Inflammatory hepatocellular adenoma, focal nodular hyperplasia and hepatic granulomas in one single patient : possible physiopathologic explanations

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Abstract

We report the case of a hepatocellular adenoma associated with focal nodular hyperplasia and hepatic granulomas in a 30-years-old woman. This association has rarely been described before but might be explained by underlying common pathophysiologic mechanisms. In this manuscript possible links between the three entities are discussed. (Acta gastroenterol. belg., **2020**, 83, **83-85**).

Keywords : liver, hepatocytes, pathophysiology.

Introduction

Hepatocellular adenoma (HCA) is a tumoural lesion due to a monoclonal expansion of hepatocytes. Although exact pathogenic mechanisms of HCA remain unknown, an association between HCA and use of oral contraceptives or androgens is assumed. Hepatocellular adenoma is not a single entity but different subtypes exist, with specific underlying gene mutations (1). These subtypes are hepatocyte nuclear factor-1α (HNF-1α)-mutated HCA, β-catenin-mutated HCA, inflammatory HCAs (I-HCA) and unclassified HCA.

There are two major complications of HCA. The first is the risk of rupture or spontaneous bleeding when the lesion is larger than 5 cm. In this condition a surgical resection is recommended. The second is malignant transformation of HCA into hepatocellular carcinoma. However, that remains a rare phenomenon, especially in the inflammatory hepatocellular adenoma subtype.

Contrariwise focal nodular hyperplasia (FNH) is a non-neoplastic lesion and is considered a consequence of vascular disturbance with hyperplastic response of hepatic parenchyma. Unlike adenoma, oral contraceptives do not play a direct role in the pathogenesis of FNH (2). FNH does not bear any risk of malignant transformation and therapeutic abstention is preferred if the lesion is asymptomatic and of reasonable size (3).

Hepatic granulomas result of multiple causes including sarcoidosis, tuberculosis, primary biliary cholangitis and viral and bacterial infections although often a cause cannot be identified.

In this case report we aim at a better understanding of links between these entities in light of recent advances in liver pathology.

Case report

A 30-years-old woman presented in the hospital for asthenia. Her weight was 86 kg, height 163 cm and body mass index (BMI) 32,4.

She stopped taking oral contraceptives one year before. Biological investigations revealed an increase of C-reactive protein (CRP) and abnormal liver tests (elevation of gamma-glutamyl transferase and alkaline phosphatase). She did not have metabolic syndrome. Abdominal ultrasonography and hepatic MRI demonstrated a nodular subcapsular hepatic lesion in segment V. The lesion measured 73 mm x 69 mm and had an arterial-phase enhancing (Fig. 1).

The radiological features were in favour of a benign tumour, possibly an adenoma whereas FNH could not be excluded. It was decided to perform MRI control at 6 months.

The control MRI showed a slowly growing lesion and revealed a second lesion in segments IV and VIII presenting comparable radiological characteristics. Both lesions were resected because of risk of bleeding in lesions suspicious for adenoma.

At macroscopic examination in the pathology department, an orange-brown multinodular mass was found in

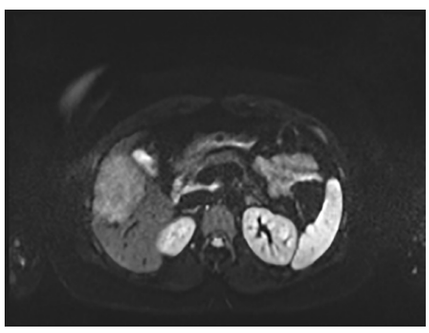

Figure 1. — MRI (diffusion phase) showing a lesion in liver segment V.

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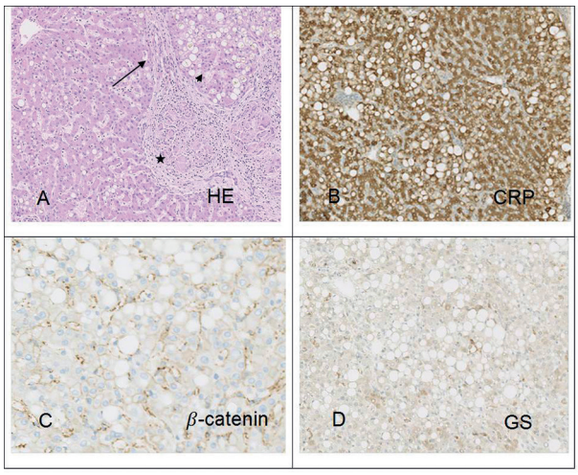

Figure 2. — Hepatocellular adenoma, inflammatory subtype. (A) Characteristic features of this subtype include fibrous septa (arrow) with dystrophic vessels and mild chronic inflammatory infiltrates. We also noted mild steatotic changes (arrowhead) and granulomas with giant cells (asterisk) (HE: haematoxylin-eosin staining). (B) Strong expression of CRP as detected by immunohistochemistry. (C) Normal membranous expression of β-catenin. (D) Absence of expression of glutamine synthetase (GS).

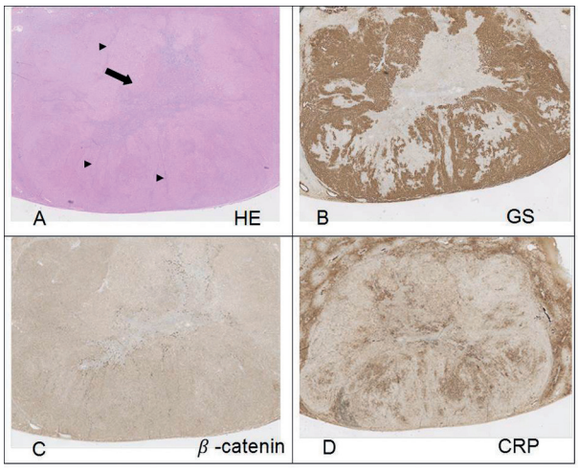

Figure 3. — Focal nodular hyperplasia. (A) Unencapsulated lesion composed of hyperplastic nodules (arrowheads) separated by fibrous septa radiating from a central scar (arrow) (HE: haematoxylin-eosin staining) (B) Characteristic map-like glutamine synthetase (GS) expression as detected by immunohistochemistry. (C) Absence of nuclear staining of β-catenin. (D) Periseptal expression of CRP.

segment V whereas segments IV and VIII contained a well circumscribed yellowish nodule.

Histopathological examination of the segment V lesion demonstrated a well-demarcated and unencapsulated nodule. It showed a relatively uniform cell population resembling normal liver, with cell plates 1-3 layers thick, and an intact reticulin framework. There were steatotic changes but we did not see any mitotic activity. Immunohistochemistry revealed an overexpression of CRP with normal membranous expression of β-catenin. There was expression of liver fatty acid binding protein (LFABP) but not of glutamine synthetase (GS). This histological aspect and the immunohistochemical analysis were in favour of an I-HCA (Fig. 2).

The lesion in segments IV and VIII was characterized by nodules of mature hepatocytes separated by large fibrous septa containing dystrophic vessels and inflammatory infiltrates. We also observed a bile ductular proliferation adjacent to fibrous tracts. Immunohistochemical staining showed a map-like pattern of GS and a periseptal expression of CRP. LFABP and β-catenin were normally expressed. These data were compatible with a FNH (Fig. 3).

Moreover, noncaseating granulomas with giant cells were seen in both liver lesions and in the surrounding liver parenchyma (Fig. 1). Ziehl-Neelsen, PAS and Grocott stains did not reveal any micro-organisms.

Three days after surgery biological cholestasis had disappeared. Six months later the patient had taken 4 kg, and nutritional counseling was foreseen. In the follow-up, there was no evidence of sarcoidosis, infection or auto-immune disease. No peri- or post-operative complications occurred and the patient was in good condition one year after surgery.

Discussion

Simultaneous occurrence of HCA, FNH and hepatic granulomas was already described by Grazi *et al.* in 2007 (4), but without any explanation on the links between them.

HCA and FNH occur predominantly, but not exclusively in women of child bearing age with an otherwise normal liver. These lesions can be difficult to distinguish on radiological and pathological examination, especially when they are small or in case of I-HCA. This latter lesion can be very challenging due to overlap features with FNH such as fibrous septa or ductular reaction. In difficult cases immunohistochemical results can be used as diagnostic criteria. Map-like GS expression pattern is highly characteristic of FNH and is not seen in I-HCA. Moreover, inflammatory markers such as CRP are typically present in I-HCA in a diffuse manner while CRP in FNH is usually restricted to periseptal areas.

The association between lesions is probably not fortuitous. FNH is often seen in context of adenomatosis. It is well known that liver vascular diseases are prone to the development of FNH, but they may also play a role in the development of HCA (5-6).

Wanless tried to precise the mechanism of association between hepatic neoplasms and FNH (7). According to him, neoplasms are sources of angiogenic growth factors that cause increased perfusion of lesions but also adjacent tissues leading to FNH formation close to neoplasms.

On the other hand, development of FNH remote of neoplasms might be a consequence of systemic increase

in these angiogenic growth factors. Even if such factors represent a diffuse stimulus, they are, however, unlikely to produce a focal lesion. An additional local stimulus such as vascular disturbance may be required to distant FNH formation.

Another study directed by Bioulac-Sage concluded that the association could be coincidental or due to shared causal mechanisms. Local and systemic angiogenic abnormalities induced by oral contraceptives, tumour-induced growth factors and vascular abnormalities are described as possible causes (8).

On the other hand, the link between FNH and granulomas is not well documented. In our case, granulomas were localized in the fibrovascular stroma of the FNH which might be a consequence of the release of inflammatory mediators by the inflammatory infiltrates.

Finally, coexistence of HCA and liver granulomas is reported in few papers (4,9-11). Bioulac-Sage *et al.* postulate that the association might be due to three mechanisms. First, chronic irritation and inflammatory stress caused by inflammatory HCA might trigger granuloma formation. Second, the presence of abnormal tumoural tissue might generate granuloma formation. Third, chronic use of oral contraceptives has been described as an etiological factor in both HCA and granuloma formation.

In view of these data, the association of I-HCA, FNH and hepatic granulomas in our patient is probably not fortuitous. She was obese and took oral contraceptives in the past, with hormonal disturbances as a consequence.

Overweight/obesity is associated with activation of the interleukin (IL)-6 signalling pathway which might lead to formation of I-HCA (12). Obesity also induces a hyperoestrogen state associated with HCA formation (13).

Furthermore, sex hormones play a role in tumourigenesis by promoting cell proliferation (14). Oestrogens have shown to induce hepatic angiogenesis in rats (15). Even though we cannot fully extrapolate this animal experiment to humans, such oestrogen-induced angiogenesis might lead to increased vascular supply with adenomatous proliferation as a consequence.

In this case, the latter phenomenon might explain the growth of the I-HCA, which contributes to an increased release of inflammatory mediators and systemic angiogenic growth factors. The inflammatory mediators contribute to overstimulation of mononuclear cells to fuse with each other, leading to formation of multinucleated giant cells and granulomas. Release of angiogenic growth factors induces increased arterial blood flow that contributes to FNH formation.

In conclusion, coexistence of HCA with FNH and hepatic granulomas is rare but might be explained in several ways. Studies on common pathophysiological pathways might lead to increased understanding of this rare phenomenon.

Conflict of interest

The authors declare no conflict of interest

References

1. BIOULAC-SAGE P., REBOUISSOU S., THOMAS C., BLANC J.F., SARIC J., SA CUNHA A., *et al.* Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. *Hepatology*, 2007, **46** : 740-748.
2. WANLESS I.R., MAWDSLEY C., ADAMS R. On the pathogenesis of focal nodular hyperplasia of the liver. *Hepatology,* 1985, **5** : 1194-1200.
3. NAVARRO A.P., GOMEZ D., LAMB C.M., BROOKS A., CAMERON I.C. Focal nodular hyperplasia: a review of current indications for and outcomes of hepatic resection. *HPB (Oxford)*, 2013, **16** : 503-511.
4. GRAZI G.L., VETRONE G., ERCOLANI G., CESCON M., RAVAIOLI M., ZANELLO M., *et al.* Associated benign liver tumors in idiopathic granulomatous hepatitis: a case report. *Hepatol. Res.*, 2007, **37** : 568-571.
5. BIOULAC-SAGE P., CUBEL G., BALABAUD C. Pathological diagnosis of hepatocellular adenoma in clinical practice. *Diagnostic Histopathology*, 2011, **17** : 521-529.
6. BIOULAC-SAGE P., BALABAUD C., BEDOSSA P., SCOAZEC J.Y., CHICHE L., DHILLON A.P., *et al*. Pathological diagnosis of liver cell adenoma and focal nodular hyperplasia: Bordeaux update. *J. Hepatol.*, 2007, **46** : 521-527.
7. WANLESS IR. Epithelioid hemangioendothelioma, multiple focal nodular hyperplasias, and cavernous hemangiomas of the liver [letter]. *Arch. Pathol. Lab. Med.*, 2000, **124** : 1105-1107.
8. LAURENT C., TRILLAUD H., LEPREUX S., BALABAUD C., BIOULAC-SAGE P. Association of adenoma and focal nodular hyperplasia: experience of a single French academic center. *Comp. Hepatol.*, 2003, **2** : 6.
9. LE BAIL B., JOUHANOLE H., DEUGNIER Y., SALAME G., PELLEGRIN J.L., SARIC J., *et al.* Liver adenomatosis with granulomas in two patients on long-term oral contraceptives. *Am. J. Surg. Pathol*, 1992, **16** : 982-987.
10. KAZI K.C., DESHPANDE R., SOMAN R., LALA M., SHAH S. Liver cell adenoma with co-existing hepatic granulomas in an HIV positive patient. *Indian J. Gastroenterol.*, 2005, **24**: 274-275.
11. BIEZE M., BIOULAC-SAGE P., VERHEIJ J., BALABAUD C., LAURENT C., VAN GULIK T.M. Hepatocellular adenomas associated with hepatic granulomas: experience in five cases. *Case Rep. Gastroenterol.,* 2012, **6** : 677-683.
12. REBOUISSOU S., AMESSOU M., COUCHY G., POUSSIN K., IMBEAUD S., PILATI C., *et al*. Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours. *Nature*, 2009, **457** : 200-204.
13. CHANG C.Y., HERNANDEZ-PRERA J.C., ROAYAIE S., SCHWARTZ M., THUNG S.N. Changing epidemiology of hepatocellular adenoma in the United States: review of the literature. *Int. J. Hepatol.* 2013, **2013** : 604860.
14. PORTER L.E., VAN THIEL D., EAGON P.K. Estrogens and progestins as tumor inducers. *Semin. Liver Dis.*, 1987, **7** : 24-31.
15. ISHII K., MATAMA S., SHIBATA H., OKABE H., OKUDAIRA M., NAGATA T., *et al.* Microcirculatory responses to estradiol benzoate in chronic liver damage induced by carbon tetrachloride in the rat. *Gastroenterol. Jpn.*, 1984, **19** : 419-423.