Differentiating IgG4-related Sclerosing Cholangiopathy from Cholangiocarcinoma using CT and MRI - Experience from a Tertiary Referring Center

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ABSTRACT

Purpose: To compare the cross-sectional imaging findings of IgG4-related Sclerosing Cholangiopathy (IgG4-SC) and Cholangiocarcinoma (CCA).

Methods: Retrospective search of radiology and pathology databases identified 24 patients with IgG4-SCand over 500 patients with CCA from January 2009 to December 2016. Patients with no pre-treatment imaging studies available on PACS, non-contrasted imaging only, presence of mass lesions, metastatic disease or biliary stents were excluded. 17 patients with IgG4-SC and a selected group of 20 (age and gender matched) patients with CCA were obtained. Images were blinded and independently reviewed by two radiologists. Differences in proportions and means between groups were analyzed using Fishers and Mann-Whitney tests respectively.

Results: Both readers identified a statistically significant difference in the presence of abrupt common bile duct narrowing between IgG4-SC and CCA (6.7% vs 68.4%, $p<0.001$; 33.3% vs 75%, $p=0.019$). No difference was seen in biliary wall thickening, wall enhancement, extrahepatic exclusive location of disease, or pancreatic duct dilation. Inter-observer variability was kappa = 0.52. Total bilirubin and CA 19-9 were unable to differentiate between IgG4-SC and CCA. Serum IgG4 was positive in 2 of 6 IgG4-SC patients who were tested.

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Conclusion: IgG4-SC and CCA share many clinical and imaging findings on CT and MRI. Abrupt bile duct cut sign strongly favors CCA. In the absence of this finding, IgG4-SC should be considered in the differential diagnosis in all cases of suspected extrahepatic CCA.

Key words:

IgG4-related sclerosing cholangiopathy, autoimmune, cholangiocarcinoma, MRI, CT

INTRODUCTION

Immunoglobulin G4 related pathologies are known to occur throughout the body [1-3], leading to a wide variety of symptoms and treatments depending on the organ involved. IgG4-related sclerosing cholangiopathy (IgG4-SC) is an IgG4 related condition for which multiple different terminologies are used, including autoimmune sclerosing cholangitis (AISC). IgG4-SC has been described in radiology and clinical literature as having certain suggestive radiologic features [4,5], but also demonstrating overlap with hilar and extrahepatic cholangiocarcinoma (CCA), as well as primary sclerosing cholangitis (PSC) [6-9]. Case reports [10] and experience at our institution have shown that differentiating between IgG4-SC and CCA can be difficult radiologically and clinically, which can lead to challenges in patient management.

Patients with IgG4-SC are classically male, often in the 6^{th} or 7^{th} decade of life, presenting with vague symptoms and/or elevated of bilirubin or jaundice [11]. It is thought to be the most common extra-pancreatic manifestation of patients with autoimmune pancreatitis (AIP), with up to 70 percent of patients with type 1 AIP demonstrating some changes in the biliary tree [12]. IgG4-SC is a rare condition, with limited epidemiologic data available. Data from Japan in 2011 suggests annual incidence of 1.4/100,000 and prevalence of 4.6/100,000 [13]. Steroids are the mainstay of treatment of both AIP and IgG4-SC, and generally the overall prognosis is favorable. [13]. Patients can manifest IgG4-SC without obvious findings of AIP, however, and in these cases the radiologic and clinical overlap with hilar or extrahepatic cholangiocarcinoma can be especially striking.

This overlap presents a challenge for the radiologist. Cholangiocarcinoma is a varied and often aggressive malignancy, and successful treatment depends on accurate and early diagnosis followed by aggressive surgical resection. Even with surgery, five year survival rates are less

than 50 percent [14]. The striking dichotomy for medical professionals comes from this major difference in treatment and prognosis between IgG4-SC and CCA. Correctly identifying patients with IgG4-SC could help avoid more aggressive therapies and the associated morbidity.

Current literature, especially on the North American population with IgG4-SC, is limited and without consensus on this issue. The purpose of this study was to report our experience from a tertiary referring center for hepatobiliary diseases, specifically to compare the cross-sectional imaging findings of IgG4-SC and CCA, and to ascertain the ability of radiologists to differentiate these entities.

MATERIALS AND METHODS

Following obtaining a waiver from the institutional review board, a retrospective evaluation was performed by searching the radiology and pathology databases from 2010-2017 to identify patients with histologically proven cases of IgG4-SC. Histopathologic diagnosis was confirmed in patients by staining tissue samples with IgG4. These samples were obtained either from endoscopic biopsy or from surgical specimens obtained after initial imaging. Conflicting data exists regarding the cutoff value for a positive stain. Published consensus data suggests a cutoff value of 10 IgG4 positive cells per high powered field, while also stating that the IgG4/IgG plasma cell ratio may be a more powerful tool in establishing the diagnosis [15]. Since this ratio is not routinely performed at our institution, the cutoff value was utilized in identifying patients.

This initial search yielded 24 patients with a diagnosis of IgG4-SC, and CT or MRI scans of these patients were identified. Patients were referred for imaging either by a primary care

physician or gastroenterologist. MRI/MRCP imaging protocol is described in Table 1. CT imaging was performed utilizing either single or multiphasic technique. Intravenous contrast was give n in all patients using a power injector. Isotopic reconstructions were performed in coronal and sagittal planes. These scans were then reviewed, and the patients who had only non-contrast exams, hepatic or other metastatic disease, and those patients who already had biliary stents at the time of presentation were excluded, yielding a total of 17 patients with IgG4-SC.

Review of the pathology database identified over 500 patients with either biopsy or surgically proven CCA. CT and MRI scans were evaluated, and the same exclusion criteria were applied for this cohort as for the patients with IgG4-SC, yielding twenty age and gender matched subjects.

The anonymized images were reviewed in a blinded fashion by two fellowship trained staff radiologists with 16 and 7 years of experience. The readers were blinded to the electronic health record and did not know the serum levels of bilirubin, CA 19-9, and IgG4. The radiologists were tasked with evaluating the images for a number of specific criteria suggested by previous literature as possible differentiating features of IgG4-SC [16]. Data was collected on the location of the dominant biliary stricture, if the stricture was smooth or abrupt, the subjective degree of biliary enhancement as compared to the liver maximum bile duct wall thickness and presence or absence of pancreatic duct dilation.

Differences in proportions and means between groups were analyzed using Fishers and Mann-Whitney tests respectively. Inter-observer variability was assessed with Cohen's kappa test. If the resulting P value is <0.05, a statistically significant difference between the two samples was accepted. Statistical analyses were performed using MedCalc version 18.11.3 (MedCalc Software, Mariakerke, Belgium).

RESULTS

The mean ages of the IgG4-SC and CCA groups were 62.2 and 69.6 years (p=0.09). There were 12/17 males in the IgG4-SCand 10/20 males in the CCA cohorts (p=0.43). All of the imaging features examined are listed in Table 2. Only the abrupt bile duct cutoff demonstrated a statistically significant difference between IgG4-SC and CCA (Reader 1: 6.7% compared to 68.4%, p<0.001) (Reader 2: 33.3% vs 75%, p=0.019) [Figures 1 and 2]. Patients with IgG4-SC demonstrated a gradual or funneled change in duct caliber significantly more often than patients with CCA (Reader 1: 93.3% compared to 31.6%, p<0.001) (Reader 2: 66.7% compared to 25%, p=0.019). Inter-observer variability for these findings was kappa=0.52.

For both readers, there was no statistically significant difference between IgG4-SC and CCA when comparing whether extrahepatic biliary disease alone was present. The degree of biliary enhancement as compared to background liver was similarly not significant. In addition, the maximum thickness of the bile duct wall and the presence of main pancreatic duct dilation were not significantly different between the two cohorts (Table 2).

Evaluation of biochemical markers of disease between IgG4-SC and CCA also did not demonstrate a significant difference. Total serum bilirubin at time of presentation in mg/dl (7.9 compared to 12.8, p=0.17) and CA 19-9 in U/mL (233.8 compared to 102.8 p=0.20) were evaluated quantitatively. Serum IgG4 levels were only drawn at the time of presentation in six of the IgG4-SC patients, and were only positive in two cases.

DISCUSSION

Our work was designed to retrospectively evaluate the ability of CT and MRI to differentiate IgG4-related sclerosing cholangiopathy from hilar and extrahepatic cholangiocarcinoma. Previous work on this subject predominately from outside the North American population has suggested a number of radiologic features that may be more specific for IgG4-SC than other disease entities, including potential ways to isolate it from cases of CCA [4,5,6,8,16,17]. Our work did not recapitulate the majority of these findings, with the important exception of gradual tapering at the site of bile duct stricture being a statistically significant hallmark of IgG4-SC. This has been described as a "funnel" appearance of the common bile duct.

Other possible differentiating features did not reach the level of statistical significance in our exam. Importantly, we did not find that the degree of enhancement of the biliary wall or the thickness of the biliary wall provided benefit in separating cases of IgG4-SC and CCA. Also of interest was the lack of a significant difference between which disease process showed dilation of the main pancreatic duct. This was used as an adjunct for involvement of the pancreatic head by disease, something that has been described in AIP and other literature on IgG4-SC [2].

Evaluation of biochemical features of the cases was also illuminating. Interrogation of serum bilirubin and CA 19-9 levels at the time of CT or MRI also did not demonstrate a significant difference between cases of IgG4-SC and CCA. Levels of CA 19-9 are not clinically specific for CCA [18] so this finding is less unexpected.

Taken together, the findings in our work highlight the difficulty of reliably differentiating IgG4-SC from CCA in practice of radiology and medicine. Gradual bile duct tapering appears to be a prevalent sign in cases of IgG4-SC, but alone is far from enough to allow for consistent

differentiation from CCA. And given the uncommon nature of IgG4-SC, it is unlikely that most radiologists, surgeons, and gastroenterologists will be exposed to a large number of cases that would help them consider the diagnosis in a patient's initial workup. Only four of the 17 IgG4-SC patients in our study had serum IgG4 levels drawn prior to diagnosis, which highlights how infrequently IgG4-SC is considered before tissue sampling is performed.

These difficulties and the lack of consensus in the literature present a challenge in approaching possible cases of IgG4-SC and CCA. Clearly, in cases of underlying hepatic or hilar mass or suspicious abdominal adenopathy, CCA presents itself more clearly. An abrupt cutoff of the common bile duct in the absence of these findings is also concerning. But there is enough overlap in presenting complaints and radiology findings between these two disease entities that IgG4-SC should always be considered in cases of possible CCA. Conversations with referring hepatic surgeons and gastroenterologists may assist in these cases as well, to help decide on which patients may benefit from tissue sampling for IgG4 staining.

This has led to the creation of more holistic guidelines for the diagnosis of IgG4-SC such as the HISORt criteria from Mayo Clinic [11] and separate criteria from Japanese working groups [19]. These rely on radiologic and clinical data, and in some cases suggest trials of steroid therapy in patients who have findings suggestive of IgG4-SC. This alone can be another diagnostic feature, as effectiveness of steroid therapy is used as another optional diagnostic criterion in the Japanese schema.

The study is limited by its retrospective nature and relatively low number of patients. However, this is not atypical for studies involving IgG4-SC, given its relatively rarity and underlying challenges in diagnosis, and in fact our study includes more patients than previous reports [4.8]. The study also included a mix of CT and MRI studies in different patients, which

while realistic in clinical practice does limit the study's ability to differentiate between the ability of one modality or the other to provide more information.

In conclusion, our study showed the presence of a gradually tapering stricture, as opposed to an abrupt cutoff of the common bile duct can serve as a significant differentiator between these disease entities. However, challenges inherent in differentiating IgG4-SC from CCA remain, and an interdisciplinary approach to these cases may benefit patient care. IgG4-SC should be considered in the differential diagnosis in patients being evaluated for CCA without evidence of a mass

TABLES

Table 1. Representative MRI/MRCP image acquisition parameters

PARAMETER	AX HASTE FS	AX T1 VIBE DIXON	Coronal HASTE	AX T1 VIBE FS	Ax Test Bolus	AX T1 VIBE FS+C	Radial HASTE Slab	Coronal T2 3D SPACE	Coronal HASTE slab (Secretin)
PULSE SEQ	HASTE*	VIBE** DIXON	HASTE	VIBE	3D FLASH	VIBE	HASTE	SPACE+	HASTE
# of slices	36	52	30	88	1	88	8	64	1
TE	90	Min 2.39	90	1.78	1.32	1.78	756	698	603
TR	1400	Min 6.7	1400	3.75	34.66	3.75	2000	2400	4500
FOV	360	360	360	360	450	360	290	360	300
MATRIX	320/60%	320/65%	320/60%	256/75%	256/96%	256/75%	256/100%	384/98%	384/70%
Sat	FatSat	Dixon		FatSat		FatSat	FatSat	FatSat	FatSat

* HASTE- Half Fourier single shot turbo spin echo

** VIBE- Volumetric interpolated breath-hold examination

+ SPACE- Sampling perfection with application optimized contrasts using different flip angle evolution

Table 2. Imaging and biochemical findings in IgG4-related sclerosing cholangiopathy (IgG4-SC) and cholangiocarcinoma (CCA) cohorts.

	READER 1			***READER 2***		
	IgG4-SC	**CCA**	**p**	**IgG4-SC**	**CCA**	**p**
CT, MRI and ERCP exams reviewed (n)	18	26		18	26	
Total bilirubin at presentation (mg/dL)	7.9	12.8	0.17			
CA 19-9 (U/mL)	233.8	102.8	0.2			
Extrahepatic duct disease only	10 (71%)	16 (84%)	0.38	12 (80%)	17 (85%)	1.0
Abrupt bile duct stricture	1 (7%)	13 (68%)	<0.001	5 (33%)	15 (75%)	0.019
Enhancement of bile duct wall (†)	14 (93%)	16 (80%)	0.27	14 (93%)	19 (95%)	1.0
Maximum thickness of bile duct wall (mm)	3.5	3.7	0.74	2.5	2.2	0.78
Pancreatic duct dilation	4 (27%)	3 (15%)	0.4	2 (13%)	2 (10%)	1.0

(**†**) enhancement as much or more than the liver

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FIGURES

Figure 1a. Coronal CT of a patient with IgG4-SC. Arrows demonstrate gradual, funnel-shaped narrowing of the proximal common bile duct.

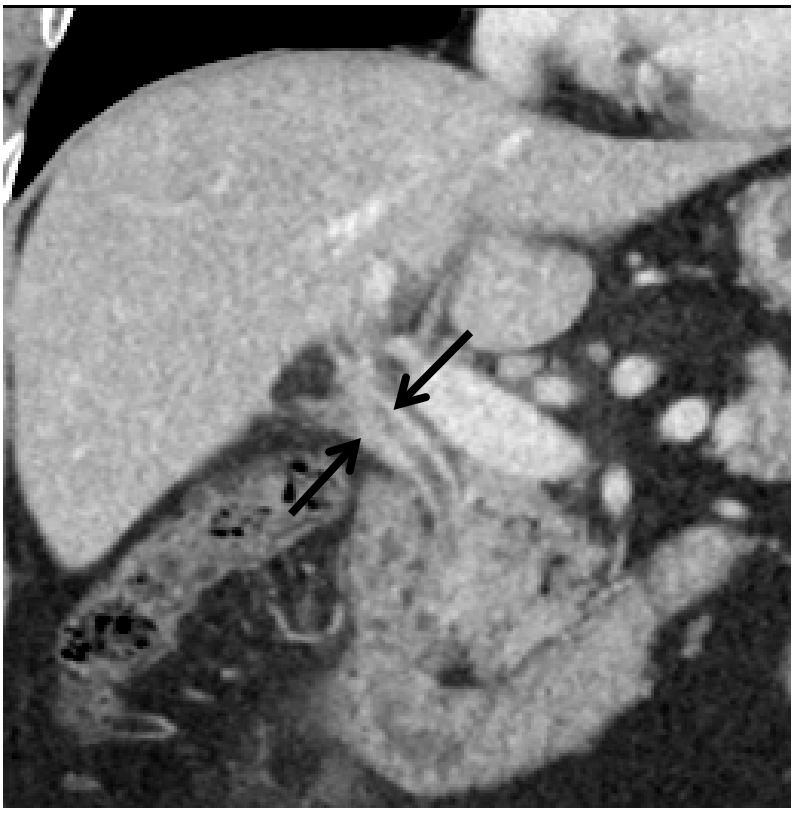

Figure 1b. Coronal T2 HASTE MRI sequence of a different patient with IgG4-SC. Again note the gradual narrowing of the upstream common bile duct (arrow).

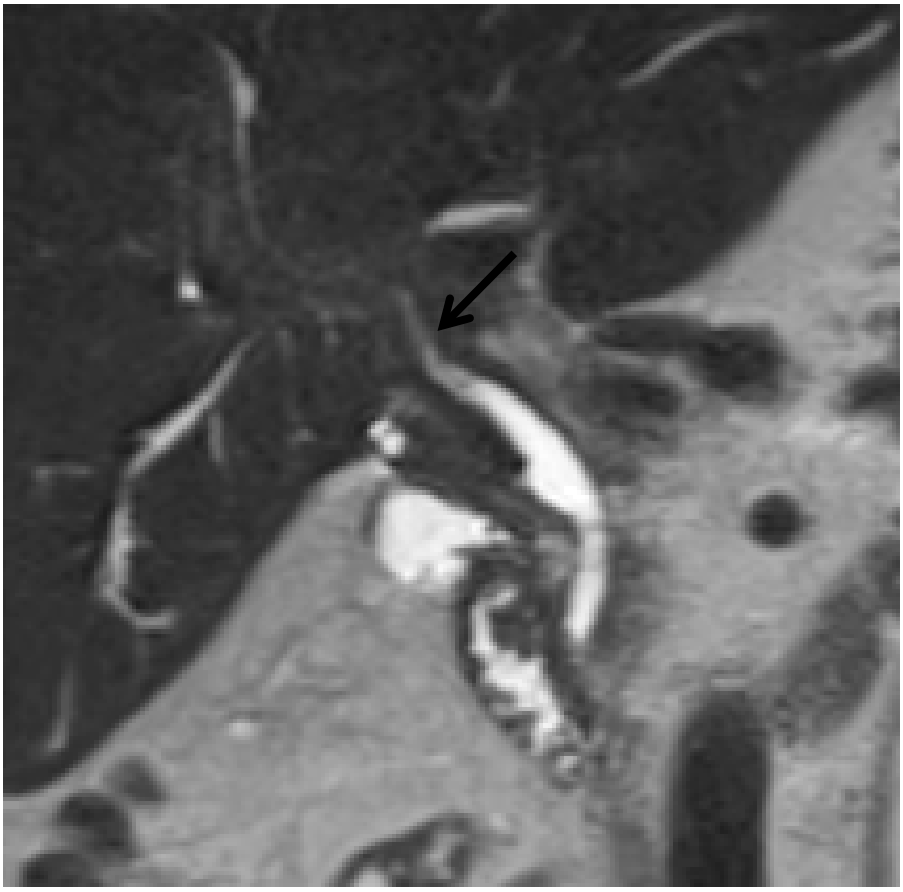

Figure 1c. Axial T1 VIBE post contrast image demonstrating gradual narrowing of the common bile duct at the hepatic hilum (arrow). Periductal wall thickening and enhancement are also noted.

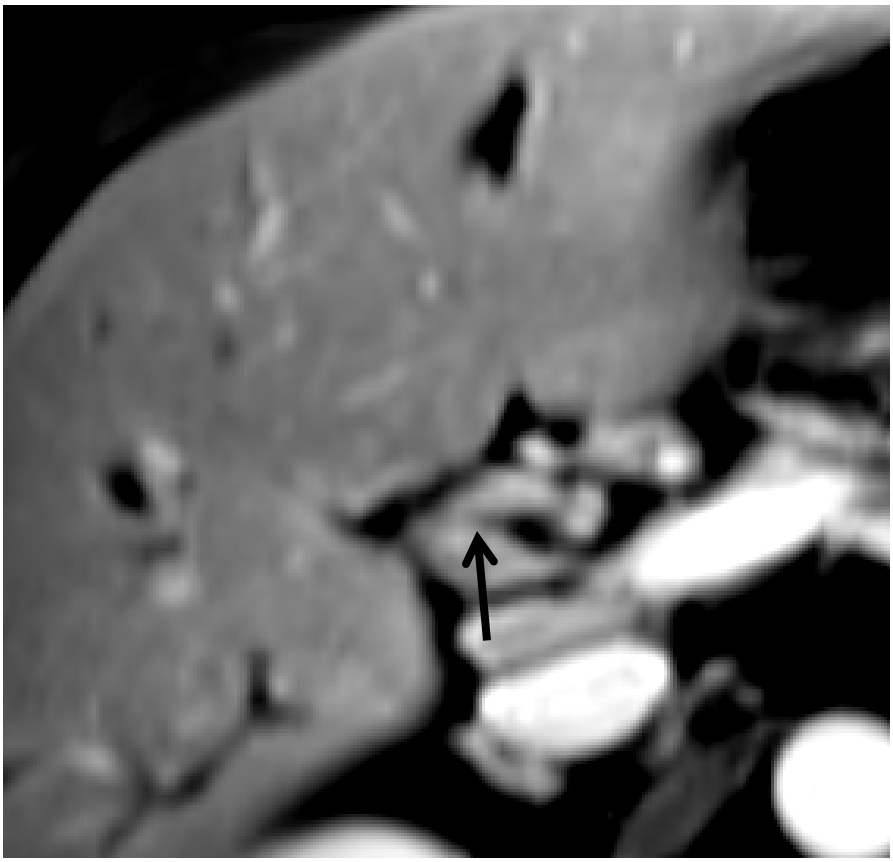

Figure 2. Radial 2D Slab MRCP image from a patient with CCA. Note the abrupt cutoff of the common bile duct (arrow) with an irregular structure between. (GB=gallbladder)