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TOPIC HIGHLIGHT

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Autoimmune pancreatitis in the context of IgG4-related disease: Review of imaging findings

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Abstract

Current understanding of autoimmune pancreatitis (AIP) recognizes a histopathological subtype of the disease to fall within the spectrum of IgG4-related disease. Along with clinical, laboratory, and histopathological data, imaging plays an important role in the diagnosis and management of AIP, and more broadly, within the spectrum of IgG4-related disease. In addition to the defined role of imaging in consensus diagnostic protocols, an array of imaging modalities can provide complementary data to address specific clinical concerns. These include contrast-enhanced computed tomography (CT) and magnetic resonance (MR) imaging for pancreatic parenchymal lesion localization and characterization, endoscopic retrograde and magnetic resonance cholangiopancreatography (ERCP and MRCP) to assess for duct involvement, and more recently, positron emission tomography (PET) imaging to assess for extra-pancreatic sites of involvement. While the imaging appearance of AIP varies widely, certain imaging features are more likely to represent AIP than alternate diagnoses, such as pancreatic cancer. While nonspecific, imaging findings which favor a diagnosis of AIP rather than pancreatic cancer include: delayed enhancement of affected pancreas, mild dilatation of the main pancreatic duct over a long segment, the "capsule" and "penetrating duct" signs, and responsiveness to corticosteroid therapy. Systemic, extra-pancreatic sites of involvement are also often seen in AIP and IgG4-related disease, and typically respond to corticosteroid therapy. Imaging by CT, MR, and PET also play a role in the diagnosis and monitoring after treatment of involved sites.

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Key words: Autoimmune pancreatitis; IgG4-related disease; Pancreatic cancer; Imaging; Computed tomography; Magnetic resonance; Positron emission tomography; Review

Core tip: The imaging appearance of autoimmune pancreatitis (AIP) varies widely. The literature is reviewed for imaging characteristics that favor a diagnosis of AIP rather than differential considerations such as pancreatic cancer. Response to steroid therapy and the presence of extra-pancreatic lesions are often seen in AIP and in IgG4-related disease. Extra-pancreatic findings and the role of imaging in monitoring their response to therapy are also reviewed, including recent developments in positron emission tomography imaging.

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INTRODUCTION

Autoimmune pancreatitis (AIP) was first described by Yoshida *et al*[1] in 1995 as a form of chronic pancreatitis. In the interval, the associated finding of abnormally elevated serum concentrations of IgG4 among AIP patients was first reported in 2001[2], and extra-pancreatic manifestations of disease were first identified among AIP patients in 2003[3]. These and other developments have contributed to the evolution of the understanding of the disease[4] and AIP is now recognized to represent a manifestation of IgG4-related disease[5,6].

AIP IN THE CONTEXT OF IGG4-RELATED DISEASE

IgG4-related disease has been recently-recognized as a systemic inflammatory disorder characterized by stereotypic histopathological features of a dense lymphoplasmacytic infiltrate, "storiform" fibrosis, and obliterative phlebitis[7,8]. It is a systemic process which may involve one or multiple organs, either synchronously or metachronously. IgG4-related disease has been described in virtually every organ system, including the pancreas[5,6], demonstrating common histopathological findings. As a result, a host of organ-specific pathologies previously thought to be unrelated are now recognized in the spectrum of IgG4-related disease, including: salivary glands (Mikulicz's syndrome), thyroid gland (Riedel's thyroiditis), orbit (orbital pseudotumor), aorta (non-infectious/inflammatory aortitis or periaortitis), pancreas (AIP), retroperitoneum (Ormond's disease or retroperitoneal fibrosis), and kidneys (tubulointerstitial nephritis).

Two types of AIP, 1 and 2, are presently recognized, found to share overlapping histopathological and clinical characteristics, but also important differences[9-11]. Of note, while Type 1 disease demonstrates IgG4-related infiltrates and serologic abnormalities, these features are absent in Type 2 disease. Additionally, extra-pancreatic organ involvement and disease relapse are associated with Type 1 and not Type 2 disease[12]. International consensus diagnostic criteria have been established for AIP, predicated on clinical, laboratory, imaging, and histopathologic data. In addition to characteristic histopathological findings, diagnostic characteristics of AIP include abnormal elevations of serum IgG4 levels, extra-pancreatic organ involvement, and responsiveness to a trial of corticosteroids. By imaging, while certain features are considered diagnostic, Types 1 and 2 cannot be reliably distinguished[9,11].

Demographics

An uncommon entity, the global burden of IgG4-related disease is difficult to assess, a problem made more challenging by its evolving characterization encompassing various organ-based pathologies which were previously thought to be disparate. However, population-based epidemiological data are available relating to AIP in Japan, where estimates based on national survey data estimate the prevalence of AIP as 0.82-2.2 per 100000 individuals[13,14]. The disease typically involves men more than women, at a ratio of 2.9-3.7 to 1, and typically involves individuals older than 50 years of age. Pertaining to AIP, groups around the world have also reported on their clinical experience[15-18].

Diagnostic features of IgG4-related disease

The diagnosis of IgG4 disease relies on the synthesis of clinical, laboratory, radiologic and histopathologic findings[5,9,11,12]. National consensus criteria for diagnosis from Japan[19] are comprised of two central, specific, findings: the first, of abnormally elevated serum IgG4 concentration > 135 mg/dL; and the second, in histopathologic analysis, of > 40% of IgG+ plasma cell positive for IgG4, and > 10 IgG4+ cells per high power field. Additional clinical, laboratory, and histopathological findings may be less specific, but increase the sensitivity for detection of organ-specific pathology in the IgG4-related disease spectrum.

Clinically, IgG4-related disease typically presents in subacute fashion. Most patients are not constitutionally ill, and fever as a symptom is unusual; the myriad clinical presentations of IgG4-related disease have previously been summarized[5]. Symptoms are typically nonspecific, and further investigations are typically necessary before the diagnosis is reached. Laboratory evaluation for IgG4-related disease has centered on serum concentration of IgG4, since this finding was first reported in AIP patients in 2001[2]. However, elevated serum IgG4 levels are detected in other types of immune-mediated and allergic disorders, as well as in infectious and malignant conditions[20]. Nonetheless, the generally accepted upper limit of normal of serum IgG4 concentration is 135 mg/dL; levels elevated beyond this are considered abnormal, including in the Japanese national consensus criteria. It should be noted that serum IgG4 abnormalities are not seen in Type 2 AIP, and at the diagnostic threshold of 135 mg/dL, up to 30% of patients with IgG4-related disease may have normal serum IgG4 levels[21].

Given the nonspecific nature of presenting symptoms, laboratory and radiologic investigation present complementary data in reaching a diagnosis of IgG4-related disease. Imaging may be of particular utility in identifying focal abnormalities that may represent biopsy targets. Even so, the characteristic of the disease to form tumefactive lesions often necessitates biopsy to exclude a malignant or neoplastic process.

IMAGING FINDINGS OF AIP

Cross-sectional imaging findings of AIP were initially described in 1998[22,23]. Clinical investigators since then have reported on the imaging appearance of AIP by a multitude of imaging characteristics, including morphology of the pancreatic parenchyma and main pancreatic duct, associated tissue (fat, lymph nodes), signal, and response

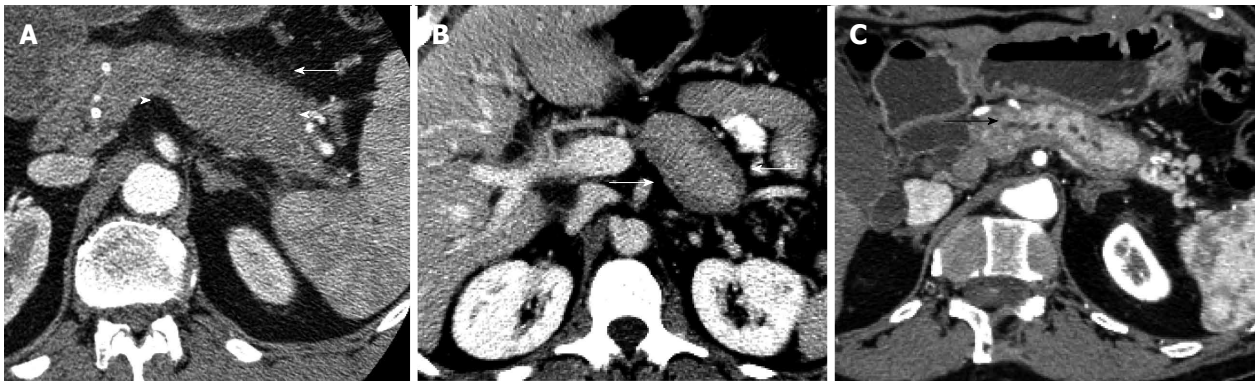

Figure 1 Contrast-enhanced computed tomography findings in autoimmune pancreatitis. A: Enlargement of the distal pancreatic body and tail (between arrowheads), with fine peri-pancreatic stranding of the adjacent fat (small arrow); B: The "capsule" or "rim" sign, a hypo-attenuating rim encircling the anterior and posterior margin of the pancreas (white arrows); C: Multifocal main pancreatic duct narrowing (black arrow).

to administration of intravenous contrast agents. Modalities employed by investigators include cross-sectional techniques of computed tomography (CT) and magnetic resonance (MR) imaging, endoscopic techniques such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS), and more recently, positron emission tomography (PET).

CT and MR imaging

Morphologic and signal characteristics: The CT appearance of AIP was first described in 1998. In two case series' of five and three patients[22,23], CT demonstrated a diffusely enlarged pancreas in all patients. Since then, studies of patients with AIP have demonstrated heterogeneity of the morphologic presentation on both CT and MR imaging: diffuse enlargement has been shown among 11%-56% of patients; focal or mass-like enlargement among 28%-59% of patients (Figure 1A); and no enlargement, or a normal appearance of the pancreas, in a minority of patients, 9%-16%[15,16,24,25]. In another series, investigators also characterized a 'mixed' appearance of diffuse and focal enlargement in 56% of 36 patients[25].

Peri-pancreatic fat planes are typically preserved on cross-sectional imaging[23]. Minimal peri-pancreatic stranding (Figure 1A), without vascular encasement, parenchymal calcification, or peripancreatic fluid collection, was seen in six patients with diffuse pancreatic enlargement, in a study of 25 patients with AIP[15]. By comparison, in that study, an accessory finding more commonly observed was one of enlarged peripancreatic lymph nodes. Imaging presentation with acute pancreatitis has rarely been reported: in one series of imaging findings on 22 patients with AIP, the authors noted the appearance of one case consistent with acute pancreatitis[16].

By MR imaging, signal abnormality representing AIP typically demonstrates relative T1 hypo-intensity, and relative T2 hyper-intensity[22,25,26]. Recent studies have sought to distinguish AIP from differential considerations such as pancreatic cancer using MR diffusion characteristics, and other imaging features (Section 4, below).

Enhancement characteristics: Classically, upon administration of intravenous contrast material, AIP demonstrates diminished enhancement in the early, or arterial phase, and relatively increased or prolonged enhancement in the delayed or venous phase (Figure 2)[22,23]. Despite variation in acquisition and definition, subsequent studies have typically supported this pattern of enhancement by both CT[27,28] and MR[24] imaging. Takahashi *et al*[27] quantitatively assessed dual-phase contrast enhanced CT among 43 AIP patients and 25 patients with normal pancreas. In the pancreatic phase, the mean CT attenuation of pancreatic parenchyma among AIP patients (85 HU) was significantly lower than that among the control group (104 HU). Delayed enhancement, defined as a 15HU or greater increase from the pancreatic phase to the hepatic phase, was observed in seven of the 13 patients (54%) with focal AIP. In separate study of imaging related to 36 patients with AIP comprising 86 contrast-enhanced CT and MRI scans[25], investigators noted hypo-enhancement in the arterial phase in 58% and 52% for CT and MRI, respectively. In that study however, delayed enhancement was found to be significantly more pronounced by MR imaging: whereas 75% of late-venous phase enhancement in CT was iso-attenuating, 74% of late-venous enhancement was hyper-enhancing by MR.

An early report[22] also noted that on CT, in 4 of 5 patients, "a capsule-like low density rim surrounded the pancreas on both early and delayed [contrast-enhanced] images," giving rise to the "capsule" or "rim" sign of AIP (Figure 1B). The correlate on MR imaging is of a T1 and T2 hypo-intense rim, with delayed enhancement, demonstrated in three of four patients. The sensitivity of this finding for AIP has been subsequently shown to be generally low for both CT and MR imaging, ranging from 12%-40%, but may potentially distinguish AIP from pancreatic malignancy[15,24-27,29].

Endoscopic techniques: ERCP and EUS

Abnormality of the intra- and extra-hepatic biliary system, including the main pancreatic duct (MPD), is common in AIP. MPD involvement varies widely, and may demonstrate irregular narrowing, in either a diffuse or segmental distribution (Figure 3)[26]. In one series of 20

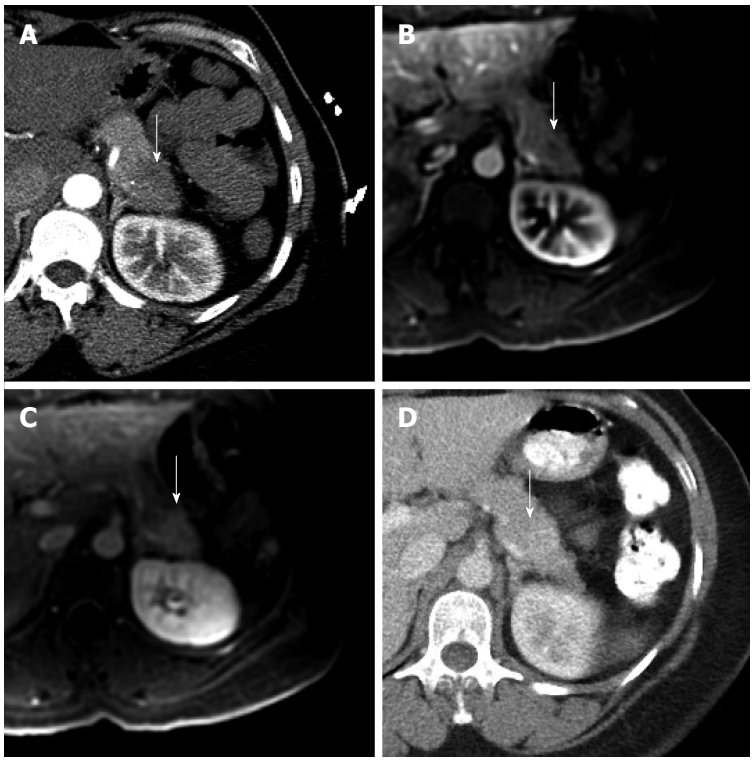

Figure 2 Delayed enhancement on computed tomography and magnetic resonance imaging in autoimmune pancreatitis. A, B, C: Focal autoimmune pancreatitis in the pancreatic tail (white arrow) with delayed early arterial enhancement on arterial phase computed tomography (CT) (A) and magnetic resonance (B, fat-saturated T1-weighted image, 30 s post-injection), with subsequent delayed enhancement (C, fat-saturated T1-weighted image, 180 s post-injection); D: Follow-up CT after corticosteroid therapy demonstrating resolution of prior enhancement abnormality (white arrow).

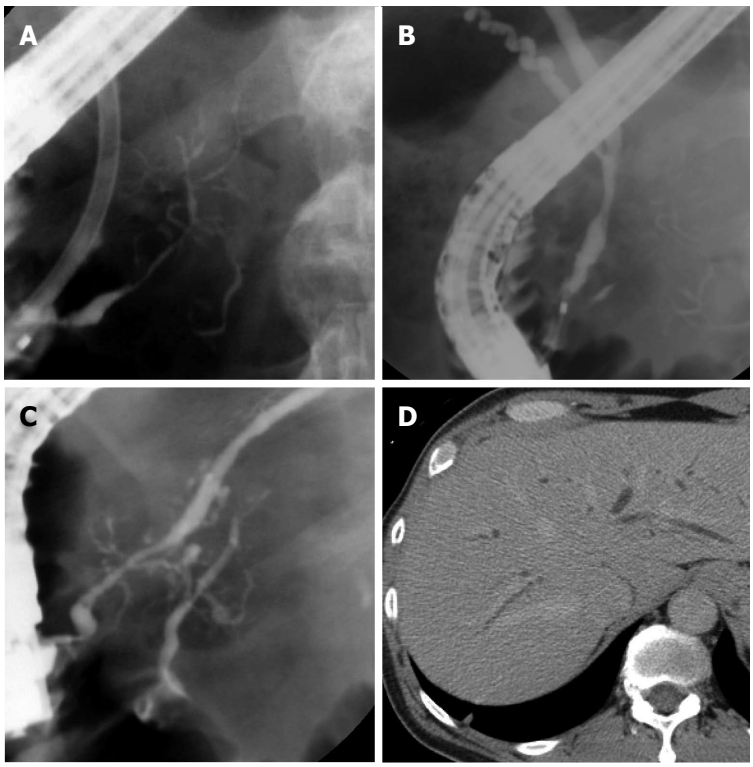

Figure 3 Biliary involvement in autoimmune pancreatitis. A, B, C: Endoscopic retrograde cholangiopancreatographydemonstrating diffuse narrowing of the main pancreatic duct (A) and segmental narrowing of the lower common bile duct (B), with improvement of main pancreatic duct narrowing after therapy (C); D: Computed tomographic image demonstrating intrahepatic biliary ductal dilatation in a patient with biliary involvement from IgG4-related disease.

patients who underwent ERCP, diffuse narrowing was found in six patients (30%), and segmental narrowing was found in nine patients (45%)[26]. The length of MPD narrowing was longer than 3 cm in 18 patients (90%). In another series of 19 patients who underwent ERCP, diffuse irregularity and narrowing of the MPD was observed in nine patients (47%), while focal stricture in the proximal MPD was seen in six patients (32%)[15]. Biliary duct abnormalities were seen in 16 of 19 patients who underwent ERCP (84%). The most common abnormality was stricture of the distal common bile duct, present in 12 patients (60%), while multiple short-segment intrahepatic duct strictures were present in six patients (30%). Biliary involvement varies widely, and multifocal narrowing of the MPD (Figure 1C) and narrowing of the lower common bile duct have been reported in as high a proportion as 85% and 90%, respectively[30]. Readers are additionally referred to a recent review for detailed discussion of IgG4-related sclerosing cholangitis, which has overlapping features[31].

The sensitivity of ERCP to diagnose AIP is limited, but can be improved with directed training of key features. A multicenter, international study[32] identified four key features of AIP from a series of 20 patients: long stricture (greater than one-third the length of the MPD); upstream dilatation from the stricture less than 5 mm; multiple strictures; and side branches arising from a strictured segment. Following training with a teaching module principled upon these features, the sensitivity of an international group of physicians to detect AIP increased significantly from 44% to 71%, with specificity of 83%.

Consistent with the varied morphologic presentation of AIP seen on CT and MR imaging, endoscopic ultrasound may reveal diffuse enlargement of the pancreas with altered echotexture, or may demonstrate a focal hypoechoic mass[33]. In one study among 21 patients who underwent EUS[15], diffuse enlargement with altered echotexture was seen in 13 patients (62%), while six patients had focal enlargement of the head of the pancreas (29%).

Magnetic resonance cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP) can provide complementary data in the diagnosis of AIP and assessment of MPD involvement, depending on the pattern of involvement[26]. In a series of 20 AIP patients, MRCP findings were compared with ERCP findings[34]. Among patients with focal AIP, the narrowed portion of the MPD was not visualized, while among patients with diffuse AIP, the MPD was incompletely visualized or not visualized. In the latter setting, non-visualization of the MPD may limit detection of duct involvement, yet MRCP may still be helpful in follow-up after therapy. In a separate study comparing MRCP findings among cohorts of 38 AIP patients, 40 pancreatic cancer patients, and 40 normal controls, ERCP was used as the gold standard[35]. The authors found MRCP to be 65% accurate (22 of 34 patients) for depicting MPD morphology among patients with AIP, significantly less than that of the cohort of patients with pancreatic cancer (89%, 23 of 26 patients) or those with normal pancreas (100%, 40 of 40 patients).

Angiography and peripancreatic vascular findings

Angiographic findings related to AIP were reported by Kamisawa *et al*[36] in 2003. Among 13 patients with AIP, angiography demonstrated irregular narrowing of the anterior superior pancreaticoduodenal artery in seven (54%) and of the posterior superior pancreaticoduodenal artery in 4 patients (31%). Deviation of the portal or splenic vein was observed in 4 cases (31%); collateral venous circulation was observed on account of stenosis or obstruction in 3 cases (23%). The presence of irregular narrowing of the pancreatic arteries similar to encasement sometimes detected in pancreatic carcinoma; these angiographic findings can cause confusion in the diagnosis of AIP.

Subsequent studies with cross sectional imaging have reported similar rates of peripancreatic vascular involvement. Takahashi *et al*[37] reported vascular involvement in 11 of 25 (44%) of AIP patients. Raina *et al*[38] demonstrated splenic vein and/or artery involvement was seen in six of 26 patients (23%). Vlachou *et al*[39] noted narrowing of the splenic vein with collateral vessel formation was seen in 9 of 57 patients (16%), with normalization of vessel caliber following resolution of AIP. Ishikawa *et al*[40] reviewed CT imaging among 54 AIP patients, finding 24 cases (44%) which demonstrated peripancreatic vascular involvement, with stenosis or occlusion of the splenic vein in 22 cases, of the superior mesenteric or portal vein in 13 cases, and development of collaterals in 18 cases. Among 16 patients who underwent steroid therapy, 14 demonstrated improvement in vascular involvement (87%).

Positron emission tomography

PET, typically used in clinical oncology to localize areas of normal or abnormal physiology based on uptake of radiopharmaceutical imaging agents[41] has found useful application in the imaging of inflammatory disease[42]. PET imaging following intravenous administration of a radiopharmaceutical such as 2-(18)F-fluoro-2-deoxy-d-glucose (^{18}F-FDG), either alone or in combination with concurrent CT imaging (PET/CT), allows for whole body imaging to identify areas of abnormally increased cellular metabolism[43].

With regard to AIP, ^{18}F-FDG uptake at pancreatic and extra-pancreatic lesions have been shown in case reports of AIP/IgG4-related disease since 1999[44-47]. Nakamoto *et al*[44] initially described two cases of AIP demonstrating diffusely and focally intense pancreatic uptake, with resolution after steroid therapy. Kajiwara *et al*[47] described two cases with multifocal ^{18}F-FDG uptake of the pancreas, corresponding to focal pancreatic masses of AIP. Kawamura *et al*[45] and Sato *et al*[46] additionally reported extrapancreatic findings in cases of AIP associated with sclerosing cholangitis, sialadenitis, and lymphadenopathy.

Table 1 Imaging findings favoring a diagnosis of autoimmune pancreatitis rather than pancreatic cancer

Diffuse pancreatic enlargement
Delayed enhancement of affected pancreas
Long segment MPD narrowing
MPD dilatation not in excess of 4-5 mm
Multiple sites of MPD narrowing
"Capsule" sign
"Penetrating duct" sign
Low ADC value reflecting restricted diffusion on diffusion weighted MR imaging[51,52]
Improvement of findings following short course of corticosteroid therapy

MPD: Main pancreatic duct; ADC: Apparent diffusion coefficient.

As with its accepted application in clinical oncology, in the context of IgG4-related disease, ^{18}F-FDG PET may prove valuable in providing complementary data in the delineating the extent of organ involvement, staging the extent of disease, guiding biopsy early in the diagnostic evaluation, and monitoring response to therapy[42].

DISTINCTION OF AIP FROM PANCREATIC MALIGNANCY

The varied appearance on cross-sectional imaging of AIP can make for a diagnostic quandary. For example, in a case series of the early clinical experience encompassing 37 patients with AIP between the years 1989 and 2005[48], 6 patients had been initially misdiagnosed with pancreatic cancer, and two patients had been initially misdiagnosed with biliary malignancy. Authors noted that 5 cases were misdiagnosed on account of the non-existence of, or unfamiliarity with, the entity of AIP. In another early report, 9 patients among a series of 17 patients with AIP were initially suspected to have pancreatic cancer[36]. The authors cited a number of variables of the cohort that raised concern for pancreatic malignancy, including: demographics (14 patients were male, 16 patients older than 60 years), clinical presentation (jaundice in 13 patients), serum studies (9 patients had elevated tumor markers), and radiologic evidence of biliary duct stenosis (16 patients).

Given the potential of overlapping clinical and radiologic presentations of AIP and important differential considerations such as pancreatic malignancy, numerous subsequent investigations have sought to discern AIP from a malignant etiology. In an early study, investigators retrospectively compared findings from nine patients with focal AIP with 80 patients with pancreatic cancer, and 11 patients with alcohol-related pancreatitis[49]. Significant factors differentiating focal AIP from pancreatic cancer included: homogeneous delayed enhancement on contrast-enhanced CT, and ERCP findings of long-segment stenosis of the MPD, and a lesser degree of MPD dilatation proximal to stricture. Other groups have subsequently employed clinical and radiologic means to differentiate AIP from pancreatic cancer, using CT, MR and PET imaging, and the imaging response to a trial of steroid therapy in diagnostic protocols[11,50]. Imaging features favoring a diagnosis of AIP rather than pancreatic cancer are summarized in Table 1.

Signal and enhancement characteristics

Discerning imaging features of AIP *vs* pancreatic cancer include morphology, attenuation, signal, and enhancement characteristics, and certain specific signs ("capsule" and "penetrating duct" signs).

International consensus guidelines recognize diffuse pancreatic enlargement with delayed enhancement to represent typical findings of AIP[11]. Quantitatively, CT studies on enhancement patterns of pancreatic AIP lesions *vs* malignancy have demonstrated mean CT attenuation in the delayed or hepatic phase of imaging to be significantly greater in AIP than in pancreatic cancer[27,51]. Contrasting data were reported however regarding enhancement in the early or pancreatic phase, possibly due to differences in contrast administration and timing. Among those two studies, Takahashi *et al*[37] found peri-pancreatic stranding and calcifications significantly associated with AIP, while Muhi *et al*[51] observed that the frequency at which calcifications were seen was not statistically significant.

The capsule sign of AIP, as previously described (Figure 1B), while of variable sensitivity, favors a diagnosis of AIP rather than pancreatic cancer when present: studies have shown the capsule sign is significantly more frequently associated with AIP[37,51,52], and rarely reported in pancreatic cancer.

The finding of greater delayed enhancement in AIP (Figure 2B and C) was demonstrated on MR imaging by Hur *et al*[52]. Two groups were assessed at the lesion level, 14 among AIP patients, 28 among pancreatic cancer patients. There was significantly greater delayed enhancement at 3-min post contrast administration in the AIP group (10/14, 71%) in the AIP group compared to the pancreatic cancer group (57%). Signal intensity in the arterial and portal venous phase following contrast administration did not differ significantly.

Using MR imaging, other investigators have sought to discern AIP from pancreatic cancer *via* diffusion weighted sequences. In diffusion weighted MR imaging, the apparent diffusion coefficient (ADC) can be calculated as a measure of free diffusion of assessed water molecules; lower ADC values indicate restricted diffusion[53]. Histopathological correlation of tissue with ADC values bear an inverse association of ADC value and cell density, *i.e.* low ADC values are associated with tissue of high cell density[54]. Early AIP data using diffusion weighted imaging demonstrated significantly decreased ADC in AIP cases, compared to cases of chronic alcoholic pancreatitis and normal controls[55]. Subsequently, investigators have quantitatively shown that ADC values are significantly lower in AIP than in pancreatic cancer. Following steroid therapy among AIP patients, foci of restricted diffusion decreased markedly or resolved, with ADC values increasing almost to that of normal pancreas[51,52,55,56].

In receiver-operating curve analysis, Hur *et al*[52] found that a threshold ADC value of 1.26×10^{-3} mm^2/s, below which would distinguish AIP from pancreatic cancer, yielded a sensitivity of 83.3% and a specificity of 79.2%. Similarly, in sensitivity analysis of ten patients with AIP and 70 patients with pathologically proven pancreatic carcinoma, Muhi *et al*[51] applied two criteria in tandem, delayed enhancement and ADC less than 0.88×10^{-3} mm^2/s, to suspected cases of focal AIP, achieving sensitivity and specificity of 100%.

Main pancreatic duct involvement

Dilatation of the MPD may be seen in both AIP and pancreatic cancer. However, AIP demonstrates a lesser degree of MPD dilatation by both conventional and MR/MRCP imaging than that seen in pancreatic cancer, typically less than 4 mm[34,35,51,52]. This pattern reflects that seen by ERCP, where AIP typically demonstrates long segment narrowing over a segment greater than 3 cm (Figure 3A), with upstream dilatation less than 4 mm[49]. In receiver-operating curve analysis conducted by Muhi *et al*[51], the group found that a threshold value of 4 mm of upstream MPD dilatation on MRCP yielded sensitivity of 100% and specificity of 76% for AIP. Additionally, multiple sites of MPD narrowing (Figure 1C) favor the diagnosis of AIP rather than pancreatic cancer, as per international consensus guidelines[11,35]. Complete obstruction of the MPD and abrupt cut-off of the MPD however, are findings differentially associated with pancreatic cancer rather than AIP[37,51].

Studies have also evaluated the value of the 'penetrating duct sign' in differentiating AIP from pancreatic cancer. Initially associated with ultrasound or ERCP findings of focal pancreatitis[57], this sign represents the finding of a non-obstructed MPD penetrating a focal pancreatic mass lesion. Ichikawa *et al*[58] previously assessed the penetrating duct sign on MRCP to have high specificity in determining inflammatory pancreatic mass lesions, and for distinguishing AIP from pancreatic cancer. Carbognin *et al*[24] found the penetrating duct sign to be present in 6 of 14 AIP cases (43%) by secretin-MRCP. In studies comparing cohorts of AIP patients and pancreatic cancer patients, MRCP studies have found the penetrating duct sign to be of variable sensitivity, but with high specificity for AIP when present. Hur *et al*[52] observed the penetrating duct sign in 3 of 9 AIP patients (33%) and in none of 29 pancreatic cancer patients (0%). Muhi *et al*[51] observed the penetrating duct sign in 8 of 11 AIP patients (73%) and in 3 of 70 pancreatic cancer patients (4%).

Advanced endoscopic techniques, such as intraductal ultrasound may further discern the etiology of existing stricture, whether from mass effect, edema, or wall thickening; Hirano *et al*[59] demonstrated advanced intrapancreatic biliary wall thickening was associated with increased severity of stricturing. Finally, EUS-guided fine needle aspiration with a 19-gauge needle allows for minimally-invasive tissue sampling, and is commonly used to exclude pancreatic malignancy[60]. Endoscopic techniques and devices specific to IgG4-related disease have been recently reviewed[61].

^{18}F-FDG PET findings

As ^{18}F-FDG PET imaging also has high sensitivity for pancreatic cancer[62], investigators have also evaluated the ability of ^{18}F-FDG PET imaging to differentiate AIP from pancreatic cancer[63-66]. Ozaki *et al*[63] detected ^{18}F-FDG uptake in all 15 patients (100%) with autoimmune pancreatitis, compared to 19 of 26 patients (73%) with pancreatic cancer. Lee *et al*[64] detected ^{18}F-FDG uptake in 17 of 17 AIP patients (100%), *vs* 124 of 151 (82%) of patients with pancreatic cancer. Shigekawa *et al*[65] compared ^{18}F-FDG PET between 18 patients with AIP and 20 patients with pancreatic cancer, with uptake observed in 16 (89%) and 18 (90%) patients, respectively. Described patterns of uptake favoring AIP rather than pancreatic cancer include: 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)[63,64]. Extra-pancreatic ^{18}F-FDG uptake at the lacrimal glands, salivary glands, thoracic lymph nodes, biliary duct, kidneys, retroperitoneal space, and prostate have been observed in cases of AIP[63-66].

Overall, studies have demonstrated high sensitivity of ^{18}F-FDG PET among patients with AIP, as well as in patients with pancreatic cancer. Extra-pancreatic foci of ^{18}F-FDG uptake may represent associated lesions in IgG4-related disease, or metastatic foci in pancreatic cancer; the role of ^{18}F-FDG PET imaging in the staging of IgG4-related disease is discussed below. While the existing literature suggest certain patterns of uptake that favor one diagnosis *vs* another, correlative clinical and histopathological data remain essential to the course of management.

IMAGING RESPONSE TO CORTICOSTEROID THERAPY

AIP has been widely shown to be responsive to corticosteroid therapy[4,5,10-12]. Imaging plays a role both in diagnostic protocols that aim to discern AIP from pancreatic cancer by the response to a course of corticosteroids, as well as in the assessment of response to therapy.

Improvement, if not complete resolution, of imaging abnormalities in AIP is commonly seen after steroid therapy. Manfredi *et al*[67] specifically evaluated CT examinations of 21 patients with AIP were reviewed before and after steroid therapy. Notably, baseline studies demonstrated hypo-attenuation of affected parenchyma in 19 patients (90%), contrast enhancement abnormality with contrast material retention at the portal venous phase in 18 (86%) patients and contrast material washout in three (14%), and non-visualized of the MPD within affected parenchyma in all patients (100%). Following steroid therapy, CT demonstrated size reduction of affected pancreatic parenchyma, normalization of pancreatic enhancement in 15 (71%), and normalization of the ap-

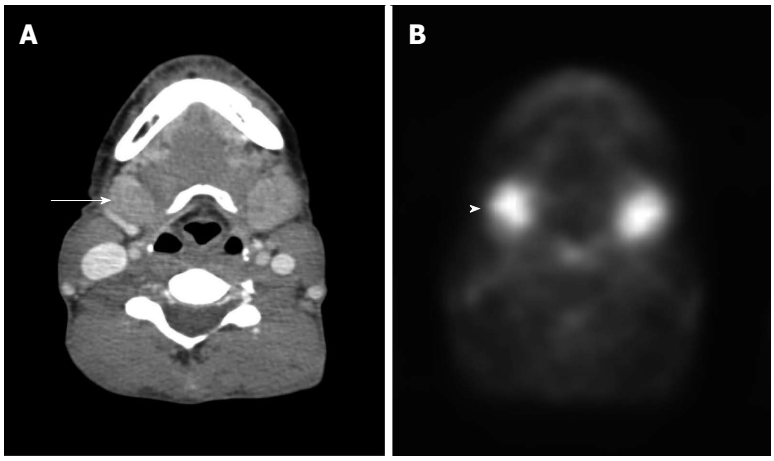

Figure 4 Head and neck findings in IgG4-related disease demonstrated by 2-(18)F-fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography. A: Bilateral, enlarged submandibular glands on computed tomography (arrow); B: Corresponding intense 2-(18)F-fluoro-2-deoxy-d-glucose uptake at the submandibular glands (arrowhead).

pearance of the MPD at affected areas.

Sahani *et al*[68] assessed follow-up CT imaging of 15 AIP patients for imaging factors associated with complete *vs* partial clinical response after steroid therapy. Complete response to treatment was associated with baseline features of diffuse pancreatic parenchymal involvement, and peri-pancreatic stranding. By comparison, partial response was associated with cases with persistent ductal stricture and persistent focal mass-like swelling after resolution of diffuse changes.

Typically, normalization of ^{18}F-FDG uptake abnormalities has also been observed by PET imaging following steroid therapy. In the series reported by Lee *et al*[64], follow-up PET/CT after steroid therapy was performed for eight patients with AIP, whereby residual intense FDG uptake was not observed in each of the eight patients. Matsubayashi *et al*[69] reported on findings of 11 AIP cases with PET imaging both before and three months after the initiation of steroid therapy. ^{18}F-FDG uptake was analyzed semi-quantitatively *via* measure of standardized uptake value (SUV). The mean of maximum SUV among pancreatic lesions differed significantly with therapy, decreasing from 5.12 at baseline to 2.69 following therapy ($P < 0.001$). By the group's SUV criteria, FDG uptake resolved completely in 6 patients (55%), diminished to a faint level in 2 patients (18%), diminished but remained abnormal in 2 patients (18%), and increased after steroid therapy in 1 patient (9%).

Repeat imaging following a trial of steroid therapy of two weeks' duration is recommended in the setting of a new AIP diagnosis, according to international consensus guidelines[11]. Moon *et al*[70] reported imaging (contrast-enhanced CT and ERCP/MRCP) results following a two-week course of steroid therapy among 22 patients with indeterminate imaging for AIP *vs* pancreatic cancer. After the two-week trial, surgical intervention was performed where reduction of pancreatic mass or MPD narrowing was not observed; each of the seven patients who did not demonstrate an imaging response were subsequently diagnosed with pancreatic cancer. Similarly, in the series of Shigekawa *et al*[65], follow-up PET was performed in six AIP patients and in three pancreatic cancer patients, and maximum SUV at follow-up was recorded within one week in five AIP patients and in all three pancreatic cancer patients. In four AIP patients, the change in maximum SUV was greater than 10%, while this value was increased or within 10% of baseline in the three patients with pancreatic cancer.

IMAGING OF IGG4-RELATED DISEASE: EXTRA-PANCREATIC FINDINGS

The observation of extra-pancreatic abnormalities among patients with AIP contributed to the understanding of IgG4-related disease[3,5]. The imaging of extra-pancreatic findings of IgG4-related disease has been reviewed previously[28,39]. Extra-pancreatic organs that may be involved include: the biliary tree, gallbladder, kidneys, retroperitoneum, mesentery, thyroid, lacrimal glands and orbits, salivary glands, lymph nodes, lungs, gastrointestinal tract, and large and medium-caliber arteries (Figures 4 and 5). In a large retrospective series of cross-sectional imaging of 90 patients with AIP, extra-pancreatic lesions were detected in 92% of cases[71]. Extra-pancreatic imaging abnormalities included: hilar lymphadenopathy (78%), wall thickening of bile ducts (78%), peri-pancreatic or para-aortic lymphadenopathy (56%), lung lesions (51%), swelling of lachrymal and salivary gland lesions (47%), retroperitoneal fibrosis (20%), renal lesions (14%), and mass lesions of the ligamentum teres (2%).

While the majority of reports on extra-pancreatic findings of IgG4-related disease center on conventional cross-sectional modalities such as CT and MR, radiopharmaceutical imaging, predominantly with ^{18}F-FDG PET but also with gallium-67, has also been reported. In the case of gallium-67, a case series among 24 AIP patients demonstrated high pancreatic uptake in

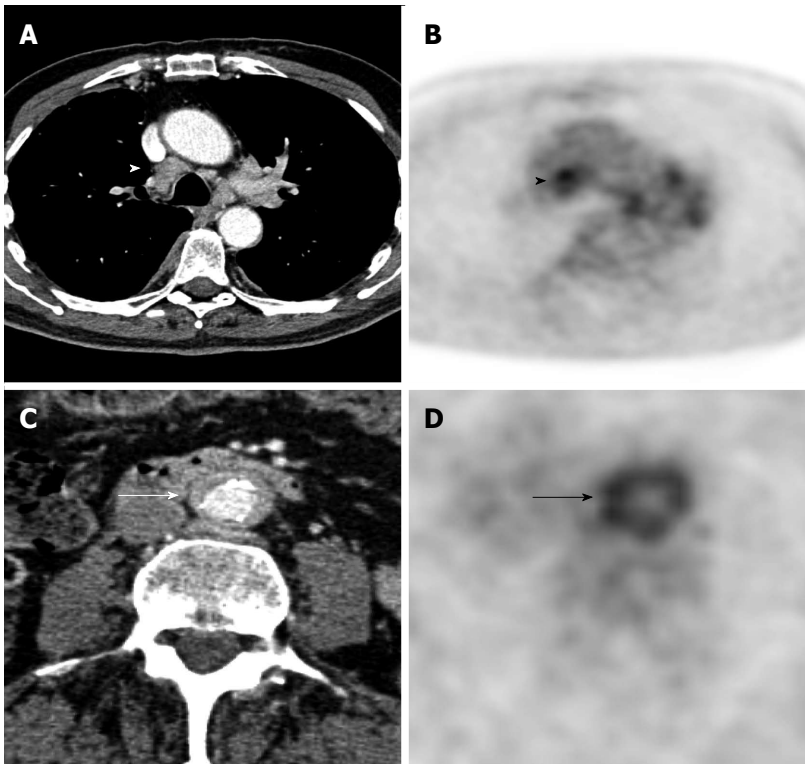

Figure 5 Thoracic and abdominal findings in IgG4-related disease demonstrated by 2-(18)F-fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography. A, B: Paratracheal mediastinal lymphadenopathy on computed tomography (CT) (A, white arrowhead) and positron emission tomography (PET) (B, black arrowhead); C, D: Retroperitoneal fibrosis on CT (C, white arrow) and PET (D, black arrow).

16 patients (67%), which resolved after corticosteroid therapy[72]. Pancreatic uptake was significantly associated with elevated serum IgG4 levels, as was hilar gallium-67 uptake. In a series of 13 patients who underwent gallium-67 imaging, high uptake was detected in the pancreas, bilateral hila, salivary glands, lacrimal glands, and periaortic lesions in 10 (77%), 10 (77%), 7 (54%), 7 (54%), and 2 (15%) patients, respectively[73]. Compared with gallium-67, imaging with ^{18}F-FDG is more commonly performed and reported on account of its favorable dosimetry and signal localization characteristics, and is discussed in further detail below.

Renal findings

Certain extra-pancreatic findings have been specifically investigated among patients with AIP. A retrospective study of 2007 investigated renal findings on CT and MRI among patients with AIP[74]. Of 40 patients with CT or MR imaging at presentation, 14 (35%) had renal involvement (12 with parenchymal involvement and 5 with extra-parenchymal involvement). Renal parenchymal lesions had decreased enhancement, and appeared as small peripheral cortical nodules, as round or wedge-shaped lesions, or as diffuse patchy involvement. Thirteen patients with underwent a follow-up study; renal lesions in 10 patients (77%) regressed (9 after steroid treatment, 1 spontaneously) but progressed in three patients without steroid treatment.

In another study of 18 patients with AIP and no history of renal disease, seven patients were found to have renal involvement (39%)[75]. In 4 patients, lesions appeared as multiple renal parenchymal nodules showing decreased enhancement; in 2 cases, diffuse thickening of the renal pelvis wall was seen; in 1 patient, an ill-defined low-attenuation mass-like lesion was identified. None of the lesions was visible on non-contrast-enhanced CT scan. In each of these seven patients, renal lesions regressed after steroid treatment (100%).

Head and neck findings

Pertaining to the head and neck, IgG4-related disease may affect a variety of sites[76], but typically are iso- to hypo-intense on T2-weighted MR imaging. Affected sites include: salivary glands, lacrimal glands, orbits, thyroid gland, lymph nodes, sinonasal cavities, pituitary gland, and larynx (Figure 2). Multiples sites are typically involved. CT imaging of involved organs may demonstrate enlargement or decreased attenuation. MR findings vary, but lesions typically have relatively low signal T2-weighted signal intensity on account of increased cellularity and fibrosis. A retrospective study of 17 patients with IgG4-related disease of the head, neck and brain demonstrated the following distribution of abnormalities: parotid gland 14 (82%), submandibular gland 10 (59%), lacrimal gland 7 (41%), pterygopalatine fossa 3 (18%), pituitary gland 2 (12%), and skull base dura mater 2 (12%)[77]. Lesions presented as either an enlarged gland or glands, or as focal nodules or masses. All lesions were well-defined, showed

homogeneous enhancement, and appeared iso- to hypo-intense on T2-weighted MR imaging. No lesion showed vascular occlusion or compression, or destruction of adjacent bony structures. In a separate study of 15 patients with IgG4-related disease of the head, neck and brain[78], the distribution was as follows: lacrimal gland 8 (53%), cranial nerve involvement 7 (47%), with the infraorbital nerve involved in 4, orbital pseudotumor 5 (33%), and pituitary gland 5 (33%). All lesions were hypo-intense on T2-weighted MR images.

^{18}F-FDG PET imaging in IgG4-related disease

Extra-pancreatic findings have been described by ^{18}F-FDG PET imaging in IgG4-related disease in case reports[79-82] and case series' (Figures 2 and 3)[69,83,84]. In one study of six patients with AIP, whole-body ^{18}F-FDG PET or PET/CT examinations were reviewed at baseline and during or following steroid therapy in 5 patients (and in one patient who did not receive steroid therapy)[82]. Baseline PET imaging revealed intense pancreatic in all six patients. Intense ^{18}F-FDG uptake at pancreatic and extra-pancreatic sites resolved during or following steroid therapy in five patients; in the one other patient, who did not receive steroid therapy, pancreatic uptake resolved while uptake persisted at salivary glands and lymph nodes. In the series of Matsubayashi *et al*[69], extra-pancreatic uptake abnormalities were observed in 11 of 13 (85%) of cases; among 11 cases with follow-up PET imaging, abnormalities either resolved or decreased at three-month follow-up PET imaging in seven of nine (78%) cases.

The utility of FDG-PET in the staging and monitoring of IgG4-related disease was evaluated in a multicenter retrospective study involving 46 ^{18}F-FDG PET/CT examinations among 21 patients[83,84]. Imaging at diagnosis or onset of relapsed disease was available for 19 patients, with abnormal ^{18}F-FDG uptake detected among all 19 patients (100%). Results of FDG-PET/CT before and after treatment were available for 12 patients. Follow-up ^{18}F-FDG PET imaging demonstrated the following: complete normalization of ^{18}F-FDG uptake in five patients (42%); mixed response in three patients (25%), with sites of complete resolution, increase in uptake at existing sites, and foci of new uptake; no change in uptake abnormality in two patients (17%); and increased ^{18}F-FDG uptake despite treatment in two patients (17%), leading to new diagnoses of B-cell lymphoma and Castleman's disease. Correlative concurrent imaging *via* other modalities (US, CT, MRI) was available for 31 PET/CT evaluations. When abnormal findings from clinical examination or other imaging modalities were taken as the reference standard, the sensitivity for the PET/CT and CT to detect IgG4-RD organ involvement was 83% and 73%, respectively. False-negative PET/CT findings were associated with small focal lesions of the lacrimal glands, kidneys, lungs, and pachymeninges, or for inactive disease.

Given the multiple modalities available by which to diagnose and monitor the response to treatment in IgG4-related disease, further investigation correlating patient outcomes to imaging features, to assess for prognostic and predictive factors of treatment response and optimize patient care, are warranted.

CONCLUSION

Along with clinical, laboratory, and histopathological data, imaging plays an important role in the diagnosis and management of AIP, and more broadly, within the spectrum of IgG4-related disease. In addition to the defined role of imaging in consensus diagnostic protocols which have been established in order to discern AIP from important differential considerations such as pancreatic cancer, various imaging modalities can provide complementary data to address specific clinical concerns. These include contrast-enhanced CT and MR for pancreatic parenchymal lesion localization and characterization and ERCP and MRCP to assess for duct involvement. While the imaging appearance of AIP varies widely, certain imaging features are more likely to represent AIP than alternate diagnoses such as pancreatic cancer. Multiple systemic sites of involvement are often seen in AIP and IgG4-related disease, are amenable to CT, MR, and ^{18}F-FDG PET localization, and typically respond to corticosteroid therapy. Areas of further investigation include prognostic factors of treatment outcome, and optimal selection of imaging follow-up for treatment monitoring.

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