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Endoscopic retrograde cholangiography does not reliably distinguish IgG4-associated cholangitis from PSC or cholangiocarcinoma

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Abstract

BACKGROUND & AIMS—Distinction of IgG4-associated cholangitis (IAC) from primary sclerosing cholangitis (PSC) or cholangiocarcinoma is challenging. We aimed to assess the performance characteristics of endoscopic retrograde cholangiography (ERC) for the diagnosis of IAC.

METHODS—Seventeen physicians from centers in USA, Japan, and UK, unaware of other clinical data, reviewed 40 preselected ERCs of patients with IAC (n=20), PSC (n=10), and cholangiocarcinoma (n=10). The performance characteristics of ERC for IAC diagnosis, as well as the kappa statistic for intra- and inter-observer agreement, were calculated.

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RESULTS—The overall specificity, sensitivity, and interobserver agreement for the diagnosis of IAC were 88%, 45%, and 0.18 respectively. Reviewer origin, specialty, or years of experience had no statistically significant effect on reporting success ($p>0.05$). The overall intraobserver agreement was fair (0.74). The operating characteristics of different ERC features for the diagnosis of IAC were poor.

CONCLUSION—Despite high specificity of ERC for diagnosing IAC, sensitivity is poor, suggesting that many patients with IAC may be misdiagnosed with PSC or cholangiocarcinoma. Additional diagnostic strategies are likely to be vital in distinguishing these diseases.

Keywords

IgG4-associated cholangitis; endoscopic retrograde cholangiopancreatography; immunoglobulin G4; autoimmune pancreatitis

Introduction

IgG4-associated cholangitis (IAC) is a steroid-responsive, fibroinflammatory biliary disease, which is considered as part of a systemic disease involving a range of organs (immunoglobulin G4 (IgG4)-associated systemic disease) ^{1–4}. Although previous studies have reported that cholangiography alone or in combination with other clinical data may allow differentiation of IAC from primary sclerosing cholangitis (PSC), ^{5–7} in clinical practice discrimination between these two conditions is often very challenging. In addition, the common presence of an inflammatory mass lesion and hilar stricturing in IAC makes differentiation from cholangiocarcinoma particularly difficult ^{2, 4, 8, 9}.

The principal aim of the current study was to evaluate the performance characteristics of endoscopic retrograde cholangiography (ERC) for the diagnosis of IAC.

Methods

ERCs (n=104) from histologically and/or clinically confirmed cases of IAC, PSC, and cholangiocarcinoma were solicited from participating centers in the UK, Japan, and USA. The ERC images were screened for quality by an experienced endoscopist (GJW) unaware of the clinical diagnoses. A final set of 48 good-quality ERCs (20 IAC, 10 PSC, 10 cholangiocarcinoma, and 8 internal IAC duplicates) were selected by the lead author (EK). The diagnosis of IAC had been made using the HISORT criteria for IAC ⁸ and all ERCs of IAC cases were obtained prior to any steroid therapy. All the cholangiocarcinomas (hilar or distal) had had a tissue diagnosis and typical clinical course. The diagnosis of PSC had been based on characteristic cholangiography features ^{10, 11} and typical histopathologic features on liver biopsy in all patients. The 48 images were shuffled, and a random number generator was used to generate numbers for the images. The final set of images was sent to 17 physicians in the UK (n=7), USA (n=4), and Japan (n=6) by e-mail (Figure 1). Readers were not aware of any clinical data, underlying diagnoses, or the relative frequency of each diagnosis within the image set. The lead author (EK) did not interpret images.

Each physician completed a data abstraction sheet (supplementary data file 1) on each image. In short, the presence of single or multiple strictures, stricture location and length, as well as prestenotic dilatation were evaluated ^{5, 6}. Four features known to be commonly associated mainly with PSC (beading, diverticulum-like outpouchings, shaggy bile duct appearance, pruned peripheral duct appearance) ^{10, 11} were also recorded. During this retrospective review of images, physicians were asked to provide the most probable diagnoses based on ERC findings. Up to 3 diagnoses could be listed by percentage

confidence. The sum of the confidences had to add up to 100%. To be considered a correct interpretation a given ERC had to be read with at least 75% confidence for that condition¹².

Statistics

The sensitivity, specificity and kappa statistic for inter- and intra-observer agreement for the diagnosis IAC were calculated. The sensitivity and specificity are in reference to the external gold standard (HISORt criteria for IAC, tissue diagnosis for cholangiocarcinoma, and tissue diagnosis as well as cholangiographic appearance for PSC). In addition the sensitivity and specificity of specific ERC features for IAC (each one alone or in differing combinations) was computed. Likelihood ratios for positive and negative test results were calculated¹³. Data are presented as mean and 95% confidence intervals (CI). Groups were compared by means of the Mann-Whitney test. A p-value < 0.05 was considered statistically significant.

Results

Performance characteristics of ERC for the diagnosis of IAC

The specificity of ERC for detecting IAC was high (88–90%), but sensitivity was uniformly low (42–51%), without any significant differences between centers (table 1). Similar results were obtained after taking into consideration correct image interpretations even if they were read with <75% of confidence (data not shown). Intra-observer agreement was fair and inter-observer agreement was poor (table 1), indicating that although different readers did not frequently assign the diagnosis of IAC to the same images, each single reader agreed more commonly with their previous assignment of the diagnosis of IAC (on duplicate images). Neither stratification according to specialty nor according to experience revealed any significant differences (Supplementary file 2).

Performance characteristics of specific ERC features for the diagnosis of IAC

No single ERC feature showed satisfactory operating characteristics to be used as a single criterion for the diagnosis of IAC (supplementary file 3). The likelihood ratios for the presence of IAC according to any cholangiographic feature were low (generally between 1 and 2) whereas the likelihood ratios for the absence of IAC were high (generally between 0.5 and 1), further indicating that no cholangiographic feature may be used to rule in or exclude the disease. Segmental or long biliary strictures as well as isolated strictures with prestenotic dilatation showed a high sensitivity but a low specificity for the diagnosis of IAC. The presence or absence of ERC features of beading, diverticulum-like formations, shaggy bile duct, and pruned-tree appearance showed fair specificity (68%–79%) but low sensitivity (supplementary file 3).

Discussion

IgG4-associated cholangitis is a recently described disease⁴ with the HISORt criteria for IAC being published only in 2008⁸. Although the presence of biliary stricturing is a prerequisite for the diagnosis of IAC to be considered⁸, to date, the performance characteristics of ERC in IAC have not been systematically studied.

We found that the use of ERC alone to diagnose IAC and differentiate it from other important alternative diagnoses was uniformly poor. This is despite the fact that the centers and clinicians involved in this study have been at the forefront of reporting and managing this disease. The overall sensitivity of ERC for IAC was particularly low. This suggests that many patients with IAC may be misdiagnosed as having PSC or cholangiocarcinoma. In a review of 185 patients who underwent major liver resections for presumed hilar

cholangiocarcinoma, Erdogan et al⁹ reported that 17% had no evidence of malignancy, and of these nearly 50% had histological features consistent with IAC. Conversely, increased clinical awareness of IAC also runs the risk of false negative diagnoses of malignancy being made, particularly if based solely on cholangiography. Where any clinical doubt exists a pathological diagnosis (of malignancy, IAC or PSC) should be intensively sought.

Despite the overall poor performance of ERC for the diagnosis of IAC, specificity was good, suggesting that particular ERC features might support the diagnosis. According to previously published data, lower common bile duct strictures and segmental or long strictures⁵⁻⁷ with prestenotic dilatation⁵ are more common in IAC compared to PSC. In our study segmental and long strictures, as well as isolated strictures with prestenotic dilatation, had high sensitivity but poor specificity for IAC. In clinical practice, however, isolated low common bile duct strictures are more likely to be due to other benign (e.g. chronic pancreatitis) or malignant (e.g. pancreatic cancer) aetiologies, rather than IAC. Overall no cholangiographic feature could be used to reliably rule in or rule out the diagnosis of IAC as all had likelihood ratios close to 1. It appears that the high specificity of ERC for IAC results from the amalgamation of a range of cholangiographic features, rather than an isolated abnormality.

The inability in our study to reliably differentiate IAC from PSC based on cholangiography alone contrasts with the report of Nakazawa et al⁵. An explanation for this may be that in their study the diagnoses were determined by consensus between two radiologists, and the operating characteristics of cholangiography for the diagnosis of IAC were not specifically evaluated⁵. Nevertheless, it is of note that cholangiographic features that have been thought to be specific for PSC^{10, 11}, were found to have fair specificity (albeit poor sensitivity) for IAC. These findings contribute to an accumulating body of evidence indicating a potential overlap between IAC and PSC¹⁴.

Our findings support the conclusion of Nishino et al that cholangiographic features alone cannot be used to reliably differentiate IAC from PSC⁶. In clinical practice, is it important to distinguish between IAC and PSC? There appear to be differing frequencies of extra-biliary disease, which may affect management. Favorable clinical and cholangiographic responses to steroids may be seen in patients with IAC^{4, 8, 15}, but not in those with PSC¹⁶. The finding that in patients with PSC and raised levels of serum¹⁷ and intrahepatic¹⁸ IgG4 the disease progresses more rapidly to a need for liver transplantation is intriguing. It has not been established whether steroid therapy would benefit the disease course in these patients.

The main limitation of our study is that participants were deliberately not provided any other information about the patients. In clinical practice, physicians would usually have access to patient information, including clinical presentation, previous medical history, and findings on imaging. This may be particularly important in the diagnosis of IAC, in whom imaging and pathological evidence of autoimmune pancreatitis and extra-biliary evidence of IgG4-associated systemic disease may greatly support the diagnosis.

In conclusion, this multicenter study shows that the performance of ERC alone for the diagnosis of IAC is uniformly poor. Additional diagnostic strategies, including aggressive attempts to achieve a pathological diagnosis, are likely to be vital in distinguishing these diseases, and so defining optimal management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

IAC	IgG4-associated cholangitis
IgG4	immunoglobulin G4
AIP	autoimmune pancreatitis
PSC	primary sclerosing cholangitis
ERC	endoscopic retrograde cholangiography
CI	confidence interval

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Figure 1.
Examples of endoscopic retrograde cholangiograms of IgG4-associated cholangitis (A), primary sclerosing cholangitis (B), and cholangiocarcinoma (C) used in the study.

Table 1

ERC performance characteristics and inter- and intra-observer agreement for the diagnosis of IAC

	All n=17	USA n=4	UK n=7	Japan n=6
Sensitivity (95% CI)	45% (36–54%)	51% (25–78%)	42% (25–59%)	44% (24–64%)
Specificity (95% CI)	88% (83–93%)	88% (68–100%)	86% (77–95%)	90% (82–98%)
Interobserver agreement for IAC (kappa)	0.18	–0.02	0.18	0.17
Intraobserver agreement for IAC (kappa)	0.74	0.69	0.76	0.75

ERC, endoscopic retrograde cholangiogram; IAC, IgG4-associate cholangitis; CI, confidence interval

No statistically significant differences were detected between groups ($p>0.05$)