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REVIEW

Imaging in pancreatitis: current status and recent advances

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ABSTRACT

Introduction: Imaging of the pancreas has been challenging because of its retroperitoneal location but this has evolved significantly the past decade.

Areas covered: Based on an enhanced understanding of the natural course, the terminology to address the various complications of acute pancreatitis has been updated. These new terminologies and the various complications have been reviewed. The role of imaging for evaluating the etiology of recurrent acute pancreatitis, to recognize complications and assess the need for interventions have been discussed in detail. The role of imaging for diagnosis of early non-calcific chronic pancreatitis and distinguishing inflammatory masses from neoplastic masses have been elucidated. Imaging features of autoimmune pancreatitis and its extra-pancreatic manifestations have been covered in a separate section.

Expert opinion: A detailed understanding of the recent advances in the imaging modalities is crucial as it impacts management.

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KEYWORDS
Acute pancreatitis; chronic pancreatitis; necrotizing pancreatitis; imaging

1. Introduction

Imaging of pancreas is daunting given its relatively small size and retroperitoneal location [1]. The terminology of pancreatitis particularly acute pancreatitis and its myriad complications has been redefined based on our improved understanding of the natural course of the disease process. It is crucial to understand these updates as it may impact management decisions particularly interventions. This review article will primarily focus on briefly reviewing the latest terminology associated with pancreatitis and give an insight into the various imaging features of pancreatitis that influences management. We will also evaluate the current evidence for the efficacy of these imaging modalities in the assessment of acute and chronic pancreatitis.

2. Acute pancreatitis

Acute pancreatitis (AP) is a dynamic inflammatory process involving the pancreas, peripancreatic tissues and less commonly remote organ systems [1–3]. Diagnosis of AP is based on at least two of the three criteria: abdominal pain consistent with pancreatitis (classically epigastric pain radiating to the back), a threefold increase in serum amylase or lipase levels and imaging findings consistent with acute pancreatitis [2]. In 1992, the Atlanta classification was introduced as the first systematic attempt to categorize the severity of AP [4]. In this classification, patients were categorized as mild or severe acute pancreatitis on the basis of absence or presence of organ failure, respectively, [4]. The initial Atlanta classification represented significant progress, but improved knowledge of disease course, evolving imaging and management options demanded an urgent need to revise and update the Atlanta classification [5]. Accordingly, a new subset of AP patients with local complications with substantial morbidity but little mortality was added to the new classification- moderately severe acute pancreatitis [6]. As per the revised Atlanta classification, AP was stratified into two morphologic subtypes based on imaging findings: interstitial edematous pancreatitis and necrotizing pancreatitis (NP) [3]. Interstitial edematous pancreatitis is characterized by focal or diffuse pancreatic enlargement and homogenous enhancement of the gland with peripancreatic fat showing some inflammatory haziness or mild stranding [3]. The enhancement of the gland may be less avid than that of the normal pancreas due to interstitial edema [7]. Nearly 5–10% of patients with AP develop NP [2,3]. Necrosis of the pancreas itself is defined by non-enhancement of pancreatic parenchyma on contrast-enhanced computed tomography (CECT) [2,3,8]. There are three subtypes of NP based on the anatomic area of necrotic involvement: (a) pancreatic only, (b) peripancreatic only, and (c) combined pancreatic and peripancreatic. Pancreatic parenchymal necrosis alone is seen in lesser than 5% of patients [5] and appears on CECT as lack of pancreatic enhancement [9]. The extent of parenchymal necrosis is divided on CECT into two categories: less than 30% and more than 30% [10]. Peripancreatic necrosis alone is recognized in approximately 20% of patients [11]. Peripancreatic necrosis causes fewer clinical complications and carries a better prognosis than pancreatic parenchymal necrosis [12]. Acute pancreatic parenchymal necrosis with peripancreatic necrosis is the most common type and can be seen in 75–80% of patients with acute necrotizing pancreatitis

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Article highlights

- Contrast-enhanced CT (CECT) is essential to define the extent and severity of necrotizing pancreatitis and guide minimally invasive interventions.
- Secretin Magnetic resonance cholangiopancreatography (sMRCP) permits better visualization of subtle changes and thus is useful for diagnosis of early chronic pancreatitis.
- Endoscopic ultrasound (EUS) as the lone imaging modality has been shown to have poor correlation with histopathology and should therefore be combined with secretin-stimulated MRCP to improve the accuracy of diagnosis of chronic pancreatitis
- Endoscopic ultrasound EUS elastography and contrast-enhanced endoscopic ultrasound (CE-EUS) are new modalities to evaluate for malignancy in advanced CP
- For patients with idiopathic recurrent pancreatitis, there is increasing evidence that endoscopic ultrasound (EUS) is useful to evaluate for gallbladder microlithiasis or sludge as possible etiologies

This box summarizes key points contained in the article.

2.1. Local complications of acute pancreatitis-pancreatic and peripancreatic collections

In the revised Atlanta classification, an important distinction is made between fluid and non-liquefied collection [3,5]. The acute collections are referred to as acute peripancreatic fluid collections (APFC) or as acute necrotic collections (ANC) depending on the absence or presence of necrosis. Interstitial edematous pancreatitis is usually associated with APFC and over time with pancreatic pseudocyst. Necrotizing pancreatitis can be associated with ANC and over time with walled off necrosis (WON). All of the collections can be sterile or infected.

2.1.1. Acute peripancreatic fluid collections (APFC)

These collections usually occur during the first 4 weeks after onset of AP. They predominantly contain only fluid and are visualized as homogenous fluid-attenuation collections that lack a wall and tend to conform to the retroperitoneal spaces. They are caused by pancreatic and peri-pancreatic inflammation or by rupture of one or more small peripheral pancreatic side duct branches [9]. Most APFCs usually remain sterile and resolves spontaneously without intervention [3,13]. Very rarely, a localized APFC persists beyond 4 weeks and evolves into a pancreatic pseudocyst [3].

2.1.2. Pancreatic pseudocyst

Pancreatic pseudocyst refers to a fluid collection surrounded by a well-defined wall with essentially no solid material. It is usually peripancreatic but may be partly or wholly intra-pancreatic [3]. It is thought to arise from disruption of the main pancreatic duct or a side-branch and consequently, aspiration of pseudocyst usually shows fluid with increased amylase [3]. Presence or absence of communication of pseudocyst to pancreatic duct may have implications towards management and is best visualized on the magnetic resonance cholangiopancreatography owing to superior contrast resolution [3]. Occasionally many pseudocysts seal off such communication and will resolve spontaneously [5]. Development of a pancreatic pseudocyst is extremely rare in AP. It can also occur in the setting of 'disconnected pancreatic duct syndrome' (Figure 3) where it arises from leakage from the disconnected duct into the necrosectomy cavity.

2.1.3. Acute necrotic collection (ANC)

These collections are present within the first four weeks of symptoms onset, and are poorly organized often containing varying amounts of solid necrotic material and fluid, may be multiple with a loculated appearance [3]. ANCs often extend from the lesser sac and para-renal spaces into the pancreas within areas of parenchymal necrosis and inferiorly as far as the pelvic sidewalls [7]. During the first week distinction between APFC and ANC may be challenging as both collections appear as areas of nonenhancement on the CECT [5]. Often these non-enhancing areas may have variable attenuation because of non-liquefied components such as hemorrhage, fat and/or necrotic fat [5]. However, any peripancreatic collection associated with established pancreatic parenchymal necrosis should be termed as acute necrotic collection, even if it is homogenous and contains no non-liquefied debris [3]. After four weeks, the ANC typically develops mature encapsulation referred to as walled off necrosis (WON).

2.1.4. Walled off necrosis (WON)

WON consists of a mature encapsulated collection of pancreatic and/or peripancreatic necrosis within a well-defined inflammatory wall [3].

Although any collection could potentially become infected, infections are more frequently encountered in necrotic collections. Diagnosis of infected necrosis is usually made clinically, and the only imaging finding of an infected collection is the presence of gas within the collection [3]. Although gas bubbles in infected necrosis are usually present because of gas-forming organisms, it can also occur as a result of spontaneous fistula to the stomach, small bowel or colon) [14]. Thus, presence of gas in the necrotic collection warrants careful evaluation of the adjacent gastrointestinal wall as this may have implications in endoscopic management. Although image-guided fine needle aspiration has traditionally been used to diagnose infection with a positive aspirate thought to immediately mandate surgical intervention [15]. However, since there is a paradigm shift away from open surgical necrosectomy and towards minimally invasive interventions, the clinical relevance of fine needle aspiration has substantially diminished [8,14]. Besides, there is risk for substantial false-negative (when sampling is attempted too early) and false positive (secondary to contamination) [25% and 15% respectively] [16]. Currently, the indications for purely diagnostic fine needle aspiration is when fungal superinfection is suspected in patients with presumed infected necrosis not improving on broad-spectrum antibiotics [14]

A recent international study assessed the interobserver agreement among expert and nonexpert radiologists, surgeons and gastroenterologists on representative CT of all stages of AP as per the revised Atlanta classification. This study demonstrated good interobserver agreement with the revised Atlanta classification particularly among the expert radiologists, which lends strong support for the widespread

adoption of this revised classification for clinical and research communications [17].

2.2. Vascular complications of acute pancreatitis

Vascular complications are common in moderate severe and severe AP and include splanchnic vein thrombosis, arterial pseudoaneurysm and hemorrhage secondary to erosion of arteries, veins and capillaries either spontaneously from pancreatic enzymes or following surgical, percutaneous and endoscopic interventions. Splanchnic vein thrombosis may frequently involve the splenic vein followed by portal vein, and superior mesenteric vein either alone or in combination Irrespective of the etiology, splanchnic vein thrombosis is known to occur in up to 24% of patients with acute pancreatitis [18]. Although pathogenesis is unclear, the systemic inflammatory cascade associated with AP together with action of proteolytic enzymes weakens vessel wall and precipitates stasis of blood flow [19,20]. Acute portomesentric venous thrombosis appears as persistent, well-defined intraluminal filling defects with central low attenuation which may be surrounded by well-defined, rim-enhancing venous walls. In case of chronic thrombosis, collaterals can be seen in addition as well. Acute thromboses are accompanied by bowel ischemia which presents as alternating intramural areas of high and low attenuation resulting from submucosal edema or hemorrhage [18]. Small bowel and colonic ischemia with subsequent necrosis and perforation are rare but dreaded complications of severe AP. It is crucial to recognize the CT findings of bowel necrosis including presence of pneumatosis intestinalis, gas in the portomesentric veins and diminished or absent bowel wall enhancement as it carries substantial mortality if not managed expectantly.

Pseudoaneurysms develop when an arterial wall is weakened by proteolytic enzymes and is usually considered a late but possible life-threatening complication of pancreatic necrosis. Pseudoaneurysms often rupture resulting in spontaneous hemorrhage into the necrotic collection, gastrointestinal tract, peritoneum and/or pancreatic parenchyma. They are best recognized in the later-arterial or portal venous phase on a CECT. On CT, MR imaging or angiography, a pseudoaneurysm appears as a focal outpouching of a vessel within the necrotic collection [21].

2.3. Extrapancreatic parenchymal complications

AP is capable of inflicting damage to adjacent parenchymal organs such as kidney, spleen and liver. Splenic involvement may include hematoma, infarction and perisplenic fluid collection secondary to pancreatic enzymes dissecting into splenic hilum as the splenic capsule is contiguous with the peritoneum covering the anterior surface of the pancreas. Renal involvement includes renal infarcts, peri-renal fluid collections and rarely complications with clinical impact such as obstructive hydronephrosis arising from extrinsic compression of the proximal ureter by retroperitoneal collections.

2.4. Role of imaging in acute pancreatitis

Although the diagnosis of AP is essentially clinical, cross-sectional imaging such as CT assessment is indicated when there is a diagnostic uncertainty, detection of gallstones or biliary obstruction, to confirm severity based on clinical predictors or in the setting of clinical deterioration despite conventional management [2]. A subsequent follow-up CT or MR assessment is warranted if there is no significant clinical improvement, clinical deterioration or especially when invasive intervention is contemplated [2]. A multidetector CT with thin collimation and slice thickness (5 mm or less) with 100–150 cc of non-ionic intravenous contrast material at a rate of 3 ml/s, during the pancreatic and/or portal venous phase is recommended. During follow-up a monophasic (portal venous phase) is sufficient. In addition to establishing the diagnosis, CECT can also be used to evaluate the extent and severity of necrotizing pancreatitis, to evaluate for local complications described above, and reassess after interventions for planning further management. Balthazar's CT severity index grades pancreatitis based on the degree of inflammation, presence of fluid collections, and extent of necrosis. A higher CT severity index score is associated with increased morbidity and mortality [22,23]. A modified CT severity index score which incorporates extra-pancreatic complications (e.g. ascites) and vascular complications has a stronger correlation with patient outcomes [24].

Magnetic Resonance Imaging (MRI) is an acceptable alternative to CT in patients with allergy to iodinated contrast material. Since imaging may need to be performed repeatedly, it is preferred in young and pregnant women to minimize exposure to ionizing radiation [21]. For MR, an axial FS-T2 and FS-T1 scanning before and after intravenous gadolinium contrast administration are recommended [2]. Pancreatic necrosis appears as a region of pancreatic parenchyma which does not enhance. Peripancreatic stranding, fat heterogeneity, and necrotic collections are best assessed on T2-weighted images, with liquefied components appearing hyperintense and nonliquefied components appearing hypointense. Hemorrhage is best seen on T1- weighted images [21]. Gadolinium contrast can be administered as long as the glomerular filtration rate is greater than 30 ml/min to avoid the risk of nephrogenic systemic fibrosis [25]. Unenhanced MR imaging can be considered in patients with renal impairment [21]. Magnetic resonance cholangiopancreatography (MRCP) is useful for identifying bile duct stones and stricture. MRCP with secretin administration is typically performed after resolution of the acute inflammatory changes to avoid exacerbating pancreatitis [26]. Secretin-stimulated MRCP is useful to assess the pancreatic duct integrity for disruption or fistulae or stricture [27].

Transabdominal ultrasonography (USG) is sensitive to evaluate for cholelithiasis but less sensitive for distal choledocholithiasis especially microlithiasis. Further, it has a limited role in evaluating the extent of necrosis and its complications as pancreas may be obscured with bowel gas.

Endoscopic ultrasound(EUS) involves using an echoendoscope which generates high-frequency sound waves and is passed through the stomach and duodenum, to evaluate

pancreatic parenchyma and ductal system. When compared to USG, EUS has closer proximity to the pancreas and non-interference of the intestinal gases with image acquisition. EUS is not generally needed for the diagnosis of acute pancreatitis (AP). If performed at the time of diagnosis, pancreas appears diffusely hypoechoic from pancreatic edema. Less common findings include pancreatic enlargement and peripancreatic fluid collection [28]. Although imaging with CT and MRI is more relevant in assessing severity of pancreatitis, few studies have explored the role of EUS in severity of AP. One study concluded that a geographic hyperechoic area with the pancreas was an adverse clinical predictor of severity [29]. However increasingly, it has emerged as a reliable modality for the diagnostic evaluation of patients with idiopathic acute pancreatitis since studies have suggested that gallbladder microlithiasis or sludge can explain cases of idiopathic pancreatitis in up to 75% of the patients [2]. Additionally, congenital anomalies such as annular pancreas, choledochocele, anomalous pancreato-biliary junction and pancreatic divisum can be diagnosed using EUS. It is additionally valuable in detecting undiagnosed chronic pancreatitis in patients with idiopathic recurrent attacks of pancreatitis. A recent prospective study evaluating use of EUS in patients with acute idiopathic pancreatitis revealed a diagnosis in 46% of the cases who had a single episode and 85% of the cases with multiple episodes [30]. In a recent systematic review of 13 studies, EUS identified additional diagnostic information in 61% of patients with IAP, with 41% having biliary tract disease [31]. Currently there is a slight debate regarding the initial work-up after an idiopathic episode of pancreatitis [32]. EUS is superior to MRCP in excluding the presence of small (<5mm) gallstones but MRCP is less invasive, less operator-dependent and probably more widely available than EUS [2]. In a recent prospective study to compare the results of EUS and MRCP to diagnose etiology for idiopathic pancreatitis, the diagnostic yield of EUS was higher than MRCP (29 vs. 10.5%). EUS was more accurate in identifying biliary etiology whereas MRCP identified pancreatic duct abnormalities, such as intraductal papillary mucinous neoplasm of the pancreas or chronic pancreatitis. The combination of EUS and MRCP revealed 50% of etiologies and was successful in reducing recurrent attacks in two-third of patients [33]. Thus, EUS should be considered as the first strategy towards the etiological evaluation of IAP irrespective of presence of gallbladder and secretin-stimulated MRCP should be considered as a complimentary tool rather than competitive [32].

The timing of EUS examination after an acute episode of pancreatitis is controversial as different studies have used different timing [32]. Majority of the studies have performed EUS, a month after an episode of AP, when patients are asymptomatic and are able to resume oral diet [30,33–36]. This usually allows time for the parenchymal changes from an acute episode to resolve, as inflammation and/or necrosis can mask and prevent visualization of subtle pancreatic lesions during the acute phase [33]. Although there is a risk of missing papillary/ampullary stones and early/small periampullary tumors as patients may be lost to follow up after discharge, delaying EUS for 4 weeks after an acute episode of pancreatitis is currently recommended.

3. Chronic pancreatitis

CP has been defined as 'a continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and/or permanent loss of function' [37]. Common features of well-established advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications (Figures 1 and 2), pancreatic exocrine insufficiency, pancreatic endocrine dysfunction and dysplasia [37]. It has been postulated that CP progresses from minimal patchy focal disease characterized by mononuclear infiltrate and fibrosis to a more diffuse distribution with overt signs of chronic inflammation such as calcification [38]. Very frequently acute exacerbation of chronic pancreatitis may result in focal edema making it indistinguishable from a neoplastic mass. Imaging is critical to

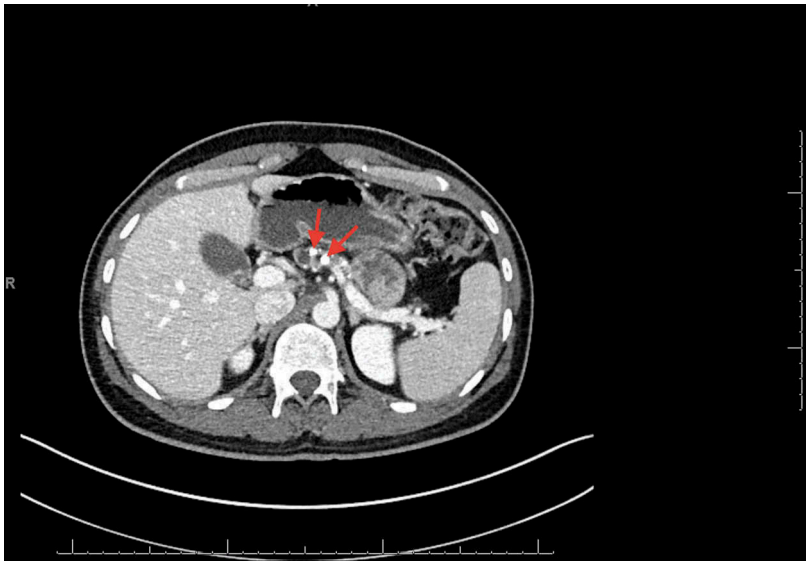

Figure 1. Axial view of Abdominal CT scan showing pancreatic duct calculi in a patient with chronic calcific pancreatitis.

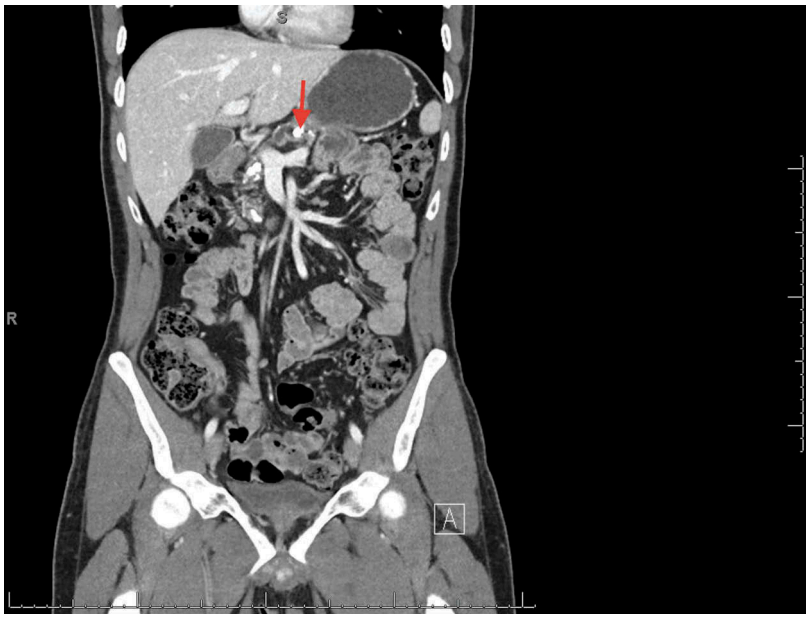

Figure 2. Coronal view of Abdominal CT scan showing a pancreatic duct calculus in a patient with chronic calcific pancreatitis

distinguish such inflammatory pseudotumor from malignancy which is common in this population.

3.1. Early diagnosis of chronic pancreatitis

This could potentiate early behavioral modification (such as smoking cessation and alcohol abstinence) which could alter the course of the disease and also facilitate timely referral to appropriate sub-specialties to prevent and monitor long-term complications of CP [39]. An accurate diagnosis of CP at its early stages remains challenging however, since the characteristic signs of chronic pancreatitis take years to decades to develop, and early parenchymal inflammatory and fibrotic changes may be very subtle [38]. The ideal imaging test should be able to reliably identify pancreatic pathologies at early stages. Discussion of imaging modalities below will touch on the ability of each of these methods to detect both early and advanced chronic pancreatitis.

3.2. Role of imaging in chronic pancreatitis

Transabdominal ultrasound, despite being noninvasive and inexpensive is limited in its diagnostic utility since bowel gas and patient's body habitus may obscure visualization of the pancreas [40]. Classic sonographic findings of CP are pancreatic calcifications (Figures 2 and 3) which are seen as multiple echogenic foci in as many as 40% of patients [41]. While transabdominal USG may be useful to visualize pseudocyst, and complications of chronic pancreatitis such as biliary strictures and splenic vein thrombosis, majority of findings are neither sensitive nor specific in aiding a diagnosis of CP [40].

CECT, with its wide availability is considered to be the best initial imaging for CP. Multidetector CT with multiple phase imaging following contrast enhancement and thinner collimation allows comprehensive evaluation of the pancreas [40]. Classical CT findings in CP include dilatation of the pancreatic duct with side-branches, pancreatic calcifications and parenchymal atrophy. Main pancreatic duct is classically beaded and irregular. It is to be noted that pancreatic parenchymal atrophy is neither sensitive nor specific and could represent normal aging process [40]. CT also aids in identifying complications attributable to CP including pseudocysts, splanchnic vein thrombosis, arterial pseudo-aneurysms and pancreatico-pleural fistulas [40]. The presence of a 'duct-penetrating' sign wherein a dilated duct or its branch penetrates the apparent mass favors pseudotumoral pancreatitis. While pancreatic ductal dilation with

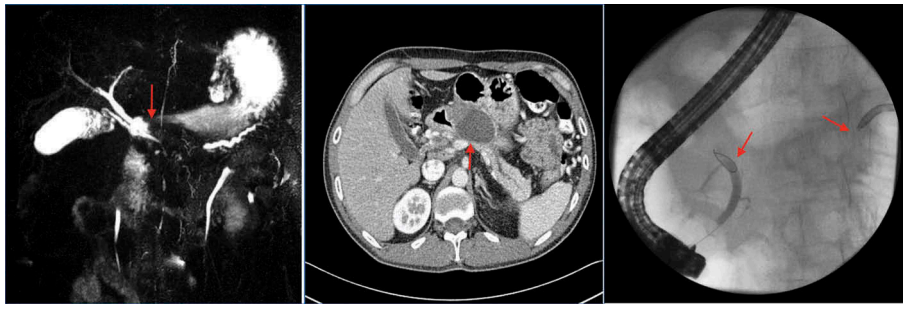

Figure 3. Disconnected pancreatic duct is shown on three different imaging modalities: MRCP, Axial CT view and ERCP (arrows show point of discontinuity.

associated mass at the site of obstruction and resultant atrophy, vascular invasion and metastasis favors malignancy [42].

While making a diagnosis of advanced chronic calcific chronic pancreatitis is fairly straightforward by standard imaging techniques, making a diagnosis of non-calcific chronic pancreatitis in patients presenting with chronic abdominal pain is difficult and controversial [43]. An accurate diagnosis of CP in the absence of overt manifestations is challenging, given its heterogeneous initiation, patchy distribution of disease, and variable progression [38].

MRI with secretin-stimulated MRCP (sMRCP) is another useful modality, particularly in the case of early chronic pancreatitis as it permits a more accurate visualization of subtle ductal changes in the early stages of CP and an indirect estimation of exocrine pancreatic reserve [43]. Pancreatic parenchyma is best assessed on non-contrast, T1-weighted, fat-suppressed images and arterial phase post contrast images [42]. Normal pancreas shows high signal on T1-weighted sequences because of abundant protein within the gland. With the aid of fat suppression, the contrast between suppressed retroperitoneal fat and the gland increases which enhances the sensitivity to detect pathology when present. Initial morphologic changes in the pancreatic parenchyma in early chronic pancreatitis include segmental or diffuse decrease in the anteroposterior diameter of the pancreas due to acinar atrophy. Pancreas signal then decreases on T1-weighted fat-suppressed images with progressive loss of the pancreatic glandular acini [42].Contrast enhancement in normal pancreas peaks arterially and the contrast washes out in a linear fashion in the venous phase. In CP, capillary blood flow is impaired secondary to fibrosis and the gland reaches it maximal enhancement in the venous phase [42].

Secretin-stimulated MRCP involves intravenous administration of secretin based on body weight with T2-weighted MRCP sequences taken every 15–30 s for 15 min after infusion which enables dynamic visualization of changes in the pancreatic ductal system [38]. Main pancreatic duct which usually measures less than 3 mm distends about 66% in response to secretin and then returns to baseline in about 10 min. Secretin administration in CP demonstrates less distension of the pancreatic duct and superior visualization of subtle irregularities and side-branches due to decreased pancreatic secretion and fibrosis. Further secretin stimulates the production of water and bicarbonate-rich fluid in the duodenum. In normal individuals, fluid appears rapidly in the periampullary duodenum, fills and distends the duodenal bulb, and then progresses past the genu. In CP, there is a delay in filling and entry in to the duodenum and decreased distension of the duodenum. Although calcifications are more readily seen in CT scans, MRI imaging is superior in detecting complications such as pseudocysts, fistulae formation, biliary strictures, and vascular complications [42].

In a recent study, Trikudanathan et al. found that two or more MRI/s-MRCP features (pancreatic ductal irregularity, stenosis, dilation, side branches, cysts, atrophy, decreased T1 signal intestinal, and duodenal filling) provided the best balance of sensitivity (65%), specificity (89%), and accuracy (68%) to differentiate abnormal (fibrosis score at least 2) from normal pancreatic tissue [43]. Three or more of these features were more accurate in diagnosing advanced fibrosis. There was also a significant correlation between the number of s-MRCP features and the severity of fibrosis ($r = 0.6$, $P < 0.0001$). A linear regression after taking age, smoking, and body mass index into consideration showed that main pancreatic duct irregularity, T1-weighted signal intensity ratio between pancreas and paraspinal muscle, and duodenal filling after secretin injection were independent predictors of CP [43]. Another recent study from the Indiana University showed that T1 weighted MR signal has a high sensitivity (77%) and specificity (83%) for detection pancreatic exocrine dysfunction and is helpful in evaluation of early CP [44].

Recent MRI advances in the horizon include the universal use of high field strength magnets which enables higher signal to noise in the pancreas, and using these high field strength magnets permits visualization of more subtle abnormalities in the pancreas [40]. Since CP has decreased and delayed enhancement, perfusion MRI can detect subtle alterations in pancreatic parenchymal perfusion. Diffusion-weighted MR imaging is a T2 weighted modality that assesses the restriction of free Brownian motion (diffusion) of water molecules in the gland [40,42]. More the fibrosis, there is less likely diffusion of water molecules in the gland as measured by the 'apparent diffusion coefficient (ADC)'. This is especially prominent when a focal region of the pancreas is fibrosed and is particularly useful to distinguish pseudotumor pancreatitis from pancreatic cancer as ADC values are distinct [45]. Other emerging innovative technologies including MRI elastography which evaluates tissue stiffness, T1- mapping for the quantification of fibrosis and pancreatic fluid flow dynamics imaging await prospective evaluation [46–49] To summarize, while MRI is a great tool to detect subtle ductal and parenchymal features of CP, without risk of ionizing radiation, there is an urgent need to validate a staging system for CP based on the emerging innovations.

Endoscopic ultrasound (EUS) is often useful to diagnose early CP as it has the ability to visualize subtle alterations in pancreatic parenchyma and duct before other imaging modalities and functional tests are abnormal [40]. EUS diagnosis of CP is based on ductal and parenchymal criteria described by the International Working Group using minimum standard terminology (MST) [50]. Parenchymal features include hyperechoic foci, hyperechoic strands, lobularity and cysts. Ductal features include main pancreatic duct stricture, dilation, irregularity, and side-branches. Among individual features only duct dilatation and lobularity had good interobserver agreement, although there was moderately good overall agreement for the final diagnosis of CP [51]. It was hoped that the use of weighted criteria and stricter definition would reduce interobserver variability among endosonographers and would decrease over diagnosis [39]. In order to resolve these controversies, the consensus-based Rosemont classification was developed to standardize EUS diagnosis of CP [14]. This classification integrates weighted criteria into a four-level diagnostic stratification system which grades the likelihood of CP (normal, indeterminate, suggestive and consistent with CP) [52]. Both the standard scoring system and the Rosemont classification appear to have a fair degree of concordance, although the Rosemont classification was more restrictive in

making a diagnosis [53]. However, contrary to expectations, use of the Rosemont classification did not significantly improve interobserver agreement compared with the standard scoring [54].

Multiple studies have attempted to validate the standard EUS features with the gold standard namely histopathology [54–57]. In a study which was the largest study which exclusively included only non-calcific chronic pancreatitis and correlated histopathology from the entire pancreas showed that EUS criteria correlates poorly with fibrosis with a sensitivity of only 61% [58]. Six or more features is needed to establish a definitive diagnosis of CP. Rosemont classification also did not show significant correlation with histopathology [39]. Thus, there is an urgent need to come up with an evidence-based, more stringent EUS criteria for early diagnosis of CP which takes into account patient characteristics such as age, sex and BMI, as well as smoking and alcohol exposure. From the authors' experience the combination of EUS along with secretin-stimulated MRCP provides a reliable imaging strategy to diagnose CP which needs to be corroborated further with multicenter studies. Elastography which provides a real-time method for evaluation of tissue stiffness has been combined with conventional EUS. Preliminary retrospective studies show a direct relationship between the strain ratio and probability of exocrine pancreatic insufficiency [59]. Although not widely available in United States, contrast-enhanced EUS appears to be promising particularly to evaluate for malignancy in advanced CP.

4. Autoimmune pancreatitis

Autoimmune pancreatitis (AIP), a chronic fibro-inflammatory steroid-responsive disease of the pancreas, was first proposed by Yoshida et al., to describe an inflammatory pancreatic disease reminiscent of autoimmune hepatitis [60]. The international consensus diagnostic criteria (ICDC) for AIP recognizes two sub-types for AIP based on their distinct natural history, clinical, and histologic features [61].

Type I AIP also known as lymphoplasmacytic sclerosing pancreatitis (LPSP) has often been described as the pancreatic manifestation of multi-organ IgG4 related disease and accounts for >95% of cases [61,62]. IgG4 related disease refers to a multi-organ syndrome characterized histologically by dense lymphoplasmacytic infiltrate, fibrosis without granulocyte infiltration, storiform fibrosis, obliterative phlebitis in affected organs, frequent elevation of serum IgG4 levels, abundant IgG4 plasma cells in affected organs (>10 per high power field) and dramatic response to steroids [61,63]. Most common clinical presentation is painless jaundice (60–75%), but other potential presentation includes pancreatic mass or focal pancreatic enlargement without jaundice (Figure 4(a)), pancreatic insufficiency in the form of new or worsening diabetes and steatorrhea and rarely acute pancreatitis [62,63]. Common previous or concurrent extra-pancreatic involvement includes proximal biliary stricture from sclerosing cholangitis, retroperitoneal fibrosis and/or chronic aortitis (Figure 4(b)), bilateral sub-mandibular enlargement with sclerosing sialadenitis, renal parenchymal lesions (Figure 4(c),(d)) with interstitial nephritis and orbits with pseudolymphoma [61–63].

Type II AIP also referred to as idiopathic duct-centric chronic pancreatitis (IDCP) is characterized by predominant periductal disruption with extensive infiltration by neutrophils (GEL) and occasionally lobular neutrophilic infiltration [64,65]. It is much less common, partly due to the challenges in establishing a

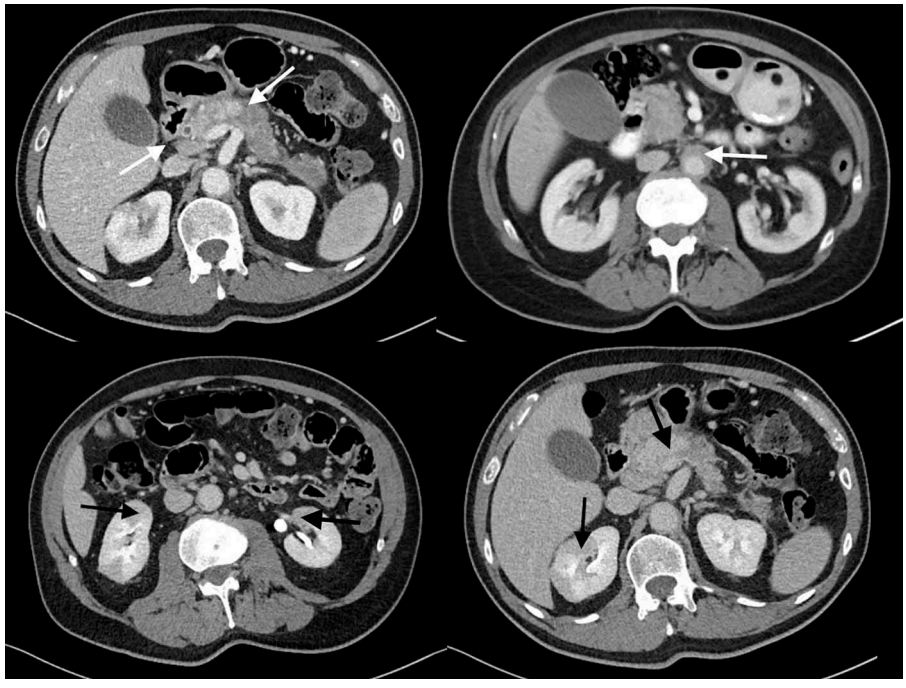

Figure 4. Axial view of Abdominal CT scan Autoimmune pancreatitis. (a) Autoimmune pancreatitis with diffuse enlarged sausage shaped pancreas with decreased attenuation on CECT and diffusely dilated bile duct. (b) Autoimmune pancreatitis with descending aortic involvement (periaortitis). (c) Autoimmune pancreatitis with renal involvement causing multiple low attenuating bilateral cortical renal lesions. (d) Diffusely enlarged sausage shaped pancreas due to autoimmune involvement along with multiple right-sided low attenuating cortical renal lesions.

diagnosis and has been mainly described in Europeans and in North America [63]. It equally affects younger males and females (average age of presentation is 31 years) with approximately 15% of patients with concurrent inflammatory bowel disease [66]. Most common clinical presentation is acute pancreatitis which is seen in nearly 50% of the patients. Other presentations include focal pancreatic mass, symptomatic pancreatic duct stricture, jaundice from the extrinsic compression of the distal bile duct from the pancreatic enlargement, and rarely abdominal pain and imaging abnormalities (Figure 4) without biochemical evidence of pancreatitis [62,63,66].

4.1. Role of imaging in the diagnosis of autoimmune pancreatitis

Imaging serves as adjunct in establishing the diagnosis of AIP, distinguishing it from pancreatic cancer and also to evaluate for extra-pancreatic manifestations in type 1 AIP. Classical appearance of AIP on cross-sectional imaging seen in 30–50% of patients is diffuse 'sausage like' enlargement of the pancreas with effacement of the lobular contours [63]. On CECT, there is a decreased enhancement during the early phase and delayed enhancement in the late phase of contrast due to inflammation [67]. There are corresponding perfusion abnormalities on MRI, including hypointensity of the parenchyma on T1-weighted images with slight hyperintensity on T2-weighted images and delayed enhancement during the late phases of contrast [68]. The low-attenuating rim (termed as capsule or halo sign) is highly specific for AIP, but is seen only in 30–40% of patients at diagnosis [67]. This peripheral rim is thought to represent fibrous tissue due to inflammatory changes of the peripancreatic tissues [69] Other less common parenchymal changes include focal or multi-focal mass-like enlargement, segmental low-density area without mass and diffuse pancreatic atrophy. A morphologic evolution of the imaging findings have been suggested with AIP initially presenting as a focal swelling and progressing into diffuse, featureless, sausage-shaped pancreas. Atrophic pancreatic parenchyma represents a late-burnt-out phase of the disease.

Characteristic ductal changes include long irregular (greater than one-third of the length of the pancreatic duct) or multifocal strictures without marked upstream dilation (<5 mm) and side branches arising from a strictured segment [70]. It is to be noted that dilated main pancreatic duct is distinctly uncommon on initial presentation and should raise a suspicion for an alternative diagnosis [63]. Previously pancreatic stones were thought to be absent in AIP; however, it has been noted in up to 18% of patients, particularly those with recurrent symptoms due to incomplete obstruction and irregularity of the MPD leading to stasis of pancreatic juices [71].Bile duct abnormalities such as smooth tapering of the intrapancreatic portion of the common bile duct or irregularity and stricturing of the intra- and extra-hepatic duct and enhanced bile duct wall thickening are recognized

Although MRCP is less invasive and more easily performed than endoscopic retrograde cholangiopancreatography (ERCP), they are considered less reliable since a portion of the pancreatic duct may not be visible even in healthy people [72]. Since diagnostic ERCP is seldom performed, it is recommended for collateral evidence only when imaging finding are not typical or in seronegative patients without other organ involvement [70]. Secretin administration during MRCP is useful in detecting focal AIP whereby the main duct which is not completely obstructed tends to penetrate the mass after secretin stimulation [69]. At diffusion-weighted imaging, although both pancreatic cancer and AIP are both detected as high signal intensity areas, pancreatic cancer usually presents as a solitary area, while diffuse or multiple high-intensity areas are suggestive of AIP [69]. Furthermore the mean apparent diffusion coefficient (ADC) values are significantly lower in AIP than pancreatic cancer [73].

Although there are no pathognomonic imaging characteristics on EUS for AIP, diffuse pancreatic enlargement with parenchyma that is hypoechoic, patchy and heterogeneous has a high probability of AIP when all these EUS features are present [74]. EUS may also demonstrate a focal hypoechoic mass with main pancreatic duct narrowing, duct wall thickening and upstream dilation of pancreatic duct, with associated enlarged peripancreatic lymph nodes, mimicking pancreatic cancer. Diffuse hypoechoic regions, diffuse pancreatic enlargement, hypoechoic thickened bile duct wall and peri-pancreatic hypoechoic margins favor AIP diagnosis [74]. Biliary tree is usually the most common site of extra-pancreatic organ involvement in AIP and imaging is impacted by the timing of procedure relative to disease onset, therapies provided, presence of indwelling stent and disease course. IgG4 related strictures are typically segmental or long and often extend into the cystic duct and gallbladder. Typical findings involve regular homogenous symmetric bile duct thickening with a hyper-hypo-hyperechoic series of layers of the duct wall [74]. Renal involvement is known to occur in roughly a third of patients with AIP and is classically parenchymal, but may also involve peri-renal tissue, renal sinus or the renal pelvis wall. Renal lesions exhibit low attenuation on CECT, isointensity on T1-weighted MRI and hypointensity on T2- weighted MRI. Renal parenchymal involvement has various patterns, with lesions being multiple and predominantly involving renal cortex. While small peripheral cortical nodules represent a very early stage of renal involvement, round lesions, well-defined wedge-shaped lesions and diffuse patchy involvement reflects the evolution of the renal parenchymal involvement [75]. Other organ involvement includes aortitis seen as thick soft tissue mass around the aorta and its branches, Sclerosing mesenteritis with soft tissue mass encasing mesenteric vessels and involving small bowel mesentery, retroperitoneal fibrosis which results in hydronephrosis. Besides imaging, EUS guided tissue acquisition is vital particularly for the diagnosis of type 2 AIP. The presence of three of the four key histopathogic findings are considered to provide the highest level of diagnostic reliability: lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis and >10 IgG4- positive cells per high power field [74]. The main limitation of fine needle aspiration cytology is that it does not provide tissue architecture to allow histopathologic diagnosis.

Many patients undergo 18F-fluorodeoxyglucose positron emission tomography/CT as a part of work-up for suspected pancreatic cancer. Classical FDG-PET findings for AIP include heterogeneous longitudinal accumulation and multiple localizations, where those for pancreatic cancer are nodular homogenous accumulation and solitary localization. .Although it has limited value in differentiating AIP from pancreatic cancer, characteristic FDG uptake by extrapancreatic organs may assist in distinguishing the two conditions [76].

5. Expert opinion

Adoption of the standard terminology is crucial for the appropriate understanding and management of acute pancreatitis and its complications. Contrast-enhanced computed tomography is vital to define the extent and severity of necrotizing pancreatitis and guides minimally invasive interventions which constitutes the current paradigm of management. Secretin MRCP permits a more accurate visualization of subtle ductal changes in the early stages and provides an indirect estimation of exocrine pancreatic reserve. EUS and secretin MRCP are useful to evaluate for etiology for recurrent pancreatitis. EUS when used as the lone modality has poor correlation with histopathology and should be combined with secretin MRCP to aid in the early and accurate diagnosis of chronic pancreatitis. There is an urgent need for an evidence-based EUS and MRI combined scoring system which evaluates ductal and parenchymal changes and takes into account age, sex, smoking and alcohol exposure for reliable diagnosis of CP. EUS elastography and contrast-enhanced EUS should be explored further.

Looking to the future, there are a few imaging advances on the horizon. The use of elastography which provides a real-time method for evaluation of tissue stiffness in combination with conventional EUS in diagnosing CP is currently being studied. Preliminary retrospective studies show a direct relationship between the strain ratio and probability of exocrine pancreatic insufficiency. The application of contrast-enhanced EUS to evaluate for malignancy in advanced CP is promising. There is also an urgent need for an evidence-based EUS and MRI combined scoring system which evaluates ductal and parenchymal changes and considers age, sex, smoking and alcohol exposure for reliable diagnosis of CP.

Declaration of interest

G Trikudanathan is on the advisory board for Abbvie. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures

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