Evaluation of hepatic findings by magnetic resonance after use of gadoxetic acid

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Abstract
Objective: To evaluate the use of post-contrast sequences using a hepatospecific contrast medium (gadoxetic acid) in patients with suspected liver nodules or masses, and to identify and describe the main findings in these images.

Methods: We performed a retrospective study with 67 outpatients, who underwent abdominal magnetic resonance examination with injection of disodium gadoxetate to investigate suspicious nodules or masses. The patients were submitted to the examination on medical request.

Results: The mean age was 41 ± 11.59 years. The most frequent histological types were focal nodular hyperplasia (31.3%), hemangioma (31.3%), and adenoma (22.4%). In focal nodular hyperplasia and adenoma, there was a greater distribution of hypointense and hyperintense enhancement in the pre-contrast phase. Isointense enhancement was much more prevalent in the arterial, portal, equilibrium, and hepatobiliary phases 15–20. In hemangiomas, hypointense enhancement was prominent in all phases.

Conclusion: Based on the behavior of liver injuries in this study after the use of the substance studied, it allowed for a better characterization of liver injuries, which can contribute to the medical practice at the time of clinical diagnosis.

KEYWORDS
gadoxetic acid, hepatic nodules, magnetic resonance imaging

1 INTRODUCTION

The contrast agents used in magnetic resonance imaging (MRI) have shown their clinical utility in a large number of organs, detecting and characterizing numerous injuries and functional abnormalities. This is important, as studies carried out with contrast media add important morphological and functional information compared with those without.1–3 Since the 1980s, a variety of contrast agents have been used to study the liver on MRI, most of them based on chelates of the paramagnetic ion, gadolinium. Currently, contrast media can be classified into two categories: non-specific extracellular and specific intracellular. The main difference being that the chelating molecule carries gadolinium.4 In this sense, the classes of hepatospecific contrasts are superparamagnetic iron oxide, which is selectively absorbed...
by the reticuloendothelial system (mainly the liver and spleen) and hepatic biary contrasts, which are captured by hepatocytes and excreted through the kidney and bile.5–7

In Brazil, the use and commercialization of a hepatobiliary contrast agent, gadoliniummethoxybenzyl dimeglumine (Gd-EOB-DTPA, disodium gadoxetate, gadoacetic disodium acid, Primovist), has recently been approved by the National Health Surveillance Agency as gadoxetic acid.

Gadoxetic acid (Gd-EOB-DTPA) is a water-soluble paramagnetic contrast medium that has extracellular and bile excretion properties. It was developed to improve the detection and characterization of focal liver lesions through MRI. It was approved for use in Europe, the USA, and Asia at a concentration of 0.25 mmol/L and a dose of 0.025 mmol/kg.8,9 Gd-EOB-DTPA has a good safety profile, which is very similar to that of other conventional gadolinium agents.8–10 The fact that it is excreted through bile makes it a relatively safe contrast agent in patients with renal dysfunction. One of its main applications is the characterization of focal hepatocellular lesions, being vital in helping to establish a clinical diagnosis.11

The objective of the present study was to evaluate the use of post-contrast sequences using a hepatospecific contrast medium (gadoxetic acid) in patients with suspected liver nodules or masses.

2 METHODS

We carried out a retrospective study in one center of radiological specialists with a group of 67 outpatients who underwent abdominal MRI with disodium gadobenate (Primovist). We sought to investigate the malignant potential of suspicious nodules or masses, from January 2018 to June 2019. The patients underwent a routine MRI on medical request, without additional cost, volume, or risk.

The collection procedure followed the following criteria: all patients received an intravenous injection of 10 mL of contrast medium through a gauge port.12–14 The injection lasted on average 14 s, with subsequent injection of saline solution to facilitate the spread of the contrast medium into the body.

The research protocol followed the standardized sequences: coronal T2, in/out phase, T1 pre-contrast, dynamic post-contrast (arterial, portal, and equilibrium), T2 diffusion, T2 fat, pure T2, hepatospecific (after 10 min), visualizations in axial and coronal section, hepatospecific (after 20 min), and axial and coronal section views. The examinations and reports were checked systematically. The evidence described and analyzed respected international criteria for the standardization of enhancement and types of enhancement. All data were contained and stored in the picture archiving and communication system of the referenced service. Exploratory data analysis was carried out by calculating measures (mean, standard deviation, minimum, median, maximum, frequency, and percentage), and drawing graphs and tables.

3 RESULTS

Of the 67 patients who participated in the survey, the mean age was 41 ± 11.59 years, with a higher frequency between the ages of 30 and 40 years, the minimum was 2 years with an age range reaching up to 72 years. Regarding the distribution by sex, the analysis shows that women were more prevalent. The most frequent histological types were: focal nodular hyperplasia (31.3%), hemangioma (31.3%) and adenoma (22.4%), atypical adenoma (6.0%), cysts (4.5%), atypical hemangioma (1.5%), and hypovascular metastasis (1.5%; Table 1).

Of the 21 patients diagnosed with focal nodular hyperplasia, there was a greater distribution of the hypointense (10) and hyperintense (11) enhancement in the pre-contrast phase. Isointense enhancement was much more prevalent in the arterial (19), portal (16), equilibrium (16), and hepatobiliary phases 15–20 (18) with the use of Primovist (Figure 1 and Table 1). Regarding adenoma, of the 15 patients diagnosed with this histological type, there was a higher prevalence of hypointense enhancement in the pre-contrast phase (11), and isointense enhancement in the arterial (10), portal (9), equilibrium (9), and hepatobiliary 15–20 (9; Figure 2 and Table 1). Regarding hypovascular metastasis, only one patient was diagnosed with this histological type, with hypointense enhancement in all analyzed phases (pre-contrast, arterial, portal, equilibrium, and hepatobiliary 15–20; Table 1).

Atypical adenomas were present in four patients who had a higher prevalence of hypointense enhancement in the pre-contrast (4) and hepatobiliary phases 15–20 (4), whereas in the arterial and portal phases, the hyperintense enhancement was more prevalent with the use Primovist (Figure 4 and Table 1). The histological type of cysts was found in three patients who presented only with hypointense enhancement in all analyzed phases (Figure 5 and Table 1). Regarding hemangioma, 21 patients were diagnosed with this histological type, for which hypointense enhancement prevailed in all phases, pre-contrast (19), arterial (16), portal (14), equilibrium (14), and hepatobiliary 15–20 (19; Figure 3 and Table 1). Only one patient presented with an atypical hemangioma presenting with hypointense enhancement in the pre-contrast, portal, and hepatobiliary 15–20 phases, and hyperintense enhancement in the arterial and equilibrium phases using Primovist (Table 1).

Sequentially, the image frames obtained by MRI using gadoxetic acid were presented.

4 DISCUSSION

When a liver injury is diagnosed, one of the main objectives is to differentiate potentially malignant lesions from benign lesions, with consequent different clinical and prognostic attitudes.12,13 The MRI protocol for studying the liver includes T1-weighted sequences in-phase and out-of-phase, usually with fat suppression, in the axial and coronal planes. Depending on the clinical suspicion and the existence of alterations in the MRI sequences obtained, dynamic evaluation of the lesions with intravenous contrast administration is carried out at several phases (arterial, portal, and equilibrium), using T1-weighted sequences 3-D gradient recalled echo.12,13

In the arterial phase (15–30 s), maximum contrast is observed in the hepatic artery, which is an important phase for the detection of hypervascular lesions and the assessment of the hepatic arterial
| Histological types observed in the sample | Phase                      | Highlight/no. patients |          |          |          |          |
|------------------------------------------|----------------------------|------------------------|----------|----------|----------|----------|
|                                          |                            | Hypotensive | Isointense | Hyperintense | n   | %        |
| Focal nodular hyperplasia                | Pre-contrast               | 10          | 0          | 11         | 21  | 31.3     |
|                                          | Arterial                   | 0           | 19         | 5          | 2   |          |
|                                          | Portal                     | 0           | 16         | 5          | 5   |          |
|                                          | Balance                    | 0           | 16         | 5          | 5   |          |
|                                          | Hepatobiliary (15–20)      | 0           | 18         | 3          | 3   |          |
| Adenoma                                  | Pre-contrast               | 11          | 1          | 3          | 15  | 22.4     |
|                                          | Arterial                   | 1           | 10         | 4          | 4   |          |
|                                          | Portal                     | 4           | 9          | 2          | 2   |          |
|                                          | Balance                    | 3           | 9          | 3          | 3   |          |
|                                          | Hepatobiliary (15–20)      | 4           | 9          | 2          | 2   |          |
| Hypovascular metastasis                  | Pre-contrast               | 1           | 0          | 0          | 1   | 1.5      |
|                                          | Arterial                   | 1           | 0          | 0          | 0   |          |
|                                          | Portal                     | 1           | 0          | 0          | 0   |          |
|                                          | Balance                    | 1           | 0          | 0          | 0   |          |
|                                          | Hepatobiliary (15–20)      | 1           | 0          | 0          | 0   |          |
| Atypical adenoma                         | Pre-contrast               | 4           | 0          | 0          | 4   | 6        |
|                                          | Arterial                   | 1           | 0          | 0          | 0   |          |
|                                          | Portal                     | 1           | 0          | 0          | 0   |          |
|                                          | Balance                    | 2           | 0          | 2          | 2   |          |
|                                          | Hepatobiliary (15–20)      | 4           | 0          | 0          | 0   |          |
| Cysts                                    | Pre-contrast               | 3           | 0          | 0          | 3   | 4.5      |
|                                          | Arterial                   | 3           | 0          | 0          | 0   |          |
|                                          | Portal                     | 3           | 0          | 0          | 0   |          |
|                                          | Balance                    | 3           | 0          | 0          | 0   |          |
|                                          | Hepatobiliary (15–20)      | 3           | 0          | 0          | 0   |          |
| Hemangioma                               | Pre - Contrast             | 19          | 0          | 2          | 21  | 31.3     |
|                                          | Arterial                   | 16          | 1          | 4          | 4   |          |
|                                          | Portal                     | 14          | 1          | 6          | 6   |          |
|                                          | Balance                    | 14          | 1          | 6          | 6   |          |
|                                          | Hepatobiliary (15–20)      | 19          | 1          | 1          | 1   |          |
| Atypical Hemangioma                      | Pre-contrast               | 1           | 0          | 0          | 1   | 1.5      |
|                                          | Arterial                   | 0           | 0          | 1          | 1   |          |
|                                          | Portal                     | 1           | 0          | 0          | 0   |          |
|                                          | Balance                    | 0           | 0          | 1          | 1   |          |
|                                          | Hepatobiliary (15–20)      | 1           | 0          | 0          | 0   |          |

Total \( n = 67 \).

In the present study, we used a hepatospecific contrast (Gd-EOB-DTPA, disodium gadoxetate, gadoacetic disodium acid, Primovist), known as gadoxetic acid. This intravenous contrast agent has great diagnostic value in assessing liver lesions, as it not only improves the detection of lesions, but the determination of the uptake characteristics often allows a specific diagnosis.
From the histological findings in the present study, focal nodular hyperplasia (FNH) occurred in 21 patients who presented with isointense enhancement in some phases (arterial, portal, equilibrium, and hepatobiliary 15–20) and hypointense in the pre-contrast phase when using Primovist. Currently, FNH is considered to result from a hyperplastic reaction of the liver tissue to a pre-existing vascular malformation.14,15 Two types of FNHs are described: typical (80%) and atypical (20%). Histologically, typical FNH is characterized by the presence of hepatocytes, Kupffer cells, bile ducts, and blood vessels in an abnormal structural pattern. Meanwhile, in the atypical form, the difference is the lack of malformed vessels and/or nodular architecture.14,15

Studies in the literature have shown that MRI has greater sensitivity and specificity for the diagnosis of FNH than ultrasound and computed tomography. In MR, typical FNH is isointense or slightly hypointense in T1-weighted sequences, and isointense or slightly hyperintense in weighted sequences in T2. The central scar is hypointense at T1 and hyperintense at T2.16–19 After administration of contrast, the typical
FIGURE 3  Magnetic resonance imaging of the abdomen, axial section. (a) Pre-contrast phase hemangioma. (b) Arterial phase hemangioma. (c) Portal phase hemangioma. (d) Equilibrium phase hemangioma. (e) Hepatobiliary phase hemangioma

FIGURE 4  Magnetic resonance imaging of the abdomen, axial section. (a) Pre-contrast phase atypical adenoma. (b) Arterial phase atypical adenoma. (c) Portal phase atypical adenoma. (d) Equilibrium phase atypical adenoma. (e) Hepatobiliary phase atypical adenoma

lesion presents rapid homogeneous hypercapture in the arterial phase; becoming isointense or slightly hypointense in the portal and equilibrium phase, these data corroborate the findings of the present study that showed an isointense predominance after administration of the contrast. The central scar is typically hyperintense in the equilibrium phase by diffusion-contrast impregnation. Studies also point out that after the administration of Gd-BOPTA, FNH is slightly hyperintense or isointense in the hepatobiliary phase, reflecting the presence of hepatocytes with abnormal biliary drainage. Gd-EOB-DTPA is more accurate, because it combines interstitial vascular uptake with specific hepatobiliary uptake.\textsuperscript{18,19}

In the present study, it was also observed that 15 patients had adenoma with a predominance of hypointense enhancements in the pre-contrast phase and isointense in the arterial, portal, equilibrium, and hepatobiliary phases 15–20. Studies have shown that on MRI, the lesion is generally heterogeneous and presents variable signals in T1-
FIGURE 5   Magnetic resonance imaging of the abdomen, axial section. (a) Pre-contrast phase cysts. (b) Arterial phase cysts. (c) Portal phase cysts. (d) Equilibrium phase atypical cysts. (e) Hepatobiliary phase cysts

weighted sequences: areas of hyper signal correspond to intracellular lipids (lose signal in out-of-phase sequences), glycogen, or recent hemorrhage; hypointense areas correspond to necrosis, old hemorrhage, or calcification. In T2-weighted sequences, the signal is equally variable, but they are usually hyperintense lesions regarding the liver parenchyma. The pseudocapsule is typically hypointense in T1 and has a variable signal in T2 (hypo, iso, hyperintense).16,17,19–21

In the dynamic study, they present a characteristic enhancement: in the arterial phase, in a ring, and progressive to the periphery in the porto-venous phase.56 The use of hepatic-specific contrast improves the detection of liver metastases, because the greater tissue discrimination in the hepatobiliary phase allows the detection of a greater number of metastases.16

In the present study, three patients presented histological type cysts with a predominance of hypointense enhancement. Studies have shown that cysts are among the most common lesions (5–14%), and can be single or multiple. It is suggested that they originate in the biliary epithelium. They tend to increase in number and dimension with age.

MRI results in well-defined lesions, which are homogeneously hypointense in the T1-weighted sequences and hyperintense in the T2-weighted sequences. Their appearance on MRI might be indistinguishable from hemangiomas; however, they do not capture contrast. In T2-weighted sequences with longer ET, the cysts maintain an intense hyper signal.17–20

Twenty-one patients presented the histological hemangioma type, and its enhancement characteristics were hypointense in all phases. Hemangioma consists of interconnected vascular channels, nourished by branches of the hepatic artery. Most remain stable; growth or involution might occur, and they might become completely fibrous. They can be single or multiple, are usually asymptomatic and discovered incidentally. The presence of symptoms might be due to the mass effect on adjacent structures or complications (hemorrhage).20

The literature has shown that MRI hemangioma presents as homogeneous and hypointense lesions in T1-weighted sequences and hyperintense lesions in T2-weighted sequences. Occasionally, they have hypointense areas at T1 and T2 corresponding to fibrosis or calcification. They present an increase in signal in sequences with a longer echo time, in which the lesion becomes more hyperintense regarding the liver, a characteristic that might be useful in differentiating it from neoplastic lesions, in which there is no increase in signal.17,20 The typical hemangioma presents as a homogeneous hypointense nodule in T1 and hyperintense in T2 without a significant signal drop when using sequences with longer echo time (TE > 130 ms). After the injection of the paramagnetic contrast medium, the enhancement pattern is similar to that seen in tomographic sections.21

The enhancement of hemangioma in MRI with Gd-EOB-DTPA has some peculiarities. The lesion tends to follow the blood signal from the abdominal vessels in the extracellular phase. In contrast, unlike what occurs when using extracellular contrast media, in the hepatobiliary phase, the hemangioma does not present progressive or persistent enhancement, but rather, hypointense, contrasting with the adjacent normal parenchyma, which represents intense uptake of Gd-EOB-DTPA in this phase, due to the absence of hepatocytes. This phenomenon is called inversion of the liver-injury enhancement gradient.22,23
CONCLUSION

This study aimed to assess the behavior of hepatic nodules using hepatospecific contrast through MRI. The findings of the present study were described in the literature. In this context, compared with other techniques, the study with MRI has great advantages, in view of the possibility of combining its greater tissue resolution with the dynamic study and the possibility of administering specific contrasts.

It was observed that the use of hepatobiliary contrast media allows an initial assessment of tumor perfusion, in the same way as extracellular contrast agents, in addition to a late assessment of uptake by functioning hepatocytes, providing additional information that allows a better characterization of the injuries. Thus, the information obtained, combined with the characteristics of the other techniques, can effectively diagnose many liver injuries. Lower accessibility and higher cost are the main disadvantages in this case.

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