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Abstract
Focal nodular hyperplasia (FNH) is a hepatic disease first described in 1958. The existence of an accessible and minimally invasive imagistic investigation to establish the diagnosis in a large number of cases would be desirable, especially because once diagnosed, the disease needs no treatment. We present the case of a young woman with long term use of oral contraceptives in which the diagnosis of FNH was established at a routine ultrasound. Evolution of disease during the pregnancy and the atypical imagistic aspect of liver lesions raised many problems of differential diagnosis.

Keywords: focal nodular hyperplasia, liver, contrast-enhanced ultrasound, pregnancy, oral contraceptives.

Introduction
Focal nodular hyperplasia (FNH) is a benign liver disorder with pathogenesis and evolution frequently associated with high estrogenic levels, situation sustained by the disease’s prevalence in women between 20 and 50 years of age [1]. The exact pathogenesis of FNH remains uncertain, the possible cause being a hyperplastic response to a regenerative nonneoplastic nodule caused by a congenital vascular malformation [2,3]. The association between multiples FNH and hemangiomas is known as the syndrome of multiples FNH [4]. The differential diagnosis includes other hypervascular liver lesions (adenomas, hepatocarcinomas, hypervascular metastasis) [5]. Although the condition usually has no clinical significance, the recognition of its imagistic issues is important to avoid inutile diagnostic procedures (biopsy, surgery). In cases in which the imagistic diagnosis cannot be done certainly, biopsy (percutaneous or laparoscopic) or surgery are necessary [6].

We present the case of a young woman with FNH in which the evolution of liver lesions during pregnancy, along with the imagistic appearance has raised problems of differential diagnosis, requiring histopathological examination.

Case report
A 34 years old woman, pregnant in the first trimester (first pregnancy), was evaluated by abdominal ultrasound (US) during a routine visit. A hypoechoic, well defined, 6/4.5 cm focal liver lesion (FLL) in the fourth hepatic seg-
ment was described (fig 1a). Doppler examination identified two arterial axes crossing the lesion and giving radial spoke-wheel-like branches. The suggestive echographic appearance, the absence of clinical symptoms and the use of oral contraceptives for a long time (about 11 years), have focused the diagnostic towards FNH. For a more accurate diagnosis, a contrast-enhanced ultrasound (CEUS) was recommended, but the examination was postponed (the procedure is contraindicated in pregnancy).

Pregnancy and birth have been normal and at four month postpartum, the patient was reevaluated. This time many FLLs have been detected (at least eight). In the fourth hepatic segment there were three adjacent lesions stretching over an area of 10/5 cm (fig 1b). The other lesions, having dimensions between 1 and 3 cm, were localized at the level of both hepatic lobes. It was considered that the condition has a progressive feature, raising questions about the diagnosis of FNH and further investigation was decided.

A computed-tomography (CT) has been performed. The lesions were hypodense on the native examination, with intense, homogenous enhancement in early arterial phase (fig 2a), becoming isoenhanced with the surrounding liver parenchyma during the portal venous phase (fig 2b) and slightly hypoenhanced during the late phase, at 3 minutes after contrast agent injection. The central scar was sketched at the level of the biggest lesions during the late phase, at 45 minutes after contrast-agent injection. The imagistic aspect further supported the initial diagnosis of FNH but, given their large number and the rapid evolution in time, the patients was referred to our department.

The liver US was repeated and completed with CEUS centered on the largest lesions from segment IV. The behavior of the followed lesions emphasized early and intense intake of the contrast agent, with filling from center to periphery, with complete enhancement at 20 seconds after injection and with intense “wash-out” from the portal phase, the lesions being completely washed in late

![Fig 1. Grey scale ultrasonography, transversal section: a) hypoechoic focal liver lesion, at the level of segment IV, well defined, having dimensions of ~ 6/4.5 cm; b) in evolution, three adjacent focal liver lesions, located in segment IV, occupying an area of ~ 10/5 cm.](image)

![Fig 2. Abdominal CT, axial sections: a) the lesions show intense, homogenous contrast agent enhancement, with central scar unenhanced during early arterial phase; b) the lesions became isoenhanced compared to the surrounding liver parenchyma during portal venous phase.](image)

![Fig 3. CEUS examination, centered on the lesions from the segment IV: a) the lesions are hyperenhanced during arterial phase, showing early and homogenous enhancement; b) early “wash-out” in portal phase; c) the lesions being completely washed during the late phase.](image)
venous phase (fig 3). The other lesions have been appreciated also during the venous phase, these presenting in their turn a hypoenhanced aspect. Behavior described in arterial phase claimed the FNH diagnosis, but the portal and venous phases were atypical.

Completely blood tests have been done, all the results being in normal ranges.

For a better characterization of the FLL an abdominal magnetic resonance (MRI) was made. Four of the liver lesions have had a typical FNH aspect, appearing hypointense during non-enhanced T1 phase, hyperintense T2 with hypersignal at the level of central scar. The scar was hypoenhanced during the arterial phase and became hyperenhanced during late venous phase (fig 4). The remaining lesions presented an atypical behavior, with the absence at their level of the central scar in hypersignal T2 and respectively without scar hyperenhancement during late postcontrast phase.

The results of the imaging being inconsistent and atypical, the exploratory laparoscopy was performed with biopsy sampling from the superficial lesions of the both hepatic lobes. Of note: the macroscopic appearance of the lesions was also different (fig 5). The anatomo-pathological results were of FNH for all the examined pieces.

Discussion

FNH is the second most common benign hepatic tumor after hemangioma, with an incidence of approximately 3-5% in general population and higher prevalence in women (12:1) [7,8]. Usually is asymptomatic, rarely grows or bleeds, and has no malignant potential [9]. Most of the times it is incidentally discovered [10]. Reported incidence of the symptomatic cases is largely variable (from 10% to 59%), the most frequent symptom being the right upper quadrant pain [9].

The disease is divided from a morphopathological point of view in two groups: typical and atypical [5]. The typical cases (80%) of FNH are characterized by the presence of three coexisting histological changes: abnormal nodular architecture, malformed vessels and proliferation of bile ducts. In atypical cases, the abnormal architecture or the malformed vessels are missing, the proliferation of biliary ducts being always present [4].

US is the first method used for detection of this lesion. In gray scale, FNH has a variable aspect: hypo-, iso-, or slightly hyperechoic. Sometimes a peripheral hyperechoic halo can be seen, due to the compression of the surrounding liver parenchyma or the presence of some blood vessels [5]. The lesions become more visible when the central scar is evident. The color Doppler
examination brings additional information about vascularization [11].

At CEUS, the particular pattern of enhancement of FNH during the arterial time is a centrifugal, “spoke-wheels”-like fill-in that starts less than 30 seconds after contrast-agent injection (aspect presents in > 90 % lesions larger than 3 cm) [12]. Usually, the enhancement is maintained in the portal and late venous phases [13]. Explanation lies in the abundance of the portal circulatory bed from inside the lesion. In case of FLLs, the “wash-out”-phenomena is directly related to the existence of numerous arteriovenous shunts, suggesting usually a pathological, neoplastic circulation. Surprisingly, in our case, all the lesions have presented early washout. Any lesion which present washout in portal phase is proposed for biopsy, being well known that both adenomas and malignant lesions could present this aspect.

CT examination is considered the imagistic standard for FNH’s characterization. The method has proved performance [14]. Typical CT appearance is that of native hypo- or isodense FLL, with homogenous enhancement during the arterial phase, becoming hyperdense, except for the central scar which remains unenhanced. The lesion is isodense during the portal phase and in the late phase the enhanced, hyperdense central scar can be seen [5,15].

MRI has sensibility of 70% and specificity of 98% for FNH diagnosis [16]. The lesions typically appears iso- or hypointense on T1 sequences (94-100%), are slightly hyperintense or isointense (94-100%), homogenous (96%), with a hyperintense central scar on T2 sequences, aspect which appears in 84% of cases of FNH [16,17]. Based on the vascular and tissue features, MRI is able, in most cases, to differentiate FNH from other FLLs [5].

Final diagnosis of FNH can be made when two imagistic examinations formulates the same result, in clinical characteristic conditions. When there are discordances, tumoral biopsy is needed. A score system for analysis of major and minor diagnostic aspects is used [18].

The particularity of our case resides in the increasing of nodules number during pregnancy and in their atypical aspect at CEUS and MRI. The numerical evolution of nodules can be correlated both with pregnancy and with use of oral contraceptives. Because the malignant histology was excluded the presence of some preexistent circulatory anomalies which have not been detected by US at the onset of pregnancy can be assumed. Hormonal conditioning of these lesions is known, under use of oral contraceptives being proved the increase in volume of FNH. This could be the explanation for increasing of nodules number during pregnancy in our patient. Our observation might suggest surveillance utility of hepatic nodules during pregnancy and in postpartum conditions.

In conclusion the imagistic appearance of FNH is well established and it is found in most typical cases but the existence of atypical cases, both clinical and imagistic, should still be considered. In these situations a major role has the hystopathological diagnosis.

References


