

Benign hepatocellular tumors: Problem diagnoses and applications of new pathomolecular classifications

Valérie Paradis, Pathology Department, Beaujon Hospital, Clichy

INSERM U773 Paris, France

vparadis@teaser.fr

Introduction

Benign hepatocellular tumors gather 2 separate groups of lesions according to their pathogenesis. Such classification has been successfully achieved owing to molecular studies, especially assessing their biological behaviour. Therefore, one distinguishes polyclonal disorders that concern regenerative non-neoplastic processes, such as focal nodular hyperplasia (FNH), and monoclonal lesions that are consistent with neoplastic tumors, including liver cell adenomas (1, 2). Both lesions are predominantly encountered in young women, usually in the context of oral contraception use.

Focal Nodular Hyperplasia

Focal nodular hyperplasia accounts for the second most common benign liver process. It is a benign tumor-like condition considered as a hyperplastic reaction resulting from arterial malformation (3). FNH displays a typical pathological pattern for both radiologists and pathologists. Grossly, FNH is a well-circumscribed, unencapsulated, usually solitary mass, characterized by a central fibrous scar that radiates into the liver parenchyma. Histologically, FNH is composed of benign-appearing hepatocytes arranged in nodules that are delineated by fibrous septa originating from the central scar. In the fibrous septa, large and dystrophic vessels, ductular proliferation and inflammatory cells are observed. The hepatocytes are hyperplastic, arranged in liver plates of normal or slightly increased thickness.

Besides this classic form of FNH, several variant lesions are described with increased frequency, and commonly classified as “non-typical FNH” by radiologists. This group is somehow heterogeneous, including FNH without central fibrous scar, lesions displaying telangiectatic or steatotic changes (4). On histological examination, FNH without macroscopic central fibrous scar exhibits all the pathological elementary features of classic FNH. However, molecular studies demonstrated that in this group of atypical FNH, lesions displaying telangiectatic changes, initially so-called “telangiectatic form of FNH”, are clonal processes and should be regarded rather as variant form of liver cell adenoma than truly FNH (5). They will be further described in the group of liver cell adenomas.

Complications of FNH such as rupture or bleeding are exceptional. No malignant transformation of FNH has been reported. Therefore, whatever the size and the number of lesions, no treatment is required for asymptomatic FNH when the diagnosis is firmly established.

Liver cell adenomas: A heterogeneous group of lesions

Liver cell adenoma is a rare, benign liver neoplasm that is strongly associated with oral contraceptive use and androgen steroid therapy. Hepatocellular adenoma can also occur spontaneously or be associated with underlying metabolic diseases, including type 1 glycogen storage disease, iron overload related to betathalassemia and diabetes mellitus (6).

Hepatocellular adenoma is usually solitary, sometimes pedunculated, with a diameter that can reach 30 cm. Large subcapsular vessels are commonly found on macroscopic examination. On cut sections, the tumor is well-delineated, sometimes encapsulated, of fleshy appearance ranging in color from white to brown. Adenoma frequently displays heterogeneous areas of necrosis and/or hemorrhage. Histologically, hepatocellular adenoma consists of a proliferation of benign hepatocytes arranged in a trabecular pattern. Small thin vessels are

usually found throughout the tumor. Hepatocytes may have intracellular fat or increased glycogen.

It has been recently proposed that liver cell adenomas are heterogeneous, with regard to their morphological pattern, with steatotic, telangiectatic or inflammatory adenomas and adenomas with cell atypias. Interestingly, specific gene alterations have been found to be associated with some of these variants (see below) (7). The latter form of adenomas may especially be encountered in patients who have taken steroids for many years. In that context, differential diagnosis with a hepatocellular carcinoma may be difficult.

Finally, it is now admitted that some atypical forms of FNH, i.e. “telangiectatic” and “mixed hyperplastic and adenomatous FNH” should be regarded as hepatocellular adenomas, as already discussed. Macroscopically, so-called “telangiectatic FNH” are well-delineated, unencapsulated and showed significant areas of vascular changes, without any fibrous scar. They were initially described by Wanless et al. as multiple nodules and were labelled as multiple FNH syndrome (8). Microscopic examination of these lesions shows transitional morphological features between adenoma and FNH. In all cases, there is no central fibrous scar. Few and short fibrous septa containing several small vessels without significant ductular proliferation are observed throughout the tumor which displays significant vascular changes of telangiectatic type. The “hyperplastic and adenomatous form of FNH” is histologically characterized by two alternating aspects: one resembling telangiectatic type, the other simulating adenoma. Taken together, these forms represent less than 20% of atypical FNH in large surgical series (9). It is of note that both lesions are now recognized as variant forms of hepatocellular adenomas and may be managed as adenomas. At last, a small group of adenomas do not display any specific morphological features.

Several complications may occur, such as bleeding, rupture and malignant transformation. The risk of malignant transformation of adenoma is in the order

of 10%. This risk appears to be higher in males and patients with large adenoma. Most cases of hepatocellular carcinoma develop at the site of the liver cell adenoma and malignancy is most often discovered on the analysis of the specimen.

Molecular diagnosis of benign hepatocellular tumors

Several changes in gene expression have been described in FNH, especially regarding molecules involved in vasculature remodelling, such as angiopoietins (ANGPT1 and ANGPT 2 (10). Such results certainly reinforced the hypothesis of vascular disorder in the pathogenesis of this lesion. A β -catenin activation, without associated mutation of this gene or axin, was recently reported in FNH (11).

In the last few years, very important progress based on molecular studies has been made in the field of liver cell adenomas that enabled to define different subtypes of adenomas associated with specific clinical and pathological features. Therefore, at least 4 subtypes of adenomas may be described. HNF1- α mutated adenomas, which account for approximately for 40% of liver cell adenomas, are characterized by a prominent steatosis, usually of marked intensity. These adenomas may be multiple and observed in the setting of adenomatosis (12). β -catenin mutated adenomas, morphologically characterized by the presence of cellular atypias, are preferentially encountered in male patients. It has been shown that these adenomas display a higher risk of malignant transformation (7). Very recently, a marked activation of interleukin 6 signalling pathway, related to mutations in the IL6ST gene encoding the signalling co-receptor gp130, has been described in the group of telangiectatic (or “inflammatory”) adenomas (13). Finally, a small group of adenomas without any specific clinical, morphological or genetic characteristics is still encountered.

Impact of molecular data on pathological diagnosis

Based upon the molecular abnormalities described, a set of several antibodies may be used in the sub-typing of benign hepatocellular tumors with a high sensitivity and specificity, especially in liver cell adenomas (14). For instance, steatotic adenomas displaying HNF1- α mutations do not express L-FABP, a protein involved in the fatty acid trafficking normally expressed by normal hepatocytes. In addition, β -catenin mutated adenomas display glutamine synthetase overexpression and express β -catenin both in the cytoplasm and the nucleus of the tumoral hepatocytes. At last, telangiectatic adenomas may show positive immunostaining with markers of the acute-phase inflammatory response, including serum amyloid A and C reactive protein.

In conclusion, molecular studies undoubtedly gained further insights into the understanding of benign hepatocellular tumors, and especially in the group of liver cell adenomas. Whether diagnosis and sub-typing of those lesions may rely on relevant and specific morphological features in most cases, additional studies using molecular markers may be helpful, in cases of atypical lesions and on biopsy samples.

References

- 1- Paradis V, Laurent A, Fléjou 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
- 2- Gaffey MJ, Iezzoni JC, Weiss LM. Clonal analysis of focal nodular hyperplasia of the liver. *Am J Pathol*1996;148: 1089-1096
- 3- Wanless IR, Mawdsley C, Adams R. On the pathogenesis of focal nodular hyperplasia. *Hepatology* 1985; 5:1194-11200
- 4- Nguyen BN, Fléjou JF, Terris B, Belghiti J, Degott C. Focal nodular hyperplasia of the liver. A comprehensive pathologic study of 305 lesions and recognition of new histologic forms. *Am J Surg Pathol* 1999;23:1441-1454
- 5- Paradis V, Benzekri A, Dargère D, Bièche I, Laurendeau I, Vilgrain V, Belghiti J, Vidaud M, Degott C, Bedossa P. Telangiectatic focal nodular hyperplasia: a variant of hepatocellular adenoma. *Gastroenterology*2004;126: 1323-1329
- 6- Barthelemes L, Tait IS. Liver cell adenomas and liver cell adenomatosis. *HBP* 2005; 7: 186-196.
- 7- Zucman-Rossi J, Jeannot E, Tran Van Nhieu J, Scoazec JY, Guettier C, Rebouissou S, et al. Genotype-phenotype correlation in hepatocellular adenomas: new classification and relationship with HCC. *Hepatology* 2006; 43:515-524

8- Wanless IR, Albrecht S, Bilbao J. Multiple focal nodular hyperplasia of the liver associated with vascular malformations of various organs and neoplasia of the brain. *Modern Pathol* 1989; 2:456-462

9- Fabre A, Audet P, Vilgrain V, Nguyen BN, Valla D, Belghiti J, Degott C. Histological scoring of liver biopsy in focal nodular hyperplasia with atypical presentation. *Hepatology* 2002; 35:414-42

10- Paradis V, Bièche I, Dargère D, Laurendeau I, Nectoux J, Degott C, Belghiti J, Vidaud M, Bedossa P. A quantitative gene expression study suggests a role for angiopoietins in focal nodular hyperplasia. *Gastroenterology* 2003; 124:651-659

11- Rebouissou S, Bioulac-Sage P, Zucman-Rossi J. Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma. *J Hepatol* 2008; 48:163-170

12- Bluteau O, Jeannot E, Bioulac-Sage P, Marques JM, Blanc JF, Bui H, Beaudoin JC, Franco D, Balabaud C, Laurent-Puig P, Zucman-Rossi J. Biallelic inactivation of TCF1 in hepatic adenomas. *Nature genetics* 2002;32:312-315

13- Rebouissou S, Amessou M, Couchy G, Poussin K, Imbeaub S, Pilati C, Iazard T, Balabaud C, Bioulac-Sage P, Zucman-Rossi J. Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours. *Nature on line*.

14- Bioulac-Sage P, Rebouissou S, Thomas C, Blanc JF, Sa Cunha A, Rullier A, et al. Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. *Hepatology* 2007; 46 :740-748