HCAs occurring in females of childbearing age.[6] The male-to-female ratio is approximately 1:10 and most patients are between 15 to 45 years of age at presentation.[7,8] A greater HCA incidence is recognised in the last several decades due to the introduction of the oral contraceptive pill (OCP).[9] In addition, HCAs are increasingly discovered as incidental findings in patients undergoing imaging tests for non-specific complaints or unrelated clinical indications. This is likely a reflection of an overall

* Guarantor and correspondent: H. Dharmana, Department of Radiology & Diagnostic Imaging, University of Alberta Hospital, 2A2.41 WMC, 8440-112 Street, Edmonton, AB T6G 2B7, Canada. Tel.: +1 780 407 6907; fax: +1 780 4073853.

E-mail address: hdharmana@gmail.com (H. Dharmana).

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increase in the volume of imaging performed on a per population basis over time.

Associations/risk factors

OCP

HCA was rarely reported before the advent of the OCP in the 1960s. A strong causal association between OCP and the development of HCA was first recognised by Baum in 1973.[10] Subsequent studies have confirmed this link and demonstrated that the development of HCA is related to higher doses and longer duration of OCP use.[9] The incidence of HCA in women on the long-term OCP (3–4 per 100,000) is approximately 25 times greater than that of the general population.[10] A few studies have also suggested that OCP discontinuation may lead to tumour regression, but this is controversial.[11] In China, a male predominance (62.3%) has been reported for HCA, possibly due to limited OCP use in this country.[6] Although OCP is considered the most important risk factor, HCAs can also develop de novo or in association with other conditions.

Anabolic steroids

Long-term misuse of anabolic androgenic steroids (AAS) has been implicated in HCA development.[12] Since the 1990s, there have been a growing number of reports of AAS misuse amongst athletes and bodybuilders for the purpose of increasing muscle mass.[13] AAS are synthetically manufactured hormones of testosterone. The liver is a hormone-sensitive organ that expresses oestrogen and androgen receptors. It is thought that excess androgenic stimulation of hepatocytes leads to abnormal cell proliferation and HCA development.[14] Some studies have documented tumour regression following AAS discontinuation.[15,16]

Glycogen storage disorders

HCA has been described in patients with glycogen storage disorders (GSDs), particularly type 1 (Von Gierke's disease) and type 3.[17] GSDs are hereditary disorders with an autosomal recessive transmission. They are characterised by abnormal glycogen accumulation in the liver, which causes chronic inflammation and predisposes to HCA development. HCAs associated with GSDs commonly affect males (male to female ratio of 2:1) and typically develop in patients <20 years of age.[18,19] These HCAs are more likely to be multiple[17] and have a higher risk of malignant transformation into HCC.[17]

Hepatic adenomatosis

Hepatic adenomatosis refers to cases where there are > 10 HCAs in the liver (Fig. 1). The condition was first described by Flejou *et al.* in 1985.[20] Unlike solitary HCAs, hepatic adenomatosis generally develops in the absence of predisposing factors and may be associated with a higher risk of complications.[21] One study suggests that

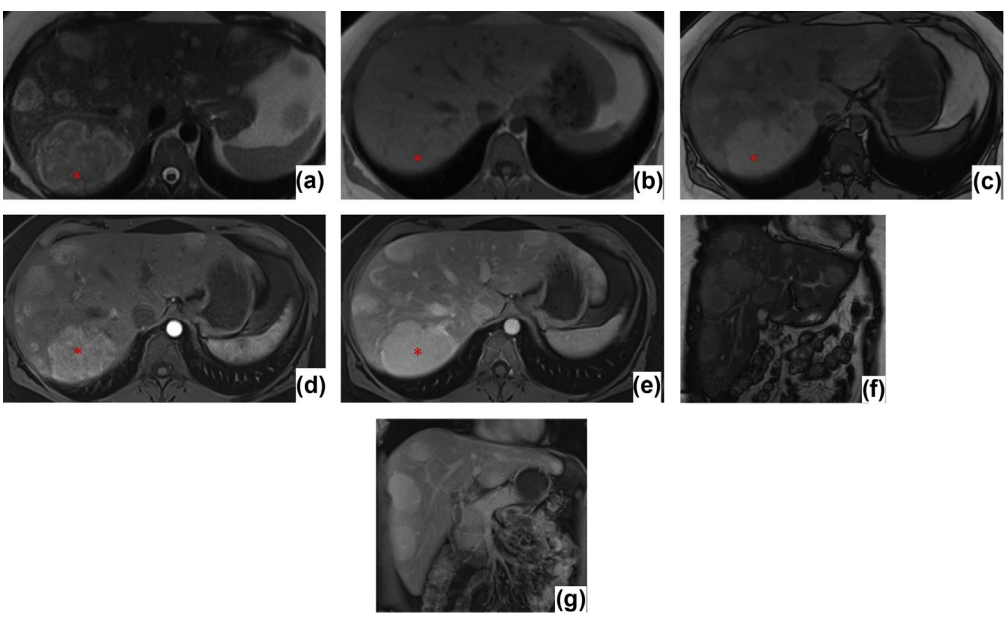

Figure 1 (a–e) A 34-year-old woman with histopathologically proven hepatic adenomatosis due to inflammatory adenomas (I-HCA) with the index mass in segment 7 (asterisk). (a) An axial T2-weighted image shows multifocal well-marginated masses (>10) of intermediate to high signal intensity in both lobes of the liver. Signal loss in the background liver but not in the masses is noted on the opposed-phase image (c) compared with the in-phase (b) T1-weighted image, denoting hepatic steatosis. Axial gadolinium-enhanced T1-weighted fat-saturated MRI images show that the masses exhibit diffuse hyperenhancement on the arterial (d) and portal (e) phases. (f–g) A 34-year-old woman with histopathologically proven hepatic adenomatosis due inflammatory adenomas (I-HCA). (f) A coronal T2-weighted image shows multifocal well-marginated masses (>10) of intermediate to high signal intensity in both lobes of the liver. (g) A coronal gadolinium-enhanced T1-weighted fat-saturated MRI image shows that the masses exhibit diffuse hyperenhancement on the portal phase.

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