Regression of benign hepatic lesions associated with exogenous estrogens withdrawal

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Learning objectives

1. To describe the changes observed in contrast-enhanced Magnetic Resonance Imaging (MRI) in the event of regression of benign hepatic lesions, such as focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA)
2. To speculate on the possible mechanism of regression.
3. To review the literature.
Background

The most common types of benign focal liver lesions are cyst, hemangioma, FNH and HCA.

**FNH** is the second most common benign tumor of the liver. Like hepatic adenoma, FNH is most often found in women of reproductive age. It is usually asymptomatic and is often discovered incidentally during a radiologic investigation for other reasons. FNH is a benign epithelial liver tumor arising from a polyclonal proliferation of hepatocytes, Kupffer cells, vascular structures, and biliary ductules. The lesion demonstrates a complex architecture, with well-differentiated hepatocytes forming nodules subdivided by fibrous septa, which coalesce to form a characteristic central vascular stellate scar [1].

**HCA** is a rare benign hepatic neoplasm that is etiologically associated with the use of steroids and especially with oral contraceptives (OC). Approximately 70%-80% of HCA are solitary; they are more often multiple in the setting of anabolic androgen therapy or glycogen storage disease. HCA is characterized by areas of necrosis, hemorrhage, myxoid stroma, or calcification. It is usually unencapsulated, although a pseudocapsule of compressed adjacent hepatic parenchyma may be present. Bile ducts are absent. Large peritumoral arteries feed the sinusoids in combination with poor connective tissue support; this feature is thought to predispose these neoplasms to hemorrhage [1].

HCA, FNH and hemangioma can be associated. Most frequent association is FNH-hemangioma reported in 20-26% [2, 3, 4, 5]. Several authors have speculated that both lesions may have causative factors in common, including focal disturbance of the hepatic blood supply that facilitates the hyperplastic development of these benign lesions. Furthermore, although endogenous and exogenous estrogens play a role in the pathogenesis of HCA, their relationship with liver hemangioma and FNH has been suspected although highly debated.

FNH can be associated with HCA: Nguyen et al reported a surgical pathologic series of 305 FNH lesions in 168 patients and found hepatic adenomas in 3.6% and one case of adenomatosis [6]. In our following experience, there is the association between FNH/ HCA and multiple hepatic hemangiomas, too.

Spontaneous regression of focal hepatic lesions is an uncommon event. In literature we found reported cases of regression of hepatic cell carcinoma (HCC). Spontaneous regression of HCC is a very rare event, with an incidence rate of 1 in 140,000 cases of HCC; nearly 62 case reports of spontaneous regression of HCC have been published from 1982 to January 2007 [7].
In literature many cases of HCA regressions are correlated with discontinuation of OC; in fact a strong association between OC use and the development of hepatic adenoma is known since 1973: about 90% of patients with hepatic adenoma had continuously taken OC in the USA [8].

Hiroko Iijima et al. reported also a case of HCA regression after hemodialysis in a patient glycogen storage disease type I (GSD-type I). The pathogenesis of hepatic adenoma in GSD-type I remains incompletely understood, though the association between hepatic adenoma and the use of oral contraceptives is well known. Recurrent and prolonged hypoglycemia with secondary stimulation such as glucagon, epinephrine, or insulin has been postulated to be responsible for the development of hepatic adenoma in GSD-type I. In contrast, however, a regression of hepatic adenomas with dietary therapy or nightly glucose infusion has been reported. Moreover it is possible that hemodialysis may have had some favorable effect by correct some metabolic imbalance [9].

Even if the role of OC in the pathogenesis of FNH has never been confirmed, some cases of regression after OC withdrawal have been reported in literature. Spontaneous regression of FNH is not uncommon, but cases of near-complete regression or complete involution are rare.
Findings and procedure details

The typical imaging findings of FNH and HCA are summarized in Table 1.

In Table 2 we instead summarize the frequent atypical aspects of the lesions. These atypical findings could make more difficult the differential diagnosis with other lesions; in these cases, the use of a hepatospecific contrast agent is very useful.

We describe a case of a 33-year-old woman who took OC; during a routine US, some hyperechoic hepatic lesions were observed. She was subjected to CT and MR examinations, with and without contrast agent.

In particular, the following sequences are used for MRI of the liver:

1) SPGR T1, in and out phase
2) T2 TSE Fat sat
3) Dynamic LAVA T1 with and without contrast agent (gadoxetic acid) in arterial, portal, delayed and hepatospecific phases.

MRI showed 4 hepatic hemangiomas (70x54, 65x56, 30x30, 45x20 mm respectively) and a homogeneous lesion (70x40 mm) that was hypointense on T1-weighted images (Fig. 1, 3) and slightly hyperintense on T2-weighted images (Fig. 2) with a homogeneous arterial phase enhancement and iso-hyperintensity during the portal venous phase (Fig. 5); the lesion shows a central scar that appears hypointense on T1 weighted images (Fig. 4).

During hepatospecific phase it was inhomogeneously hyperintense with hypointense areas in the contest (Fig. 6).

MRI with a hepatocyte-specific contrast agent confirmed the hepatocellular origin of the mass, even if the lesion had got a posterior area relatively hypointense. Some of these findings were typical for FNH, but the atypical aspects oriented for a mixed lesion FNH/Adenoma.

In view of the hypothesis of benign nature of the lesion, the patient was subjected to US and MR follow-up. We evaluated the evolution of this FNH/HCA with dynamic hepatocyte-specific contrast-enhanced MRI in a four-year period after OC withdrawal.

We considered two parameters:

1. size
2. contrast enhancement
Two years later, during the first follow-up MRI, the lesion showed a reduction of global diameters (70x40 versus 40x20 mm) (Fig. 7, 8, 9). We observed also a reduced enhancement during the arterial phase (Fig. 10, 11) and a strong reduction of enhancement after hepatospecific agent administration (Fig. 12) than the first MRI. The posterior area relatively hypointense was present, but it was reduced in volume (maximum diameter: 15 versus 22 mm).

The second MRI follow-up (three years later), showed a further reduction of global diameters of the lesion (27x19 mm versus 40x20 mm) (Fig. 13, 14, 15) and a further reduced enhancement during the arterial (Fig. 16, 17) and the hepatospecific acquisitions (Fig. 18); the posterior area had a further reduced maximum diameter (12 versus 15 mm) (Fig. 18).

In summary we observed a progressive volumetric reduction to a near complete regression of the FNH/HCA both of the principal mass and the posterior area.

The residual lesion during the arterial phase showed also a progressive decreased contrast-enhancement.

Since the 1970s, many cases of FNH have been reported in patients taking both high- and low-dose OC [10]. Scaroli et al.'s case-control study shows an association between FNH and OC use in 83% of cases versus 59% of controls and the trend in risk with duration was statistically significant [11]. Some authors have suggested that OC are not the pathophysiologic cause of FNH (as in hepatic adenoma); however, the correlation between regression of FNH and the discontinuation of OC in several cases have suggested that exogenous estrogens may act as trophic agents.

Sarma et al. quote only 9 cases of complete radiologic regression and among the lesions that completely involuted, no pattern can be discerned with regard to OC use status. Six FNH lesions disappeared in patients with no significant history of OC use, two disappeared in spite of ongoing OC use, and one disappeared 5 years after the discontinuation of OC [10].

Kuo et al reported a complete radiologic involution of FNH lesions associated with patients of older age, and nodule diameter of <2 cm. We can't confirm this result because our patient was younger and the maximum diameter was 7 cm [12].

Due to the amount of conflicting data in the FNH literature, and the fact that many conclusions on the effect of exogenous estrogens are founded on weakly significant data, further study is necessary to firmly establish the role of OC in the natural history of FNH.
**Table 1**

<table>
<thead>
<tr>
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<th>US</th>
<th>CEUS</th>
<th>Precontrast CT</th>
<th>Arterial phase</th>
<th>Portal phase</th>
<th>Delayed phase</th>
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<tr>
<td><strong>FNH</strong></td>
<td>Iso/ Hypo/ Hyperechoic</td>
<td>Hypervascular lesion (spoke-wheel sign, centrifugal filling)</td>
<td>Iso/ Hypoattenuating lesion</td>
<td>Central scar: hypovascular</td>
<td>Hyperattenuating lesion</td>
<td>Variable wash-out, isocountenating lesion</td>
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<tr>
<td><strong>HCA</strong></td>
<td>Variable, often hyperechoic (Table 2)</td>
<td>Mixed filling, generally centripetal</td>
<td>Persistent enhancement</td>
<td>Heterogeneous mass (generally hypovascular lesion with areas of hyperattenuation due to recent hemorrhage in approximately 15%–47%)</td>
<td>Heterogeneous hypovascular lesion, with a pseudocapsule in 25%–30%</td>
<td>Isocountenating lesion</td>
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<th><strong>MRI</strong></th>
<th><strong>CT</strong></th>
<th><strong>MRI</strong></th>
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<tr>
<td><strong>FNH</strong></td>
<td>Lack of the central scar</td>
<td>Presence of areas of lipid or fat seen at CT in 7%–10% and calcification in 5%–15%</td>
<td>Lack of the central scar</td>
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<td>Rapid washout of contrast material in the portal venous phase</td>
<td>HCA have variable signal intensity but can show hypointense foci on unenhanced T1-weighted images secondary to hemorrhage or intracellular lipid.</td>
<td>Hypointense on T2-weighted images central scar</td>
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<td>Lack of enhancement of the central scar on delayed images</td>
<td>T1-hypointense enhancing pseudocapsule due to compression of surrounding parenchyma with mild fibrosis,</td>
<td>T1-hypointense enhancing pseudocapsule due to compression of surrounding parenchyma with mild fibrosis,</td>
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<td></td>
<td>Early draining veins</td>
<td>Strongly hypointense lesion on T2-weighted images</td>
<td>Strongly hypointense lesion on T2-weighted images</td>
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<td></td>
<td>Partial peripheral rim-like enhancement on delayed images</td>
<td>Diffusely hypointense lesion on T1-weighted images</td>
<td>Diffusely hypointense lesion on T1-weighted images</td>
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**Table 2**

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Fig. 1: First MR examination: axial in phase T1-weighted image. FNH appears slightly hypointense respect to a normal liver; left lobe hemangioma shows highly hypointense

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Fig. 2: First MR examination: axial fat-suppressed T2-weighted image. FNH appears slightly hyperintense respect to a normal liver and hypointense respect to left lobe hemangioma

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**Fig. 3:** First MR examination: unenhanced T1 LAVA sequence. FNH appears hypo intense respect to a normal liver; left lobe hemangioma shows highly hypointense.

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**Fig. 4:** First MR examination: dynamic contrast-enhanced T1 LAVA sequences after administration of gadoxetic acid during arterial phase. FNH shows high contrast enhancement with hypointense central scar; globular contrast enhancement of the left lobe hemangioma.

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**Fig. 5:** First MR examination: dynamic contrast-enhanced T1 LAVA sequences after administration of gadoxetic acid during portal venous phase. FNH shows iso-hyperintensity respect normal liver; globular enhancement of the left lobe hemangioma

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**Fig. 6:** First MR examination: axial image during hepatospecific phase. FNH shows hyperintensity with posterior area of low signal suspect for HCA. Left lobe hemangioma shows hypo intensity respect to a normal liver

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Fig. 7: MRI performed two years after diagnosis and OC withdrawal: axial in phase T1-weighted image

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Fig. 8: MRI performed two years after diagnosis and OC withdrawal: fat-suppressed T2-weighted image

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**Fig. 9:** MRI performed two years after diagnosis and OC withdrawal: axial T1 LAVA sequence without contrast agent

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Fig. 10: MRI performed two years after diagnosis and OC withdrawal: axial T1 LAVA after gadoxetic acid administration during arterial phase

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**Fig. 11:** MRI performed two years after diagnosis and OC withdrawal: axial T1 LAVA after gadoxetic acid administration during portal phase

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Fig. 12: MRI performed two years after diagnosis and OC withdrawal: axial T1 LAVA after gadoxetic acid administration during hepatospecific (axial sequence) phase

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Fig. 13: MRI performed three years after diagnosis and OC withdrawal: axial in phase T1-weighted image

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**Fig. 14**: MRI performed three years after diagnosis and OC withdrawal: fat-suppressed T2-weighted image

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Fig. 15: MRI performed three years after diagnosis and OC withdrawal: axial T1 LAVA sequence without contrast agent

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**Fig. 16:** MRI performed three years after diagnosis and OC withdrawal: axial T1 LAVA after gadoxetic acid administration during arterial phase

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Fig. 17: MRI performed three years after diagnosis and OC withdrawal: axial T1 LAVA after gadoxetic acid administration during portal phase

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Fig. 18: MRI performed three years after diagnosis and OC withdrawal: axial T1 LAVA after gadoxetic acid administration during hepatospecific phase

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Conclusion

There is not sufficient data to conclude that the natural history of our patient's lesion can be attributed to their cessation of exogenous estrogen use, nor is there sufficient data to conclude contrarily. Indeed, there is a concrete possibility that these lesions would have involuted regardless of exogenous estrogen status. Our cases, however, provide yet more anecdotal evidence to the body of literature that suggests that exogenous estrogens may contribute to the growth or maintenance of FNH lesions and the role of OC.

MRI is now an ideal modality for the diagnosis and follow-up of FNH, as it has well-defined diagnostic criteria for FNH and eliminates the carcinogenic ionizing radiation of CT and operator dependence of ultrasound. MRI may show regression of FNH and HCA in terms of size and contrast enhancement after discontinuation of OC.
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