MRI of Hepatic Adenomatosis: Initial Observations with Gadoxetic Acid Contrast Agent in Three Patients

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OBJECTIVE. The purpose of our study was to describe the MR signal characteristics of histologically proven liver adenomatosis in three patients using gadoxetic acid, a newly developed liver-specific MR contrast agent.

CONCLUSION. In all three patients, more than 100 liver adenomas revealed no metabolism of the new liver-specific contrast agent in the delayed phase. Because of absent or strongly reduced intracellular uptake of gadoxetic acid in all adenomas during delayed contrast-enhanced series, differentiation of adenomas from dysplastic or malignant lesions was not possible.

Liver adenomatosis is a rare condition of unknown cause, which occurs predominantly in young women [1–3]. The presence of more than 10 adenomas is usually required to fulfill the criteria of liver adenomatosis [4]. To our knowledge, only 70 cases of liver adenomatosis have been previously reported, although the number of affected individuals may well be underestimated [3]. Patients with liver adenomatosis are clinically asymptomatic, and the condition is often found by coincidence during radiologic workup of another suspected abnormality.

Initial radiologic workup may be difficult to evaluate because routine imaging criteria do not allow confident differentiation of this benign entity from malignant or dysplastic liver lesions. Recognition of potential dysplastic transformation of adenomas during follow-up examinations is also difficult because MRI features are not specific even after contrast administration [2, 3].

Gadoxetic acid disodium is a new liver-specific MR contrast agent. In addition to dynamic imaging, gadoxetic acid allows delayed imaging of functional liver tissue because of its highly specific uptake by hepatocytes [5]. Benign lesions containing well-differentiated hepatocytes have been shown to metabolize and take up gadoxetic acid, whereas malignant and dysplastic tumors generally show no uptake [6].

Administration of liver-specific contrast media such as gadoxetic acid may therefore be of use for initial workup of patients with newly discovered liver adenomatosis and for follow-up of these patients in search of potential dysplastic growth of adenomas. We describe the initial findings in gadoxetic acid-enhanced MRI as observed in three patients with liver adenomatosis.

Materials and Methods

Patients

Institutional review board approval was obtained before performance of this study; informed consent was waived for retrospective review of records and images. Three women were examined. The first patient was 41 years old (patient 1) and had been diagnosed with endometriosis. She had been treated with lynestrenol for the past 7 years. After elevated transaminases were found on a routine follow-up examination, sonography was performed, which revealed multiple liver masses. MRI was ordered for further workup of the liver lesions. Because of the size of the largest lesion in the left liver lobe and its potential for complications, this patient underwent left hemihepatectomy after MRI. Pathohistologic analysis revealed multiple typical liver adenomas without atypical cells.

The second patient was 27 years old (patient 2). She suffered from glycogen storage disease type 1b, had multiple known liver adenomas, and was referred to us for a baseline MRI to rule out potential dysplastic lesions. Two years previously, one large adenoma (> 7 cm in diameter) and several small adenomas had been surgically resected in this patient; no dysplastic cells were observed.
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found at histologic analysis. Follow-up sonography revealed no enlargement of the liver adenomas over 2 years. The third patient was 53 years old (patient 3). She had multiple known liver adenomas and was referred for routine follow-up MRI of the liver. Two years previously, one hepatic lesion in segment III had been surgically removed; histologic analysis showed a liver adenoma without cytologic atypia. The patient had never taken oral contraceptives or other estrogen-containing medications.

Imaging Techniques

MRI was performed using a 1.5-T unit (Achieva, Philips Medical Systems) and a phased-array body coil. T1- and T2-weighted sequences were acquired with the following parameters: T1-weighted fast-field echo (FFE) transverse (TR/TE, 23/4.6), dual T1-weighted FFE in-phase and opposed-phase transverse (237/opposed-phase 2.3, in-phase 4.6), T2-weighted single-shot transverse (391/80) and coronal (587/80), and T2-weighted spectral inversion recovery transverse (416/80).

After IV injection of 10 mL (0.25 mmol/mL) of gadoxetic acid–based contrast medium (gadoxetic acid disodium [Gd-EOB-DTPA] [Primovist, Bayer Schering Pharma]), T1-weighted transverse gradient-echo sequences (high-resolution isotropic volume examination [THRIVE]) with spectral presaturation inversion recovery [SPIR], 4.3/2.1) were obtained during arterial (25 seconds), portal venous (70 seconds), and delayed (3, 10, or 15 or 20 minutes) phases. Gadoxetic acid was injected manually and flushed with saline solution.

Image Interpretation

Two radiologists with 8 and 3 years of experience in gastrointestinal MRI reviewed the MR images in consensus. The total number of liver lesions was counted and the size of each lesion was measured on a PACS workstation (ProVision, Cerner). Signal intensity of all liver lesions was graded on T1-weighted, T2-weighted, and contrast-enhanced images as isointense, hypointense, or hyperintense in relation to normal liver tissue. In the delayed contrast-enhanced images, signal intensity of the liver parenchyma was hyperintense compared with unenhanced T1-weighted images because of intracellular uptake of gadoxetic acid by normal liver tissue.

Results

MRI

All three patients showed multiple, well-delineated focal liver lesions. Approximately 50, 75, and 30 lesions greater than 3 mm in diameter were counted in patients 1, 2, and 3, respectively, the largest lesions measuring 76 × 60, 45 × 28, and 16 × 13 mm, respectively. Patients 1 and 2 featured innumerable smaller lesions. All lesions were hyperintense on T2-weighted images but only slightly so in patient 3. On unenhanced T1-weighted images, many lesions were barely visible and mostly isointense or slightly hyper- or hypointense in comparison with normal liver parenchyma. In patient 3, most lesions were clearly hypointense. On the arterial phase, the lesions showed considerable contrast uptake in patient 1 and slight uptake in patients 2 and 3. All lesions appeared isointense in relation to the adjacent liver parenchyma during venous phase imaging in patients 1 and 2; in patient 3, many lesions were hypointense in relation to the surrounding liver tissue. On delayed phase imaging, most lesions were homogeneously hypointense due to much stronger gadoxetic acid uptake of the surrounding normal liver parenchyma (Fig. 1). However, three of the larger lesions in patient 1 differed by showing strong peripheral contrast enhancement, and few lesions in patient 2 appeared slightly heterogeneous with weak peripheral contrast enhancement (Fig. 2).

Discussion

Liver adenomatosis is a rare condition usually defined by the presence of more than 10 adenomas in otherwise normal liver parenchyma [4]. Unlike solitary hepatic adenomas, liver adenomatosis is believed to have no association with oral contraceptives or steroids [2, 4], although some published data

Fig 1—27-year-old woman with histologically proven liver adenomatosis and underlying glycogen storage disease type Ib. A and B, Lesions are barely visible on unenhanced T1-weighted image (A) and hyperintense on T2-weighted image (B). C, On 20-minute delayed image after gadoxetic acid administration, all lesions are strongly hypointense in relation to strong gadoxetic acid uptake by surrounding normal liver parenchyma.
suggest a possible association with estrogens [7]. Patients with underlying glycogen storage disease have often been excluded from the diagnosis of liver adenomatosis on the basis of the classification by Flejou et al. [4] from 1985.

Liver adenomatosis and solitary hepatic adenomas are similar histologically, with extensive sinusoids and feeding arteries and a lack of biliary ductules [8], although unusual histology of liver adenomatosis has been reported in patients with glycogen storage disease [9]. Three histologic forms of liver adenomatosis have been recently described: steatotic, peliotic, and mixed [3].

On unenhanced MRI and in comparison with normal liver parenchyma, adenomas in liver adenomatosis have been described as hyperintense on T2-weighted images and mostly hyper- to isointense on T1-weighted images, although some lesions can appear hypointense. With extracellular gadolinium-based contrast media, a majority of lesions show arterial phase enhancement; on venous and delayed phases, contrast enhancement differs depending on histologic type, with enhancement of all peliotic adenomas, partial enhancement of mixed adenomas, and minimal or absent enhancement of steatotic adenomas [3]. Our findings match these published data, although contrast behavior on the delayed phase cannot be compared because of liver-specific intracellular uptake of gadoxetic acid.

Gadoxetic acid is a recently developed gadolinium-based MR contrast agent with high intracellular specificity to hepatocytes. It is administered IV and first distributed in the extracellular vascular compartment, allowing dynamic imaging of liver lesions. Uptake of about 50% of injected gadoxetic acid occurs by the anionic transporter protein of hepatocytes and leads to intracellular accumulation and thus increased signal intensity of liver parenchyma on delayed T1-weighted MR images. Intracellular gadoxetic acid is excreted through the bile ducts, in our experience beginning roughly 10 minutes after contrast administration. The remaining 50% of injected gadoxetic acid is excreted renally [6, 10].

Because of its high specificity to liver cells, gadoxetic acid allows distinction of hepatocyte-containing from non-hepatocyte-containing tissue, although only tumors containing highly differentiated hepatocytes have been shown to enhance in delayed phase imaging [6]. Previous reports have described gadoxetic acid enhancement in hepatic adenomas during delayed phases [5, 6, 11]; one atypical adenoma showing no late enhancement has been reported [6]. These findings indicate the potential of gadoxetic acid to reliably diagnose hepatic adenomatosis during initial workup and even allow recognition of potential dysplastic growth during follow-up.

Contrary to these reports, most adenomas in our three patients showed no gadoxetic acid uptake during delayed phase imaging. Only a few adenomas showed weak and diffuse delayed uptake, and three large adenomas showed strong peripheral enhancement. Absence of delayed phase enhancement did not permit confident diagnosis of benign liver adenomas in our patients; instead, we were left with a differential diagnosis that included dysplastic adenomas, metastases, and multifocal hepatocellular carcinoma [6].

On gadobenate dimeglumine–enhanced (MultiHance, Bracco) MRI, Grazioli et al. [8] described identical behavior of solitary hepatic adenomas and adenomas in liver adenomatosis during delayed imaging. Solitary adenomas and adenomas in liver adenomatosis could be reliably differentiated from focal nodular hyperplasia because of a lack of hepatic metabolism. Gadobenate dimeglumine is also partially specific to hepatocytes, but only 3–5% is metabolized as opposed to 50% of gadoxetic acid [6, 8, 10]. The reason for the absence of hepatic metabolism of gadobenate dimeglumine in adenomas is not known. Grazioli et al. discussed two possible explanations. Adenomas may have an altered cell structure compared with normal hepatocytes and therefore a lack of gadobenate dimeglumine uptake. On the other hand, the absence of biliary ductules in adenomas—and therefore reduced biliary excretion mechanisms—may lead to decreased uptake gradients of gadoxetic acid into hepatocytes of adenomas.

In conclusion, we observed absent or strongly reduced intracellular uptake of gadoxetic acid in all adenomas during delayed phase imaging. Lack of metabolism of gadoxetic acid in liver adenomas did not allow differentiation from malignant or dysplastic nodules in all three patients with liver adenomatosis.

References

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