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CORRESPONDENCE

Focal nodular hyperplasia and hepatocellular carcinoma: uncommon companions?

Sir,

Focal nodular hyperplasia (FNH) is a benign condition of the liver characterised by nodules of hyperplastic hepatocytes divided by fibrous septa radiating from a fibrous scar. The fibrous scar contains abnormal vessels and FNH are thought to develop from a hypertrophic response of hepatocytes to an increase in local blood flow.[1] It is widely accepted that FNH has an indolent natural history with minimal risk of haemorrhage or rupture and no acknowledged potential for malignant transformation.[2] However our own experience with two patients with hepatocellular carcinoma (HCC) arising within an FNH, and a total of 20 reported patients with hepatocellular carcinoma occurring in close association with FNH[3–18] (Table 1), indicates that FNH and HCC can occur in the same hepatic lesion.

A 34-year-old female was noted to have abnormal liver function tests. Clinical examination was normal. An abdominal ultrasound demonstrated a large mass in the left side of the liver and this was further investigated with an abdominal CT scan. Arterial phase images showed a hypervascular mass in segments 2 and 3 without a central scar and with partial washout in the portal venous phase. Other investigations demonstrated a normal full blood count, plasma urea and electrolytes. Hepatitis B and C serology was negative and tumour markers including α-fetoprotein were within the normal range. Her liver function tests were mildly deranged with an alkaline phosphatase (ALP) of 142 U/L (normal range 40–100U/L) and a gamma glutamyl transferase (γGT) of 282 U/L (normal range <50 U/L). A diagnosis of a large adenoma or possible fibrolamellar carcinoma was made and a left hepatectomy was performed without complication. Her subsequent clinical course was uneventful. The patient is alive and well 5 years post-resection.

Pathological analysis showed a lesion with the histological appearances of FNH with a small HCC contained within the substance of the FNH (Fig. 1A). The surrounding FNH showed numerous large, unpaired, abnormal blood vessels consistent with a large vascular abnormality, such as a haemangioma. Further staining with a specific marker for glutamine synthetase demonstrated perivenular uptake in normal liver (Fig. 1B) with a more widespread geographic distribution in FNH (Fig. 1C) and diffuse intense uptake with the HCC (Fig. 1D). Glutamine synthetase staining also highlighted an area of large cell change adjacent to the HCC (Fig. 1E).

A 45-year-old Caucasian male was referred with an abdominal mass. This had been incidentally noted during routine assessment of an incisional hernia. At age of 12 years the patient had been found to have portal hypertension and a mesocaval shunt was performed. At assessment the patient denied any medication use and drank less than 1 unit of alcohol per week although admitted to heavy alcohol intake 10 years previously. Examination was unremarkable except for a palpable mass in the epigastrium. Investigations showed a normal full blood count, urea and electrolytes, and an elevated α-fetoprotein of 23170 μg/L (normal range <10 μg/L). Liver function tests showed an elevated ALP of 455 U/L, γGT of 910 U/L, alanine transferase 147 U/L (normal range 0–45 U/L), and aspartate transferase of 90 U/L (normal range 0–45 U/L). A magnetic resonance scan showed a large hypervascular mass involving segments 2 and 3 and a diagnosis of hepatocellular carcinoma was made. A left hepatectomy was performed with the procedure and recovery uncomplicated and the patient discharged on day 5. The α-fetoprotein decreased to <5 μg/L

Table 1 Summary of reported patients with hepatocellular carcinoma (HCC) and focal nodular hyperplasia (FNH)

Reference	Age	Sex	Risk factors HCC	Cirrhosis	αFP	Tumour diameter, cm	Histotype HCC	Histotype FNH	Lesions adjacent
Saul *et al.* 1987[18]	19	F	Nil	Nil	Normal	FNH 9 cm; HCC smaller	Fibrolamellar	NS	Yes
Davidson *et al.* 1990[17]	16	M	Nil	Nil	Normal	FNH NS; HCC 6 cm	Fibrolamellar	NS	Yes
Saxena *et al.* 1994[15]	14	F	Nil	Nil	NS	NS	Fibrolamellar	NS	Yes
Muguti *et al.* 1992[16]	3 patients, 2 ordinary HCC, 1 fibrolamellar. Age, sex, risk factors, tumour site not stated. αFP normal in all 3 patients								
Chen *et al.* 2001[14]	65	F	Nil	Nil	Raised	20 cm tumour	Ordinary	NS	Yes
Coopersmith *et al.* 2002[13]	43	F	Nil	Nil	Raised	7 cm tumour	Ordinary	NS; Diffuse	Yes
Cucchetti *et al.* 2003[12]	55	F	Nil	Nil	Normal	7 cm tumour	Ordinary	NS	No
Zhang *et al.* 2004[11]	56	M	Hepatitis B carrier	Present	Raised	FNH 3 cm; HCC 2 cm	Ordinary	NS	Yes
Imkie *et al.* 2005[10]	27	F	Nil	Nil	Normal	FNH 20 cm; HCC 6 cm	Fibrolamellar	NS	Yes
	45	F	Nil	Nil	Normal	FNH 14 cm; HCC NS	Fibrolamellar	NS	Yes
Kataoka *et al.* 2006[9]	64	M	Nil	Nil	NS	NS	Ordinary, also lymphoma	Regenerative hyperplasia	Yes
Langrehr *et al.* 2005[8]	46	F	Nil	Nil	NS	FNH 14 cm; HCC 5 cm	Ordinary	NS	Yes
	50	F	Nil	Nil	NS	FNH 12 cm; HCC 3 cm	Ordinary	NS	Yes
Petsas *et al.* 2006[7]	23	F	Nil	Nil	Normal	FNH 4.5 cm; HCC 1 cm	Ordinary	NS	Yes
Sotiropoulos *et al.* 2008[6]	31	F	Nil	Nil	Normal	FNH 15 cm; HCC 7 cm	Ordinary	NS	Yes
Morise *et al.* 2009[5]	59	M	Hepatitis B & C carrier	Nil	Raised	FNH 2 cm; HCC 0.9 cm	Ordinary	NS	Yes
Haubert *et al.* 2010[4]	86	F	Nil	Nil	Normal	NS	Ordinary	NS	Yes
Scheuermann *et al.* 2012[3]	38	F	Nil	Nil	Normal	NS	Fibrolamellar	NS	Yes, absent portal vein

αFP, α fetoprotein; NS, not stated.

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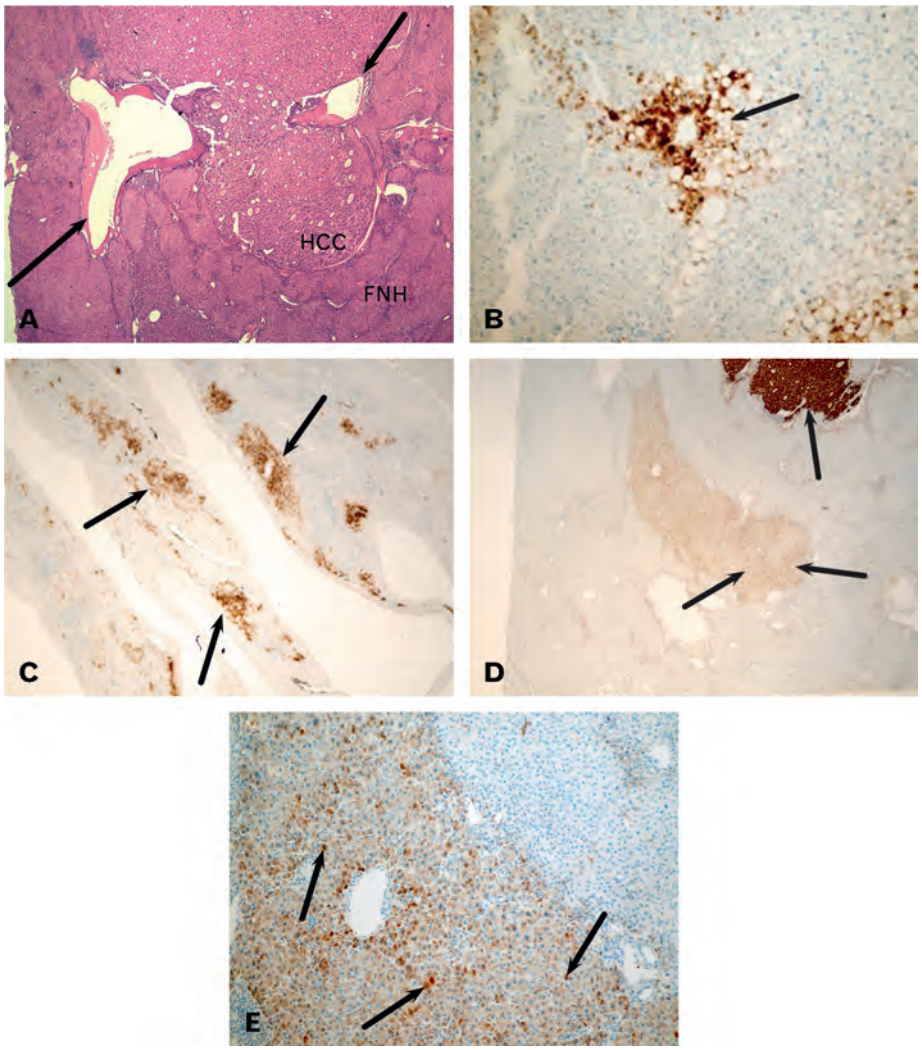

Fig. 1 (A) H&E stained tissue from Patient 1 demonstrating multiple abnormal vascular channels (arrow), hyperplastic hepatic tissue (FNH) and a small HCC (HCC). (B) Glutamine synthetase staining in normal liver demonstrating uptake in perivenular hepatocytes (arrow). (C) Glutamine synthetase staining in hyperplastic tissue showing more widespread uptake (arrows). (D) Glutamine synthetase staining in HCC demonstrating intense diffuse staining (single arrow) and an adjacent area of dysplastic change with increased, diffuse staining compared to normal (double arrows). (E) Detail of the area of dysplastic change demonstrating multiple atypical nuclei (arrows).

1 month post-resection and has remained normal. The patient is alive and well with no signs of recurrent disease at 4 years post-resection.

Pathological analysis showed a large, lobulated lesion, which occupied most of the resected liver and contained a pale stellate scar. About one-third of the lesion was occupied by a cholestatic and haemorrhagic lesion which also bore a pale nodule (Fig. 2). Histology confirmed a large FNH associated with HCC and a similar immunohistochemical staining profile to Patient 1.

In 1980 Berman *et al.*[19] suggested that FNH was a precursor lesion to fibrolamellar HCC in the same way that hepatic adenomas can undergo malignant transformation into non-fibrolamellar HCC. Subsequent clonal analysis of FNH has shown that these lesions are largely polyclonal suggesting a hyperplastic rather than a neoplastic growth pattern while HCC are monoclonal consistent with malignant transformation.[20] However, there are a number of reports in the literature of HCC arising in close association to FNH indicating that these lesions can co-exist in the same patient (Table 1).

Co-existence of HCC and FNH is rare. Only 22 instances have been reported although there is a high incidence of HCC

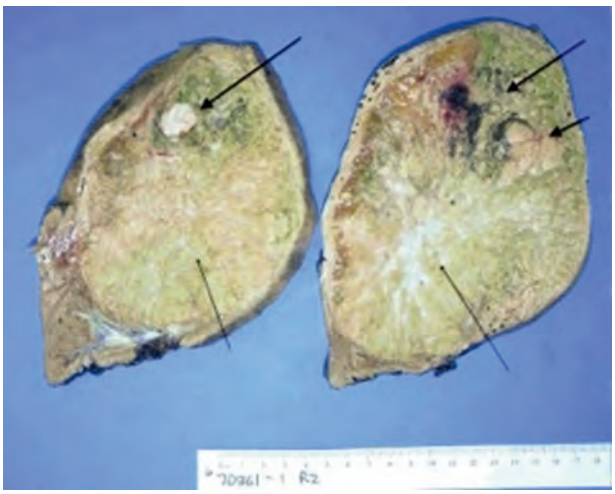

Fig. 2 Macroscopic specimen from Patient 2 demonstrating a large nodular lesion with a stellate scar (thin arrows) with the histological features of focal nodular hyperplasia and the hepatocellular carcinoma arising in this (thick arrows). This shows haemorrhage and cholestasis.