Co-existence of hepatocellular adenoma and focal nodular hyperplasia in a young female

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INTRODUCTION

Focal nodular hyperplasia (FNH) and hepatocellular adenoma (HA) are both benign nodular hepatocellular lesions, presenting mainly in women of childbearing age in non-cirrhotic, non-fibrotic livers. Simultaneous occurrence of these two lesions is extremely rare. We herein report a case of a young female without any predisposing risk factors who presented to our emergency department complaining of acute abdominal pain. Imaging studies revealed a 6 cm lesion in the right hepatic lobe and a 2.5 cm lesion in the left hepatic lobe, respectively. In view of the patient’s symptoms and lack of a confirmed diagnosis based on imaging, we performed a bisegmentectomy V- VI and a wedge resection of the lesion in segment III by laparotomy. Postoperative course was uneventful and the patient was discharged on the fourth postoperative day. The pathology report demonstrated an HA in segments V -VI and FNH in segment III, respectively. Six months later, the patient remains asymptomatic with normal liver function tests, ultrasound and magnetic resonance imaging follow-up. To our best knowledge, this is the first case to describe simultaneous occurrence of HA and FNH without the presence of any known risk factors for these entities. The uncertainty in diagnosis and acuteness of presenting symptoms were established criteria for prompt surgical intervention.

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of patients, while hepatomegaly and fever occur in less than 1 percent of cases. Spontaneous rupture leading to hemorrhage is extremely rare and there is no incidence of malignant transformation of FNH[4,5]. Levels of serum alpha-fetoprotein are within normal range[6,7].

HA is the third most common benign liver lesion in adults, after hepatic hemangiomia and FNH, and is 3 to 10 times less common than FNH[6,7]. A 30 to 40 fold increase in the incidence of HA has been assumed in long term users of oral contraceptives, with a base level incidence of 1 per million in women using oral contraceptives for less than 24 mo or not at all[8,9]. As in FNH, patients with HA are often asymptomatic. Atypical abdominal discomfort is reported in about 30% to 40% of patients and in a small number of cases a palpable mass is present. Large lesions may cause more severe complaints such as abdominal pain; hypovolemic shock after rupture or intratumoral hemorrhage has been observed in some cases. As with FNH, serum alpha-fetoprotein levels are within normal range[6,10].

Simultaneous presence of FNH and HA is very rare and only few cases have been published in the pertinent literature[11-14]. We report a case of a young female without any predisposing risk factors with simultaneous existence of FNH and HA. The diagnostic procedure, therapeutic management and possible pathogenic setting are discussed herein.

CASE REPORT

An 18 year old nulliparous female patient presented to the emergency department complaining of acute abdominal pain. She was 1.65 m tall and weighed about 55 kg upon admission (body mass index 20.2). The patient denied any oral contraceptive pill use, tobacco or alcohol consumption and there was no history of hepatitis. Hepatitis infection markers were negative. Gynecological history was unremarkable, with normal pubertal/postpubertal development and menstruation. Past medical history was likewise unremarkable. The pain was localized in the right upper quadrant of the abdomen and was accompanied by a slight elevation of body temperature (37.2 °C). The patient did not complain of vomiting, change in bowel habits or any urinary symptoms. Clinical examination did not demonstrate any suspicious signs of high endogenous androgen activity. Routine laboratory studies, including a complete blood count, biochemical profile with liver function tests and α-fetoprotein measurement, were within normal range.

Emergency ultrasound showed a mass of approximately 6 cm in diameter located in the right liver lobe. Upper abdominal magnetic resonance imaging (MRI) revealed a 6 cm lesion in the right liver lobe (segments V and VI) and a smaller one (2.5 cm) in the left lobe (segment III), respectively (Figure 1). However, the MRI findings were not specific for the larger lesion in the right lobe (Figure 1A). In view of the patient’s symptoms and the lack of a confirmed diagnosis based on preoperative imaging examinations, we opted for prompt surgery.

The patient underwent a bissegmentectomy V-VI and a wedge resection of the lesion in segment III by laparotomy. Total operating time was 125 min and blood loss was minimal. Portal triad clamping was not performed at any stage of the operation. Perioperative or postoperative blood or plasma products transfusion was not required. The postoperative course ran uneventfully and the patient was discharged on the fourth postoperative day in good general condition.

Pathology report of the larger lesion in segments V and VI revealed a non-encapsulated hepatocellular neoplasm composed of benign-looking hepatocytes, arranged in sheets and thin cords, occasionally forming rosette-like structures (Figure 2A and B). Isolated arteries were also present. Two different hepatocellular populations were discernible, demonstrating a zonal distribution. In the periphery of the lesion, eosinophilic hepatocytes were present alternately with larger hepatocytes, thus forming a vague lobulation. Absent portal-tract like structures with thin fibrous septa and mild ductular reaction were observed mainly towards the periphery of the lesion. Overall, the tumor was characterized by mild to moderate steatosis, lipofuscinosis, a well-developed reticulin network, no cytological abnormalities and no inflammatory infiltrates. Immunohistochemical examination showed absence of nuclear expression of beta catenin, while serum amyloid A gave a weak, non-specific reaction. Cytokeratin 7 was positive in the abor-
tive bile ducts and ductules and in a few tumor cells at the periphery of the fibrous septa. Cytokeratin 19 was positive only in rare ductular structures. Glutamine synthetase exhibited a patchy positive expression, while L-FABP antibody was not attenuated compared to normal parenchyma. Pathology and immunohistochemistry findings supported the diagnosis of hepatocellular adenoma partly featuring a telangiectatic variant.

The pathology report of the resected segment Ⅲ revealed a non-encapsulated, circumscribed hyperplastic hepatocellular lesion. The tumor was divided into smaller nodules by fibrous septa, which contained dystrophic arteries (Figure 2C). Prominent ductular reaction and mild to moderate inflammatory infiltrates were also observed (Figure 2D). A well-developed reticulin network supported the tumoral hepatocytes that showed no cytological atypia and minimal steatosis. The diagnosis was that of focal nodular hyperplasia.

At present, 6 mo after the operation, the patient remains asymptomatic with normal hepatic function tests and ultrasound and MRI imaging show liver regeneration without signs of tumor relapse.

**DISCUSSION**

We herein describe a case of a young female patient, with no history of oral contraceptive use or other risk factors, exhibiting simultaneous occurrence of FNH and HA in different liver segments.

FNH and HA are two benign liver lesions that very seldom co-exist. The pathogenesis of FNH and HA is considered to be different. On one hand, the exact etiology of FNH is not completely understood. It is generally suggested that FNH originates from arterial malformation, which causes a hyperplastic reaction of normal liver cells to either hyperperfusion or hypoxia. As hyperplastic reactions respond to cell proliferation mechanisms, FNH does not undergo any malignant transformation. Several clinical observations strengthen the above hypothesis as FNH may coexist with hepatic hemangioma or telangiectasia. Scalori et al. suggested that cigarette smoking might be an elevated risk index for FNH. On the other hand, HA seems to have a causal relationship with exogenous administration of male and female sex hormones. The use of oral contraceptives provides convincing evidence that the incidence and size of HA is dose and duration dependent. Moreover, the pertinent literature reports sporadic cases of HAs occurring in patients with elevated levels of endogenous androgens, sex hormone imbalance or exogenous administration of androgens as a treatment option for aplastic anemia. A special form of HA has been described where multiple adenomas occur with at least ten lesions in the liver parenchyma, a condition designated as liver adenomatosis. The etiology of liver adenomatosis is unknown but there is some evidence supporting common pathways with HA. The fact that this condition is often found in women with a history of estrogen exposure could imply that liver adenomatosis is an advanced form of HA. Obesity, positive history of viral hepatitis, alcohol abuse and metabolic diseases, such as Von Gierke glucogen storage disease, have also been depicted as possible risk factors for HA by some authors.

Recently, a meticulous analysis of a large series of HA by a French collaborative group resulted in their
classification of 4 subtypes\textsuperscript{[10]}. The first group includes heavily steatotic adenomas exhibiting biallelic inactivation of hepatocyte nuclear factor 1 alpha. The second group is characterized by activating mutation of beta catenin and a higher risk for malignant transformation. The third group is defined by the presence of inflammatory infiltrates, sinusoidal dilation, fibrous septa with ductular reaction and abortive portal tracts, while the fourth group includes adenomas that cannot be classified in any of the above three subtypes. Of note, the newly characterized entity previously called telangiectatic FNH, now believed to be a variant of liver cell adenoma, is classified in the third group of inflammatory/telangiectatic adenomas\textsuperscript{[20,26,30]}. The adenoma described herein shared some morphological features with the telangiectatic subtype. However, it was categorized into the fourth group (adenoma not otherwise classified) due to the absence of pathognomonic telangiectatic and inflammatory findings.

It is well established that HA and FNH are two distinct entities with specific histological and molecular features. However, differential diagnosis between them may be difficult in liver resection specimens or liver biopsy-obtained material. It is most likely that in the near future diagnosis will be facilitated by the molecular alterations detected in such lesions. Liver cell adenomas, including subtypes previously called telangiectatic FNH, are monoclonal tumors\textsuperscript{[26,30]}. Conversely, clonal analysis on FNH lesions indicated a monoclonal origin in 14% to 50% of cases, depending on the samples examined and molecular techniques carried out. Furthermore, the mRNA ratio of angiopoietin genes (ANGPT-1 and ANGPT-2, respectively) is found to be attenuated in typical FNH compared to HA\textsuperscript{[31]}. The simultaneous presence of both FNH and HA in the same patient is very rare and only a few cases have been described in the pertinent literature\textsuperscript{[11-14]}. The largest report is the work of a French group that studied the co-existence of benign liver tumors\textsuperscript{[11,14]}. In this study, HA and FNH were found in the same liver in 5 out of 30 cases with multiple benign liver lesions over a period of 12 years\textsuperscript{[14]}. It is of note that in all cases published in the literature, patients were either on exogenous administration of oral contraceptives or had endogenous elevated sex hormones, conversely to our case presented herein. Laurent et al\textsuperscript{[12]} reported that simultaneous occurrence of HA and FNH could be generated secondary to systemic and local angiogenic abnormalities by oral contraceptives, tumor induced growth factors or thrombosis and local arterio-venous shunting.

In our case, the young female patient had no clinical signs of androgen hyperactivity, nor did she receive any oral contraceptives. She did not consume any tobacco or alcohol and her BMI was within normal range. She also had a negative history of viral hepatitis with normal serum hepatitis virus infection assays. Thus, our report is the first in the literature to describe the simultaneous occurrence of HA and FNH without the presence of any known risk factors. In our case, there is no obvious common pathogenic mechanism and the co-existence of the lesions could be incidental. However, the presence of some morphological overlapping features does not exclude the possibility of a commonly shared causative relationship. Deeper knowledge of the molecular background of those two tumors could help to recognize the exact association between them.

In recent years, there has been an increased incidence in the diagnosis of FNH and HA. The reason for this fact is increased administration of oral contraceptives on one hand and, on the other hand, imaging modalities evolution. This reality urges the need for providing secure preoperative diagnostic criteria in order to avoid an unnecessary operation and, more importantly, not to skip a necessary resection of a potential malignant tumor in a young or middle aged female. Many imaging modalities are used to diagnose FNH and HA. Especially for FNH, diagnosis can be achieved with high certainty on several imaging studies based on typical features. However, there are atypical imaging findings in both FNH and HA\textsuperscript{[12]}. Sensitivity and specificity of diagnostic imaging has been improved for the diagnosis of FNH, while the gold standard for HA is still liver biopsy. In our case, we decided to proceed to surgery mainly due to preoperative diagnostic uncertainty and acute symptomaticology.

In this report, we present a case of a young female patient with co-existence of FNH and HA of the liver without any previous exogenous administration of oral contraceptives or any other known risk factors predisposing to these liver lesions. This fact, together with the absence of typical radiological characteristics, could imply a common pathway in the pathogenesis of these two benign liver lesions or the presence of an intermediate form with interesting radiological, molecular or pathological features. The uncertainty in diagnosis and acuteness of presenting symptoms were established criteria for prompt surgical management. However, in cases of diagnosed benign tumors, surgery should be performed only when tumors are symptomatic or have a risk of complications such as hemorrhage, rupture or malignant potential.

\textbf{REFERENCES}

1. Fukukura Y, Nakashima O, Kusaba A, Kage M, Kojiro M. Angioarchitecture and blood circulation in focal nodular hyperplasia of the liver. \textit{J Hepatol} 1998; 29: 470-475
2. Choi BY, Nguyen MH. The diagnosis and management of benign hepatic tumors. \textit{J Clin Gastroenterol} 2005; 39: 401-412
3. Buell JF, Tranchart H, Cannon R, Dagher I. Management of benign hepatic tumors. \textit{Surg Clin N Amer} 2010; 90: 719-735
4. Weimann A, Ringe B, Klemmnauer J, Lamesch P, Gratz KF, Prokop M, Maschek H, Tusch G, Pichlmayr R. Benign liver tumors: differential diagnosis and indications for surgery. \textit{World J Surg} 1997; 21: 985-990; discussion 990-991
5. Nguyen BN, Fléjou JF, Terris B, Belghiti J, Degott C. Focal nodular hyperplasia of the liver: a comprehensive pathological study of 305 lesions and recognition of new histologic forms. \textit{Am J Surg Pathol} 1999; 23: 1441-1454
6. Karhunen PJ. Benign hepatic tumours and tumour like conditions in men. \textit{J Clin Pathol} 1986; 39: 183-188
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1 Cherqui D, Mathieu D, Zafrani ES, Dhumeaux D. [Focal nodular hyperplasia and hepatocellular adenoma in women. Current data]. Gastroenterol Clin Biol 1997; 21: 929-935
2 Rooks JB, Ory HW, Ishak KG, Strauss LT, Greenspan J, Hill AP, Tyler CW. Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. JAMA 1979; 242: 644-648
3 Giannitrapani L, Soresi M, La Spada E, Cervello M, D'Alessandro N, Montalto G. Sex hormones and risk of liver tumor. Ann N Y Acad Sci 2006; 1089: 228-236
4 Bioulac-Sage P, Blanc JF, Rebouissou S, Balabaud C, Zucman-Rossi J. Genotype phenotype classification of hepatocellular adenoma. World J Gastroenterol 2007; 13: 2649-2654
5 Reichlin B, Stalder GA, Rüedi T, Bianchi L. [Co-occurring liver cell adenoma and focal nodular hyperplasia due to contraceptives. Case report]. Schweiz Med Wochenschr 1980; 110: 873-874
6 Grangé JD, Guéchot 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
7 Di Carlo I, Urrico GS, Ursino V, Russello D, Puleo S, Latteri F. Simultaneous occurrence of adenoma, focal nodular hyperplasia, and hemangiomat of the liver: are they derived from a common origin? J Gastroenterol Hepatol 2003; 18: 227-230
8 Laurent C, Trillaud H, Lepreux S, Balabaud C, Bioulac-Sage P. Association of adenoma and focal nodular hyperplasia: experience of a single French center. Comp Hepatol 2003; 2: 6
9 Wantess IR, Albrecht S, Bilbao J, Frei JV, Heathcote EJ, Roberts EA, Chiasson 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
10 Toshikuni N, Kawaguchi K, Miki H, Kihara Y, Sawayama T, Yamakazi S, Takano S, Minato T. Focal nodular hyperplasia coexistent with hemangiomat and multiple cysts of the liver. J Gastroenterol Hepatol 2001; 16: 206-211
11 Vilgrain V, Uzan F, Brancatelli G, Federle MP, Zappa M, Menu Y. Prevalence of hepatic hemangioma in patients with focal nodular hyperplasia: MR imaging analysis. Radiology 2003; 229: 75-79
12 Breden R, Chapaux X, Deltenre P, Henrion J, De Maeght S, Horsmans Y, Borbath I, Leenaerts A, Van Cauter J, Françoise S, Sersté T, Moreno C, Orlent H, Mengeot P, Lerut J, Sempoux C. Large spectrum of liver vascular lesions including high prevalence of focal nodular hyperplasia in patients with hereditary haemorrhagic telangiectasia: the Belgian Registry based on 30 patients. Eur J Gastroenterol Hepatol 2010; 22: 1253-1259
13 Buscarini E, Danesino C, Plauchi H, de Fazio C, Olivieri C, Brambilla G, Menozzi F, Reduzzi L, Blotta P, Gazzaniga P, Pagella F, Grosso M, Pongiglione C, Cappiello J, Zambelli A. High prevalence of hepatic focal nodular hyperplasia in subjects with hereditary hemorrhagic telangiectasia. Ultrasound Med Biol 2004; 30: 1089-1097
14 Scalori A, Tavani A, Gallus S, La Vecchia C, Colombo M. Risk factors for focal nodular hyperplasia of the liver: an Italian case-control study. Am J Gastroenterol 2002; 97: 2371-2373
15 Nakao A, Sakagami K, Nakata Y, Komazawa K, Amimoto T, Nakashima K, IZsaki H, Takakura N, Tanaka N. Multiple hepatic adenomas caused by long-term administration of androgenic steroids for aplastic anemia in association with familial adenomatous polyposis. J Gastroenterol 2000; 35: 557-562
16 Triantafyllopoulou M, Whittington MF, Melin-Aldana H, Benya EC, Brickman W. Hepatic adenoma in an adolescent with elevated androgen levels. J Pediatr Gastroenterol Nutr 2007; 44: 640-642
17 Beuers U, Richter Wo, Ritter MM, Wiebecke B, Schwandt P. Klinefelter’s syndrome and liver adenoma. J Clin Gastroenterol 1991; 13: 214-216
18 Veteläinen R, Erdogan D, de Graaf W, ten Kate F, Jansen PL, Gouma DJ, van Gulik TM. Liver adenomatosis: re-evaluation of aetiology and management. Liver Int 2008; 28: 499-508
19 Greaves WO, Bhattacharya B. Hepatic adenomatosis. Arch Pathol Lab Med 2008; 132: 1951-1955
20 Rebouissou S, Bioulac-Sage P, Zucman-Rossi J. Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma. J Hepatol 2008; 48: 163-170
21 McLarney JK, Rucker PT, Bender GN, Goodman ZD, Kashi tani N, Ros PR. Fibrolamellar carcinoma of the liver: the radiologic-pathologic correlation. Radiographics 1999; 19: 453-471
22 Ronald M, Woodfield J, McCall J, Koea J. Hepatic adenomas in male patients. HPB 2004; 6: 25-27
23 Bioulac-Sage P, Balabaud C, Zucman-Rossi J. What’s in a name? Hepatology 2010; 51: 1086-1087
24 Bioulac-Sage P, Rebouissou S, Sa Cunha A, Jeannot E, Lepreux S, Blanc JF, Blanché H, Le Bail B, Saric J, Laurent-Puig P, Balabaud C, Zucman-Rossi J. Clinical, morphologic, and molecular features defining so-called telangiectatic focal nodal hyperplasias of the liver. Gastroenterology 2005; 128: 1211-1218
25 Paradis V, Benzeki A, Dargère D, Béchê I, Laurendeau I, Vilgrain V, Belghiti J, Vidaud M, Degott C, Bedossa P. Telangiectatic focal nodal hyperplasia: a variant of hepatocellular lar adenoma. Gastroenterology 2004; 126: 1323-1329
26 van den Esschert JW, van Gulik TM, Phoa SS. Imaging mo dalities for focal nodular hyperplasia and hepatocellular adenoma. Dig Surg 2010; 27: 46-55

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