A case of hepatocellular carcinoma arising within large focal nodular hyperplasia with review of the literature

Theodoros Petsas, Athanasios Tsamandas, Irene Tsota, Dionisios Karavias, Chrysoula Karatza, Vassilios Vassiliou, Dimitrios Kardamakis

Abstract
Focal nodular hyperplasia (FNH) is a relatively rare benign hepatic tumor, usually presenting as a solitary lesion; however, multiple localizations have also been described. The association of FNH with other hepatic lesions, such as adenomas and haemangiomas, has been reported by various authors. We herein report a case of hepatocellular carcinoma arising within a large focal nodular hyperplasia, in a young female patient.

INTRODUCTION
Focal nodular hyperplasia (FNH) is a relatively rare benign hepatic tumor, often asymptomatic and discovered incidentally[1,2]. It occurs in both men and women, but shows a predilection for young women. FNH presents as a solitary lesion in 70% of the cases, while in 30% of patients two to five lesions are present[3]. Multiple lesions occur rarely[4-7].

Although an association with the use of oral contraceptives has been shown[6-7], its pathogenesis is still unclear.
sidered as FNHs. MR imaging was carried out at the same
time and the findings were consistent with multiple FNHs.

Due to the great increase in the size of the mass lo-
cated in the left lobe, during such a short period (3 mo), a
CT guided core liver biopsy was performed in the largest
lesion. Pathologic examination of the biopsy revealed that
the specimen composed of fibrous tissue surrounded a
nodule of hyperplastic hepatocytes, contained numerous
thin-walled vessels, as well as numerous proliferated bile
ductules. No evidence of malignancy was observed. Based
on the radiological and histopathological data, the provi-
sional diagnosis of FNH was made. In order to exclude
any coexistent brain pathology, the patient underwent
brain MR imaging, which was normal.

The surgical procedure involved the resection of the
II and III liver segments. During the operation a frozen
section was performed, revealing FNH. The surgical speci-
men measured 17.3 cm × 15.0 cm × 10.2 cm (Figure 3A).
It consisted of a portion of liver which contained two
masses, the larger measuring 9 cm × 6 cm × 5 cm and the
smaller 4.5 cm × 3.5 cm × 2.0 cm. Macroscopically, both
masses had a yellow-white cut surface and a central scar.
In addition, the smaller mass contained another smaller
tumor measuring 2.1 cm × 1.8 cm × 1.0 cm, which was
located in the periphery and showed a brown-green cut
surface (Figure 3A-inset). Microscopic examination of
the specimen revealed the presence of FNH (two discrete
tumors), whereas the smaller tumor included within the
smaller mass represented a well-differentiated hepatocel-
lular carcinoma (Figure 3B). Diagnosis of HCC was based
on morphological (HE stain) and immunohistochemical grounds (Figure 4): The neoplastic cells exhibited positive stain for hepatocyte paraffin antigen and cytokeratin 18 and negative stain for cytokeratin CK19, chromogranin, synaptophysin, common leukocyte antigen negative, CD34 antigen. In addition, polyclonal carcinoembryonic antigen displayed a canalicular pattern.

The postoperative period was uneventful. During the follow-up period, the patient underwent liver transplantation in another center abroad. Pathologic examination at that time revealed that the two small tumors in the right liver lobe represented liver angiomylolipomas (personal communication). At present time, eight years after the initial diagnosis, the patient is alive.

**DISCUSSION**

Benign liver tumors are uncommon in surgical practice (3%-5% of all liver tumors); haemangioma is the most common type (55%-60%), whereas adenomas (8%-19%) and FNH (21%-27%) are less frequent. FNH, also called focal nodular hyperplasia, is a benign tumor, with concomitant FNH and HCC; the results showed that FNH was of monoclonal origin, but the FNH clone was similar to that of HCC and therefore the potential of FNH for malignant evolution would have a common origin that should be attributed to vascular changes primarily caused by a congenital abnormality of the angioarchitecture and blood circulation of the liver. Various authors have described the coexistence of FNH with vascular cranial malformations, cystic dysplasia of the kidneys, Klippel-Trenaunay syndrome. In all cases described so far, the coexistence of the above findings were attributed to a so called syndrome or were described as coincidental. A useful diagnostic tool for the distinction between liver cell adenoma and FNH, when the routine histopathologic features are not very clear, is clonality analysis.

The histopathological features of FL-HCC suggest a direct link between this tumor and FNH and some authors hypothesize a direct evolution from FNH to FL-HCC. Also, the simultaneous presence of adjacent adenoma does not exclude the development of HCC from malignant degeneration of the adenoma. Therefore coexistence of FNH and HCC in the same patient is an exceptional event, to the best of our knowledge reported only in two cases.

Recent insight into the molecular characteristics of the clonal growth of FNH failed to support further a possible derivation of HCC from FNH; two different studies, conducted by Gaffey and Paradis, were undertaken to clarify the monoclonal or polyclonal nature of these tumors by a method that scans the molecular pattern of inactivation of chromosome X. The authors eventually came to opposite conclusions. In another study, clonal analysis was applied to macroscopically different portions having different histological features within the same tumor, with concomitant FNH and HCC; the results showed that FNH was of monoclonal origin, but the FNH clone was similar to that of HCC and therefore the authors’ conclusions did not support the hypothesis that HCC was the product of malignant transformation from FNH. The issue of an identical clonal origin of FNH and HCC therefore remains a matter of debate, although we feel it is rather imprudent at present to completely exclude any malignant potential of FNH.

The potential of FNH for malignant evolution would appear unlikely on the basis of the follow-up of patients with non-surgically excised FNH. Weimann et al observed an increase in the size of FNH lesions only in 9.5% of 53 cases, with no malignant transformation during a mean follow-up of three years. Likewise, in other studies no increase in lesion size was observed among 11 patients in a two-year follow-up, and in some cases the FNH even completely disappeared over time. This evidence...
recently led Charny et al, to conclude that, if the diagnosis is unequivocal, surgical resection is not indicated for asymptomatic FNH[25].

A clear and precise diagnosis of a benign liver tumor is difficult to obtain in every patient, particularly in the case of FNH. In the series collected by Terkivatan, difficulty in differentiating FNH from adenoma or HCC represented the indication for surgery in 32% of cases[28]. FNH was rarely encountered by radiologists prior to the current practice of helical multiphasic CT or MR imaging. It is also believed that as the imaging methods improve, FNH will be encountered more frequently. Many authors have reported the CT features of FNH. Imaging characteristics, typical of FNH, include a homogeneous well-defined hypo-, or iso-dense lesion on unenhanced scans, which shows bright enhancement during early arterial phase and becomes isodense on portal venous phase. Central scars are hypodense on early arterial and portal venous phases and become hyperdense on delayed scans[29-32]. Magnetic resonance imaging is another modality also used for the confident diagnosis of FNH. The reported sensitivity and specificity values for contrast-enhanced-MRI diagnosis of FNH was 70% and 98% respectively in an article by Cherqui et al in a series of 41 patients with clinical radiological and pathological correlations. The central scar was detected in 78% of the cases[33]. An alternative to angiography could be hepatic cholescintigraphy, which according to the study of Weimann, best reflected the vascular pattern and the typical biliary ductule proliferation of FNH (sensitivity ≥ 82%, specificity ≥ 97%)[34].

Finally, the diagnostic value of liver biopsy in suspected FNH is rather limited; the lesion itself may not be reached or the specimen may not be sufficient for an accurate diagnosis, and false negative results are deleterious for the final outcome as hepatic adenomas or HCC may bleed or seed along the needle track.

In conclusion, at present there is no clear-cut evidence supporting the potential for malignant degeneration of FNH into HCC; the indication for surgery, particularly in small lesions (≤ 4 cm) and asymptomatic patients, is therefore rather controversial. In view of this uncertainty, a correct diagnosis which differentiates between FNH and HCC must be achieved for all cases by means of a multidisciplinary approach. Due to the rarity of the association between FNH and HCC, it is difficult to draw solid conclusions for both the pathology of this entity and the appropriate management of these patients.

REFERENCES

1 Reddy KR, Kligerman S, Levi J, Livingstone A, Molina E, Franceschi D, Badalamenti S, Jeffers L, Tzakis A, Schiff ER. Benign and solid tumors of the liver: relationship to sex, age, size of tumors, and outcome. Am Surg 2001; 67: 173-178
2 Finch MD, Crosbie JL, Currie E, Garden OJ. An 8-year experience of hepatic resection: indications and outcome. Br J Surg 1998; 85: 315-319
3 Benhamou JP, Erlinger S. Maladies du foie et des voies biliaires. 3rd ed. Paris: Medicines-Sciences: Flammarion, 1995: 71-90
4 Collé L, de Beeck BO, Hoorens A, Hautekeete M. Multiple focal nodular hyperplasia. J Gastroenterol 1998; 33: 904-908
5 Vilgrain V, Flejou JF, Arrive L, Belghiti J, Najmark D, Menu Y, Zins M, Vullierme MP, Nahum H. Focal nodular hyperplasia of the liver: MR imaging and pathologic correlation in 37 patients. Radiology 1992; 184: 699-703
6 Scott LD, Katz AR, Duke JH, Cowan DF, Maklad NF. Oral contraceptives, pregnancy, and focal nodular hyperplasia of the liver. JAMA 1984; 251: 1461-1463
7 Knowles DM, Wolff M. Focal nodular hyperplasia of the liver: a clinicopathologic study and review of the literature. Hum Pathol 1976; 7: 533-545
8 Chen TC, Chou TB, Ng KP, Hsieh LL, Chou YH. Hepatocellu- lar carcinoma associated with focal nodular hyperplasia. Report of a case with clonal analysis. Virchows Arch 2001; 438: 408-411
9 Saul SH, Titelbaum DS, Gansler TS, Varelo M, Burke DR, Atkinson BF, Rosato EF. The fibrolamellar variant of hepatocellular carcinoma. Its association with focal nodular hyperplasia. Cancer 1987; 60: 3049-3055
10 Vecchio FM, Fabiano A, Ghirlanda G, Manna R, Massi G. Fibrolamellar carcinoma of the liver: the malignant counterpart of focal nodular hyperplasia with oncocytic change. Am J Clin Pathol 1984; 81: 521-526
11 Cucchetti A, Vivarelli M, De Ruvo N, Bellusci R, Cavallari A. Simultaneous presence of focal nodular hyperplasia and hepato-cellular carcinoma: case report and review of the literature. Tumori 2003; 89: 434-436
12 Gaffey MJ, Iezzoni JC, Weiss LM. Clonal analysis of focal nodular hyperplasia of the liver. Am J Pathol 1996; 148: 1089-1096
13 Paradis V, Laurent A, Flejou JF, Vidaud M, Bedossa P. Evidence for the polyclonal nature of focal nodular hyperplasia of the liver by the study of X-chromosome inactivation. Hepatology 1997; 26: 891-895
14 Wanless IR, Mawdsley C, Adams R. On the pathogenesis of focal nodular hyperplasia of the liver. Hepatology 1985; 5: 1194-1200
15 Foster BH, Berman MM. The malignant transformation of liver cell adenoma. Arch Surg 1994; 129: 712-717
16 Friedman LS, Geng DL, Hedberg SE, Hasselbacher KJ. Simultaneous occurrence of hepatic adenoma and focal nodular hyperplasia: report of a case and review of the literature. Hepatology 1984; 4: 536-540
17 Grange JD, Guechot J, Legendre C, Giboudeau J, Darnis F, Poupon R. Liver adenoma and focal nodular hyperplasia in a man with high endogenous sex steroids. Gastroenterology 1987; 93: 1409-1413
18 Mathieu D, Zafrani ES, Anglade MC, Dhumeaux D. Association of focal nodular hyperplasia and hepatic hemangiomata. Gastroenterology 1989; 97: 154-157
19 Di Carlo I, Urrico GS, Ursino V, Russello D, Pulso L, Latteri F. Simultaneous occurrence of adenoma, focal nodular hyperplasia, and hemangiomata of the liver: are they derived from a common origin? J Gastroenterol Hepatol 2003; 18: 227-230
20 Goldin RD, Rose DS. Focal nodular hyperplasia of the liver associated with intracranial vascular malformations. Gut 1990; 31: 554-555
21 Kinjo T, Aoki H, Sunagawa H, Kinjo S, Muto Y. Congenital absence of the portal vein associated with focal nodular hyperplasia of the liver and congenital choledochal cyst: a case report. J Pediatr Surg 2001; 36: 622-625
22 Bathgate A, MacGilchrist A, Piris J, Garden J. Multiple focal nodular hyperplasia in Klippel-Trenaunay syndrome. Gastroen-terology 1999; 117: 284-285
23 Wanless IR, Albrecht S, Bilbao J, Frei JV, Heathcote EJ, Roberts EA, Chasson D. Multiple focal nodular hyperplasia of the liver associated with vascular malformations of various organs and neoplasia of the brain: a new syndrome. Mod Pathol 1989; 2: 456-462
24 Gong L, Su Q, Zhang W, Li AN, Zhu SJ, Feng YM. Liver cell adenoma: a case report with clonal analysis and literature re-view. World J Gastroenterol 2006; 12: 2125-2129
25 Weimann A, Ringb B, Klemmneuer J, Lamesch P, Cratz KF, Prokop M, Mashek H, Tusch G, Pichlmayr R. Benign liver tu-mors: differential diagnosis and indications for surgery. World J Surg 1997; 21: 983-990; discussion 990-991
26. Di Stasi M, Caturelli E, De Sio I, Salmi A, Buscarini E, Buscarini L. Natural history of focal nodular hyperplasia of the liver: an ultrasound study. *J Clin Ultrasound* 1996; 24: 345-350
27. Charny CK, Jarnagin WR, Schwartz LH, Frommeyer HS, DeMatteo RP, Fong Y, Blumgart LH. Management of 155 patients with benign liver tumours. *Br J Surg* 2001; 88: 808-813
28. Terkivatan T, de Wilt JH, de Man RA, van Rijn RR, Zondervan PE, Tilanus HW, IJzermans JN. Indications and long-term outcome of treatment for benign hepatic tumors: a critical appraisal. *Arch Surg* 2001; 136: 1033-1038
29. Procacci C, Fugazzola C, Cinquino M, Mangiante G, Zonta L, Andreis IA, Nicoli N, Pistolesi GF. Contribution of CT to characterization of focal nodular hyperplasia of the liver. *Gastrointest Radiol* 1992; 17: 63-73
30. Choi CS, Freeny PC. Triphasic helical CT of hepatic focal nodular hyperplasia: incidence of atypical findings. *AJR Am J Roentgenol* 1998; 170: 391-395
31. Kehagias D, Mouloupoulos L, Antoniou A, Hatziioannou A, Smyrnios T, Trakadas S, Lahanis S, Vlahos L. Focal nodular hyperplasia: imaging findings. *Eur Radiol* 2001; 11: 202-212
32. Brancatelli G, Federle MP, Grazioli L, Blachar A, Peterson MS, Thaete L. Focal nodular hyperplasia: CT findings with emphasis on multiphasic helical CT in 78 patients. *Radiology* 2001; 219: 61-68
33. Cherqui D, Rahmouni A, Charlotte F, Boulaahdour H, Metreau JM, Meignan M, Fagniez PL, Zafrani ES, Mathieu D, Dhumeaux D. Management of focal nodular hyperplasia and hepatocellular adenoma in young women: a series of 41 patients with clinical, radiological, and pathological correlations. *Hepatology* 1995; 22: 1674-1681

S- Editor Wang J  L- Editor Zhu LH  E- Editor Bai SH