Pancreatic Disorders & Therapy
ISSN: 2165-7092

Nair and Gupta, Pancreat Disord Ther 2016, 6:2
DOI: 10.4172/2165-7092.1000171

Review Article Open Access

Igg4 Related Disease of the Pancreas – Review of Imaging Findings

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Rec date: Feb 04, 2016; **Acc date:** Feb 25, 2016; **Pub date:** Feb 29, 2016

Abstract

IgG4 related disease is a systemic fibro-inflammatory disorder which can affect any organ system in the body. Involvement of pancreas by IgG4 related disease is quite common. Imaging of the pancreas shows characteristic changes in IgG4 related disease. Imaging can also differentiate it from other mimics as pancreatic malignancy.

Keywords: IgG4 related disease; Pancreas; Imaging; Autoimmune pancreatitis; Inflammatory

Introduction

IgG4 related disease is a systemic inflammatory disorder which can affect any organ system in the body. The term IgG4 related disease was first used in a Japanese consensus conference in 2012 [1] and has evolved into common scientific parlance since then.

IgG4 related disease of the pancreas shares many common histopathological features with autoimmune pancreatitis (AIP). The concept of autoimmune pancreatitis was first put forward by Yoshida et al. [2] in 1995 after numerous authors had reported a form of chronic pancreatitis associated with Sjögren's-like syndrome. The associated finding of abnormally elevated serum concentrations of IgG4 among AIP patients was first reported in 2001 [3]. In 2003, Kamisawa et al. [4] proposed the concept of IgG4-related sclerosing disease and suggested that autoimmune pancreatitis is, in fact, a part of that disease spectrum.

Autoimmune pancreatitis is classified into two subtypes which share common histopathological and clinical characteristics. IgG4-related infiltrates and serologic abnormalities in Type 1 AIP help in differentiating it from Type 2 AIP. Type 1 AIP is now recognized as the pancreatic manifestation of IgG4-related disease [5].

The Japanese study group for the diagnostic evaluation of IgG4-related disease proposes three main diagnostic criteria which comprise of characteristic organ swelling or space-occupying mass in the clinical examination or corresponding axial imaging, raised serum IgG4 concentration and characteristic histology [6]. Elevated serum levels of IgG, IgG4 and autoantibodies like rheumatoid factor and antinuclear antibodies are helpful in diagnosis of this entity. The final diagnostic gold standard remains histo pathological confirmation [6].

However AIP is inadequately represented by these criteria [7]. The ICDC Diagnostic criteria for autoimmune pancreatitis have been proposed by various research groups on the basis of several factors such as imaging, histologic and serologic findings, extrapancreatic involvement, and response to corticosteroid therapy. Characteristic imaging findings play an important role in the diagnosis of autoimmune pancreatitis in most classification systems, although the applicability of other findings varies [8]. It is important to remember that the presence of elevated serum IgG4 alone is insufficient for a conclusive diagnosis of type 1 AIP. Infact the IgG4 levels may be normal in a subset of patients with type 1 AIP. In these patients, distinctive pancreaticobiliary imaging findings, representative clinical findings and extrapancreatic involvement help in arriving at the correct diagnosis of IgG4 related disease.

Imaging Findings

Pancreatic imaging is an essential component of the ICDC criteria for diagnosis of autoimmune pancreatitis [9]. The importance of imaging in autoimmune pancreatitis started getting recognized around 1998 once cross sectional imaging findings of this disease were first described. A wide spectrum of imaging characteristics has since been established.

Modalities employed by radiologists have evolved from conventional imaging techniques like ultrasonography, computed tomography (CT), magnetic resonance (MR) and magnetic resonance cholangio pancreaticography (MRCP) imaging to endoscopic techniques such as endoscopic ultrasound (EUS), and most recently, positron emission tomography (PET).

Ultrasound is usually the first imaging technique to be called upon in a patient with obstructive jaundice or with upper abdominal pain. In patients of IgG4 disease of pancreas, diffuse or focal hypoechoic appearance of the pancreas is seen on sonography, sometimes associated with dilatation of the common bile duct due to involvement of its intrapancreatic portion. Contrast-enhanced ultrasonography can depict vascularity of suspected area with most of the inflammatory pancreatic masses showing a pattern of enhancement similar to the normal pancreatic gland (isovascular) whereas pancreatic malignancies classically appear hypovascular to normal pancreatic parenchyma [10].

Contrast enhanced computed tomography (CT) scan done according to pancreatic protocol is considered as the imaging gold standard. It provides information comparable to MRI while being a quicker, cheaper and widely available modality which also helps in simultaneously ruling out pancreatic malignancy and metastatic disease. Three distinct imaging morphologies of IgG4 related disease of the pancreas are recognized on CT and MRI images based on extent of parenchymal involvement i.e., diffuse, focal and multifocal.

Amongst the three, diffuse form is the most common subtype. The normal pancreatic parenchyma demonstrates a lobular contour with parenchymal clefts on cross sectional imaging. In the diffuse form, the pancreas appear diffusely enlarged and hypodense on CT with featureless borders. A characteristic surrounding surrrounding capsule like rim (halo) is often seen which is attributed to peripancreatic fluid, fibrous tissue proliferation or phlegmon [11,12]. Accessory findings include narrowing of peripancreatic veins and minimal peripancreatic fat stranding / lymphadenopathy [11].

With regards to enhancement characteristics, affected pancreas show decreased enhancement in the pancreatic phase with nearly normal enhancement in the hepatic phase of imaging compared to normal subjects [13]. Studies by Bodily et al. and Carbognin et al. [14,15] further validated this assertion regarding enhancement patterns on both CT and MRI imaging. In addition, this delayed enhancement pattern was found to be significantly more pronounced on MR imaging in comparison to CT [16]. When these typical imaging features are present, supportive laboratory evidence (elevated serum IgG4 levels) is sufficient for diagnosis making core biopsy unnecessary for diagnosis and treatment initiation.

Acute pancreatitis is the main imaging differential consideration for diffuse AIP; however it has a vastly different clinical presentation with imaging features like peripancreatic collection/fat necrosis, parenchymal necrosis and mesenteric fat stranding further aiding in differentiation.

The focal form of the disease is relatively much less common and is characterized by a focal mass lesion, usually in the pancreatic head. Affected patients usually present with obstructive jaundice, unless the lesion is located in distal pancreatic body or tail. The main pancreatic duct shows characteristic irregular narrowing in affected segment of the pancreas with mild proximal upstream dilatation. In addition, the intrapancreatic portion of the common bile duct is frequently narrowed. Takahashi et al. [13] demonstrated that delayed enhancement, defined as a 15 HU or greater increase from the pancreatic phase to the hepatic phase is commonly seen in focal AIP.

The main differential diagnosis of focal AIP is pancreatic head malignancy owing to similar imaging findings and clinical features such as painless jaundice, anorexia and weight loss; however it is extremely important to differentiate between the two entities as there is a marked difference in treatment strategies. Marked pancreatic duct dilatation in malignancy serves as a useful differentiating feature. Further on multiphasic imaging, pancreatic carcinoma, unlike AIP, appears hypoattenuating to normal pancreatic parenchyma, in both the pancreatic and hepatic phases. However it is important to remember that pancreatic biopsy is mandatory to rule out pancreatic carcinoma even if clinical, radiological and serological findings indicate focal AIP. Hence the role of imaging in focal AIP is more important in biopsy guidance and for follow up once pancreatic carcinoma has been ruled out on biopsy.

In the multifocal form of the disease, multiple focal masses are seen throughout pancreatic parenchyma with mild narrowing of the pancreatic duct in affected segments.

Besides above imaging features, type 1 AIP is also associated with a number of extrapancreatic lesions like sclerosing cholangitis, retroperitoneal fibrosis, renal involvement (tubulointerstitial nephritis), salivary and lacrimal gland involvement, hilar and orbital involvement (IgG4 associated pseudolymphoma) [17]. The commonest extrapancreatic manifestation of type 1 AIP is IgG4-SC, which can mimic cholangiocarcinoma. Imaging findings of extrapancreatic disease serve as useful clues in distinguishing autoimmune pancreatitis from pancreatic cancer and serve to further consolidate the diagnosis of AIP. Other less commonly reported findings include hypophysitis and chronic thyroiditis. All these extrapancreatic lesions show pathological findings similar to IgG4 disease of pancreas such as massive lymphoplasmacytic infiltration and fibrosis and obliterating phlebitis, and presence of prominent IgG4 positive plasma cells [18]. It is this link to other organ involvement that led clinicians to consider AIP as part of a systemic IgG4 related disease in which diverse organ manifestations are linked by the same histopathological characteristics [19].

MRCP is an increasingly useful technique which generates excellent images of the pancreaticobiliary tree and is replacing diagnostic ERCP in many pancreaticobiliary diseases. The presence of multiple, long stenoses without an upstream MPD dilation at MRCP suggests the diagnosis of AIP [20]. In the diagnosis of focal AIP, it acts as a problem solving tool in the differential diagnosis of pancreatic adenocarcinoma as comparatively lesser upstream dilatation of the MPD on MRCP suggests AIP rather than pancreatic adenocarcinoma (PC) [20,21]. Newer MRCP techniques and secretin enhanced MRCP help to further refine the diagnostic differentiation between AIP and PC [21].

Endoscopic ultrasound (EUS) is a novel imaging technique for imaging of autoimmune pancreatitis with findings consisting of diffuse hypoechoic appearance or focal hypoechoic spots with absence of a discreet mass in pancreas. However its primary utility is as a means of guidance for pancreatic core biopsies, in cases of focal AIP. Addition of contrast enhanced ultrasound and elastography aids in further corroboration of the diagnosis.

PET imaging constitutes the latest weapon in the radiological arsenal for diagnosis of autoimmune pancreatitis with diffuse/focal FDG uptake depending upon the imaging pattern. A 2014 study by Ebbo et al. [22] comprehensively researched the role of PET imaging, either used alone or concurrent with CT (PET/CT) in the staging and monitoring of IgG4 related disease. The study found superior diagnostic sensitivity of PET/CT (83%) in comparison to CT alone (73%). In cases of AIP, certain characteristic uptake patterns have been determined such as diffuse pancreatic uptake, multiple foci of pancreatic uptake, elongated shape of focal uptake (vs. a nodular pattern of uptake), and heterogeneous uptake (vs. a homogeneous pattern of uptake) [23,24].

Conclusion

Patients with IgG4 related disease of the pancreas usually demonstrate a rapid and sustained response to corticosteroid therapy; therefore, an accurate timely diagnosis is essential to alleviate patient symptoms without resorting to unnecessary surgical procedures. All standard diagnostic criteria for autoimmune pancreatitis place a special emphasis on imaging findings along with clinical, laboratory and histopathological data. Imaging aids in lesion localization and characterization, provides biopsy guidance and helps in discerning AIP from other important differential considerations such as pancreatic cancer.

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