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Research

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Association of adenoma and focal nodular hyperplasia: experience of a single French academic center

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Abstract

Background: We report our experience of the simultaneous occurrence of adenoma and focal nodular hyperplasia (FNH). Liver cell adenoma together with FNH was found in five out of 30 cases of "multiple benign hepatocytic nodules" collected in our files of the Department of Pathology of the University Hospital of Bordeaux, during the last 12 years. All five cases were women on oral contraceptives. In all cases, the reason for surgery was the discovery, by imaging techniques, of an adenoma (4 cases) or of an unidentified benign tumor, possibly an adenoma.

Results: Four cases of FNH were discovered by imaging techniques, prior to surgery. Additional small nodules were diagnosed either during surgery or during the slicing of the specimen in 3 cases. Adenoma and the FNH cases identified by imaging techniques were confirmed as such by light microscopy. Some small nodules could not be categorized with certainty because they contained biliary structures without ductular reaction. In one case, the non-nodular liver was abnormal around the area in which there were multiple nodules: there was approximation of portal tracts with portal and hepatic venous thromboses, and portal tract remnants with arteries surrounded with a rim of fibrosis. In two cases, some large hepatic veins had thickened walls.

Conclusions: The association of FNH and adenoma could be coincidental or secondary to shared causal mechanisms: a) systemic and local angiogenic abnormalities induced by oral contraceptives; b) tumor-induced growth factors; c) thrombosis and local arterio-venous shunting. A better recognition of the association of adenoma and FNH, particularly in the context of multiple nodules, could be useful in clinical practice.

Background

Adenoma and focal nodular hyperplasia (FNH) are both benign nodular hepatocellular lesions occurring in child bearing women, in a liver that is otherwise histologically

normal or nearly normal. Both lesions looked like histologically quite different in their typical forms; however, some non-typical nodules, especially those of small size, could be extremely challenging to hepatologists.

A central stellate fibrous region containing malformed large arteries but usually no portal veins characterizes typical FNH. The lesion is multinodular, composed of nearly normal hepatocytes, arranged in 1–2 cell-thick plates, associated with a prominent bile ductular reaction, and intermingled with inflammatory cells (at the interface between hepatocytic nodules and fibrous bands). FNH is considered as a hyperplastic process resulting from an increased arterial flow. At the opposite, adenoma is a true benign neoplasia, composed of slightly enlarged but nearly normal hepatocytes, arranged in 1–2 cell-thick plates, with numerous thin arteries dispersed within the tumor, whereas there are no portal tracts and particularly no biliary ducts. Adenoma exhibited usually peliotic and necrotic hemorrhagic changes, steatotic areas and sometimes dysplasia. Their transformation into HCC is well documented but remains rare.

The simultaneous occurrence of adenoma and focal nodular hyperplasia (FNH) has been infrequently documented [1–6]. FNH associated with adenomas or adenomatosis has been reported [7–9], suggesting a link between these conditions.

We report the experience of a single French academic center, which supports the possibility that the association is more than by chance. Liver cell adenoma together with FNH was found in five out of 30 cases of "multiple benign hepatocytic nodules" collected in our files of the Department of Pathology of the University Hospital of Bordeaux, during the last 12 years.

Results and Discussion

Relevant clinical, radiological and surgical data are presented in Figures 1, 2 and 3. All 5 cases of liver cell adenoma together with FNH were women on oral contraceptives. In all cases, the reason for surgery was the discovery, by imaging techniques, of an adenoma (cases 1, 3, 4, 5) or of an unidentified benign tumor possibly an adenoma (case 2). In four cases (2, 3, 4, 5) FNH were discovered by imaging techniques prior to surgery. The case in which the diagnosis of FNH was missed by pre-operative imaging was case 1 that had a small 1 cm superficial FNH.

Case	1		2				3	
Age / Sex	45 / F		40 / F				38 / F	
OC (duration - in years)	+ (10)		+ (15)				+ (17)	
Main clinical signs / disease	Fatigue (alcoholism)		Increased GGT				Increased GGT	
MRI location and number of nodules (size largest one: cm)	VII, 1 (3)		VI, 1 (5)	VII, 1 (4)	LL, 1 (3)	LL, 1 (2)	RL, 1 made of 2 parts (13)	
Clinical, radiological diagnosis	Adenoma		FNH	FNH	?	FNH	Adenoma	Surrounded by FNH
Surgery (years)	RH (95)	Plus tumorectomy (III) for 1 superficial N	Biopsy	Biopsy	LH (98)		RH (98)	
Gross macroscopy diagnosis	Adenoma	FNH (1 cm)			Adenoma	FNH	Adenoma	Surrounded by FNH
Liver pathology nodules	Adenoma	FNH (1 cm)	FNH	FNH	Adenoma (steatotic)	FNH + 2 steatotic N (few mm) ?	Adenoma	Surrounded by FNH
Liver pathology of non tumoral liver	Normal		Some HV with thickened walls. Some isolated arteries and abnormal portal tracts				Normal	
Follow up (new nodule)	1 (small) probable FNH (99)		No change				No change	

Figure 1

Adenoma plus focal nodular hyperplasia (cases 1, 2 and 3). Liver segments are indicated by roman numbers. FNH – focal nodular hyperplasia; GGT – gamma glutamyl transpeptidase; Hem: hemorrhagic; HV – hepatic vein; LH – left hepatectomy; LL – left lobe; MRI – magnetic resonance imaging; N – nodule; OC – oral contraceptives; PV – portal vein; RH – right hepatectomy; RL – right lobe; T – tumorectomy. (Abbreviations are valid for Figures 2 and 3.)

Case	4						
Age / Sex	29 / F						
OC (duration - in years)	+ (2)						
Main clinical signs / disease	Abdominal pain + shock						
MRI location and number of nodules (size largest one: cm)	I (intratumural bleeding), 1 (6)	II, 1 (1)	III, 1 (1)	VII, 1 (1)	VIII, 1 (3)	VI, 1 (1)	Many small N
Clinical, radiological diagnosis	Adenoma	Adenoma	Adenoma	Adenoma	Adenoma	FNH	
Surgery (years)	LH + I (00)						3 T for superficial N (RL)
Gross macroscopy diagnosis	Adenoma (Hem)	Adenoma	Adenoma	Several small N			?
Liver pathology of nodules	Adenoma (Hem)	Adenoma	Adenoma	Adenoma - FNH - N?			2 FNH - 1N ?
Liver pathology of non tumoral liver	Some HV with thickened walls						
Follow up (new nodule)	No change						

Figure 2
Adenoma plus focal nodular hyperplasia (case 4).

A

Case	5	
Age / Sex	41 / F	
OC (duration - in years)	+ (20)	
Main clinical signs / disease	Abdominal pain	
MRI location and number of nodules (size largest one: cm)	RL, 1 (3)	RL, 1 (4)
Clinical, radiological diagnosis	FNH	Adenoma
Surgery (years)	RH (02)	
Gross macroscopy diagnosis	FNH	Adenoma + several N near the gallbladder (few mm up to 1 cm)
Liver pathology of nodules	FNH	Adenoma - FNH - N ?
Liver pathology of non tumoral liver	HV thrombosis. Areas of approximation + thrombosis of PV	
Follow up (new nodule)	No change	

B

Oral contraceptives	Cases
Levonorgestrel (0.15 - 0.20 mg), Ethinylestradiol (30 µg)	Patients 2, 3 and 5
Gestodene (50 µg), Ethinylestradiol (30 µg)	Patients 4 and 5
Cytoproterone (2 mg), Ethinylestradiol (35 µg)	Patient 2
Norethisterone (1 mg), Ethinylestradiol (30 µg)	Patient 5
Gestodene (75 µg), Ethinylestradiol (20 µg)	Patient 3

Figure 3
A - Adenoma plus focal nodular hyperplasia (case 5) **B** - Details of contraceptives, for all five cases.

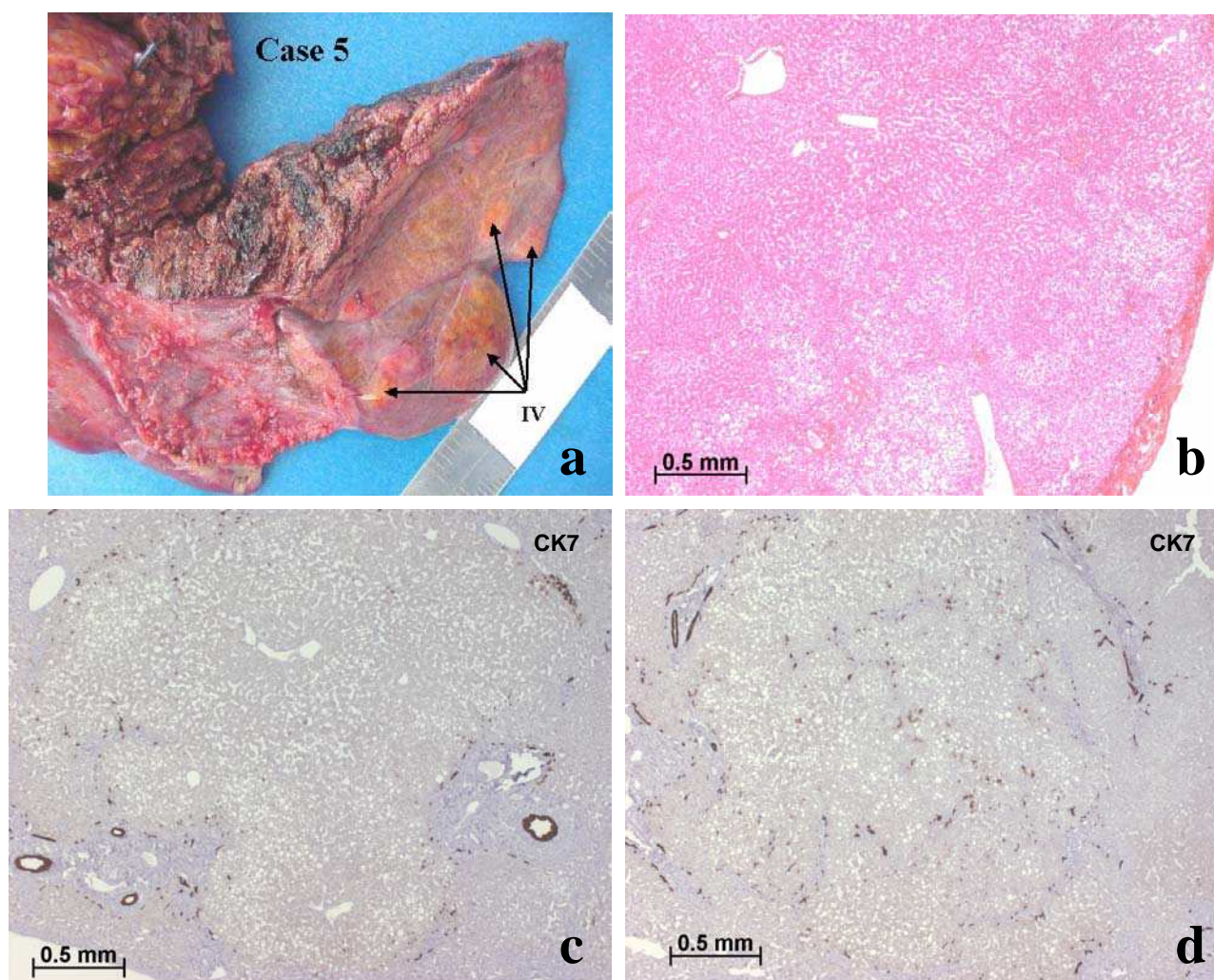


Figure 4

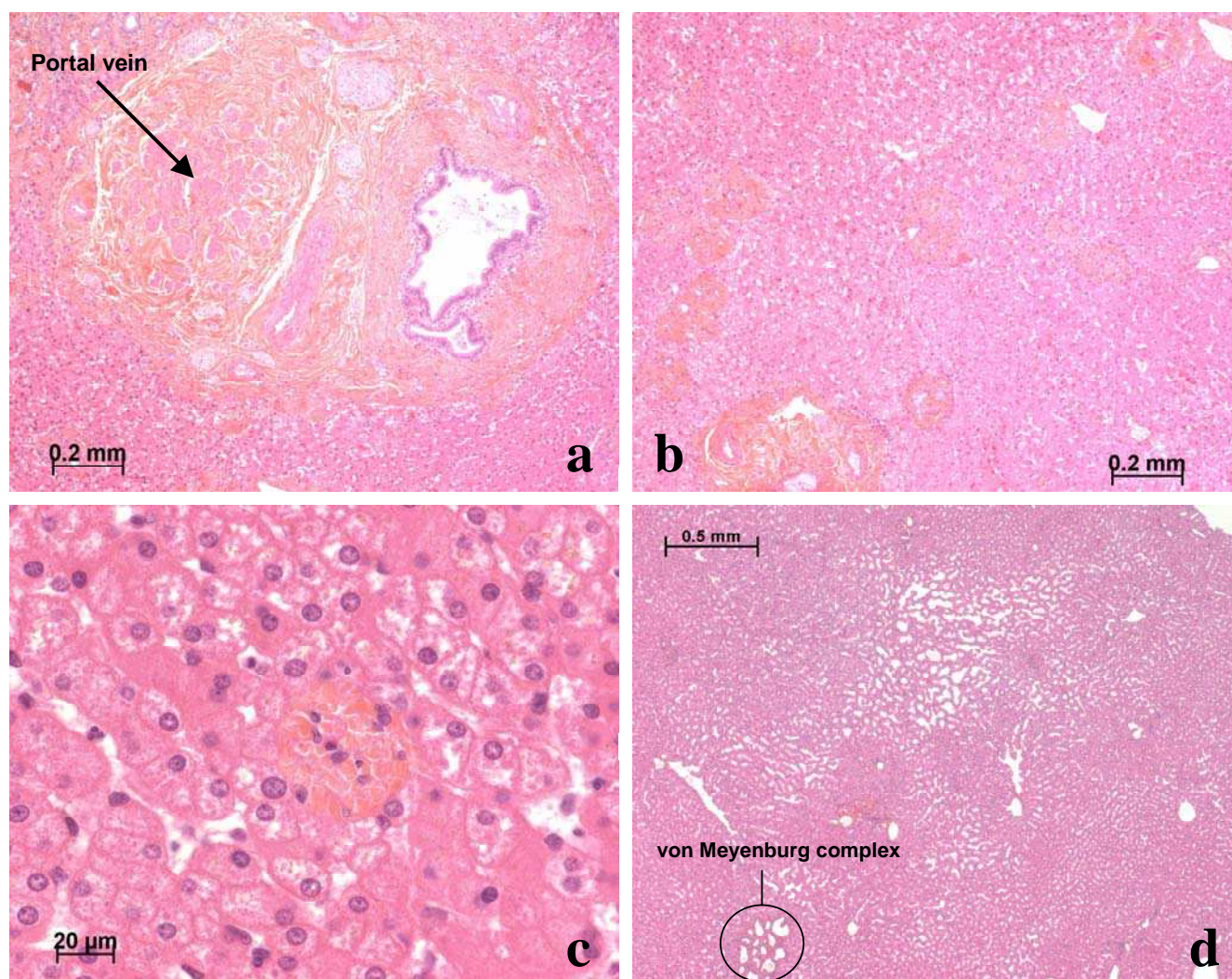
Case 5, segment IV. (a) shows several small nodules on the surface of segment IV (arrows). Among the nodules (surface and cut sections) there were several small adenomas (b, c). One nodule contained numerous CK7 positive biliary cells (d); it could not be classified with certainty, but it could be an early FNH lesion.

Additional small nodules were discovered (cases 2, 4 and 5; Figs. 4,5,6,7) either during surgery or during post-resection dissection of the specimen. Case 4 was known to have multiple nodules, one of which, at least, was identified as FNH (Fig. 6) by pre-operative imaging. Additional small superficial nodules (in case 4) were interpreted as adenomas by the surgeon and resected, and were solid FNH by light microscopy.

Adenoma and FNH recognized by imaging techniques were easily identified as such by light microscopy. Conversely, some small nodules could not be identified with

certainty because of the presence of biliary structures without ductular reaction (Figs. 4,5,6,7). To achieve a categorical assignment for the purposes of this study, we classified these small nodules with intralesional arteries and few/rare biliary cells, better identified by cytokeratin 7 (CK7) immunostaining, as adenoma [10]; and nodules with some/frequent biliary cells associated with intralesional arteries as FNH.

In one case (case 5) there were additional abnormalities in the non-nodular liver in the area around the multiple nodules that were found (Figs. 4, 5). These abnormalities

**Figure 5**

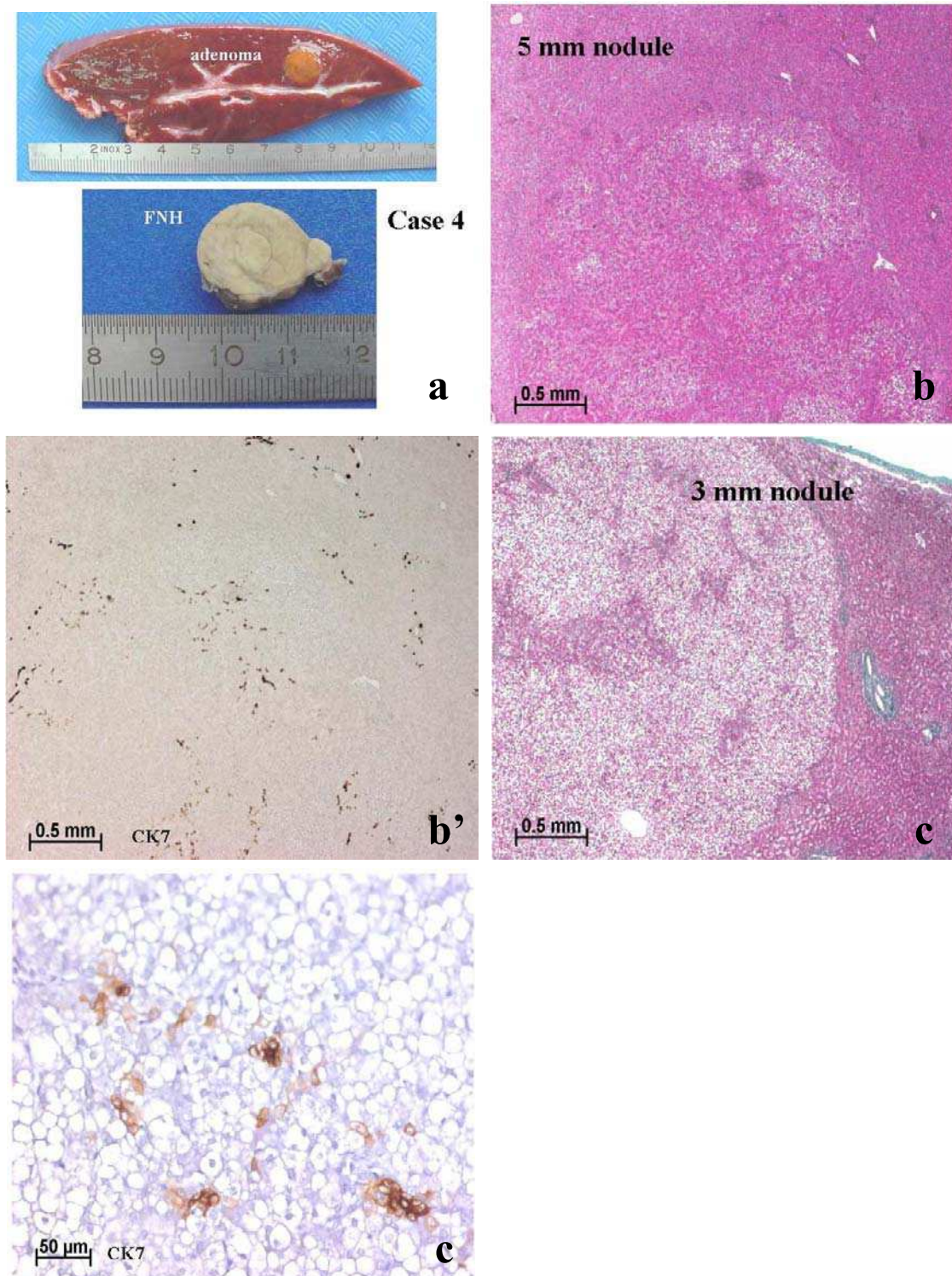
Case 5, segment IV. Around the nodules, there were many abnormalities such as obstruction of portal vein branches (a), areas of portal tract approximation (b), portal tract remnants (c), and sinusoidal dilatation (d). Some von Meyenburg complexes were also observed (d).

consisted of portal tract approximation, portal venous and hepatic venous thromboses (totally or partially), portal tract remnants with arteries surrounded with a rim of fibrosis, and some von Meyenburg complexes were also observed. In two cases (cases 2 and 4) some large hepatic veins had thick walls.

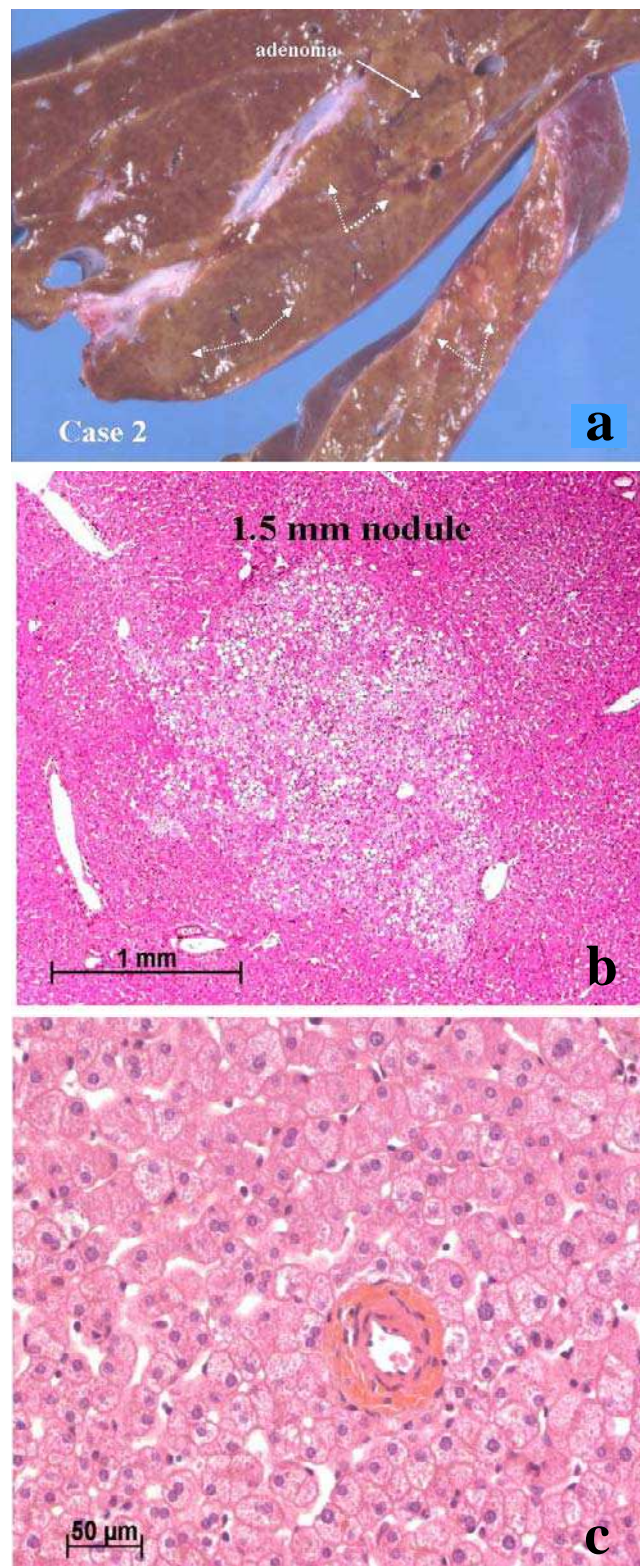
In our referral center (3 million inhabitants), we receive mainly difficult cases either because the nature of the nodule(s) is unknown or because surgery might be technically difficult. Our patients thus consist of a highly selected population. Nevertheless, our finding of liver cell adenoma together with FNH in 5 out of 30 cases of "multiple

benign hepatocytic nodules", collected in the files of the Department of Pathology of the University Hospital of Bordeaux during the last 12 years, suggests the possibility of a significant association.

If we omit case 1 which could be a co-incidental association of a known adenoma and a separate small FNH discovered incidentally during surgery, the four other cases show features that suggest a close relationship between adenoma and FNH:

**Figure 6**

Case 4. In addition to the presence of adenomas and FNH seen macroscopically (a), there were many tiny nodules (b, c). In (b) there were many CK7 positive biliary cells (b') in the vicinity of arteries. This nodule could be an early FNH lesion. In another nodule (c) CK7 positive cells were faintly stained, isolated and did not form biliary structures. This nodule (c') is more likely an adenoma than a pre-FNH lesion.

**Figure 7**

Case 2. In addition to the presence of several FNH and one adenoma (white solid arrow) (a), there were many small areas that were difficult to differentiate from the surrounding non-nodular tissue (white dotted arrows) (a). These areas corresponded to steatotic zones that could not be defined with certainty (b). In the non-nodular tissue there was an isolated hepatic artery (c).

- Case 3 is a rare example of the intermingling of the two lesions, with the FNH surrounding the adenoma [3]. The two lesions were diagnosed by pre-operative imaging.

- Case 4 demonstrates the presence of FNH in a patient with multiple adenomas (so-called adenomatosis) [8]. Here, pre-operative imaging identified at least one FNH, too.

- Case 2 illustrates the converse situation with at least, one adenoma in a patient with multiple FNH.

- Case 5 is similar to case 2 except that only one large FNH was picked up by imaging techniques.

It is thought that in FNH, increased arterial flow leads to secondary hepatocellular hyperplasia. Therefore, FNH is considered the consequence of a hyperplastic rather than a neoplastic process [11]. The association of FNH and adenoma could be coincidental or secondary to shared causal mechanisms [12–14]:

a) systemic and local abnormalities of angiogenesis induced by oral contraceptives (in our series all of the patients were women on oral contraceptives).

b) neoplastic growth factors inducing a nearby hyperplastic reaction; the surrounding of the adenoma by FNH (case 3) represents the best example.

c) thrombosis and local arterio-venous shunting [12]; in three cases, there were obvious abnormalities of veins in the non-nodular liver.

On the one hand, FNH might occur as a consequence of adenoma/adenomatosis; on the other hand, vascular abnormalities (congenital or acquired, and which are the key factor for the formation of FNH [11,13,14]), could favor the development of adenomas/adenomatosis (Fig. 8). The risk link to estrogen was thought to decrease with the use of the third generation of OC (lesser estrogens). However, the reduction of the dose of estrogens had limited effect on reducing the risk of venous thrombosis. Moreover, third generation of progestins in combination preparation increases the extent of adverse hemostatic changes and the associated risk of thrombosis [15].

One important finding shown in this study is that the number of nodules seen on the resected specimen is occasionally much greater than the number of nodules detected by imaging techniques. Some of these nodules cannot be identified with certainty [16]. This is certainly a major limitation of histopathology (and imaging). Clonality assessment [17] and gene analysis [18] could help to solve the identification of those small nodules. The size of

the nodule (and thus the stage of the development of either adenoma or FNH) are probably the main reasons for the diagnostic difficulty which could be used as an argument to postpone the resection of small yet unidentified "benign" nodules (as long as their growth remains slow).

A better knowledge of the association of adenoma and FNH particularly in the context of multiple nodules, either adenomas or FNH, should prevent clinicians to conclude a final diagnosis in patients with multiple liver lesions of either type, simply on the basis of characterizing any single lesion. This will be helpful for a better follow-up of patients thought to have only multiple FNH or only multiple adenomas.

Conclusions

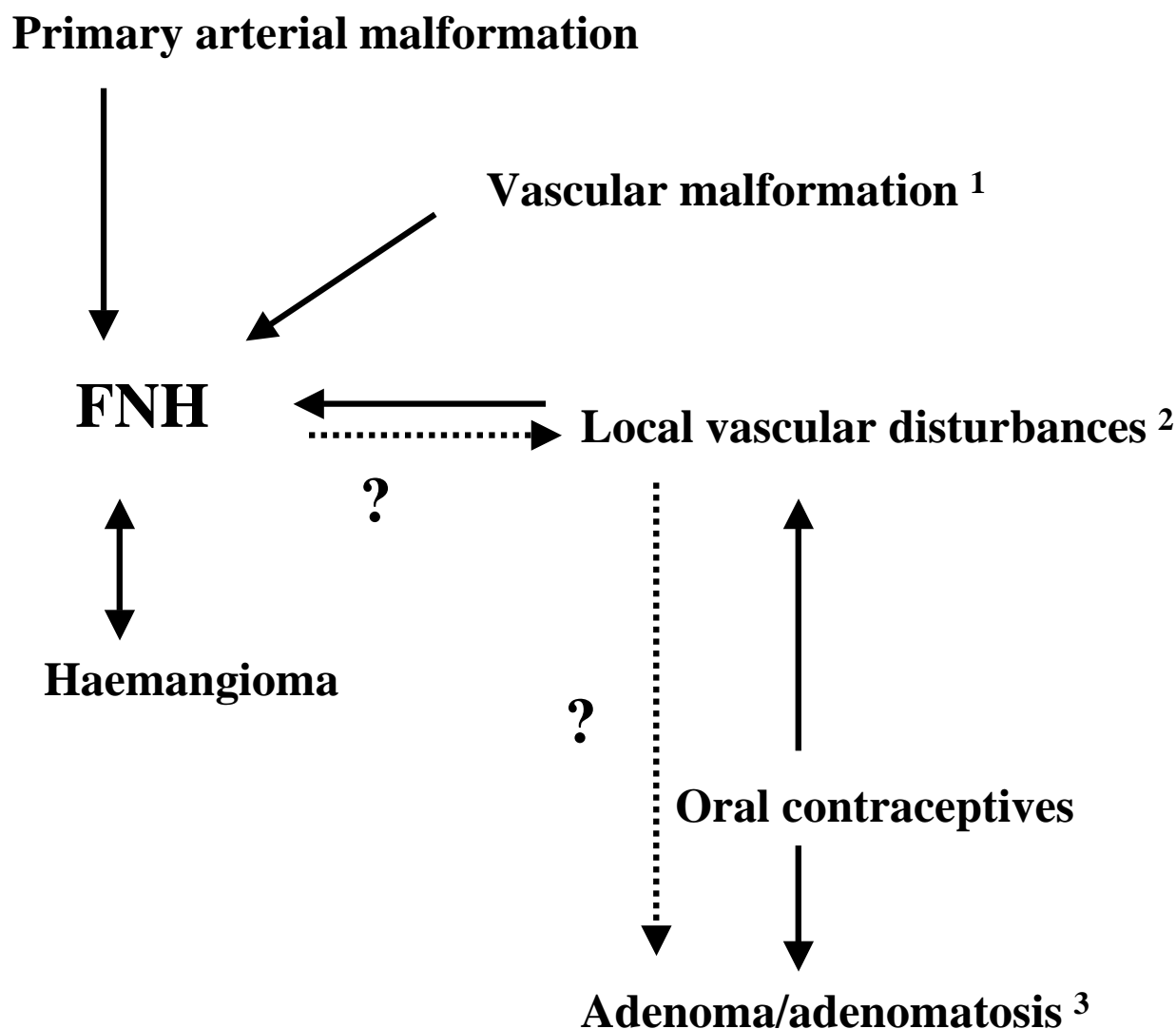
Liver adenoma and FNH in the context of multiple nodules may be significantly associated. The number of nodules seen in a resected specimen is occasionally much greater than nodules detected by imaging techniques. Small nodules present diagnostic difficulties. A better recognition of the association of adenoma and FNH, particularly in the context of multiple nodules, should be useful in clinical practice.

Methods

In the last 12 years, we collected in our files of the Department of Pathology of the University Hospital of Bordeaux, 30 cases of "multiple benign hepatocytic nodules". In our Institution, resected liver tumors are sliced thinly in the Department of Pathology. Each lesion detected prior to, or during resection or slicing is sampled. In addition, non-lesional liver near to and distant from the nodules are also sampled. Haematoxylin and eosin, Masson's trichrome, reticulin, and Perls' stains are performed routinely. For this study, slides were reviewed (by P.B-S and C.B.), and additional sections and immunostaining (CK7, alpha smooth muscle actin and CD 34) were performed whenever necessary. Standard criteria were used for the identification of adenoma and FNH [19]. Liver cell adenoma together with FNH was found in five cases out of 30 cases of "multiple benign hepatocytic nodules". Clinical, radiological and surgical data of these cases were reviewed.

Authors' Contributions

C Laurent contributed with clinical data. H Trillaud contributed with radiological data. C Balabaud reviewed slides and wrote the paper. S Lepreux contributed to the pathological examination. P Bioulac-Sage did the pathological examination and reviewed the paper. All authors read and approved the final manuscript.

**Figure 8**

Hypothetical relationships between adenoma/adenomatosis and FNH. ¹Vascular malformations: hereditary hemorrhagic telangiectasia; congenital absence of portal vein; intra hepatic venous shunt. ²Local vascular disturbances: Budd Chiari; cirrhosis; tumors (epithelioid haemangio-endothelioma; fibrolamellar hepatocellular carcinoma). ³The risk linked to estrogens.

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