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EDITORIAL

Pancreatic fluid collections: What is the ideal imaging technique?

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Abstract

Pancreatic fluid collections (PFCs) are seen in up to 50% of cases of acute pancreatitis. The Revised Atlanta classification categorized these collections on the basis of duration of disease and contents, whether liquid alone or a mixture of fluid and necrotic debris. Management of these different types of collections differs because of the variable quantity of debris; while patients with pseudocysts can be drained by straight-forward stent placement, walled-off necrosis requires multi-disciplinary approach. Differentiating these collections on the basis of clinical severity alone is not reliable, so imaging is primarily performed. Contrast-enhanced computed tomography is the commonly used modality for the diagnosis and assessment of proportion of solid contents in PFCs; however with certain limitations such as use of iodinated contrast material especially in renal failure patients and radiation exposure. Magnetic resonance imaging (MRI) performs better than computed tomography (CT) in characterization of pancreatic/peripancreatic fluid collections especially for quantification of solid debris and fat necrosis (seen as fat density globules), and is an alternative in those situations where CT is contraindicated. Also magnetic resonance cholangiopancreatography is highly sensitive for detecting pancreatic duct disruption and choledocholithiasis. Endoscopic ultrasound is an evolving technique with higher reproducibility for fluid-to-debris component estimation with the added advantage of being a single stage procedure for both diagnosis (solid debris delineation) and management (drainage of collection) in the same sitting. Recently

role of diffusion weighted MRI and positron emission tomography/CT with ^{18}F-FDG labeled autologous leukocytes is also emerging for detection of infection noninvasively. Comparative studies between these imaging modalities are still limited. However we look forward to a time when this gap in literature will be fulfilled.

Key words: Acute pancreatitis; Contrast-enhanced computed tomography; Magnetic resonance imaging; Endoscopic ultrasound; Positron emission tomography scan; Pancreatic fluid collections; Acute necrotic collections; Acute peripancreatic fluid collections; Pseudocysts; Walled-off necrosis

Core tip: Contrast-enhanced computed tomography is widely used imaging modality for the diagnosis and staging of acute pancreatitis due to its excellent capacity to demonstrate early inflammatory changes as well as local complications including fluid collections, However, magnetic resonance imaging may be a better imaging technique due to its, nonionizing nature, higher soft tissue contrast resolution, better safety profile of intravascular contrast media, noninvasive evaluation of pancreatic duct integrity and also has superiority in discrimination of internal consistency of pancreatic collections which is useful in further management plan. Role of endoscopic ultrasound and other newer techniques is still in evolving phase.

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INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas characterized by auto-digestion of pancreatic parenchyma, vasculitis and fat necrosis[1]. Two of the following three features are required for diagnosis of AP: (1) abdominal pain consistent with pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or trans-abdominal ultrasonography[2,3].

Morphologically AP can be of two types: interstitial edematous pancreatitis (IEP) and necrotizing pancreatitis (NEP). IEP constitutes a diffuse (or sometimes localized) enlargement of the pancreas due to inflammatory edema and it usually resolves within the first few days[4]. On the other hand necrotizing pancreatitis which is seen in about 5%-10% of patients, commonly manifests as necrosis involving both pancreatic and peripancreatic tissues and less commonly involving only the peripancreatic tissue, and rarely of the pancreatic parenchyma alone. Necrosis develops early in the course of severe pancreatitis and usually well establishes by 96 h after onset of clinical symptoms[5].

The basis of defining morphological classification and local complications in Revised Atlanta classification is CECT. Recent studies have shown that MRI and EUS are better imaging for quantification of solid debris which is the basis for deciding management strategies, and may replace CT in future. Role of the newer technique such as diffusion-weighted MRI (DWI-MRI) and positron emission tomography (PET) CT in the severity assessment and detection of infection noninvasively is still to be established. This editorial is to review the role of all available imaging modalities in differentiating PFCs in patients of AP.

LOCAL COMPLICATIONS OF AP

As per the Revised Atlanta classification[6] local complications of AP comprises of acute peri-pancreatic fluid collections (APFCs), pancreatic pseudocysts, acute necrotic collections (ANCs) and walled-off necrosis (WON). Other local complications include gastric outlet obstruction, splenic and portal vein thrombosis and colonic necrosis.

APFCs

They usually develop in early stage of disease, and establish its borders with retroperitoneum and adjacent organs[6,7]. They can be single or multiple, but their contents are typically homogenous, sterile and lack wall of inflammatory or granulation tissue. Patients with APFCs are asymptomatic and treatment is usually unnecessary. Most of these collections resolve on their own[7,8]. If they do not resolve within a month, they evolve in to pancreatic pseudocysts (which is rarely seen during disease course).

Pancreatic pseudocysts

Pseudocyst is a fluid collection with homogenous internal fluid contents, but without any solid material and enclosed by a clear wall of fibrous tissue. It usually arises from main pancreatic duct or its intra-pancreatic branch disruption resulting in leakage of pancreatic juice; hence high amylase levels are seen in aspirated fluid from these cysts[6]. It is rarely seen following acute pancreatitis except in setting of a disconnected duct syndrome[9] and following surgical necrosectomy.

ANCs

These collections are seen in the setting of necrotizing pancreatitis (within first 4 wk) and consist of inhomogeneous mixture of liquefied, necrotic fatty tissue along with solid pancreatic and extra-pancreatic debris. They can be single or multiple, and are sometimes multiloculated. Differentiating ANC from an APFC may be difficult in the first week of the disease. With passage of time, parenchymal necrosis becomes more obvious, which aids in the distinction between these two. They may gradually resolve, persist as wall-off necrosis or may get infected in course of disease.

WON

Necrotic tissues surrounded by enhancing inflammatory walls are referred as WONs and evolve from ANCs after 4 wk of necrotizing pancreatitis. They can be confined to the pancreatic tissue or at times be away from the pancreas. WONs can be sterile or infected as well as solitary or multiple[6].

ROLE OF IMAGING

Imaging helps in the diagnosis of clinically suspected AP or suggesting alternative diagnosis. It also helps in determination of the cause of pancreatitis like biliary duct obstruction or structural abnormalities. Additionally, imaging can be utilized for assessment of the severity of the disease by identifying pancreatic or peripancreatic necrosis and complications. It has an essential role in classifying fluid collections especially in differentiating APFCs from ANCs and pseudocysts from WON, as presence or absence of solid or necrotic debris in a fluid collection has direct bearing on the outcome as well as on the choice of management strategy.

The choice of appropriate imaging modality depends on the reason for investigation, clinical symptoms, time of onset of symptoms and lab findings.

Role of transabdominal ultrasonogram

Ultrasonogram (USG) is a widely available, cheap, non-invasive investigation and can be repeated as often as necessary. Pancreas visualization using USG is feasible in 75%-93% of patients irrespective of weight or overlying bowel gas[10], It also helpful in identification of biliary lithiasis, exclusion of other causes of acute abdominal pain (medical or surgical) and for separation of severe AP from mild or moderate which is interpreted along with clinical and biochemical parameters. American College of Gastroenterology recommended that trans-abdominal ultrasound should be performed in all patients with AP (strong recommendation, low quality of evidence)[11].

USG is also helpful in monitoring the evolution of fluid collections, which occur as a result of AP, and in guiding diagnostic and therapeutic interventions. A recently published study showed that USG accuracy is comparable to that of endoscopic ultrasound and magnetic resonance imaging in patients with WON for delineation of solid debris but with its limitations in presence of air or high solid content[12].

Advantages of this method are its portable character, high accessibility (cheap equipment, lack of invasion) and dynamic character in real time. Limitations are operator dependence and inability to reproduce images. It cannot replace more efficient examination methods such as CT/MRI especially in case when parenchymal necrosis has to be detected or when the patient suffers from high meteorism.

Role of CECT

CECT is the widely used imaging modality in AP for the diagnosis, severity assessment and morphological classification. It also provides information on presence of collections and their size along with its wall thickness and internal debris. CT is an ideal technique to guide percutaneous aspiration and drainage procedures[13].

Revised Atlanta classification recommended CECT to be done at 5 to 7 d of pancreatitis for more reliably establishing the necrosis which is easily underestimated by immediate CT[9,14]. CECT criteria are used to subdivide AP into two types: IEP and NEP. The criteria for identification of the IEP are relatively homogeneous enhancement of pancreatic parenchyma with mild haziness or peripancreatic fat stranding, whereas lack of pancreatic parenchymal enhancement or necrosis of peripancreatic tissue suggest NEP[6]. Distinction between these two types is important as studies have shown an significant relationship of necrosis with local or systemic complications, hospital stay and death[8,15,16]. The role of recently developed radiological scoring systems based on organ dysfunction and SIRS are also promising in determination of severity and early stratification[17-19].

Additionally local complications of AP are also defined based on CECT[6]. APFCs appear as homogenous collections with low attenuation value without well-defined walls, whereas ANC are heterogeneous collections with varying degree of non-liquid density and without well defined walls. Both these entities usually occur within 4 wk. Later on with progressive liquefaction of pancreatic and/or peripancreatic necrosis, ANC becomes organized and walled-off and termed as WON. The latter appears as heterogeneous collection with both solid and liquid density on CECT[16,20]. On the other hand pseudocyst appears as encapsulated collection of homogeneous fluid density with only liquid component.

Role of CECT in predicting local complications in patients with pancreatic necrosis was evaluated in a prospective study, in which multivariate analysis identified that the degree of pancreatic necrosis and presence of peripancreatic necrosis predicted the development of infected pancreatic necrosis;

whereas transparenchymal necrosis with upstream viable pancreas and no peripancreatic necrosis were associated with pseudocyst development[21]. Heiss *et al*[22] studied the correlation between various morphologic features on CECT with the outcome in a retrospective study of 80 patients with severe AP requiring percutaneous drainage therapy and found that the pancreatic parts exhibiting necrosis (head, body, tail) and the presence of distant fluid collections (posterior pararenal space and/or paracolic gutter) had a significant correlation with mortality. Mortality was 42% if two or all three parts had necrosis whereas it was 20% when none or only one part of the pancreas exhibited necrosis. On basis of presence or absence of distant fluid collections it was 46% and 22%, respectively.

Differentiating WON from pancreatic pseudocyst when visible pancreatic necrosis seen in the initial CECT, is usually not difficult. It is important to note that the necrosis of peripancreatic tissue alone however with normal enhancing pancreas can also develop into WON. Since management of these different types of collections differs, distinguishing between these is vital. Pancreatic pseudocysts can be managed easily by endoscopic methods of simple drainage; however patients with WON require more aggressive endoscopic techniques such as larger tract dilation, placement of multiple stents, aggressive irrigation, and debridement of necrotic tissue by direct endoscopic necrosectomy (DEN) or surgical necrosectomy[23,24]. Recent Studies have shown that EUS-guided drainage using a large-bore fully covered biliary self-expandable tubular metal stent or biflanged metal stent can also provide sufficient drainage, and quick fistula formation[25-27]. The factors determining outcome of standard endoscopic drainage in patients with WON are proportion of solid debris and size of collection. Patients with less than 10% solid debris usually require a one-time endoscopic drainage; multiple sessions are required in patients with 10%-40% solid debris. Patients with > 40% solid debris either need direct endoscopic or surgical necrosectomy[28].

Thus CT imaging helps in delineation of morphology of fluid collections and quantification of the presence of solid debris and fat necrosis (seen as fat density globules) to assess the presence of drainable fluid before intervention.

Although there is no consensus on which imaging modality should be preferred for assessment of organized PFCs, CECT is commonly used in symptomatic collections and for planning therapeutic interventions. Takahashi *et al*[29] retrospectively studied CT of 73 patients with PFCs (45 WON, 28 pseudocysts) to differentiate WON from pancreatic pseudocysts. CT score was also calculated for each PFC. Radiographic features that favored WON included larger size, extension to paracolic or retrocolic space, an irregular border, presence of fat attenuation and debris in the PFC, presence of pancreatic parenchymal deformity or discontinuity, and the absence of dilation of the main pancreatic duct. CT could differentiate WON from pseudocysts, using a CT score of $\geqslant$ 2, with an accuracy of 79.5%-83.6%.

The main limiting factors for CECT are ionizing radiation, use of iodinated contrast material especially in patients with renal failure or contrast allergy and moderate sensitivity in identifying gallstones and biliary stones[30]. The above limiting factors can be overcome by using MRI.

Role of MRI

Similar to CT, MRI can be also used for the diagnosis and severity grading in AP. MR severity index (MRSI) significantly correlated with Ransons score, CTSI, C-reactive protein levels, duration of hospitalization and clinical outcome[31]. It may represent a better imaging technique due to nonionizing nature, higher soft tissue contrast resolution, and better safety profile of intravascular contrast media. Newer innovations in MRI such as the use of phased-array coils, parallel imaging, triggering techniques[32] or motion resistant sequences allow for improved spatial resolution and faster acquisition times making it more practical[33]. MRI also has a role in noninvasive evaluation of peripancreatic soft tissue, pancreatic ductal system and vascular network in a single examination. The concurrent use of secretin improved the diagnostic yield of MRCP in the evaluation of the PD integrity[34].

Acute fluid collections on MR examination are hypointense on T1WI and homogeneously hyperintense on T2WI if the contents are serous; if bleed occurs it appears as hyperintense on T1WI (more evident with fat-suppressed sequences). Simple pseudocysts are hypointense on T1WI and homogeneously hyperintense on T2WI. Their wall enhances slightly in early phases and progressively increases in subsequent phases due to its fibrotic nature; multiplanar MR acquisition improves the visualization of its relationship with surrounding organs. WONs are heterogeneous on T2WI (due to the presence of necrotic debris, bleeding or infection), with proteinaceous fluid contents arranged in layers (liquid-liquid level): the necrotic debris may appear as irregularly shaped regions of low signal intensity within the necrotic collections. Breathing independent T2-weighted sequences such as single-shot echo-train spin echo are useful to evaluate these necrotic collections.

The main advantage of MRI relative to CECT in the evaluation of peripancreatic fluid collections is easier appreciation of solid debris with MRI[35]. A prospective, blinded study compared MR findings with CT and USG to depict solid debris within pancreatic collections prior to intervention. The sensitivity and specificity values, for the prediction of actual drainability were: MR imaging, 100% and 100%; CT, 25% and 100%; US, 88% and 54% respectively[36]. Another recently

published study assessed the reproducibility of CT and MRI findings for debris assessment and presence of ductal communication in patients with symptomatic organized PFCs and found that MRI was superior to CECT for the inter-reader agreement on complexity of pancreatic collections, Also pancreatic duct disruption exclusion can be done more confidently on MRI[37].

Diffusion weighted MRI (DWI-MRI) is a new MRI technique based on diffusion of water protons *in vivo* which is related to the Brownian motion of water molecules within the tissues. DW-MRI yields apparent diffusion coefficient (ADC) as a quantitative parameter. In the literature, limited number of studies have demonstrated successful application of DW-MRI in pancreatic diseases. Yencilek *et al*[38] reported that DWI-MRI and ADC values are helpful in the diagnosis of all subgroups of acute pancreatitis even grade A patients in whom usually there is lack of CT findings. DWI-MRI in AP has been recently evaluated in two studies. One study compared CECT with DWI-MRI in detection of infection and found that sensitivity and accuracy of latter were higher than CT for detection of infection[39]. Another study on use of DW-MRI to differentiate different degrees of severity of AP, showed that DW-MRI is a compatible and safe image option to differentiate tissue image patterns between patients with normal pancreas, mild AP and necrotizing AP, particularly in those with contraindications to contrast-enhanced MRI (which is classically required for determining the presence of necrosis) or CT[40].

Another advantage of MRI over CT is identification of PD disruption which is commonly associated with central gland necrosis. Endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard for detection of PD disruption but is limited by its invasive nature and potential complications such as post-ERCP pancreatitis. MRI/MRCP may serve as a first line of investigation for treatment planning of symptomatic PFCs to assess drainability and pancreatic duct integrity[34]. Drake *et al*[41] showed that MRCP achieved 95% accuracy in detecting pancreatic duct disruption; thus helps in identifying patients who might benefit from early treatment by bridging the duct. MRI also helps in differentiating fluid collections secondary to pancreatitis from other cystic neoplasms.

Therefore, the logic of using MRI over CT in AP hinges on the following points: (1) this imaging method is without radiation hazard so safe in patients with AP requiring repeated imaging; (2) comparable to CT in demonstrating the presence and extent of necrosis, the presence, site, size and extent of PFCs, but better than CT in assessment of the debris content and drainability of these collections; (3) although the definitive evidence of aggravation of pancreatic injury with the use of iodinated contrast used in CT is debatable, yet evidence of a similar injury from use of Gd-DTPA for MRI does not exist; thus MRI appears to be a safer option in this respect; (4) PD integrity can better appreciated in MRCP; and (5) upcoming role of DWI-MRI has given hope for early and noninvasive detection of infected collections in future. The main limiting factor for MRI and its advanced techniques is high cost.

Role of EUS

With a close propinquity of the EUS probe to the pancreas and better spatial resolution than CT or MRI, EUS has emerged as an invaluable tool for assessment of pancreatobiliary diseases. Moreover, EUS is a minimally invasive procedure with relatively less complication rate compared to ERCP. However data regarding the role of EUS in AP is limited.

The increasing usage of EUS for drainage of PFCs has thrown more light on the important diagnostic role which it could define prior to the drainage. Solid debris in collections can be better delineated on EUS even when CT fails to do so. Apart from identifying the small collections behind the gaseous bowel loops and presence of vascular abnormalities within the wall of fluid collection at the site of drainage, EUS always fares better in defining the solid debris and its proportion as a constituent of fluid collections. This information provided by EUS plays an important role in selecting drainage procedure. MRI also provides similar information on solid debris and the results were comparable to EUS in a recent paper[12]. EUS has the best accuracy in characterizing peripancreatic collections prior to endoscopic intervention which can alter the management decision in up to one third of patients because of alternate diagnosis or by identifying anatomical and vascular factors precluding endoscopic management[42,43]. The largest randomized trial comparing different techniques demonstrated a 91% success rate with employment of EUS, compared with 72% when not used[44]. However the disadvantages of EUS are the requirement of monitored anesthesia care, need for expert endo-sonographer, operator dependence, and interobserver variability, inability to characterize in presence of air and difficult to perform in sicker patients with respiratory distress which these patients usually are.

In our experience with pancreatic fluid collections using EUS and CT, solid debris was detected on CT in only 32% fluid collections, whereas EUS delineated solid debris in 92% fluid collections. The amount of solid debris, graded as minimal (< 10%), moderate (10%-50%) and profound (> 50%), was compared between different types of fluid collections, need for intervention and modality of intervention. While the majority of ANCs (72.2%) had profound solid debris, majority of WONs (62%) had only moderate solid debris (P < 0.001). Of the three pseudocysts labelled on CT, one had moderate (30%) solid debris on EUS (missed on CT). Amongst WONs, need for intervention was present in all patients with profound solid debris, in 40% with moderate solid debris and in none with

minimal solid debris[45]. This delineates the importance of EUS in further management planning.

Role of PET scan

Recently, we have in a pilot study evaluated role of ammonia PET-CT (PET images after intravenous injection of $^{13}NH_3$) in diagnosing and quantifying pancreatic necrosis. We found good agreement with CECT and good interobserver acceptability and concluded that ammonia PET can be an alternative to CECT with minimal radiation burden especially in patients with renal failure[46]. However the main limiting factors are limited availability and cost as compared to other imaging techniques.

Role of radionuclide-labeled leukocyte scintigraphy PET scan as noninvasive modality for diagnosing infected collection has also been evaluated in recent studies as an alternative to image guided FNAC. Earlier these studies were limited to gamma camera scintigraphy with leukocytes labeled with 111 In or ^{99m}Tc in which image quality and resolution were unsatisfactory. However feasibility of labeling leukocytes in vitro with ^{18}F-FDG has given a possible way to overcome these limitations. We have used PET/CT with ^{18}F-FDG labeled autologous leukocytes to detect infection in pancreatic or peripancreatic fluid collections in 41 patients with AP and compared with microbiologic culture of aspirated fluid from the collection and showed 100% sensitivity, specificity, and accuracy of the scan (in 35 patients in whom fluid culture reports were available). We feel that that this technique is a reliable, accurate and noninvasive imaging modality for detection and localization of infection in patients with fluid collections[47].

CONCLUSION

CECT has traditionally been accepted as the method of choice for imaging PFCs in clinical practice, however recent studies have reported a higher accuracy rate with MRI and EUS as compared to CECT especially in quantification of solid debris. This has led better understanding of the natural history of PFCs. Comparative data between these different modalities are still lacking and require further studies.

Furthermore advances in cross-sectional imaging technique such as DWI-MRI and PET/CT with ^{18}F-FDG labeled autologous leukocytes may have promising role in early detection of fluid infection by noninvasive means in near future.

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