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# HEPATIC ADENOMATOSIS: MR IMAGING FEATURES

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**Hepatocellular adenomas are rare benign liver neoplasms that commonly occur in women with a history of oral contraceptives intake for more than 2 years. Hepatic adenomatosis is characterized by the presence of multiple adenomas, arbitrarily > than 10, involving both lobes of the liver, without any history of steroid therapy or glycogen storage disease. Although the adenomas in liver adenomatosis are histologically similar to other adenomas, liver adenomatosis appears to be a separate clinical entity. Adenomas in hepatic adenomatosis may be of the inflammatory, hepatocyte nuclear factor 1alpha-mutated, or beta-catenin-mutated subtype, and accordingly show variable imaging appearances. Hepatic adenomatosis carries the risk of impaired liver function, hemorrhage and malignant degeneration. We report a case with the inflammatory subtype of hepatic adenomatosis in a 39-year-old woman with liver steatosis. The magnetic resonance imaging features using extracellular gadolinium chelates and hepatocyte-targeted contrast agents are described.**

**Key-word: Liver neoplasms, MR.**

Hepatic adenomatosis occurs predominantly in women during the 4th and 5th decades of life (1). Hepatic adenomatosis is rare, although its real frequency could be underestimated because many patients are asymptomatic. Hepatic adenomatosis is defined as the presence of multiple adenomas (arbitrarily > 10) involving both lobes of the liver. Patients with glycogen storage disease or with a history of steroid intake are not considered to have liver adenomatosis (1, 2).

Although the exact aetiology of hepatic adenomatosis is still unclear, congenital or acquired hepatic vascular abnormalities, mutations of the hepatocyte nuclear factor 1alpha (HNF1A) gene, and non-alcoholic fatty liver disease have been proposed as potential causes for the development of hepatic adenomatosis (1, 2). Hepatocellular adenomas in patients with hepatic adenomatosis may be of the inflammatory, HNF-1alpha-mutated, or beta-catenin-mutated subtypes, and as a consequence may show variable imaging findings.

We describe the magnetic resonance imaging (MRI) findings in a 39-year-old woman presenting with non-alcoholic fatty liver disease and hepatic adenomatosis characterized by the inflammatory subtype of hepatic adenomas.

## Case report

A 39-year-old female with unremarkable previous medical history was referred for MRI after detecting a large liver mass during routine ultrasound examination. Patient had taken oral contraceptives for 12 years. Physical examination showed slight overweight (body mass index 29). The laboratory evaluations and blood biochemistry profile showed elevated C-reactive protein (11,4 mg/dl; normal value < 0,5), alkaline phosphatase (417 U/L, normal values 27-126) and γ-glutamyltransferase (101 U/L, normal values 5-43) levels. Hepatitis B surface antigen, anti-hepatitis B surface antibody and anti-hepatitis C antibody were negative.Serum alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigenic determinant (CA) 19-9 were normal. On MRI, liver parenchyma showed marked signal drop-off on T1-weighted out-of-phase images and corresponded to steatosis of the liver parenchyma. Multiple, approximately 14, well-delineated focal liver lesions with variable size (1-10 cm diameter) involving both liver lobes were noted. Lesions were diffusely hyperintense on T2-weighted images, with higher signal intensity in the periphery of the lesion (Fig. 1). All lesions showed minimal or no signal drop-off on chemical shift sequences. On T1-weighted in-phase images, lesions were isointense or mildly hyperintense compared to liver parenchyma (Fig. 1). On fat suppressed T1-weighed images, due to liver steatosis, lesions were markedly hyperintense (Fig. 2). One lesion measuring 8 cm demonstrated an irregular central T1- and T2-weighted hypointense area.

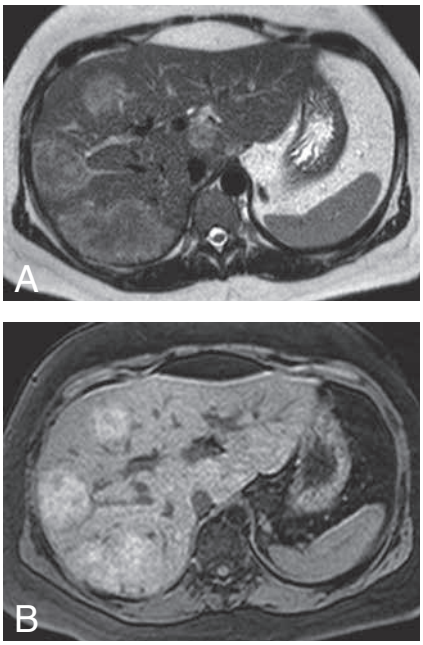


*Fig. 1.* — Axial T2- (A) and T1-weighted (B) MR images show multiple, sharply demarcated liver lesions with variable size. T2-weighted image shows a characteristic hyperintense rimlike band in the periphery of the lesions (A). On T1-weighted imaging lesions are hyperintense (B).

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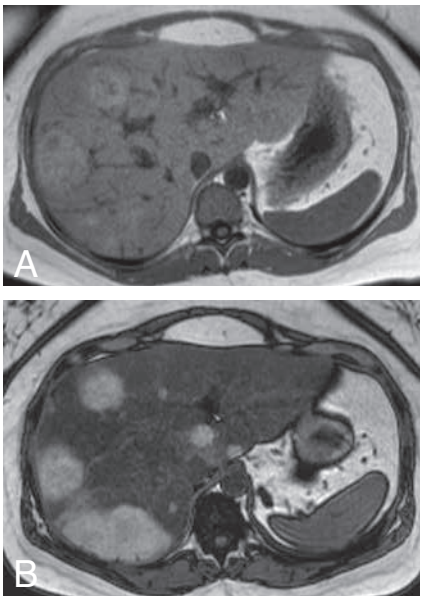


*Fig. 2.* — Axial T1 in-phase (A) and out-of-phase (B) MR images show isointense to mildly hyperintense lesions on the in-phase image (A) and clearly hyperintense lesions on the out-of-phase image (B). Notice also the signal drop-off of the liver parenchyma on the out-of-phase image due to steatosis.

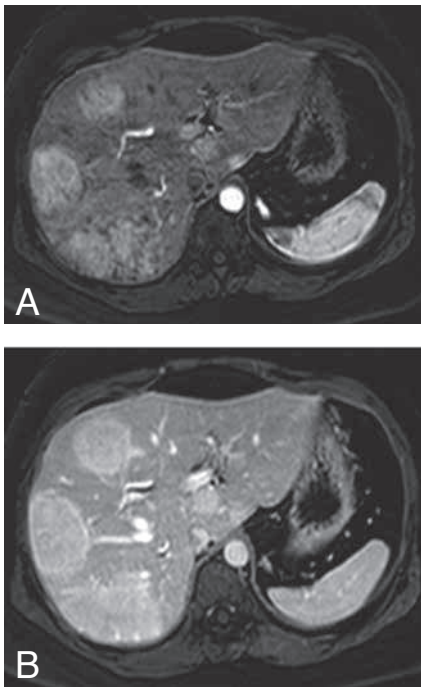


*Fig. 3.* — Axial postgadolinium MR images demonstrate the hypervascular nature of all lesions with intense enhancement in the arterial phase (A) persisting in the delayed phase (B).

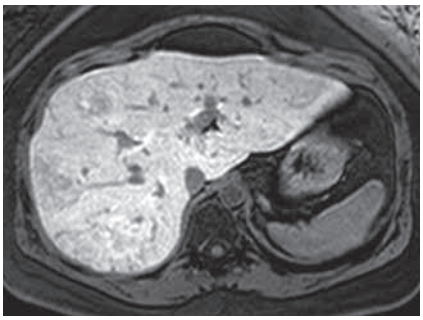

*Fig. 4.* — Axial MR image after Primovist® administration shows heterogeneous enhancement of all lesions.

After intravenous administration of gadolinium-based contrast material (Dotarem®, gadoteric acid, Guerbet, France) all lesions showed intense enhancement during the arterial phase, which persisted in the portal venous and delayed phases (Fig. 3). In a second session hepatocyte phase imaging was performed. After administration of hepatocyte specific gadolinium-based contrast material (Primovist®, gadoxetic acid disodium, Bayer Pharma AG, Germany), heterogeneous enhancement was noted and corresponded to contrast uptake by well-differentiated hepatocytes (Fig. 4).

Based on MRI features of focal liver lesions diagnosis of hepatic adenomatosis, composed of inflammatory hepatocellular adenomas, was made. Biopsy of a liver lesion was refused by the patient. Follow-up using MRI was performed and showed two years after diagnosis no morphologic change of the lesions and no change in imaging findings, supporting the diagnosis of liver adenomatosis.

## Discussion

Inflammatory hepatocellular adenomas occur most frequently in young women with a history of oral contraceptive usage and in obese patients (3). In patients with inflammatory hepatocellular adenomas, signs of chronic anemia and/or 'systemic inflammatory syndrome' characterized by fever, leukocytosis, and elevated serum levels or C-reactive protein can be seen. Abnormal liver function tests, consisting of increased serum levels of transaminases, alkaline phosphatase, and gamma-glutamyl transferase, may be present, especially if multiple adenomas or intralesional bleeding are present (4).

Hepatic adenomatosis is a rare condition usually defined by the presence of more than 10 adenomas in otherwise normal liver parenchyma (5). Non-alcoholic fatty liver disease and congenital or acquired hepatic vascular abnormalities and mutations of the HNF1A gene have been proposed as potential causes for the development of hepatic adenomatosis (6, 7). Hepatic adenomatosis has been reported to have no association with oral contraceptives or steroid use (6). However, a possible association with the use of estrogens has also been suggested (8).

At MRI, the imaging features of hepatocellular adenomas vary on the basis of the histopathologic findings and associated complications (7). In patients with hepatic adenomatosis, three MRI patterns have been described to be associated with three pathologic forms, which include steatotic, peliotic, and mixed types (9). On the basis of the genotype-phenotype classification and pathologic features hepatocellular adenomas are categorized into three distinct subtypes: inflammatory hepatocellular adenomas; HNF-1alpha-mutated hepatocellular adenomas; and beta-catenin-mutated hepatocellular adenomas (10). These different subtypes show variable clinical behaviour, imaging findings, and natural history, and thus the options for treatment surveillance may vary (7). The MRI findings of different subtypes of hepatocellular adenomas have been reported by Laumonier et al (11). HNF-1alpha-mutated hepatocellular adenomas and inflammatory hepatocellular adenomas have been described to be associated with specific MRI patterns and related to diffuse fat distribution and to sinusoidal dilatation, respectively.

At MRI, inflammatory hepatocellular adenomas are diffusely hyperintense on T2-weighted images, with higher signal intensity in the periphery of the lesion (described as "atoll sign"), because of dilated sinusoids. On T1-weighted images lesion isointensity or mildly hyperintensity compared to adjacent liver parenchyma is noted, with minimal or no signal drop-off with chemical shift sequences. After intravenous administration of gadolinium-based contrast material intense enhancement during the arterial phase is seen, with persistent enhancement in the portal venous and delayed phases (7, 11). A marked T2 hyperintensity together with delayed persistent enhancement for the diagnosis of inflammatory hepatocellular adenomas has been reported to correspond with a sensitivity of 85% and a specificity of 87% (11). HNF-1alpha-mutated hepatocellular adenomas are are isoin-

*Table I. — Overview of MR imaging features according to the pathologic subtype classification of hepatocellular adenoma versus hepatocellular carcinoma (HCC). T1WI = T1-weighted imaging. T2WI = T2-weighted imaging. T1 C+ (Gd) = T1-weighted imaging after administration of gadolinium contrast.*

| | HEPATOCELLULAR ADENOMA | | | HCC |
|---|---|---|---|---|
| | Inflammatory subtype | HNF-1alpha-mutated subtype | Beta-catenin-mutated subtype | |
| T1WI | Iso- or mildly hyperintense to liver | Iso- or hyperintense to liver | Homogeneous or heterogeneous hyperintense to liver, depending on presence of hemorrhage and/or necrosis | Variable signal intensity |
| T2WI | 'Atoll' sign | Iso- or mildly hyperintense to liver | | Usually hyperintense to liver |
| Chemical shift sequence | Minimal or no signal drop-off | Diffuse signal drop-off | No signal drop-off | Signal drop-off when presence of intracellular fat |
| T1 C+ (Gd) | Strong arterial enhancement with persisting enhancement in portal venous and delayed phase | Moderate arterial enhancement with washout in portal venous and delayed phase | Strong arterial enhancement that may or may not persist in portal venous and delayed phase | Heterogeneous arterial enhancement with washout in portal venous and delayed phase |

tense to slightly hyperintense on T2-weighted images. On T1-weighted images they are predominantly hyper- or isointense, with diffuse signal drop-off with use of the chemical shift sequence, correlating with intracellular steatosis. lesions. After gadolinium-based contrast material administration moderate enhancement is noted in the arterial phase, with absence of persistent enhancement in the portal venous and delayed phases (7, 11). A homogeneous signal drop-off on chemical shift images for the diagnosis of HNF-1alpha-mutated hepatocellular adenomas has been shown a sensitivity and specificity of 86% and 100% respectively (11). No specific MRI imaging features have been described for the diagnosis beta-catenin-mutated hepatocellular adenomas. On T1- and T2-weighted images, beta-catenin-mutated hepatocellular adenomas may show homogeneous or heterogeneous hyperintense signal intensity, depending on the presence of hemorrhage and/or necrosis. With extracellular gadolinium-based contrast media strong arterial enhancement that may or may not persist on the portal venous and delayed phases can be seen. Beta-catenin-mutated hepatocellular adenomas may mimic hepatocellular carcinoma (7, 11).

In the absence of biopsy with histopathologic confirmation, imaging findings may be helpful in the subtype characterization of hepatocellular adenomas, and therefore, may be helpful in the prediction of complications and the guidance of patient management. Hepatic adenomatosis is not associated with an increased risk of complications. The risk of bleeding with associated rupture and the development hepatocellular carcinoma depends on tumor size and adenoma subtype. As a consequence, management of hepatocellular adenomas in patients with hepatic adenomatosis is similar to management of other hepatocellular adenomas (2, 7). Liver-specific MR contrast media, e.g. gadoxetic acid disodium, allows delayed imaging of functional liver tissue because of its highly specific uptake by hepatocytes. Benign lesions containing well-differentiated hepatocytes haven been shown to take up and metabolize gadoxetic acid, whereas malignant tumors generally show no uptake (12). As a consequence, liver-specific contrast media may be used for initial workup of patients with newly discovered liver adenomatosis and for follow-up of these patients in search of potential malignant growth.

Intratumoral bleeding may be seen in 20%-25% of hepatocellular adenomas. Lesions larger than 5 cm in maximum diameter and in proximity to the capsular surface show a higher risk of bleeding with rupture (7). Of all subtypes, inflammatory hepatocellular adenomas show a higher tendency for bleeding with a frequency of up to 30%, due to the presence of sinusoidal dilatation, peliotic areas, and abnormal vessels. The complication rate of HNF-1alpha-mutated hepatocellular adenoma is lower: lesions less than 5 cm show minimal risk of bleeding with rupture or malignancy. Beta-catenin-mutated hepatocellular adenomas have also a risk of bleeding; however, the exact incidence is not known. The overall risk to develop hepatocellular carcinoma in hepatocellular adenomas has been reported between 5% and 10% (7). The beta–catenin-subtype of hepatocellular adenomas carries the highest risk of malignant transformation and these lesions should be considered as borderline lesions between hepatocellular adenoma and hepatocellular carcinoma (3). The risk to develop hepatocellular carcinoma in patients with inflammatory hepatocellular adenomas is about 10% (10). Malignant transformation of HNF-1alpha-mutated hepatocellular adenomas is low, especially when tumor size is less than 5 cm in maximum dimension. The most important risk factors for malignant transformation of hepatocellular adenomas are male sex, concomitant glycogen storage disease, anabolic steroid usage, the beta-catenin subtype and adenomas larger than 5 cm in maximum diameter (7).

Differential diagnosis varies according to the imaging features and include multifocal nodular fatty change, well-differentiated hepatocellular carcinomas (HCC), multifocal hepatocellular carcinoma in a non-cirrhotic liver, multiple focal nodular hyperplasia (FNH), fat containing metastases from renal cell cancer and hypervascular metastases from primary neuroendocrine tumors (pancreatic islet cell tumor, carcinoid tumor, and pheochromocytoma), breast cancer, thyroid carcinoma or melanoma (9).

Adenomas as well as multifocal HCC may demonstrate internal fat, hemorrhage and heterogeneity. Absence of underlying liver disease or obvious signs of cirrhosis can be very helpful to make a distinction between these two entities. An overview of the MR imaging features of the three subtypes of adenoma versus HCC is given is table I. Differentiation of liver adenomatosis from hypervascular metastases may be difficult as well. Lack of an identifiable underlying primary extra-hepatic malignancy and absence of fat within the lesions are important findings. Intratumoral fat deposition, although possible, is rarely seen in FNH. Also hyperintensity on both in- and opposed phase T1-weighted imaging, owing to intratumoral blood degradation products, has rarely been noted in FNH but is often seen in hepatocellular adenomas.

## Conclusion

Hepatic adenomatosis is rare. Hepatocellular adenomas in hepatic adenomatosis may be of the inflammatory, HNF-1alpha-mutated, or beta-catenin-mutated subtypes, and may show variable imaging findings. The risk of complications depends on tumor size and adenoma subtype. MRI may be helpful in subtype characterization and, therefore, may be helpful in the prediction of complications and the guidance of patient management. The use of liver-specific MR contrast media helps to differentiate between benign adenomas, malignant and dysplastic lesions. Liver-specific contrast media could be used for initial workup in patients with newly discovered hepatic adenomatosis and for follow-up in search for potential malignant degeneration.

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