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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Duodenogastric Gadoxetic Acid Reflux on Routine Liver Magnetic Resonance Imaging and Upper Endoscopy Findings

Rutin Karaciğer MR Görüntülemede Duodenogastrik Gadoksetik Asit Reflüsü ve Üst Gastrointestinal Sistem Endoskopisi Bulguları

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Abstract

Objectives: Bile reflux gastritis is an underdiagnosed but common type of chemical gastritis (CG) caused by bile induced irritation of gastric mucosa. Diagnosis is based on endoscopic and histologic findings. However, if bile reflux is not observed, diagnosis of bile gastritis might be challenging. We aimed to evaluate duodenogastric gadoxetic acid (GA) reflux in routine liver magnetic resonance imaging (MRI) and to compare this finding with bile reflux and gastritis findings in upper endoscopy.

Materials and Methods: A total of consecutive 45 patients who underwent GA-enhanced liver MRI with at least one delayed phase image (≥40 minutes delay) and upper endoscopy were retrospectively included. Images were reviewed by two radiologists regarding the presence and extent of gastric GA. Endoscopic and histologic results were noted.

Results: Duodenogastric GA reflux was detected in 8 patients (17.8%). In 2 of them endoscopy revealed bile reflux. In one of these two patients gastritis was also noted,whereas gastric mucosa was considered as normal in the other patient. In 6 out of 8 patients with contrast reflux gastric bile stain was not reported. In each of these 6 patients erosive/erythematous gastritis was detected. Histopathology confirmed CG in 4 out of them.

Conclusion: It might be challenging to differentiate bile induced gastritits from other types of CG, in particular, if gastric bile stain is not observed during upper endoscopy. Thus, radiologists should be aware of duodenogastric GA reflux on delayed phase MRI and report this finding. We suggest, that diagnostic performance of MRI regarding bile reflux and bile gastritis should be investigated with a multidisciplinary prospective study design.

Key Words: Magnetic Resonance Imaging, Gadoxetic Acid, Bile Reflux, Bile Gastritis

Öz

Amaç: Safra gastriti, yaygın bir kimyasal gastrit (KG) türü olup gastrik mukozanın safra kaynaklı hasarı ile ortaya çıkmaktadır. Tanı endoskopik ve histolojik bulgulara dayanmakla birlikte safra reflüsünün saptanmadığı durumlarda safra gastritini belirlemek zor olabilmektedir. Çalışmamızda, rutin karaciğer manyetik rezonans (MR) görüntülemede duodenogastrik gadoksetik asit (GA) reflüsünü değerlendirmeyi ve bu bulguyu üst endoskopide saptanan safra reflüsü ve gastrit bulguları ile karşılaştırmayı amaçladık.

Gereç ve Yöntem: Temmuz 2011-Mayıs 2021 tarihleri arasında GA ile gerçekleştirilen toplam 1543 rutin dinamik karaciğer MR inceleme retrospektif olarak tarandı. Safra kanallarında kontrast maddenin izlendiği, en az bir geç faz (≥40 dakika) MR görüntüsü bulunan ve MR çekimi ile üst GİS endoskopi arasında 1 yıldan az süre olan 45 hasta çalışmaya dahil edildi. MR görüntüleri, kontrast madde reflüsü varlığı ve uzanımı açısından iki radyolog tarafından konsensus ile değerlendirildi. Hastaların endoskopik ve histopatolojik bulguları hastane kayıt sisteminden not edildi.

Bulgular: Kırk beş hastanın 8'inde (%17,8) duodenogastrik GA reflü saptandı. Duodenogastrik GA reflü saptanan 8 hastanın 2'sinde endoskopide safra reflüsü mevcuttu. Endoskopik olarak da safra reflüsü kanıtlanan 2 hastanın birinde gastrit mevcutken, diğer hastada mide mukozası normal

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Öz

olarak değerlendirilmişti. Kontrast reflüsü olan 8 hastanın 6'sında endoskopik olarak midede safra rapor edilmemişti. Bu hastaların hepsinde (N=6) eroziv/eritemli gastrit ve 4'ünde histopatolojik olarak kanıtlanmış KG mevcuttu.

Sonuç: Endoskopi sırasında midede safra gözlenmediği durumlarda safra kaynaklı gastritleri, diğer KG tiplerinden ayırt etmek güçtür. Duodenogastrik GA reflünün safra gastritinin göstergesi olabileceği radyologlar tarafından az bilinen bir durumdur. Klinik olarak da diğer KG tiplerinden ayırt edilmesi zor olabilen bu durumun, geç faz MRG'de saptanabileceğine dair farkındalığının artması gerekmektedir. Ön çalışma olan bulgularımızın, MRG'nin safra reflüsü ve gastritinde tanısal performansının ve klinik katkısının değerlendirileceği, multidisipliner prospektif çalışmalar ile destekleneceğine inanmaktayız.

Anahtar Kelimeler: Manyetik Rezonans Görüntüleme, Gadoksetik Asit, Safra Reflüsü, Safra Gastriti

Introduction

Bile reflux is the duodenogastric backflow of alkaline duodenal and pancreatic secretions, acids, and bile salts (1). A small amount of bile reflux into the stomach is considered physiologic and might occur post-prandial or in the early morning, whereas pathologic bile reflux tends to be more excessive and more prolonged. Pathologic reflux can develop either due to an underlying pyloric sphincter dysfunction, impaired gastroduodenal motility (primary reflux), or after gallbladder removal and gastric surgery (secondary reflux) (2-5).

Diagnosis of bile reflux is made by upper gastrointestinal endoscopy, other intubation methods such as gastric pH monitoring through the nasogastric tube or measurement of bile acids in gastric aspirates and hepatobiliary scintigraphy (6,7). Depending on the amount, concentration, and duration of pathologic bile reflux, this condition may cause chemical irritation of the gastric mucosa leading to chemical gastropathy/gastritis and increasing the risk of gastric malignancy (8,9).

The presence of gastric bile stain accompanied by gastritis findings, including mucosal erythema, erosions, or ulcers, support the diagnosis of bile-induced chemical gastritis via upper endoscopy (9,10). However, this diagnosis should be confirmed by histopathologic findings such as foveolar hyperplasia, reactive glandular changes, edema, chronic inflammation, intestinal metaplasia, and gastric polyps (11,12). In this context, it has to be noted that histopathologic findings are not specific to bile-induced chemical gastritis but can also be seen in other types of chemical gastritis (10,11). Therefore, endoscopic or radiologic proof of gastric bile stain is essential for a more specific diagnosis.

Gadoxetic acid is a hepatocyte-specific contrast agent routinely used in hepatobiliary magnetic resonance imaging (MRI). Since it is taken up by hepatocytes and is biliary excreted, it provides both functional and morphologic information. In addition, due to its biliary excretion, it is expected to be seen in the biliary tree and duodenal lumen 15-20 minutes after intravenous injection (13).

In this study, we aimed to emphasize that duodenal contrast reflux into the stomach might occur during routine gadoxetic-acid enhanced hepatic MRI and to compare the presence of contrast reflux with upper endoscopy findings.

Materials and Methods

This retrospective observational study was conducted according to the Declaration of Helsinki principles and was approved by Ankara University Human Research Ethics Committee (approval no: İ10-644-21, date: 02.12.2021).

Study Population

Overall, 1543 consecutive gadoxetic acid-enhanced dynamic liver MRI examinations of adult patients obtained between July 2011 and May 2021 were retrospectively reviewed.

Considering the total MR examinations (n=1543), the prevalance of duodenogastric gadoxetic acid reflux was 2.9% (n=44). The inclusion criterion was the presence of at least one delayed phase image (≥40 minutes delay). This was met in 196 out of the total 1543 examinations.

Of the 196 studies, 151 were excluded due to the following reasons: (a) gadoxetic acid not present in the biliary system or duodenum in at least one delayed phase image (n=4); (b) upper GI endoscopy not performed (n=116); the time interval between MRI and upper GI endoscopy was more than one year (n=31). Thus, 45 patients with each MRI study were included in this study (Figure 1).

MRI Protocol

MRI was performed by using a 1.5-T system (Aera, Siemens, Erlangen, Germany; Optima 450w, GE Healthcare, Milwaukee, WI) and a 3-T system (MAGNETOM® Verio, Siemens, Erlangen, Germany; Signa PET MR, GE Healthcare, Milwaukee, WI) device with a phased array torso coil. The sequences consisted of coronal T2w single-shot fast spin echo, axial T2w fat-suppressed FSE, axial diffusion-weighted images (b=50, 400, 800), axial T1w dual-echo gradient echo (GRE) and post-contrast fat-suppressed 3D GRE T1w sequences.

Post-contrast T1w images were obtained after intravenous injection (1 mL/sec) of 0.025 mmol/kg gadoxetic acid disodium (Gd-EOB-DTPA, Primovist®) followed by a saline chaser (10 mL) using an automatic injector.

MRI Analysis

Pre- and post-contrast axial and coronal T1w images retrieved from a picture archiving and communication system (RIS/PACS; Centricity 5.0 RIS-i, GE Healthcare, Milwaukee, WI, USA) were retrospectively evaluated by two radiologists (M.K., D.K.Ö.) in consensus regarding the presence and extent (gastric antrum, corpus, fundus) of duodenogastric gadoxetic acid reflux.

Institutional electronic medical records were used to screen endoscopy results for gastric bile staining and gastritis findings. Diagnosis of bile gastritis was based on the presence of erythematous and/or exsudative gastric mucosa with gastric bile stain detected on upper endoscopy.

Statistical Analysis

Descriptive statistical analyses were performed using SPSS for Windows 11.5 (SPSS Inc., Chicago, IL, USA). Continuous variables with normal distribution were presented as mean (± standard deviation); non-normal variables were expressed as a median (minimum-maximum), and the categorical variables were summarized as counts (n) and percentages (%).

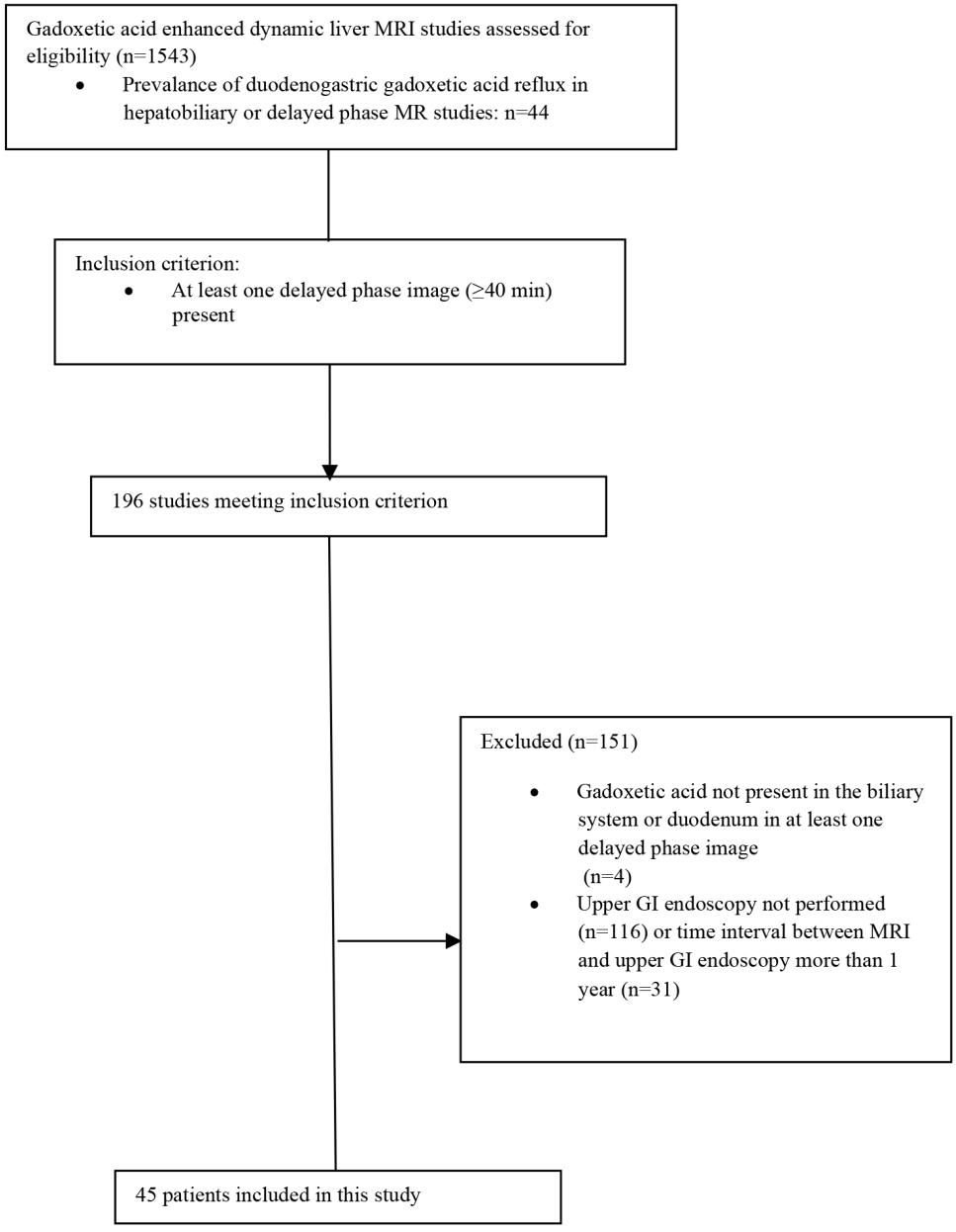

Figure 1: Flowchart

Results

Study Population

The study population consisted of 24 female (53.3%) and 21 male patients (46.6%) with a median age of 58 years (age range, 27-79 years).

While eight patients (17.7%) had a prior cholecystectomy, none of the patients had undergone gastric surgery.

Screening for early stage hepatocellular cancer in chronic hepatic parenchymal disease was the major indication for gadoxetic acid enhanced MRI (n=37, 82.2%), followed by evaluation of focal hepatic lesions (n=5, 11.1%) and cholangiocellular cancer (n=3, 6.6%).

MRI Findings

In 8 out of 45 patients (17.8%) gastric gadoxetic acid reflux was detected in delayed phase images with contrast medium extending into the gastric antrum (n=5), corpus (n=2) and fundus (n=1) (Figures 2-4). In 2 of these eight patients, reflux was also present in the hepatobiliary phase extending into the antrum and corpus, respectively (Table 1).

Imaging findings consistent with chronic liver disease were observed in each patient with and in 29 (%78.4) patients without duodenogastric contrast reflux.

Association of MRI Findings with Upper Endoscopy Results

In 2 out of 8 patients with duodenogastric gadoxetic acid reflux, gastric bile stain was also detected during upper endoscopy. While in 1 of them, endoscopic gastritis findings were present, in the other patient, endoscopy revealed normal mucosa. Gastritis findings were noted in each of the six patients without reported gastric bile staining. Biopsy revealed chemical gastritis in 4 of these 6 patients (Table 2).

Bile reflux was neither detected in the remaining 37 (82.2%) patients without contrast reflux. In 35 patients, gastritis

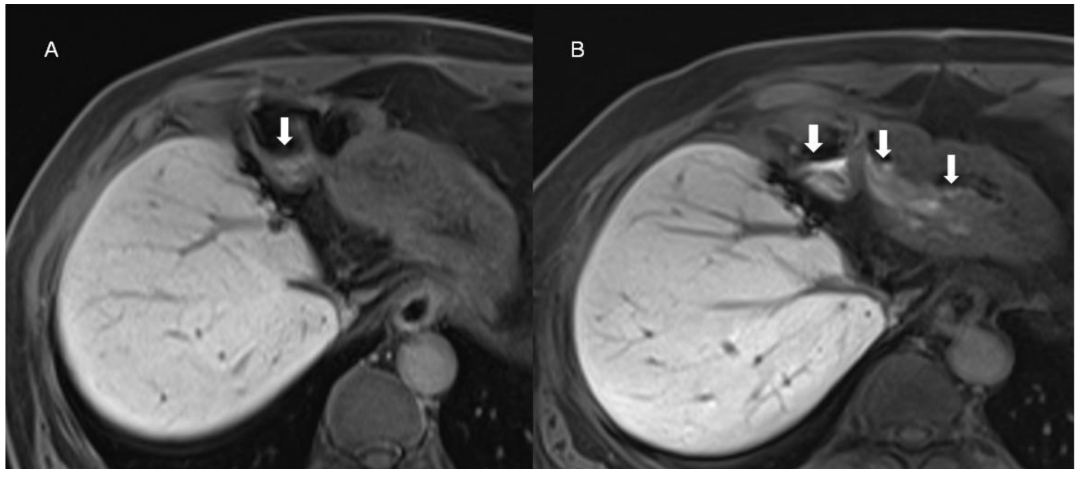

Figure 2: Axial gadoxetic-acid enhanced T1-weighted MR images of a 58-years-old male patient. Duodenogastric reflux (arrows) into the gastric antrum in the hepatobiliary phase **(A)** and into the gastric corpus (in the delayed phase (70 min after injection) **(B)**. Upper endoscopy revealed erosive gastritis but no bile reflux. Biopsy proved chemical gastritis

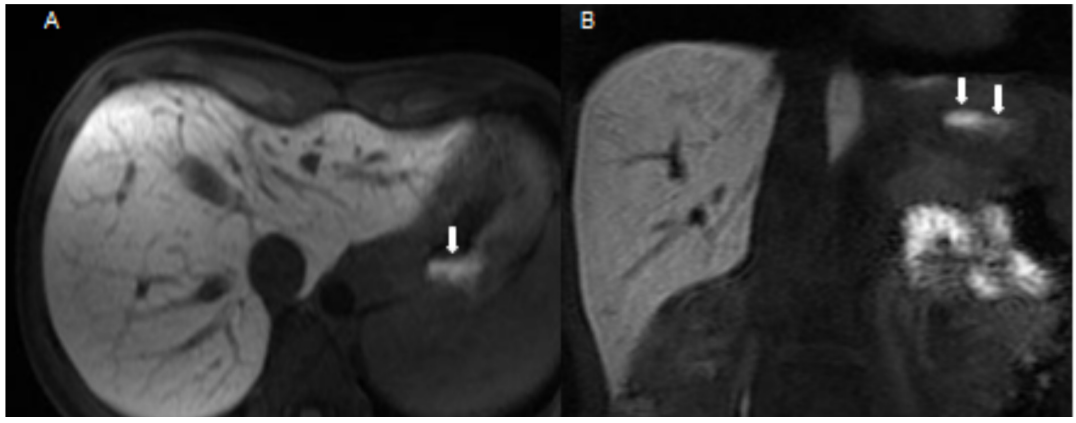

Figure 3: Axial **(A)** and coronal **(B)** gadoxetic-acid enhanced T1-weighted MR images of a 24-years-old female patient. Duodenogastric reflux into the gastric fundus in the delayed phase (75 min after injection). Upper endoscopy revealed erythematous gastritis but no bile reflux. Biopsy proved chemical gastritis

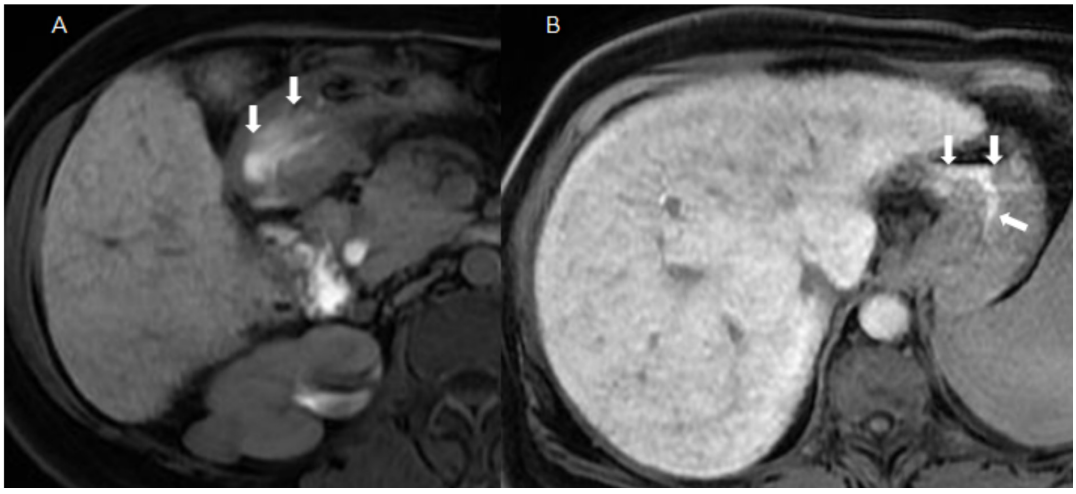

Figure 4: Axial gadoxetic-acid enhanced T1-weighted MR images of a 66-years-old female patient. Duodenogastric reflux into the gastric antrum in the hepatobiliary phase **(A)** and into the gastric corpus in the delayed phase (60 min after injection) **(B)**. Upper endoscopy revealed bile reflux but no gastritis. Biopsy was not performed

Table 1: Delay times of contrast reflux on MRI after gadoxetic acid injection

Patient	Presence of contrast reflux	
	Hepatobiliary phase (min)	Delayed phase (min)
1	-	75
2	-	50
3	20	60
4	-	60
5	20	70
6	-	120
7	-	75
8	-	60

MRI: Magnetic resonance imaging

Table 2: Endoscopic and histologic findings in patients with contrast reflux on MRI

Patient	Endoscopic findings	Histologic results
1	Erythematous gastritis Acute hemorrhagic gastritis	-
2	Erosive antral gastritis Atrophic gastritis of the gastric fundus and corpus	Chemical gastritis Chronic gastritis
3	Gastric bile stain No gastritis	-
4	Pangastritis with antral erosions	Normal antral mucosa
5	Erosive pangastritis	Chemical gastritis
6	Extensive gastric bile stain Erosive pangastritis	-
7	Mucosal hyperaemia of the gastric corpus and antrum	Chemical gastritis
8	Erythematous pangastritis Antral polyp	Chemical gastritis Antral hyperplastic polyp

MRI: Magnetic resonance imaging

findings (with concomitant portal gastropathy in 7 patients) were reported. In 22 of these 35 patients, biopsy results could be obtained and yielded chemical gastritis in 15 cases.

In 1 of the 8 patients with cholecystectomy, reflux was detected both in upper endoscopy and MRI. In another patient with cholecystectomy duodenogastric contrast reflux was present while gastric bile staining was not reported.

Discussion

Due to its alkaline ingredients, bile reflux might cause chemical gastritis, gastric ulcers, intestinal metaplasia, and gastric malignancy (6,7). Chemical gastritis results from the mucosal irritation of the gastric mucosa and may also be induced by exogenous substances such as non-steroidal anti-inflammatory drugs (NSAID) and chemotherapeutic agents (14,15).

Bile gastritis is generally diagnosed based on mucosal erosions, erythema, swelling, and gastric bile stain on upper endoscopy. These findings should be supported by a histopathologically proven chemical gastritis pattern (10). However, if gastric bile stain is not observed during endoscopy, it is not possible to distinguish bile gastritis from other forms of chemical gastritis histopathologically.

Previous studies indicated that the severity of chemical gastritis depends on the amount of bile reflux and that chronic inflammation is more severe in bile-induced gastritis than in other forms of gastritis (6,16,17). Additionally, bile gastritis has been identified as an independent risk factor for developing precancerous gastric lesions and gastric malignancy (18).

Medical treatment of bile gastritis is similar to that of the other chemical gastritis types with an additional option of prokinetic drugs and ursodeoxycholic acid administration, which might reduce the clinical symptoms due to bile reflux (19,20). Furthermore, Roux-en-Y diversion is often the only succeeding treatment in patients with bile reflux after gastric surgery (21). Thus, due to the higher risk of malignancy and therapeutical distinctions, the diagnosis of bile reflux as the underlying cause of chemical gastritis might be of clinical relevance.

Although histopathologically confirmed chemical gastritis was common in our study population, gastric bile reflux was reported in only one patient after endoscopy. This might be either since, despite the presence of bile reflux, it was considered as not clinically significant and thus was not mentioned in the endoscopy report, or was not observed during endoscopy owing to the intermittent nature of bile reflux, or else chemical gastritis was caused by exogenous substances but not by bile.

While upper endoscopy is routinely used to diagnose bile gastritis, a recent study revealed a lower accuracy and predictive value regarding the diagnosis of bile reflux compared to gastric pH monitoring and hepatobiliary scintigraphy (11). Previously, it was also concluded that accurate diagnosis of duodenogastric bile reflux is not possible with upper endoscopy and histopathology but should include the latter techniques, particularly if surgical treatment is planned (11). However, these techniques are either invasive or release radiation and, thus, are often performed with a more specific preliminary diagnosis.

To the best of our knowledge, there is only one study assessing the diagnostic utility of MRI in duodenogastric gadoxetic acid reflux (22). This study showed that duodenogastric contrast was an indication for bile reflux, and thus, gadoxetic acid-enhanced MRI might play a potential role in the diagnosis of bile reflux. The authors also stated that in several patients, MRI revealed contrast reflux in the stomach in delayed images, whereas no bile reflux was observed during endoscopy (22). In our study, out of the 8 patients with gastric contrast reflux in delayed phase MR images, gastric bile stain was noted in only 2 patients. Thus, in 75% of patients with contrast reflux into the stomach on MRI, endoscopy revealed no bile reflux or was not mentioned. In the study by Hyun et al. (22), this was the case in 53.8% of patients with positive MRI findings. This might be due to the fact, that on MR studies with delayed phase imaging, the overall examination period revealing functional information is longer than is the case with upper endoscopic studies that would rather provide a "snapshot" at the time of the study (22). With regard to the diagnosis of duodenogastric reflux, this might be listed as an additional advantage of gadoxetic acid enhanced MRI, which provides more detailed anatomic information, is a non-invasive technique, and does not use ionizing radiation. The higher rate of discrepancies between MRI and upper endoscopy findings in our study compared to the results of Hyun et al. (22) might be due to the possibility, that despite gastric bile being noticed during upper endoscopy, it was probably assumed to be physiologic and thus was not reported owing to the retrospective study design.

Hyun et al. (22) stated that duodenogastric contrast reflux corresponded to bile reflux, however, in 2/3 of cases, it was not associated with bile gastritis findings on endoscopy. In our study, in only 1 of 8 patients with duodenogastric contrast reflux, gastritis findings accompanied by gastric bile staining were present. However, it is noticeable, that in 50% of the patients with duodenogastric reflux chemical gastritis was present.

We suppose that even though bile gastritis was not diagnosed via upper endoscopy, bile might be the underlying cause of diagnosed chemical gastritis in at least some patients with duodenogastric contrast reflux. However, since bile reflux and, thus, contrast reflux into the stomach can occur physiologically, other causes of chemical gastritis could not be excluded at this point, in particular, since agents such as NSAID are widely used in the population. In addition, there was also a high prevalance of chemical gastritis among the

reflux, negative patients. Moreover, it was beyond the scope of this study to assess the diagnostic performance of MRI in bile gastritis but rather to raise awareness of duodenogastric contrast reflux which previously has been shown to be indicative of bile reflux (22).

Previous studies revealed a prevalence of 10% for bile reflux during upper endoscopy with much higher ratios of up to 80-90% after cholecystectomy (6,23). This could be both associated with increased bile flow to the duodenum owing to the lack of bile reservoir after cholecystectomy and the impairment of gastroduodenal motility (23,24). While none of our patients had undergone gastric surgery, 8 patients had cholecystectomy. In 1 of the 8 patients (12.5%) with cholecystectomy, bile reflux was detected during upper endoscopy, and in 2 patients (25%) duodenogastric contrast reflux was observed on MRI.

In our study, each patient with duodenogastric contrast reflux had chronic liver disease. Chronic liver disease is known to cause gastric paresis, and thus, duodenogastric contrast reflux might also be due to duodenogastric motility impairment (25). However, we could not presume any reliable potential association, since chronic liver disease was the most frequent diagnosis also in patients without contrast reflux.

Study Limitations

Our study has several limitations. First, this was a retrospective study. Thus, the endoscopic procedure was not standardized, and with respect to MRI, time delay after contrast injection in delayed phase imaging varied between patients. However, we included only MRI studies with a minimum delay of 40 minutes for delayed phase imaging, considering that gadoxetic acid is expected to extend to the distal common hepatic duct during the hepatobiliary phase with a progressive filling of the duodenum in delayed phases (>30 min). Consistently, we observed that duodenogastric contrast reflux occurred more frequently in delayed phase images without being apparent in the hepatobiliary phase. Second, the sample size was small. Third, we could not obtain sufficient information regarding the clinical symptoms and current or previous medication of the patients which might have induced chemical gastritis. Forth, since hepatobiliary scintigraphy or other diagnostic methods for bile reflux were not performed in our patients, diagnosis of bile reflux was limited to upper endoscopy results. Thus, we could not assess the diagnostic utility of MRI in bile reflux nor the patient-specific clinical relevance of contrast reflux. However, we could prove the existence of this finding, which, if it is being reported, might prompt a more detailed investigation for bile reflux and gastritis.

Conclusion

It might be challenging to differentiate bile-induced gastritis from other types of chemical gastritis, particularly if gastric bile stain is not observed during upper endoscopy. Thus, radiologists should be aware of duodenogastric gadoxetic acid reflux on delayed phase MRI and report this finding to support the gastroenterologist in the search for the underlying cause of gastritis. We suggest that the diagnostic performance of MRI regarding bile reflux and bile gastritis should be investigated with a multidisciplinary prospective study design.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Ankara University Human Research Ethics Committee (approval no: İ10-644-21, date: 02.12.2021).

Informed Consent: Retrospective observational study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: M.K., A.E., Design: M.K., A.E., Data Collection and Processing: M.K., D.K.Ö., O.A., A.E., Analysis or Interpretation: M.K., D.K.Ö., Literature Search: M.K., Writing: M.K., D.K.Ö.

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