Review

Differentiating Between Mass-forming Chronic Pancreatitis and Pancreatic Ductal Adenocarcinoma: A Challenging Clinical Approach

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Abstract

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is a tumor of the pancreas that has a 5-year survival rate as low as 7.8%. In cases of chronic pancreatitis, it is sometimes challenging to rule out neoplastic changes, as mass-forming pancreatitis (MFCP) that can occur secondary to long-lasting inflammation can commonly mimic the presentation of pancreatic ductal adenocarcinoma. The clinical picture, laboratory, and radiological imaging of PDAC and MFCP may sometimes overlap, resulting in a higher incidence of misdiagnosis and unnecessary surgery.

Aim: We aim to describe the various tools available to help physicians distinguish between mass-forming chronic pancreatitis and pancreatic ductal adenocarcinoma.

Methods: A literature search was conducted on "PubMed" using the following terms: pancreatic carcinoma, mass-forming chronic pancreatitis, and pancreatic mass. Several articles discussing imaging modalities including ultrasound, CT-scan, and MRI; and laboratory markers including cancer antigen 19–9 (CA 19-9), carcinoembryonic antigen (CEA), glypican-1 (GP-1), low-density lipoprotein receptor (LDLR), and K-RAS, were reviewed.

Discussion: Despite their similar presentations, the management of MFCP and PDAC is very different. The similarity in history, clinical symptoms, and imaging findings can lead to unnecessary procedures. In this review, we examined several modalities that physicians might use to avoid any misdiagnosis.

Conclusion: Although none of these tests alone has been shown to be superior to the others, a potential suggestion might be to use a combination of these tests to allow a reliable diagnosis.

Keywords: Pancreatic carcinoma, Mass-forming chronic pancreatitis, Pancreatic mass

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a tumor of the pancreas that has a 5-year survival rate as low as 7.8% [1]. Its ultimate treatment is surgical resection, even though exploratory biopsy is not always conclusive [2]. In cases of chronic pancreatitis, it is sometimes challenging to rule out neoplastic changes as mass-forming pancreatitis (MFCP), which can occur secondary to long-lasting inflammation, can commonly mimic the presentation of pancreatic ductal adenocarcinoma [2,3,4]. The clinical picture, laboratory, and radiological imaging findings of PDAC and MFCP may sometimes overlap, resulting in a higher incidence of misdiagnosis and unnecessary surgery. As a result, early and accurate diagnosis is critical to enable physicians to select the most appropriate treatment approach to avoid any mismanagement of the disease [5].

Various diagnostic strategies have been developed to differentiate MFCP from PDAC, including imaging findings and serum biomarkers [1,2,3,4,6-19]. The most frequent are transabdominal ultrasound, trans-sectional imaging, and blood tests [13]. We aim to describe the various tools available to help physicians distinguish between mass-forming chronic pancreatitis and pancreatic ductal adenocarcinoma.

Materials and Methods

Search methods

A literature search was conducted on "PubMed" using the following terms: pancreatic carcinoma, mass-forming chronic pancreatitis, and pancreatic mass. Cross-referencing was also used, and hand searches of articles were identified after an initial search. Commentaries, case reports, clinical vignettes, and articles not written in English were excluded.

Data collection

Three authors independently screened the titles and abstracts of all retrieved records in order to identify the articles that meet the inclusion criteria. The results were discussed to make a final decision.

Discussion

Despite their similar presentations, the management of MFCP and PDAC is very different. The similarity in history, clinical symptoms, and imaging findings can lead to unnecessary procedures [2,4,7,20]. In this review, we examined several modalities that physicians might use to avoid any misdiagnosis (Table 1).

1-Imaging

Imaging findings in MFCP and PDAC considerably overlap, resulting in misdiagnosis in up to 25% of cases [21]. In fact, they share numerous common imaging features including cystic lesions, fibrosis, hyperenhancement of mass, and pancreatic and biliary abnormalities [9]. However, various useful signs and imaging techniques have been found to differentiate between the two pathologies [2,4].

1.a-Morphology and Anatomic Description

One study showed that the mean diameter of the lesion was larger in patients with MFCP compared to those with Pancreatic Cancer (PC). The PC lesions were also characterized by increased lobulation when compared to the MFCP group [2]. While pancreatic calcifications may be found in both pathologies, their pattern of distribution and location can assist clinicians in differentiating between the two diseases [4]. Calcifications in MFCP are usually diffuse and found within the parenchyma and duct, whereas calcifications in PDAC tend to be more localized and do not involve the duct [2,4]. In addition, the displacement of calcifications, or the presence of a mass within diffuse areas of calcifications are alarming signs of the presence of PDAC [4,8]. Pancreatic pseudocysts or cystic lesions are additional imaging findings that are more common in MFCP, and present with characteristics not found in PC, such as honeycombing, calcification, and discontinuous wall [2].

1.b-Ducts and Vasculature

The duct-penetrating sign is another indicator of a benign condition. It is present

when the main pancreatic duct appears patent without any obstruction. It has 96% specificity, 85% sensitivity, and 94% accuracy in differentiating MFCP from PDAC [8]. It may be detected on computed tomography (CT) but is better seen on magnetic resonance cholangiopancreatography (MRCP).

The pancreatic duct is considered dilated when it exceeds two millimeters (mm) in the body and tail, or 3mm in the head, or when it develops a sudden dilatation upstream to the stenosis. It is better visualized on MRCP. Duct dilation in cholangiopancreatography (CP) is characterized by strictures and contour irregularities [4], and is observed in collateral branches localized to normal pancreatic tissue [4,8]. In contrast, duct dilation in PDAC is severe, smooth, and accompanied by severe parenchymal atrophy [4].

The duct-to-parenchyma ratio is obtained from endoscopic ultrasound (EUS) and is a useful measure to differentiate between the two pathologies [8]. In fact, when the ratio is greater than 0.34, more ductal dilation and pancreatic atrophy are observed, further reinforcing the PDAC diagnosis. However, when this ratio is less than 0.34, it is more likely that this mass is associated with inflammatory causes, as ductal dilatation and parenchymal atrophy are less pronounced [8].

The double duct sign represents the simultaneous dilatation of the pancreatic and common bile ducts. It highly favors PDAC over inflammatory conditions [4,8] and is present in 80% of PDAC, but it can also occur in MFCP. In most cases, we can rely on the degree of stenosis to differentiate between the two. In most cases of MFCP, the stenosis, and dilation is less severe than those seen in PDAC. However, severe cases of stenosis and dilation in MFCP have been reported, making it very challenging to differentiate MFCP from PDAC [4]. Moreover, involvement of the pancreatic vasculature can also be a useful tool in detecting PDAC, as any change ranging from vessel obstruction, vessel encasement by soft tissue, vessel narrowing, and vessel deformities is strongly suggestive of PDAC [8].

1.c-Imaging techniques

Perfusion CT (PCT) scan is a technique that studies tissue hemodynamics over a period of time to assess its perfusion parameters in different phases of contrast distribution. On PCT, blood volume (BV), mean blood flow (BF), permeability surface area product (PS), and peak enhancement intensity (PEI) are decreased in MFCP and PDAC when compared to a normal pancreas [7]. However, a greater decrease in these parameters was recorded in PDAC than in MFCP [2,4,7].

Computed tomography texture analysis (CTTA) is a combination of CT imaging and image texture processing that allows the quantification of tissue heterogeneity. This texture analysis with CT imaging would have an improved specificity (92%), sensitivity (94%), and accuracy (94%) to help in differentiating between MFCP and PDAC [1]. In one study, a machine learning algorithm "radiomics" based on MRI imaging, was created to differentiate between MFCP and PDAC. Interestingly enough, this model was more accurate in differentiating between the two pathologies in the training and validation sets than clinicians and radiologists [6].

EUS is another technique that creates high-resolution images allowing better visualization of the pancreas. However, its accuracy in differentiating benign pancreatic masses from cancerous ones does not exceed 75%. EUS-guided fine needle aspirate (FNA) has been shown to have a low sensitivity of 54% in diagnosing pancreatic masses when it was associated with chronic pancreatitis [12]. These drawbacks were overcome by implementing other techniques such as contrast agents and elastography in endoscopic ultrasound. Elastography is a technique that classifies tissues based on their response to pressure applied by the EUS probe [12,20]. On one hand, qualitative analysis of pancreatic masses' elasticity based on a color scale had a poor diagnostic ability in differentiating between MFCP and

PDAC. On the other hand, quantitative analysis using a mean value or the ratio of elasticity of the mass over soft reference tissue showed very promising results. EUS elastography has been shown to have a high sensitivity (93.4%) and positive predictive value (92.5%). It has low specificity (66.0%) and a negative predictive value (68.9%) with an accuracy of 85.4% overall for the mean of the hue-histogram in the detection of malignancy [12]. Ultimately, Elastography would improve the accuracy, sensitivity, and specificity of EUS-guided FNA to differentiate between malignancy and chronic inflammation [8,20]. Contrast-enhanced EUS had also been found useful to differentiate between MFCP and PDAC. Despite the fact that both MFCP and PDAC showed hypo-enhancement on contrast-enhanced harmonic EUS (CEH-EUS), it was found that the contrast uptake ratio was significantly lower in PDAC than in MFCP.

Markers

Metabolomics is a technique used to discover, test, and validate biomarker signatures that can be used to differentiate between similar pathologies [14]. A biomarker signature made of 9 metabolites in addition to CA 19-9 was developed (table 2) and showed promising results in differentiating between PDAC and chronic pancreatitis [13]. Furthermore, it was able to detect PDAC in the early stages with an accuracy of 90.5%, making it a very effective tool in solving this dilemma. One study showed that levels of GP-1 circulating exomes are a promising marker for MFCP and PDAC differentiation as their levels were significantly higher in PDAC than in MFCP. This marker had a high sensitivity (98.3%) and a moderate specificity (86.2%) in differentiating between the two pathologies, outperforming CA 19-93.

The Low-density lipoprotein receptor (LDLR) is a cell-surface receptor that is upregulated in PDAC. In one study, LDLR was found to be significantly lower in PDAC than in MFCP and had very low accumulation early after injection of LDLR Fc fragments [16]. Thus, LDLR was found to be a very useful marker

differentiating between PDAC and MFCP. K-RAS mutant epithelial cells are another marker that was found to be significantly higher in PC than in MFCP22. The simultaneous analysis of K-RAS mutations with the aspirate's cytopathological and histopathological analysis may significantly improve the diagnostic ability of clinicians. Effectively, the absence of K-RAS mutations in inconclusive cytopathology studies or inconclusive diagnosis strongly predicts pseudotumoral chronic pancreatitis over PC [17]. Some studies combined imaging techniques with markers to better differentiate between pancreatic cancer and chronic inflammation. A model capable of differentiating between the two pathologies with a high degree of accuracy was built on two parameters, the first one being mass heterogeneity that was quantified by the multiparametric MRI-based radiomics analysis, and the second one being specific serum markers, namely CA 19-9 and CEA. This model was successfully tested and validated against each of these tests alone for the diagnosis of PC and MFCP [19]. Another imaging modality deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography/CT (18F-FDG PET/CT)was used in adjunct to CA19-9 and was shown to be useful in differentiating between CMFP and PC. When combined, they reached a sensitivity, specificity, and accuracy to differentiate PDAC from MFCP of 90% [18].

Conclusion

In conclusion, differentiating between MFCP and PDAC remains a dilemma as they may share overlapping clinical, laboratory, and imaging findings. As described in this article, clinicians are using several tools to assist them in choosing the appropriate diagnosis and managing it accordingly. Although none of these tests alone has been shown to be superior to the others, a potential suggestion might be to use a combination of these tests to allow a reliable diagnosis. Most importantly, identifying the correct pathology would avoid using unnecessary resources and exposing patients to unnecessary procedures.

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Annex

Table 1: Summary of modalities used to differentiate between PDAC and MFCP

Abbreviations: MFCP (mass forming pancreatitis); PDAC (pancreatic ductal adenocarcinoma); CP (chronic pancreatitis); BF (blood flow); BV (blood volume); PEI (peak enhancement intensity); PS (permeability surface area product); CT (computed tomography); CTTA (computed tomography texture analysis); EUS (endoscopic ultrasound); EUS-guided FNA (endoscopic ultrasound guided-fine needle aspiration); CA19-9 (cancer antigen 19-9); GP-1 (glypican-1); LDLR (low density lipoprotein receptor); K-RAS (kirsten rat sarcoma viral oncogene homolog); MRI (magnetic resonance imaging); CEA (carcinoembryonic antigen); 18F-FDG PET/CT (18F-fluorodeoxyglucose-positron emission tomography/computed tomography)

	Presentations of MFCP and PDAC using different modalities	
Imaging	MFCP	PDAC
Morphology and Anatomic Description	Lesions with a larger mean diameter	Lesions with increased lobulations
	Diffuse calcifications located within the parenchyma and duct	Localized calcifications that do not involve the duct
	Higher incidence of pseudocysts or cystic lesions with honey-combing, calcifications and discontinuous wall	Displacement of calcifications or the presence of a mass within diffuse areas of calcifications
Ducts and Vasculature	Positive duct-penetrating sign	Positive double duct sign associated with severe stenosis and dilation
	Duct dilation characterized by strictures and contour irregularities, observed in collateral branches localized to normal pancreatic tissue.	Severe and smooth duct dilation accompanied by severe parenchymal atrophy
	Duct-to-parenchyma ratio less than 0.34	Duct-to-parenchyma ratio more than 0.34
		Pancreatic vasculature

		involvement (obstruction of the vessels, encasement of vessels by soft tissue, narrowing of vessels, and vessel deformities)
Imaging techniques		Perfusion CT shows a greater decrease in mean blood flow (BF), blood volume (BV), peak enhancement intensity (PEI) and permeability surface area product (PS) in PDAC compared to MFCP
		CTTA outperforms regular CT imaging in differentiating between MFCP and PDAC
		The radiomics model was shown to differentiate between MFCP and PDAC better than clinicians and radiologists
		EUS combined with elastography outmatches EUS-guided FNA in differentiating between MFCP and PDAC
		Contrast-enhanced EUS shows a significantly lower contrast uptake ratio in PDAC compared to MFCP
Markers		
Biomarker signature		The biomarker signature composed of 9 metabolites in addition to CA 19-99 showed high accuracy in detection of PDAC in early stages and promising results in the differentiation between PDAC and MFCP
GP-1 circulating exomes		Higher levels of GP-1 circulating exomes in PDAC compared to MFCP
Low-density lipoprotein receptor (LDRL)		Lower LDLR levels in PDAC compared to MFCP, with a very low accumulation early after injection of LDLR Fc
K-RAS mutant epithelial cells		Higher K-RAS mutant epithelial cells in PC compared to MFCP
Combination of imaging techniques and markers		
Multiparametric MRI-based radiomics analysis combined with CA 19-99 and CEA.		This model was proved superior in diagnosing PC and MFCP compared to these tests alone
18F-FDG PET/CT combined with CA19-9		This combination reached a 90% sensitivity, specificity, and accuracy in differentiating PDAC from MFCP

Table 2: Metabolites selected for metabolic biomarker signature

Abbreviations: CA 19-9: Cancer Antigen 19-9

Biomarkers used
CA 19-9
Proline
Sphingomyelin (d18:2, C17:0)
Phosphatidylcholine (C18:0, C22:6)
Isocitrate
Sphinganine-1-phosphate (d18:0)
Histidine
Pyruvate
Ceramide (d18:1, C24:0)
Sphingomyelin (d17:1, C18:0)