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Igg4 Related Sclerosing Disease Masquerading as Primary Malignancies –Role of Cross-Sectional Imaging in Hepatobiliary and Pancreatic Manifestations

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Abstract

Background and objectives: IgG4-related disease is rare multisystem disorder mimicking inflammatory and neoplastic process and is underreported disorder due to lack of awareness. This study aims to discusses the intra-abdominal manifestations of this disease on cross-sectional imaging which help to distinguish it from other major differentials.

Methods: A Cross sectional observational study (retrospective and prospective) was done in our department over a period of two years. Study population involved all patients in whom Cross sectional imaging of the abdomen was done (n = 1200). Out of these, patients with IgG4 disease as the final diagnosis (according to Japanese criteria) in whom Cross section abdominal imaging was done, were included in the study (n = 6). Serum IgG4 values taken. Final histopathological diagnosis was obtained.

Results: The Radiological diagnosis of these lesions was distributed as follows: Sclerosing cholangitis (n = 4); Hepatic involvement (n = 3); Gall bladder involvement (n = 1); Autoimmune pancreatitis (n = 1); Lymph nodal involvement (n = 3). All of lesions mentioned above showed fibrosis and immunohistochemistry features of IgG4 related disease on histopathology. All except one case had elevated Serum IgG4 levels.

Conclusions: Due to the systemic nature of the disease, imaging workup of IgG4-related disease should always include whole-body examinations to detect multiple organ involvement. Although definitive diagnosis requires histopathologic analysis, the radiologists should be familiar with its clinical and imaging manifestations to avoid misdiagnosis and unnecessary surgical interventions thus improving the overall prognosis and clinical outcome of the patient.

Keywords: IgG4; cholangitis; pancreatitis; fibrosis, sclerosis

Introduction

Immunoglobulin G4 (IgG4)-related disease is a disorder with multiorgan involvement mimicking inflammatory and neoplastic processes. It is a recently proposed clinical-pathologic entity that consists of by fibro-inflammatory lesions rich in IgG4-positive plasma cells and often but not always, elevated serum IgG4 concentrations [1]. Its pathogenesis is poorly understood but are consistent with both an autoimmune and an allergic disorder. Due to the systemic nature of the disease, imaging workup of IgG4-related disease should always include whole-body examinations to detect multiple organ involvement. The pancreas is most commonly involved organ but has been described in various other organs including the biliary tree, orbits, lacrimal glands, salivary glands, lungs, kidneys, aorta, retroperitoneum, lymph nodes, pachymeninges, prostate and pituitary gland [2]. Although definitive diagnosis requires histopathologic analysis, the radiologists should be familiar with its clinical and imaging manifestations to avoid misdiagnosis and unnecessary surgical interventions [1].

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Literature Review

Epidemology

Only little Epidemiologic understanding of IgG4-related disease is known due to insufficient awareness of the diagnosis and its only recent appearance in the medical literature. It is observed that IgG4-RD usually affects individuals of middle to upper age, with an onset at 50–70 years, although rare pediatric cases have been described in some studies [3]. The higher disease prevalence in the male population is higher in this spectrum in contrast to other autoimmune diseases hallmarked by female. However, this difference in manifestation between the two sexes are unclear [4]. Male predominance is much more seen in disease involving the kidney and retroperitoneum, with reported prevalence as high as 90%. However, IgG4-related sialadenitis and dacryoadenitis have been frequently reported among females.

Pathogenesis

Our overall understanding of the pathogenesis of IgG4-related disease is vague and still to date immature in scientific studies, and there are findings consistent with both an autoimmune and an allergic disorder [4]. Possibly, environmental exposure could be important in disease initiation, but other triggers such as microbial antigens or auto-antigens could also contribute to the causation of the disease process. Few mechanisms have been studied in the pathogenesis of IgG4 related disorders. Identifying these mechanisms will possibly help to prevent irreversible tissue damage. The two prevailing theories underlying observed pathology include: 1) induction of a polarized CD4 + T cell that activates innate immune cells responsible for the development of fibrosis; 2) a negative feedback process involving generation of IgG4 secreting plasmablasts, plasma cells, and IgG4 antibodies responsible for preventing autoimmunity. Autoimmunity has been hypothesized to be a potential initial immunologic stimulus for the Th2-cell response in IgG4 related disease [5]. The Japanese group [6] proposed three major diagnostic criteria for practical use as shown in Table 1. Because clinical symptoms and pathologic features depend on the location of the lesion, it is very challenging to establish criteria that include all patients with IgG4-related disease. The above-mentioned diagnostic criteria are not organ specific but are intended to help physicians differentiate IgG4-related disease from other inflammatory or malignant diseases [3].

Table 1. The proposed diagnostic criteria in IgG4 related disease.

(a) Clinical examination	Showing characteristic diffuse or localized swelling or masses in one or more organs.
(b) Hematologic examination	Showing elevated serum IgG4 concentrations (≥ 135 mg/dL).
(c) Histopathologic examination	Showing marked lymphoplasmacytic infiltration and storiform fibrosis, as well as organ infiltration by IgG4-positive plasma cells.

- *Diagnosis definite : If all three criteria are met*
- *Diagnosis probable : If clinical/imaging + HPE criteria are met*
- *Diagnosis possible : If the clinical/imaging + lab criteria are met*

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Histopathological features of IgG4-related disease

Histologic examination of biopsy specimens is observed to be the gold standard in diagnosing IgG4-related disease. The histopathological findings include a dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. The presence of these findings, with or without tissue eosinophilia, is strongly suggestive of IgG4-related disease [1]. Although IgG4-related disease has a highly characteristic histologic appearance, it cannot be definitively diagnosed without immunohistochemical staining for IgG4 [7]. However, it has been suggested that the disease is more suggestive if accompanied by increased numbers of IgG4-positive plasma cells in the form of dense infiltrates of IgG4-plasma cells (> 10–50 per high-power microscopic field), depending on the affected organ are highly specific for IgG4-related disease [4,8]. A ratio of IgG4-positive to IgG-positive plasma cells higher than 40% is also helpful in distinguishing between IgG4-related disease and non-IgG4-related inflammatory conditions [6,8]. Elevated serum IgG4 concentration is common but not specific for IgG4-related disease. On the other hand, serum IgG4 concentration may be normal in sizeable minority of cases which are classical biopsy- proved IgG4-related disease [4,8]. Thus, neither an increase in serum IgG4 concentration nor an elevated number of IgG4-positive plasma cells in tissue is specific for IgG4-related disease [8]. Hence, the early diagnosis of the disease requires meticulous correlation with the histopathological features of the lesion along with its clinical and radiologic findings.

Role of Imaging

Radiologic imaging plays an important role even though definitive diagnosis of IgG4-related disease requires histopathology analysis, in demonstrating features suggestive of the diagnosis. Adequate Imaging workup for IgG4-related disease should include a CT scan of the chest, abdomen, and pelvis to identify possible multiorgan involvement. Cross sectional imaging, especially CT can supplement diagnostic criteria for IgG4-related disease. Key features can be seen based on the involved organ. In general, radiological studies will demonstrate infiltration and enlargement of involved organs. Other general radiologic features include glandular swelling, nodularity, organ wall thickening, fibrosis, and lymphadenopathy. Knowledge of the radiologic findings can help avoid delays in diagnosis, unnecessary surgical procedures, establish a biopsy site for histologic analysis, and allow for early diagnosis and management of the disease [4].

Methods and Methodology

Patients

This cross-sectional observational study (retrospective and prospective) was done in our department and approved by the Institute Ethics Committee, and that the need for informed consent from the patients was waived. In our investigation, study population involved all patients in whom cross sectional imaging of the abdomen was done (n = 1200). Patients referred to the department for such studies of contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) as well as patients in whom final diagnosis is available regarding the lesions were included. The final diagnosis in lesions were arrived at based on pathological diagnosis and serum IgG4 levels. Five patients with a histopathological diagnosis of IgG4 disease and elevated serum IgG4 levels were included, who received contrast-enhanced CT examination and surgical resection at

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SriRamachandra Institute of higher education and research. A convenient sampling method was used, and the study was done over a period of two years. Patients in whom final histopathology diagnosis and serum IgG4 level were not available, were excluded from the study. Extra hepatobiliary and pancreatic lesions were excluded from the study.

CT acquisition

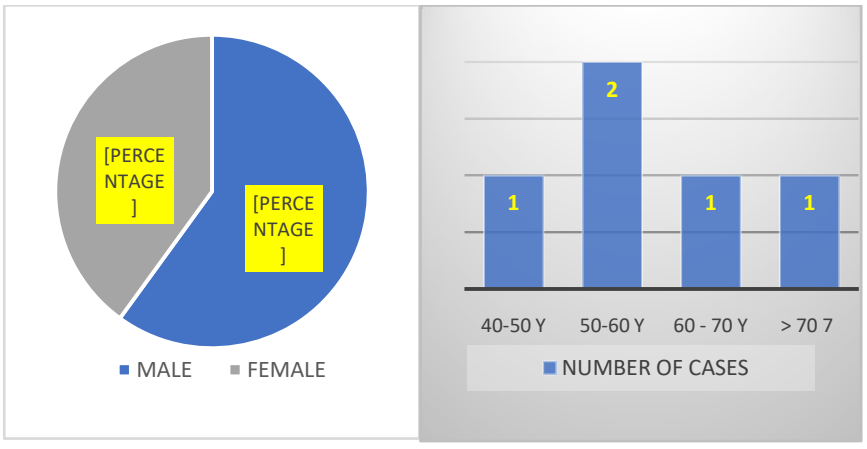
Contrast-enhanced CT examinations were performed using one of the following multislice computed tomography (MDCT) scanners: Phillips–brilliance 16 (Philips Medical Systems, Cleveland, USA); GE EVO evolution 128 slice (GE Healthcare, Princeton, USA). The patients were fasted for at least 8 h before examination. CT images were obtained during breath holding with the following parameters: 120 kV, 250 mA. The section thickness and reconstruction interval were 5.0 mm. An 80–100 mL dose of nonionic intravenous contrast material was administered with a power injector at a rate of 3.0 mL/s. Then, at 28 and 60 s after injection with the agent, contrast-enhanced scans in the arterial phase and portal venous phase were done. The CT scans were sent to a picture archiving and communication system (PACS) to be interpreted at workstations. Contrast-enhanced MR examinations were performed using one of the following MRI scanners: GE SignaHDxt 1.5 Tesla (GE Healthcare, Princeton, USA) or in Siemens Magneto Avanto 1.5 Tesla (Siemens, Forchheim, Germany).

Data / Image analysis

Abdominal CT and MRI scans of the five patients were read by two radiologists with three and ten years of experience, who were blinded to the pathological features. The maximum size, contour, boundary of the lesion with attention to the presence of strictures of the biliary tree, enlargement of involved organs, glandular swelling, nodularity, organ wall thickening, fibrosis, and lymphadenopathy, pattern of enhancement and enhancement degree were observed. Following this Histopathology and serum IgG4 levels were obrained for these cases were analysed.

Results

Demographic Details



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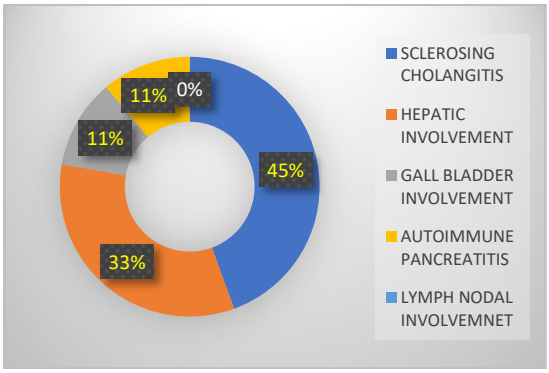
The radiological diagnosis of these lesions was distributed as follows:



Sclerosing cholangitis (*n* = 4);
Hepatic involvement (*n* = 3);
Gall bladder involvement (*n* = 1);
Autoimmune pancreatitis (*n* = 1);
Lymph nodal involvement (*n* = 3)

All of lesions mentioned above showed fibrosis and immunohistochemistry features of IgG4 related disease on histopathology and elevated serum IgG4 levels (Table 2).

Table 2. Histopathological Examination details.

S.No.	Age / Sex	Radiology	Serum IgG4	Histopathological Examination
1.	50 / M	Sclerosing cholangitis with IHBR involvement -? IGG4	Elevated 2.9	Acute cholestatic hepatitis
2.	73 / F	Hepatobiliary, pancreatitis? IGG4	Elevated 3.1	Fibrotic process with inflammatory cells
3.	65 / F	Sclerosing cholangitis with chronic liver disease	Elevated 6.7	Chronic active hepatitis with cirrhosis - ? IgG4
4.	55 / M	Diffuse enhancing soft tissue mass involving the confluence of the cystic duct and the common hepatic duct	Elevated	Acute inflammatory process - ? igG4)
5.	43 / M	Cholangitis, mediastinitis ? IGG4	Elevated	Acute inflammatory process

Discussion

Recently, IgG4-related sclerosing disease has become an emergingclinico-radio-pathologic entity in the hepatobiliary and pancreatic sytem. The pathology includes diffuse or focal organ enlargement and mass forming or thickening lesions, caused by heavy infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis in various organs, which may lead to autoimmune pancreatitis, sclerosing cholangitis, cholecystitis orhepatopathy. However, the exact pathogenesis and patho-physiology of IgG4-related sclerosing disease remains unclear. IgG4

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sometimes mimicks malignancy both clinically and radiologically and must be included in the differentials when clinical and imaging features merits consideration.

Autoimmune Pancreatitis

The pancreas was the first organ recognized as related to IgG4 disease. Classic autoimmune pancreatitis presents with diffusely or focally enlarged pancreas [2-4]. In the last few years, clinical, laboratory, and histopathological analyses of several studies from revealed two different entities of AIP with distinct histopathology and clinical profiles [9]. Type-I autoimmune pancreatitis presents with mild abdominal pain, weight loss, and painless and often obstructive jaundice. It is characterized histopathologically by lymphoplasmacystic sclerosing pancreatitis. As widely reported, type-I AIP is considered an IgG4-related systemic disease with pancreatic and extrapancreatic involvement [9,11]. Type-II AIP has a histological pattern distinct from type-I, although they share some features. Periductal infiltrate is seen in both AIP subtypes; otherwise, diffuse inflammation, fibrosis, and phlebitis are less prominent in type-II. It presents with normal IgG4 serum levels and is considered a pancreas-specific disorder, except from the well-known association with inflammatory bowel diseases [9].

Specific imaging findings of autoimmune pancreatitis: A specific finding of autoimmune pancreatitis that has not been described in any other pancreatic disorder is a capsule like rim or halo of low attenuation surrounding the pancreas at contrast material-enhanced CT and MR imaging (Fig. 1C). This finding is presumed to represent a fluid collection, a phlegmon, or fibrosis. Autoimmune pancreatitis are Less likely to have pancreatic duct dilation than adenocarcinoma. Another imaging feature that helps us differentiate AIP from adenocarcinoma is Penetrating duct sign (Fig. 1C), whichis a feature of AIP pancreatitis [7,10]. The focal type usually presents in the pancreatic head (Fig. 1D) and is difficult to distinguish from Pancreatic Adenocarcinoma. However, they demonstrate delayed enhancement and greater restricted diffusion than Pancreatic Adenocarcinoma [11].

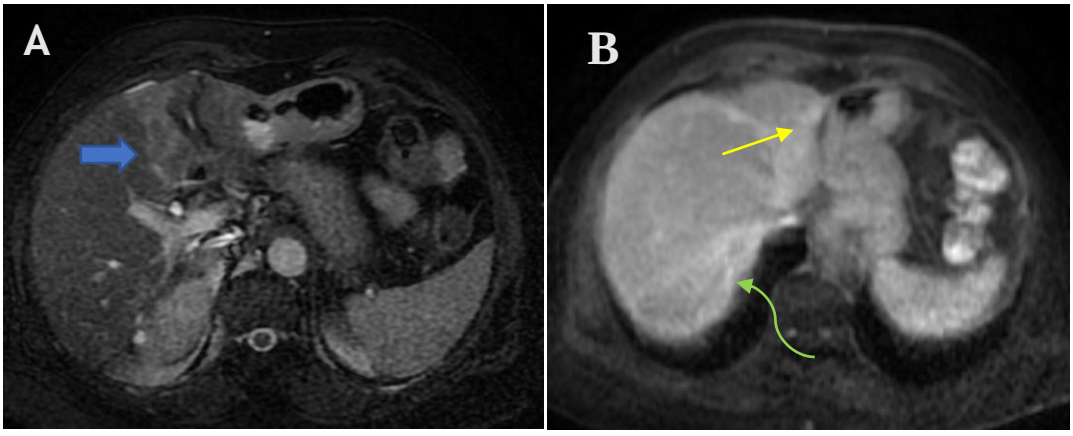

Figure 1A & 1B: A seventy-three-year-old female, presented with abdominal pain; Axial T2 W and post contrast axial T1 W MRI of the abdomen at the level of the liver shows ill defined T2 hyperintense lesion (block arrow) involving the left lobe of the liver which is seen to extend upto the capsule of the liver showing persistent progressive contrast enhancement (yellow arrow). Similar enhancing ill defined lesion is also seen involving the subcapsular region of right lobe of liver (curved arrow) involving segment VII extending upto the hilum of the liver.

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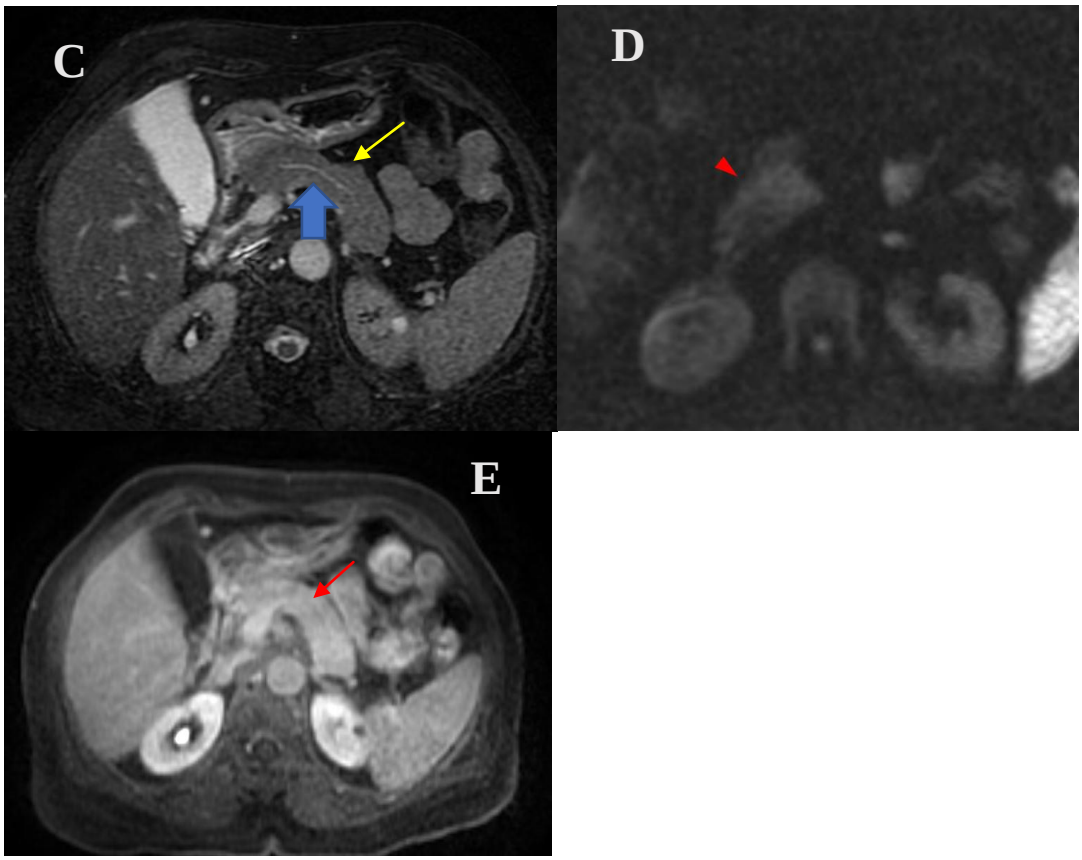

Figure 1C, 1D& 1E: A seventy-three-year-old female, presented with abdominal pain; Axial T2 W,DWI and post contrast axial T1 W MRI of the abdomen at the level of the pancreas shows sausage shaped bulky pancreas (yellow arrow) with diffusion restirction on DWI arrow head) showing heterogenous enhancement with few patchy areas of peristent enhancement (red arrow) predominantly in the tail of pancreas. There is mild irregularity of the pancreatic duct blue arrow) in the body and tail region of pancreas.

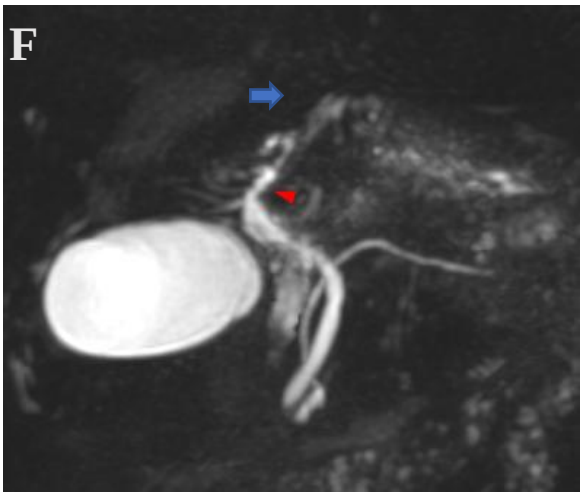

Figure 1F: A seventy-three-year-old female, presented with abdominal pain; Reformatted 3D-MRCP

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shows luminal irregularity with multiple areas of narrowing of the left hepatic duct (arrowhead) and left lobe intrahepatic biliary radicles giving beaded appearance (block arrow) representing chronic cholangitis.

IgG4-related sclerosing cholangitis

IgG4-related sclerosing cholangitis is commonly associated with type I autoimmune pancreatitis. If untreated, it can progress to end-stage liver disease and is extremely difficult to differentiate from primary sclerosing cholangitis. On, histopathology, obliterative phlebitis and transmural fibrosis. Dense infiltrates of IgG4-positive plasma cells and T cells can be seen. IgG4-related disease can similarly affect the liver. Patients present with mass lesions and clinically with obstructive jaundice. If the mass lesions occlude the bile ducts, presentation may resemble cholangiocarcinoma. Imaging may show focal or diffuse bile duct thickening (Fig. 1C,4B) often associated with stenosis (Fig. 1A) or upstream dilatation (Fig. 1B). These findings may similarly be depicted on ERCP or MRCP [4] 60-80% with AIP will have biliary duct involvement leads to bile duct stenosis and upstream dilation (3C) of the bile ductswall thickening [7,10].

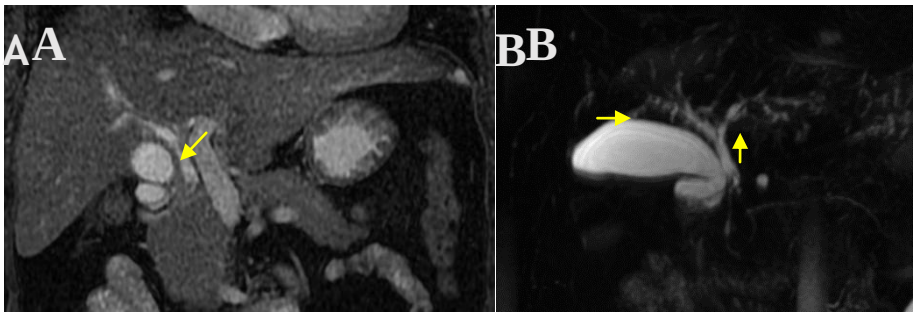

Figure 2A &2B: A fifty-year-old male, H/o jaundice; Coronal T2 W MRI and Reformatted 3D MRCP images shows diffuse irregularity of the intrahepatic biliary radicles in the form of narrowing (arrow), stenosis, strictures (right arrow) and ectasia up arrow) of the involved bile ducts.

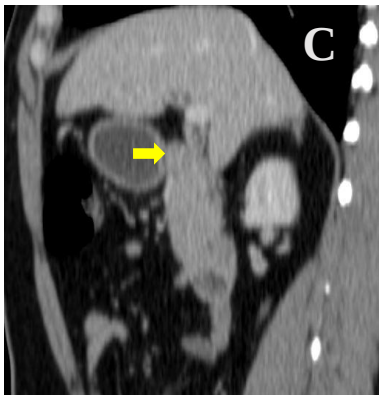

Figure 2C: Reformatted sagittal view of contrast enhanced abdomen in venous phase at the level of porta hepatis shows diffuse smooth wall enhancement (block arrow) of common hepatic duct noted with abrupt narrowing of the common bile duct just below cystic duct insertion causing diffuse long segment stricture

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of the supraduodenal, retro duodenal and intrapancreatic segments of the CBD.

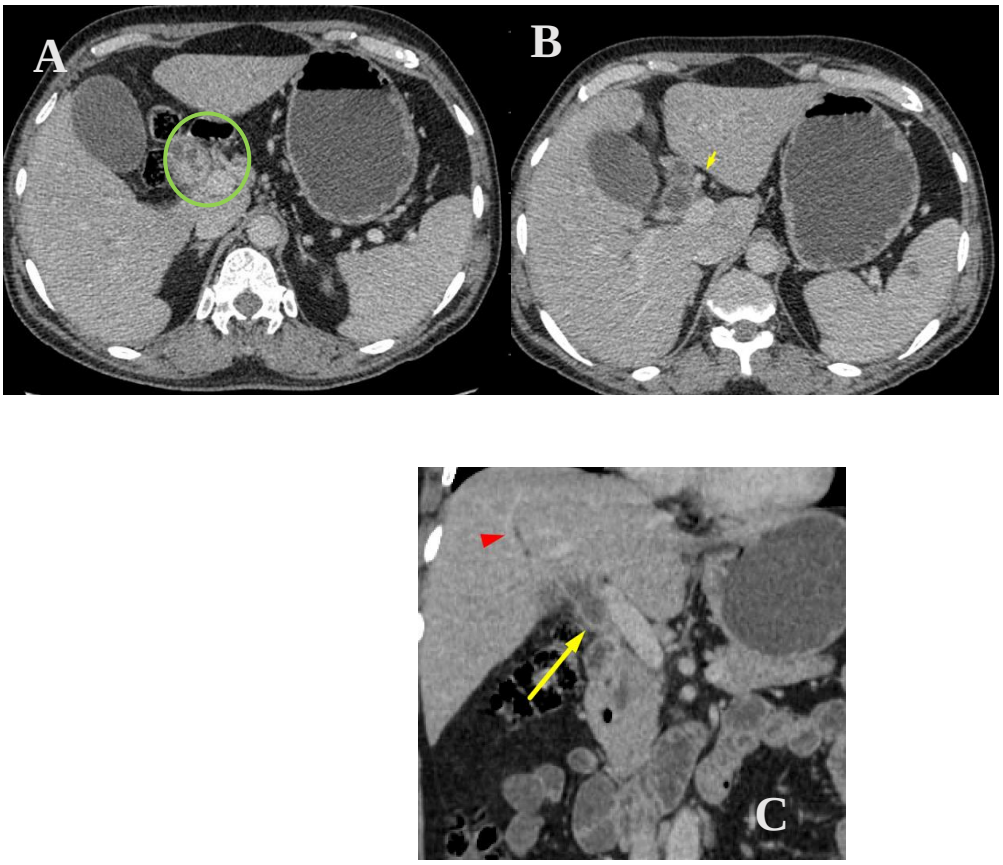

Figure 3A, 3B & 3C: A fifty-five-year-old male, H/o jaundice; Post contrast axial view and reformatted coronal view in venous phase at the level of the porta hepatis shows diffuse enhancing soft tissue mass (circle) involving the confluence of the cystic duct and the common hepatic duct causing dilatation of the proximal biliary tree (arrowhead) with abrupt tapering of the common bile duct. No evidence of infiltration into the surrounding organs.

IgG4 related hepatopathy

Recently, IgG4-related autoimmune hepatitis is an emerging disease entity of IgG4-related disease. The term IgG4-related hepatopathy refers to any kind of hepatic parenchymal involvement of IgG4-related sclerotic disease, including inflammatory pseudotumor, but is often used to refer to any parenchymal lesion [12]. Pathologically, IgG4-related hepatopathy includes heterogeneous histological lesions in liver parenchyma. According to a previous study, pathological changes of hepatic parenchyma are present in patients with type 1 AIP, and these changes can be classified as; portal inflammation (35%), large bile duct damage (47%), portal sclerosis (47%), lobular hepatitis (29%), and cholestasis (24%) [7]; and these findings may

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coexist. However, they are not sufficient to reach a diagnosis, because pathologic findings including portal inflammation and sclerosis can be observed in IgG4-related sclerosing cholangitis and in IgG4-related hepatopathy [13]. The imaging findings of IgG4-related cholangitis and hepatopathy differ as the former presents as periductal infiltration and upstream bile duct dilatation (Fig 4B), and the latter presents as parenchymal mass or infiltration (Fig 4A) [14].

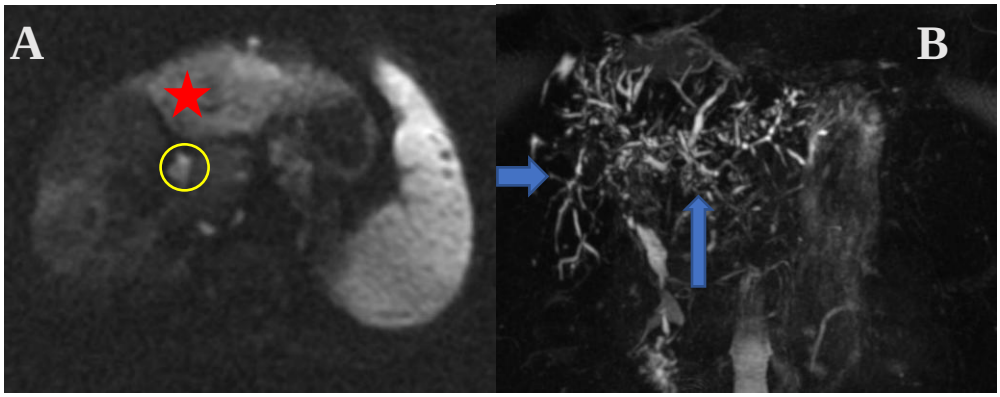

Figure 4A &4B: A sixty-five-year-old female, presented with jaundice, Axial DWI at the level of the liver shows ill defined areas of restricted diffusion (star) involving the sub capsular surface of both lobes of the liver. Few lymphnodes showing restricted diffusion (circle) is seen the porta hepatis. Reformatted 3D-MRCP shows multifocal dilatation of the intrahepatic biliary radicles with intervening segments of narrowing, giving a beaded appearance (block arrows) suggesting sclerosing cholangitis.

IgG4 related cholecystitis

IgG4-related cholecystitis is a manifestation of IgG4-related sclerosing disease in the gallbladder. In general, fibroinflammatory involvement is mainly observed in the submucosa of the gallbladder and bile duct wall (Fig. 5C), where the epithelium of these structures is said to be intact [15]. Cytological examinations were often said to be useful in establishing a differential diagnosis of gallbladder cancer, although it was difficult to obtain biopsy samples adequate for establishing characteristic histopathological findings of IgG4-related cholecystitis. In cases with suspected benign gallbladder diseases such as xanthogranulomatous cholecystitis etc, and gallbladder malignancy, IgG4-related cholecystitis must be included in the differential diagnosis and serum IgG4 should be assessed [15] for establishing definitive diagnosis.

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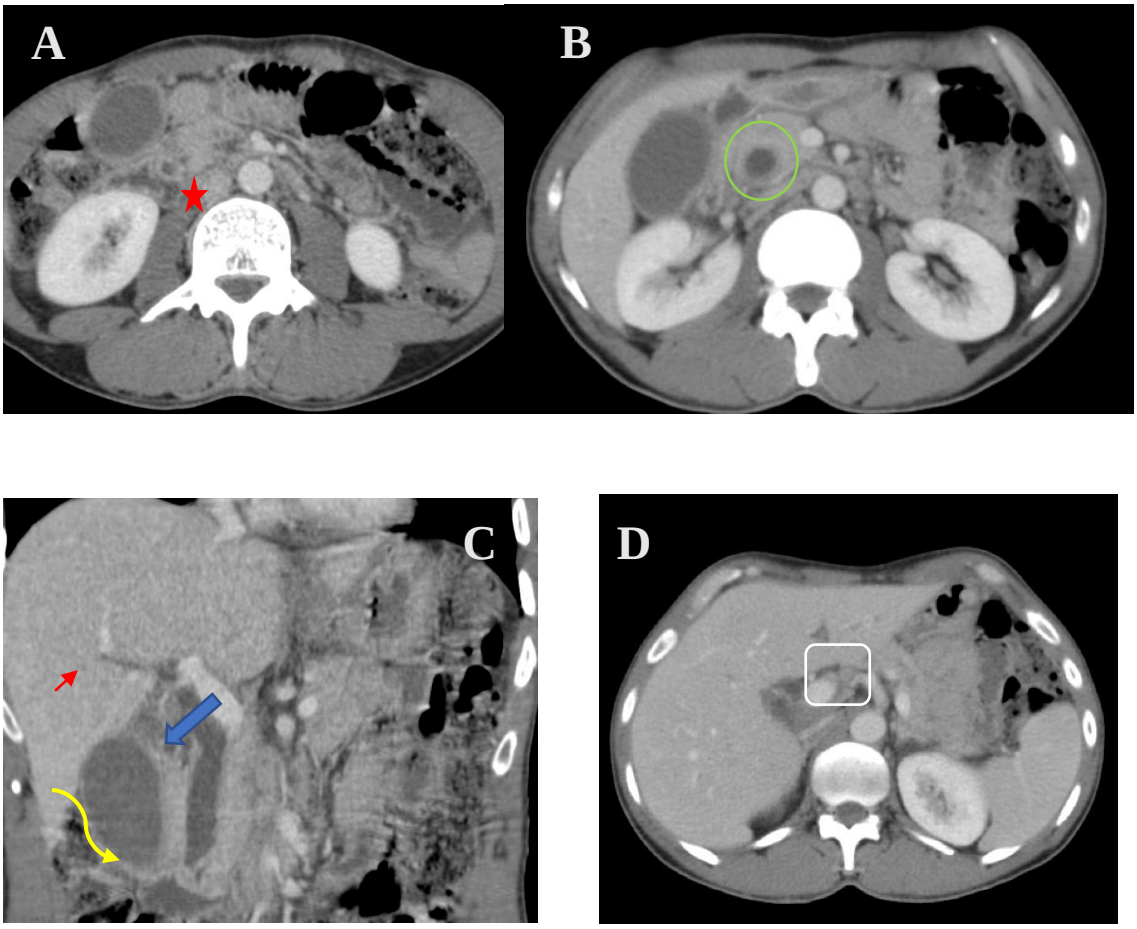

Figure 5A, 5B. 5C & 5D: A forty-three-year-old male, presented with fever and jaundice; Post contrast axial view and reformatted coronal view in venous phase at the level of distal CBD shows short segment stricture of the juxtaproximal distal CBD (star) causing upstream dilatation of the CBD (green circle), CHD (block arrow) and the right IHBR (arrow). The gallbladder is over distended with wall thickening (curved arrow). Few enlarged the periportal and para-aortic lymph nodes (white square).

Limitation

The limitations of the study were the low sample size as many of the radiologically suspected cases were not subjected to biopsy / lab investigation due to loss of follow up by the patient. Also, PET – CT and Machine learning algorithms could not be applied to our cases.

Conclusion

Due to the systemic nature of the disease, imaging workup of IgG4-related disease should always include whole-body examinations to detect multiple organ involvement. Although definitive diagnosis requires histopathologic analysis, the radiologists should be familiar with its clinical and imaging manifestations to avoid misdiagnosis and unnecessary surgical interventions thus

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improving the overall prognosis and clinical outcome of the patient.

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