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Hepatic Adenoma and Focal Nodular Hyperplasia: Differential Diagnosis and Treatment

Paulo Herman, M.D., Vincenzo Pugliese, M.D., Marcel A.C. Machado, M.D., Andre L. Montagnini, M.D., Marcelo Z. Salem, M.D., Telesforo Bacchella, M.D., Luis A.C. D'Albuquerque, M.D., William A. Saad, M.D., Marcel C.C. Machado, M.D., Henrique W. Pinotti, M.D., Ph.D.

Department of Gastroenterology, Hospital das Clinicas, University of São Paulo Medical School, R. Eneas de Carvalho Aguiar, 255, São Paulo, CEP 05403-900, Brazil

Abstract. The diagnosis of benign hepatic tumors as hepatic adenoma (HA) and focal nodular hyperplasia (FNH) remains a challenge for clinicians and surgeons. The importance of differentiating between these lesions is based on the fact that HA must be surgically resected and FNH can be only observed. A series of 23 female patients with benign liver tumors (13 FNH, 10 HA) were evaluated, and a radiologic diagnostic algorithm was employed with the aim of establishing preoperative criteria for the differential diagnosis. All patients were submitted to surgical biopsy or hepatic resection to confirm the diagnosis. Based only on clinical and laboratory data, distinction was not possible. According to the investigative algorithm, the diagnosis was correct in 82.6% of the cases; but even with the development of imaging methods, which were used in combination, the differentiation was not possible in four patients. For FNH cases scintigraphy presented a sensitivity of 38.4% and specificity of 100%, whereas for HA the sensitivity reached 60% and specificity 85.7%. Magnetic resonance imaging, employed when scintigraphic findings were not typical, presented sensitivities of 71.4% and 80% and specificities of 100% and 100% for FNH and HA, respectively. Preoperative diagnosis of FNH was possible in 10 of 13 (76.9%) patients and was confirmed by histology in all of them. In one case, FNH was misdiagnosed as HA. The diagnosis of HA was possible in 9 of 10 (90%) adenoma cases. Surgical biopsy remains the best method for the differential diagnosis between HA and FNH and must be performed in all doubtful cases. Surgical resection is the treatment of choice for all patients with adenoma and can be performed safely. With the evolution of imaging methods it seems that the preoperative diagnosis of FNH may be considered reliable, thereby avoiding unnecessary surgical resection.

Liver cell adenoma (HA) and focal nodular hyperplasia (FNH) are rare benign tumors of hepatocellular origin that usually affect young women. The incidence of HA was low until the 1970s, but recently the disease has become increasingly common in young women because of the advent of oral contraceptives, whose role in the development of this tumor has been demonstrated [1, 2]. The pathogenesis of FNH is unknown and is probably not associated with the use of oral contraceptives; they play a role not in the genesis but in tumor growth [3, 4]. During the last 15 years, with the improvement in and routine use of imaging methods, both lesions have been detected more frequently.

Correspondence to: P. Herman, M.D., Rua Pintassilgo, 210 ap. 71, São Paulo, SP, CEP 04514-030, Brazil.

The differential diagnosis between HA and FNH is often difficult, representing a challenge for clinicians and surgeons, especially because HA must be treated surgically and FNH is not. Patients with HA generally present with abdominal pain, and surgical resection is advocated based on the high incidence of bleeding complications, which are life-threatening in some instances [5]. Moreover, neoplastic degeneration of HA has also been reported [6, 7]. In contrast, FNH is generally an incidental finding in asymptomatic patients, and complications such as hemorrhage and malignant degeneration are almost always absent [8, 9]. For these reasons, patients can be just observed. In many instances, the differential diagnosis is possible only after a wedge biopsy or resection of the tumor. This study aimed to establish criteria that would allow the differential diagnosis between HA and FNH based on clinical, biochemical, and radiologic data, thus avoiding unnecessary surgical biopsy or resection.

Patients and Methods

A total of 23 female patients with benign solid liver tumors were studied between 1990 and 1998. The mean age was 31 years (range 8–50 years); and 78.3% had a history of oral contraceptive use. Abdominal pain was present in two-thirds of the patients, and in two of them it presented as an acute episode.

Liver function tests were performed in all patients, as were ultrasonography, computed tomographic scan (CT), and technitium (^{99m}Tc)-sulfur colloid and ^{99m}Tc-labeled DISIDA (dimethyliminodiacetic acid) liver scintigraphy; 11 patients were submitted to magnetic resonance imaging (MRI).

Patients with solid liver tumors, diagnosed by ultrasonography or CT, were all submitted to scintigraphy with DISIDA. If increased uptake or retention of the tracer was found, suggesting a benign tumor such as FNH or HA, the investigation continued following a diagnostic algorithm trying to establish the differential diagnosis between these two lesions (Fig. 1).

All patients were submitted to ^{99m}Tc sulfur-colloid scintigraphy, where increased or decreased uptake suggested FNH or HA, respectively. If normal uptake was found, investigation continued

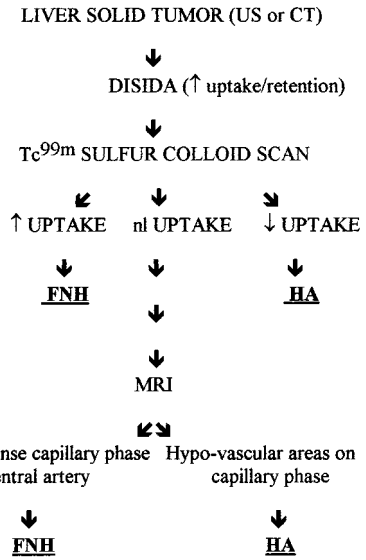

Fig. 1. Algorithm for differential diagnosis between hepatic adenoma (HA) and focal nodular hyperplasia (FNH). US: ultrasonography; CT: computed tomographic scan; MRI: magnetic resonance imaging; DISIDA: ^{99m}Tc-labeled dimethyliminodiacetic acid scintigraphy.

with MRI. In all cases the tumor was solitary and large, ranging from 4.5 to 15.0 cm in diameter.

The radiologic criteria for the diagnosis of HA or FNH were based on established literature data [4, 7, 10–14]. The criteria for the diagnosis of *adenoma* were (1) hypervascularized heterogeneous mass on CT, with intratumor necrosis or hemorrhage; (2) low uptake on ^{99m}Tc-sulfur-colloid scintigraphy; (3) the presence of a capsule or pseudocapsule, hypovascular areas on CT/MRI. The main criteria for the diagnosis of *FNH* were (1) homogeneous hypervascularized mass with a central scar on CT; (2) increased uptake on ^{99m}Tc-sulfur-colloid scintigraphy; (3) central feeding artery on CT/MRI; (4) low lesion-to-liver contrast on T1- and T2-weighted MRI images.

According to our study protocol, all patients were submitted to surgical exploration with tumor wedge biopsy or resection. Hepatic resection was performed in 20 patients and consisted of left hepatectomy in 2 cases, right hepatectomy in 4, left lateral segmentectomy in 8, segmentectomy in 3, and nodulectomy in 3. In the other three, in whom major resections would be required, frozen section biopsies diagnosed FNH and the resection was not indicated. No postoperative complications were observed.

Differences in clinical, biochemical, and radiologic data were analyzed by Student's *t*-test and χ^2 test. Significance level was set at 5% ($p < 0.05$).

Results

Clinical and biochemical findings are shown in Table 1. Patients with FNH were slightly older. The incidence of oral contraceptive intake was 90.0% and 69.2% in patients with HA and FNH, respectively. Abdominal pain was frequent in both groups (80.0% of HA patients, 61.5% of FNH patients), but acute pain was observed only in two patients with HA. Biochemical examination showed slightly elevated γ-glutamyl transpeptidase levels most frequently in adenoma cases, whereas alkaline phosphatase was elevated in only one patient with liver cell adenoma. Other liver function tests were within normal limits in all patients. Statistical analysis of the clinical and biochemical data did not show any significant difference between the two groups.

Table 1. Clinical and biochemical features in 23 patients with benign liver tumors.

Feature	HA (n = 10)	FNH (n = 13)
Mean age (years)	29.2 (22–50)	32.4 (8–50)*
RUQ abdominal pain (no.)	8/10 (80%)	8/13 (61.5%)*
Acute liver pain (no.)	2/10 (20%)	0*
Oral contraceptive use (no.)	9/10 (90%)	9/13 (69.2)*
Alkaline phosphatase ↑ (no.)	1/10 (10%)	0*
γ-Glutamyl transpeptidase ↑ (no.)	4/10 (40%)	4/13 (30.7)*

RUQ: right upper quadrant.
*No statistically significant difference ($p > 0.05$).

Table 2. Findings at radiologic investigation of hepatic adenoma and focal nodular hyperplasia.

Finding	HA (n = 10)	FNH (n = 13)
DISIDA ↑ uptake or retention	8/10 (80%)	13/13 (100%)
Sulfur colloid		
↑ Uptake	—	5/13 (38.4%)
No uptake	4/10 (40%)	7/13 (53.8%)
↓ Uptake	6/10 (60%)	1/13 (7.7%)
Computed tomography		
Heterogeneous + necrosis/hemorrhage	4/10 (40%)	0
Homogeneous + central scar	0	4/13 (30.7%)
Magnetic resonance imaging		
Hypovascular areas	3/4 (75.0%)	0
Low lesion-to-liver contrast, homogeneous lesion	0	5/7 (71.4%)

Results are number of patients.
DISIDA: ^{99m}Tc-labeled dimethyliminodiacetic acid.

Radiologic findings are shown in Table 2. Ultrasonography and CT revealed a solid hepatic mass in all cases. At CT evaluation, typical features were found in 40.0% of the adenoma patients and in 30.7% of the FNH patients. DISIDA liver scintigraphy showed increased uptake or retention of the tracer in all but two cases of liver cell adenoma (intratumor hemorrhage was present in both).

Liver scintigraphy with ^{99m}Tc-sulfur-colloid showed no abnormalities (normal uptake) in 11 of 23 cases (47.8%). Decreased uptake of ^{99m}Tc-sulfur-colloid, was found in seven patients, six of them with adenoma (60.0% sensitivity, 85.7% specificity). Increased uptake, typical in FNH, was found in five patients, all of whom had FNH (38.4% sensitivity, 100% specificity). In one case scintigraphy showed typical features of HA, but histology diagnosed FNH.

Magnetic resonance imaging was performed in 11 patients. It revealed typical features in three of four (75.0%) adenoma patients and in five of seven (71.4%) FNH patients.

A preoperative diagnosis, according to the algorithm, was established for 20 of 23 patients and was correct in 19. Three patients were submitted to surgical exploration without a pre-

Table 3. Duration of oral contraceptive intake.

Time (years)	HA (n = 10)	FNH (n = 13)
<2	1	3
2–5	4	5
>5	5	5
Mean	57 months	46 months

sumptive preoperative diagnosis. One patient was operated as having HA, but morphologic evaluation demonstrated FNH.

Histologic examination showed 13 patients with FNH and 10 with HA. No postoperative complications were observed.

Discussion

Benign liver tumors, such as HA and FNH are uncommon; they generally affect young women; and their pathogeny and outcome are completely different. Although there is a well established association between oral contraceptive use and the development of adenomas [1, 2], the etiology of FNH is still unknown but it is not associated with the use of this drug. The high prevalence of oral contraceptive use in the FNH group can be explained by the fact that most FNH is seen at an age that coincides with female fertility [3, 9]. There is some evidence that FNH develops as a response to a preexisting arterial, spider-like malformation [10] and that estrogens could have a trophic effect on this tumor [4, 11, 12]. Table 3 shows the duration of the use of oral contraceptives in both groups of our 23 patients.

Patients with HA often present with abdominal pain and, in up to 30% of the cases, acute pain due to tumor bleeding or rupture [8, 9]. On the other hand, FNH is often found incidentally in asymptomatic patients. In this study, abdominal right upper quadrant pain was frequent in all patients, but acute pain occurred in only two, both with adenoma and due to intratumor bleeding. It is known that patients with FNH are usually asymptomatic, but eight patients had low-intensity abdominal pain. Among these patients, five were submitted to endoscopic evaluation that disclosed gastroduodenitis. Maybe in these cases the pain was part of a dyspeptic syndrome.

Biochemical changes observed in patients with liver cell adenoma include elevations in alkaline phosphatase and γ-glutamyl transpeptidase serum levels probably due to the size of the tumor, which is often more than 10 cm in diameter, or to the presence of intratumoral hemorrhage [13]. In the present series, as in that of Belghiti et al. [13], alkaline phosphatase levels were increased only in patients with adenoma. Patients with FNH usually have normal liver function tests, although slightly elevated γ-glutamyl transpeptidase levels may be found. Distinction between HA and FNH is not possible based only on clinical and laboratory data.

The advances in imaging techniques improved our ability to diagnose benign liver tumors. Ultrasonography usually reveals a solid mass with increased echogenicity in both lesions, although a mass with decreased echogenicity may also be found [14]. Recently, the diagnostic efficacy to differentiate HA from FNH had been studied with color Doppler sonography and power Doppler imaging [12, 15]. According to Bartolozzi, et al., differentiation was possible in 90% of the cases with the use of power Doppler and in 68% with conventional color Doppler sonography [15]. These results are promising, and we intend to use the techniques in the future as part of our diagnostic algorithm. CT scanning shows homogeneous enhancement with a central scar in FNH and a hyperdense heterogeneous tumor sometimes with central bleeding or necrosis in HA [11]. According to the literature, typical CT features are observed in 50% of patients with FNH and 75% of those with HA [11]. In the present report, 30.7% of patients with FNH and 40% with HA presented typical CT findings.

Liver DISIDA scintigraphy usually shows increased uptake or retention of the tracer, suggesting a benign lesion, such as HA or FNH [16]. In two cases of HA with intratumor hemorrhage, DISIDA showed a nonuptake area.

On ^{99m}Tc-sulfur-colloid scintigraphy, FNH presents normal or increased uptake, and HA is shown as a nonuptake lesion [9, 14, 17]. Normal or increased labeled colloid uptake used to be considered highly specific for FNH, but now some data demonstrate a lack of specificity for liver scintigrams that can reveal normal sulfur-colloid uptake in 23% of patients with adenoma [18]. Low sulfur-colloid uptake lesions were found in seven patients, six with HA, showing a sensitivity of 60.0% and a specificity of 85.7%. Increased uptake was found in five patients, all of them with FNH, representing a sensitivity of 38.4% and a specificity of 100%. When scintigraphy findings suggested the diagnosis, no further investigation was indicated; and the patients were submitted to surgical exploration. In these patients, histologic examination confirmed the preoperative diagnosis in 11 of 12 (91.6%). In one case preoperatively diagnosed as HA, histologic examination disclosed FNH.

In 11 of 23 cases (47.8%) where typical scintigraphic abnormalities were not found, further radiologic investigation with MRI, according to the diagnostic algorithm, was performed. At MRI, focal nodular hyperplasia shows early vigorous, homogeneous contrast enhancement in 89% of the cases, and in 43% it is followed by late central enhancement [11, 19, 20]. A typical central feeding artery is found in one-third of FNH cases [13, 17, 21]. Cherqui et al. reported that for the diagnosis of FNH, enhanced MRI showed a sensitivity of 70% and a specificity of 98% [12]. Adenomas appear on MRI as a hyperintense heterogeneous mass in 51% of the cases, and a peripheral rim is observed in 31% [5]. MRI was performed in 11 patients of our series and suggested the diagnosis of FNH in five of seven (sensitivity of 71.4%, specificity of 100%) and the diagnosis of HA in three of four (sensitivity 75%, specificity 100%).

With this diagnostic approach, the preoperative diagnosis was correct in 82.6% of the studied cases. This study, like others [8, 13, 14], demonstrated that even with the use of modern imaging techniques only about 85% of patients with HA or FNH can be diagnosed preoperatively. In our series, three patients were operated without a presumptive diagnosis and one with a wrong diagnosis of adenoma.

Ultrasound- or CT-guided fine-needle percutaneous biopsy has been recommended by some for diagnosing benign liver tumors. We and many others [3, 12, 13, 21–23] do not believe this procedure is indicated, however, because the small dimension of the specimens in many instances does not allow the distinction between HA and FNH; moreover, there is a high risk of bleeding from these hypervascularized tumors. All patients of the present series were submitted to liver resection or intraoperative biopsy.

The importance of preoperative diagnosis of benign hepatic tumors is based on the fact that HA must be resected and FNH only observed. Surgical resection of adenomas is advocated be-

cause of the high incidence of bleeding complications, reported in 15% to 33% of cases [5]. Neoplastic degeneration of HA has been reported as well [6, 7, 13, 21, 24]. There are also reports of adenoma regression after discontinuation of oral contraceptives [25], but this occurrence is inconsistent. Moreover, in three cases of tumor regression or reduction, malignant degeneration was reported in the area of the previous adenoma [26–28].

Elective resection of HA has a mortality rate of less than 1% in specialized centers [9, 22, 23, 26, 29], whereas rupture into the peritoneal cavity can lead to mortality rates of 5% to 10% [3]. In the present series, hepatic resection was performed without postoperative complications. We and others [13, 21, 22, 26] recommend surgical resection of HA, rather than observation; it can be done with low or no mortality, and it eliminates the possibility of hemorrhage or eventual malignant transformation.

Focal nodular hyperplasia is often an incidental finding, and a nonoperative approach has been adopted by most hepatobiliary centers because there are no proven cases of malignant degeneration and only three cases of hemorrhage have been reported [30]. Follow-up with serial ultrasonography is then recommended. However, patients in whom a differential diagnosis is not possible or tumor growth is documented, liver resection is indicated. Among our patients there were three for whom major liver surgery would be required for resection; intraoperative biopsy was performed and FNH diagnosed. In this cases we decided not to proceed with the resection because of the potentially high morbidity risk of the resection compared with the benign clinical course of FNH.

With the advent of intraoperative ultrasonography and the ultrasonic dissector, nonanatomic resection or enucleation is advocated, especially for benign lesions where there is no need to remove the surrounding normal liver parenchyma. In the present report, liver lobectomies were performed prior to the availability of these technologic devices or when large tumors were found.

Conclusions

The differential diagnosis of such benign liver tumors as adenoma and focal nodular hyperplasia remains difficult despite the development of imaging methods. Liver scintigraphy has low sensitivity but is highly specific for the diagnosis. Among our patients, isotope scanning has been useful for the differential diagnosis in 11 of 23 (47.8%). When increased uptake or retention of DISIDA associated with increased tumour uptake of sulfur-colloid was found, the diagnosis was always FNH. MRI scanning is useful for differentiating between the two lesions [12, 17, 19]. Based on our data, when typical FNH features were seen at scintigraphy and more recently on MRI, the diagnosis was always correct. Despite the small number of patients, our results suggest that a preoperative diagnosis of FNH is reliable; and in these cases surgery may be avoided [8, 9]. However, in most cases where there is diagnostic doubt or an adenoma is suspected, intraoperative biopsy is the best method for the differential diagnosis.

Résumé

Le diagnostic de tumeur hépatique bénigne comme l'adénome hépatique (AH) ou l'hyperplasie focale nodulaire (HFN) reste problématique pour les cliniciens et les chirurgiens. L'importance de distinguer entre ces deux lésions est basée sur le fait que l'AH doit être réséqué alors que l'HFN peut être simplement observée. On a évalué 23 patientes ayant une lésion hépatique bénignes (13 HFN et 10 AF) et un algorithme de diagnostic radiologique a été employé avec le but d'établir des critères préopératoires pour le diagnostic différentiel. Tous les patients ont eu une biopsie chirurgicale ou une résection hépatique pour confirmer le diagnostic. Basé seulement sur des données cliniques et de laboratoire, cette différentiation n'est pas possible. Selon cet algorithme, le diagnostic n'était correct que dans 82.6% des cas mais, même avec le développement des méthodes d'imagerie, utilisées en combinaison, la différentiation n'a pas été possible chez 4 patients. Dans le cas d'HFN, la scintigraphie avait une sensibilité de 38.4% et une spécificité de 100% alors que pour l'AH, la sensibilité était de 60% et la spécificité de 85.7%. La résonance magnétique, employée lorsque les résultats de la scintigraphie n'étaient pas typiques, avait une sensibilité et une spécificité de 71.4% et de 80%, et de 100% et 100% pour, respectivement, l'HFN et l'AH. Le diagnostic préopératoire d'HFN était possible dans 10/13 (76.9%) des cas, toujours confirmé par l'histologie. Un cas d'HFN a été méconnu comme étant un AH. Le diagnostic d'AH a été possible dans 9/10 (90%) des cas. La biopsie chirurgicale reste la meilleure méthode pour le diagnostic différentiel entre l'AH et l'HFN et elle doit être réalisée dans tous les cas douteux. Chez tous les patients ayant un adénome, la résection chirurgicale est le traitement de choix et peut être réalisée avec sécurité. Avec l'évolution de l'imagerie, il semble que la diagnostic préopératoire d'HFN peut être considéré comme fiable, évitant alors une résection chirurgical inutile.

Resumen

Todavía constituye un reto para los internistas y cirujanos, el diagnóstico diferencial entre tumores benignos del hígado, tales como el adenoma (HA) y la hiperplasia nodular focal (FNH). La importancia de este diagnóstico radica, en que el adenoma (HA) ha de ser extirpado quirúrgicamente mientras que la FNH requiere un tratamiento expectante. Fue evaluado, en 23 mujeres con tumores benignos hepáticos (13 FNH y 10 HA), un algoritmo radiológico diagnóstico, con objeto de obtener criterios que permitiesen el diagnóstico preoperatorio diferencial, entre ambos tumores. Todas las pacientes fueron sometidas a una biopsia quirúrgica o una resección hepática, para confirmar el diagnóstico. Los datos clínicos y analíticos, por si solos, no permiten establecer un diagnóstico diferencial. De acuerdo con el algoritmo investigado, el diagnóstico fue correcto en el 82.6% de los casos, pero incluso con el concurso de técnicas de imagen, que fueron utilizadas de forma combinada, en 4 pacientes el diagnóstico diferencial no fue posible. En casos de FNH, la gammagrafía tiene una sensibilidad del 38.4% y una especificidad del 100%; por el contrario, en casos de HA la sensibilidad es del 60% y la especificidad del 85.7%. La MRI, empleada cuando los hallazgos escintográficos no fueron claros, presentó para FNH una sensibilidad del 71.4% y una especificidad del 100%; para los HA la sensibilidad fue del 80%, con una especificidad del 100%. Para la hiperplasia nodular focal, el diagnóstico preoperatorio se estableció en 10 de los 13 casos (76.7%), confirmándose éste, en todos los casos, mediante estudios histológicos. En un caso, la FNH fue falsamente diagnosticada como HA. El diagnóstico de adenoma hepático fue factible en 9 de 10 casos (90%). La biopsia

quirúrgica constituye el mejor método para establecer el diagnóstico diferencial entre el HA y la FNH y, ha de realizarse en todo caso dudoso. En todos los pacientes con adenoma, el tratamiento de elección es la resección, que puede realizarse con toda garantía de éxito. Probablemente, con el desarrollo de las técnicas de imagen podrá establecerse con certitud, el diagnóstico preoperatorio de las FNH, evitando así, resecciones quirúrgicas innecesarias.

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