Case Report

Benign liver lesions in female patients

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Liver cell adenoma and focal nodular hyperplasia are benign conditions, often encountered in young and middle aged female patients. They can present acutely, but more often are diagnosed incidentally during investigation of abnormal liver function tests or vague abdominal pain. We present four cases, which contrast the diagnosis and management of focal nodular hyperplasia (FNH) and liver cell adenoma (LCA).

CASE 1

A 33-year-old previously healthy woman was admitted with sudden onset of epigastric and left upper abdominal pain. Her only regular medication was the oral contraceptive pill, used almost continuously for the previous sixteen years. Ultrasound and CT scans were performed. These revealed a large mass in the left lobe of the liver into which bleeding had occurred (Fig. 1). In addition there was a large lesion in the posterior aspect of the right lobe. Appearance on CT scan was in keeping with a ruptured lesion in the left lobe and focal nodular hyperplasia in the right lobe. Laparotomy revealed a large tumour in
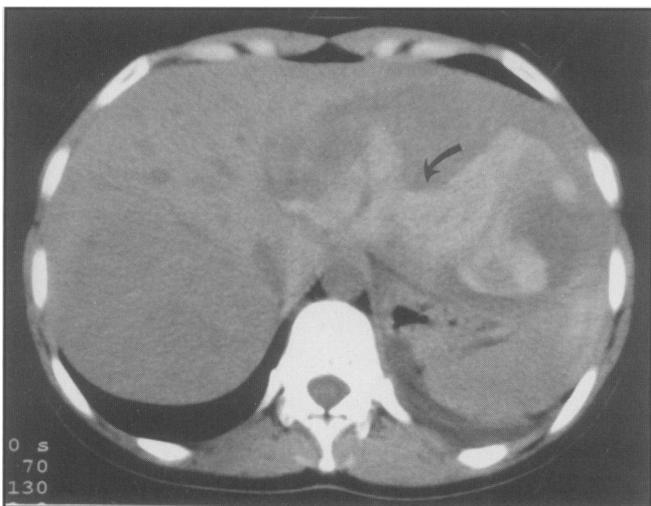

Fig 1. CT scan, from patient 1, demonstrating a large heterogeneous lesion in the left lobe, into which bleeding has occurred (curved arrow).

segments II and III with some surrounding satellite nodules. There was evidence of haemorrhage into the tumour and a haematoma, was present in the left upper quadrant. Left hepatic lobectomy was performed. Histopathology confirmed the left lobe lesion to be a liver adenoma; biopsy of the right lobe lesion revealed focal nodular hyperplasia. She remains well three years following surgery. Repeat CT scan at two years has demonstrated no change in size of the right lobe lesion.

CASE 2

A 26-year-old woman with a three year history of oral contraceptive use presented with a three-month history of right-sided abdominal pain. Clinical examination was unremarkable but USS of the abdomen showed a 5 x 7 x 8 cm hyperechoic mass in the right lobe of the liver. Contrast enhanced CT scan demonstrated the same lesion and the presence of a central scar. On repeat CT imaging six months later no significant change was seen. This is consistent with a diagnosis of focal nodular hyperplasia. Eighteen months after initial presentation she remains well.

CASE 3

A 29-year-old woman was admitted electively for laparoscopic cholecystectomy. During initial laparoscopy a tumour arising from the left lobe of the liver was noted. Conversion to open cholecystectomy allowed routine cholecystectomy and biopsy of the liver lesion to be performed. Histopathology was consistent with focal nodular hyperplasia. An enhanced CT scan,

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one month after surgery, revealed no focal hepatic abnormality. In the succeeding months, the patient experienced episodes of epigastric pain. A further CT scan six months after surgery identified a 3.8 cm diameter lesion in the left lobe with no central scar or internal haemorrhage. A third CT scan eighteen months after her initial surgery showed no change. However the patient was experiencing intermittent episodes of abdominal pain. This fact, combined with her desire to have a further child in the future, resulted in elective surgery to enucleate the FNH lesion from segment IV of the liver.

CASE 4

A 54-year-old woman was noted to have abnormal liver function tests on routine investigation of abdominal pain. Her only past medical history was essential hypertension, treated with thiazide diuretics. She had lived in Australia and had travelled to the Far East, but had no known history of hepatitis. Ultrasound revealed a 6 x 4 cm mass in the posterior aspect of the right lobe of the liver. This was irregular in outline, and mainly echogenic but with an echo-poor centre. CT scan showed a well-defined mass measuring 5 x 6 x 5 cm, which was hypodense with a central stellate scar (Fig.2). The appearances were consistent with FNH. CT guided biopsy was performed. The histology revealed unremarkable hepatic architecture, and the biopsy was not diagnostic of FNH from the material submitted. Repeat CT scan 8 months after the initial investigations showed no significant change. The patient has remained well two years later.
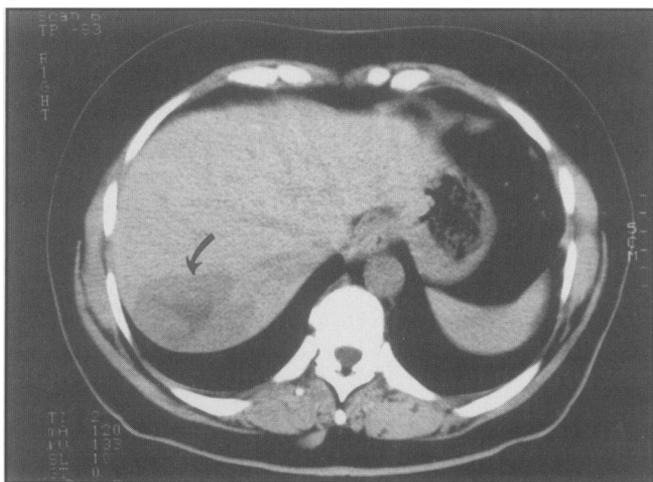

Fig 2. CT scan, from patient 4, demonstrating a hypodense mass in the right lobe, with a central stellate scar (curved arrow).

DISCUSSION

The association between the development of liver cell adenoma (LCA) and the use of oral contraceptives was first reported in 1973.[1] Early reports estimated that the risk of developing LCA increases thirty four fold in women using high oestrogen oral contraceptives.[2] Recent studies for low dose oestrogen contraceptives showed the risk to be increased only by a factor of three.[3] Prolonged duration of oral contraceptive use increases the risk of liver cell adenoma. One study demonstrated that use of oral contraceptives for five, nine or greater than nine years increases the risk by 2, 5, 7.5 and 25 respectively.[4] In contrast, focal nodular hyperplasia (FNH), although more common than LCA, is not associated with the use of oral contraceptives and the increased incidence in the past twenty five years is likely to be due to increased awareness and the more widespread use of ultrasound.[5]

The natural history of these conditions varies. LCA carries a significant risk of complications such as rupture, haemoperitoneum, shock, death and, rarely, malignant transformation.[6] FNH however is essentially benign. It is not premalignant and complications such as massive growth, rupture or haemorrhage are rare.[5] In the few reported cases with haemorrhage the histological diagnosis of FNH has been questioned.[6] This fundamental difference in long term behaviour influences the presentation and management of the two conditions.

Case 1 is typical of LCA. Eighty percent of patients with hepatic adenoma are symptomatic – half of these have signs related to a mass, such as pain, whilst the other half are symptomatic because of haemorrhage. This may be intratumoural, subcapsular or intraperitoneal. Essentially the reverse is true in FNH. Typically, only 10% of this group have symptoms, the lesion being found incidentally in the remaining 90%, as in cases 3 and 4.[7] In one case series, no patient with FNH had presented with rupture or bleeding.[8]

Radiological imaging alone is not always diagnostic, but nonetheless can help in differentiating FNH from LCA. The presence of an avascular central stellate scar, although not always found, is pathognomonic for FNH when it occurs, since it never arises in liver cell adenoma.[7] Similarly, precontrast hyperdense areas (haemorrhage) is supportive of the diagnosis of LCA. Differentiation can also be made with less

widely available imaging techniques. These include MRI with or without gadolinium enhancement, colour doppler ultrasound and radionuclide scintigraphy, with Technetium (Tc 99) sulphur colloid.

With MRI the central stellate area of FNH is hyperintense on T2 and hypointense on T1 images. Enhancement with gadolinium shows accumulation of contrast agent within the central area on delayed T1 images. For LCA, haemorrhage is hyperintense on T1 and T2 images, while necrosis is hyperintense on T2 and hypointense on T1 images. Characteristically LCA shows no accumulation of gadolinium contrast agent within the tumour.[9]

With colour doppler FNH shows arterial signals within the tumour, while LCA demonstrates venous signals. Using radio labelled colloid a focal defect is seen in LCA, compared to increased or normal uptake in FNH.[9] This stems from the histolgical difference of these lesions. LCA lacks Kupffer cells, and does not take up radioisotope. In FNH Kupffer cells are present and metabolically active resulting in increased uptake.[7]

Histologically these lesions differ.[10] Macroscopically, LCA is yellowish tan in colour with a homogeneous appearance. There is no true capsule but a pseudocapsule may be created by the compression of normal liver parenchyma. Haemorrhage, both macroscopic and microscopic, is common. Macroscopically, lobulation and a central scar are characteristic of FNH. Microscopically Kupffer cells and bile ducts are found in FNH, but are absent in LCA, which is distinguished by the presence of glycogen rich vacuoles. However, differentiation and definite diagnosis on percutaneous biopsy is often difficult as the tumour, particularly FNH, can so closely resemble normal liver parenchyma. Case 4 illustrates this point well, as the radiological diagnosis of FNH was not conclusively supported by percutaneous biopsy. Percutaneous biopsy is considered safe, but complications including haemorrhage and death do occur. However mortality rates following the procedure are extremely low (0.03-0.006%).[11] Imaging and histology, along with the clinical history may all be used to make the diagnosis of LCA or FNH. This is important because, the natural history of the two conditions differs markedly and so, therefore, does their management.

Discontinuation of oral contraceptives is obligatory in patients with LCA. Although occasionally regression has been observed after discontinuation this is not invariable, and growth, rupture and malignant transformation have been reported, despite cessation of contraceptive use.[7, 12] Most authors agree that oral contraceptives are not the causal agent of FNH. However, it has been postulated that they might have a trophic effect increasing the size and vascularity. Therefore, discontinuation of oral contraceptives is also advised in this condition.

The management of FNH requires a flexible approach. Asymptomatic lesions are best managed expectantly and can be safely observed with regular ultrasound. The only clear indications for surgery are the presence of symptoms or uncertainty about the diagnosis. In the latter case, if resection is a major hazard biopsy alone is recommended since the prognosis of FNH left undisturbed is excellent. For symptomatic FNH, resection has been demonstrated to be safe with no operative mortality and less than 1% morbidity. Relief of symptoms is also generally achieved.[13] A further indication for resection of FNH is planned pregnancy, if the tumour is easily accessible. This is because it has been well documented that these lesions may increase in size during pregnancy.[14] It is for these reasons that patient 3 underwent elective surgery. The diagnosis of LCA strongly supports surgical intervention, due to long term risks of conservative management. Elective resection of LCA is almost as safe as FNH, morbidity and mortality for this being 7% and less than 1% respectively. This increases to 5-8% for emergency resection.[5]

In summary, FNH and LCA are liver masses identified in women and the latter is clearly increased by use of oral contraceptive steroids. They differ in histological and radiological characteristics and these are often of use in making a diagnosis. While FNH is often asymptomatic and benign, LCA is, by contrast, often symptomatic with a potential for significant complications. These risks inherent in LCA make surgical intervention in this condition the treatment of choice.

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