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**REVIEW ARTICLE**

# Liver cell adenoma and liver cell adenomatosis

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**Abstract**
During the last three decades liver cell adenoma and liver cell adenomatosis have emerged as new clinical entities in hepatological practice due to the widespread use of oral contraceptives and increased imaging of the liver. On review of published series there is evidence that 10% of liver cell adenomas progress to hepatocellular carcinoma, diagnosis is best made by open or laparoscopic excision biopsy, and the preferred treatment modality is resection of the liver cell adenoma to prevent bleeding and malignant transformation. In liver cell adenomatosis, the association with oral contraceptive use is not as high as in solitary liver cell adenomas. The risk of malignant transformation is not increased compared with solitary liver cell adenomas. Treatment consists of close monitoring and imaging, resection of superficially located, large (>4 cm) or growing liver cell adenomas. Liver transplantation is the last resort in case of substantive concern about malignant transformation or for large, painful adenomas in liver cell adenomatosis after treatment attempts by liver resection.

**Key Words:** *Liver cell adenoma, liver cell adenomatosis*

The prevalence of patients with liver cell adenoma is increasingly seen within hepatology practice due to the widespread use of oestrogen-based oral contraceptives, and due to the increased use of cross-sectional imaging for a variety of unrelated reasons. Consequently many lesions are identified as incidental findings in asymptomatic patients. The clinical significance and natural history of these incidental solid liver lesions is not fully understood, and there is a need for an optimal management strategy in such patients.

Liver cell adenoma is a benign neoplasm of the liver that has significant aetiological association with the oral contraceptive pill in young women. Liver cell adenoma secondary to oestrogen/progestogen ingestion is usually solitary, but some people may develop several adenomas disseminated throughout the liver. This latter condition is known as liver cell adenomatosis, does not have the strong association with oestrogen or anabolic steroid ingestion, and affects males more readily [1].

This article presents the current knowledge and optimal therapeutic strategies for patients with solitary liver cell adenoma and liver cell adenomatosis.

## Background

Liver cell adenoma is the most important benign epithelial tumour of the liver, and has an estimated incidence of 3 per 1 000 000 per year [2]. The annual incidence is substantially higher with long-term oral contraceptive use, estimated at 3–4 per 100 000 [3], but may be less with newer oral contraceptives [4].

Liver cell adenoma was first described by Edmondson [5] in 1958 as an encapsulated liver tumour that does not contain bile ducts, when he identified two such lesions in 50 000 autopsies. In 1973, Baum [6] reported the important relationship between oral contraceptive use and the development of liver cell adenomas in seven patients. Several subsequent case series [7,8] in the 1970s supported the hypothesis of an association between the oral contraceptive pill and liver cell adenoma, and in 1976 Edmondson [9] published a case-control study giving further evidence of this association. The causal relationship between oral contraceptive medication and liver cell adenoma appears to be proportional to the hormonal dose and duration of medication [3,10,11], and is highest in women over 30 years of age after using oral contraceptives for more than 24 months. It is estimated the risk of developing an adenoma increases by a factor of 5 after 5 years, and by 25 after 9 years of oral contraceptive usage [11]. Regression of the tumour may occur after cessation of oral contraceptive usage [12], and there are reports of progression to hepatocellular carcinoma many years after stopping oral contraceptives [13–15]. Pregnancy appears to stimulate rapid

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growth in these lesions with risk of potentially fatal spontaneous rupture, and should be avoided in women of childbearing age [3].

Other possible aetiologies of liver cell adenoma include clomiphene [16], methyl testosterone [17], danazol [18], Klinefelter's syndrome [19], Types I, III and IV glycogen storage disease [20,21], and familial adenomatous polyposis [22].

Liver cell adenoma is usually a solitary nodule that may reach 30 cm in diameter. Macroscopically these lesions are smooth and soft on palpation, and range in colour from white to yellow to brown. On histological examination adenomas consist of cords of hepatocytes that have a high glycogen and fat content. The normal hepatic parenchymal architecture is lacking, with an absence of portal tracts and hepatic veins.

Liver cell adenomatosis is present in 10%–24% [23–25] of patients with liver cell adenoma and presents specific management difficulties. Liver cell adenomatosis was originally thought to affect males and females equally, but the most recent series report a female : male ratio of 7 : 1 and 15 : 1, respectively [26,27]. There is a strong association between liver cell adenomatosis and glycogen storage disease, but the association of liver cell adenomatosis and oral contraceptive or androgenic steroid use [1] is uncertain.

## Presentation and diagnosis

Symptomatic patients usually present with right upper quadrant pain secondary to bleeding within the liver cell adenoma. At initial presentation these symptoms are often attributed to cholecystitis, the most common diagnosis in this patient population. Liver function tests may be abnormal secondary to necrosis or haemorrhage, and alkaline phosphatase is often elevated in those with liver cell adenomatosis. Some present with an acute abdomen and life threatening haemorrhage secondary to an uncontained rupture and bleeding into the peritoneal cavity, but most have a more indolent clinical presentation.

Some liver cell adenomas are picked up incidentally during imaging studies of the liver or noted during laparoscopic cholecystectomy. The differential diagnosis includes focal nodular hyperplasia, a benign liver lesion of vascular origin, and well-differentiated hepatocellular carcinoma. These two lesions can be difficult to differentiate from adenoma and remain the diagnostic challenge as they have different therapeutic implications. Patients with focal nodular hyperplasia are less likely to be symptomatic or have deranged liver function tests [28,29].

The ultrasonographic features of liver cell adenomas are non-specific and may appear iso-, hypo-, or hyperechoic. The classical appearance is of a well-demarcated hyper-echoic mass, but central necrosis or haemorrhage gives rise to heterogeneous echogenicity that simulates that of focal nodular hyperplasia [30]. The CT appearances of adenoma may be quite variable, but the classical lesion characteristics are best appreciated with multi-phase helical CT scanning. Liver cell adenoma shows early phase peripheral contrast enhancement and subsequent centripetal contrast enhancement [31]. The pattern of perfusion starting at the periphery can be demonstrated on angiography and has been used to differentiate liver cell adenomas from focal nodular hyperplasia where the vascular supply arises centrally from a feeding artery leading to rapid filling of the suprahepatic vein ('spoke wheel' appearance) [32].

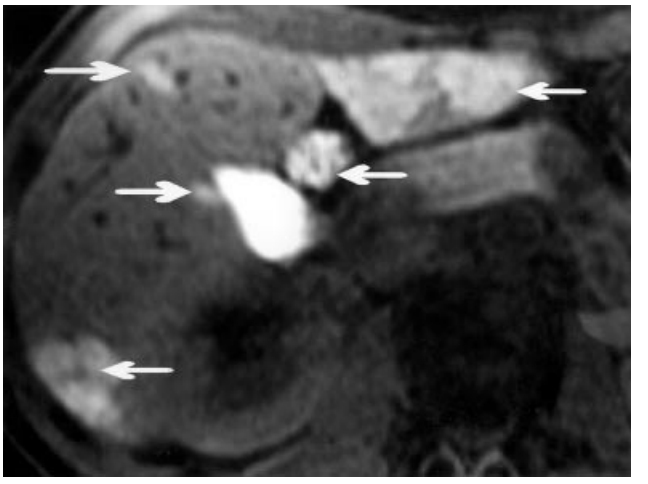

Figure 1. Teslascan MRI at 24 hours after injection: uptake of contrast in left lobe and lateral aspect of right lobe by multiple adenomas (arrows).

Magnetic resonance imaging has the optimal sensitivity for lesion detection, but again characterization of the lesion can be variable. Ultra-fast sequences with breath-holding and gadolinium contrast provide most information [27,33,34], and surveillance of patients with liver cell adenomatosis is highly effective using a delayed teslascan 24 hours after injection of gadolinium (see Figure 1). Even with these advances it may be impossible to differentiate liver cell adenoma from focal nodular hyperplasia or hepatocellular carcinoma, and a biopsy is then essential for histological clarification.

## Lesion biopsy

Percutaneous biopsy of a liver lesion is not to be recommended in young fit patients as this can induce bleeding and tumour dissemination, does not exclude malignancy if normal tissue is found, and may be inaccurate. In a study by Charny *et al.*, only 11 of 30 biopsies were accurate [35]. There are numerous case reports of women using oral contraceptives who develop hepatocellular carcinomas, but preoperative or operative liver needle biopsies reveal liver cell adenomas only [14,36–39] (Table I). Excision biopsy of liver lesions either by open surgery, or laparoscopically [40], is the gold standard method for diagnosis. Even with tumour tissue, accurate microscopic differentiation between benign liver cell adenomas and hepatocellular