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Case Report

Diminishing calcifications as a potential predictor of pancreatic ductal adenocarcinoma arising in association with IPMN in patients with chronic pancreatitis ☆

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ABSTRACT

Chronic pancreatitis (CP) is a progressive benign fibroinflammatory condition involving repeated episodes of pancreatic inflammation, which lead to fibrotic tissue replacement and subsequent pancreatic insufficiency. A lifetime risk of developing pancreatic ductal adenocarcinoma (PDAC) in patients with chronic pancreatitis is reported to be 1.5%-4%. However, diagnosis of PDAC in patients with CP can be challenging, in part due to overlapping imaging features. In rare instances, pancreatic parenchymal calcifications that are typically associated with chronic pancreatitis may diminish in the case of a developing PDAC. In this article, we present a patient with chronic pancreatitis in whom calcifications decreased at the time of pancreatic ductal adenocarcinoma diagnosis, as compared to prior CT imaging. The unique imaging features of "diminishing calcifications" associated with a hypoattenuating lesion can potentially be a useful sign of pancreatic ductal adenocarcinoma and may aid in early diagnosis and prompt treatment intervention.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) continues to be the 3rd leading cause of cancer-related death in the United States and is projected to be 2nd by 2030. With a 5-year survival rate of 12%, early diagnosis and improved control of systemic disease are essential for improved patient outcomes [1–3]. Multiple conditions and premalignant lesions of the pancreas have been identified that are associated with the development

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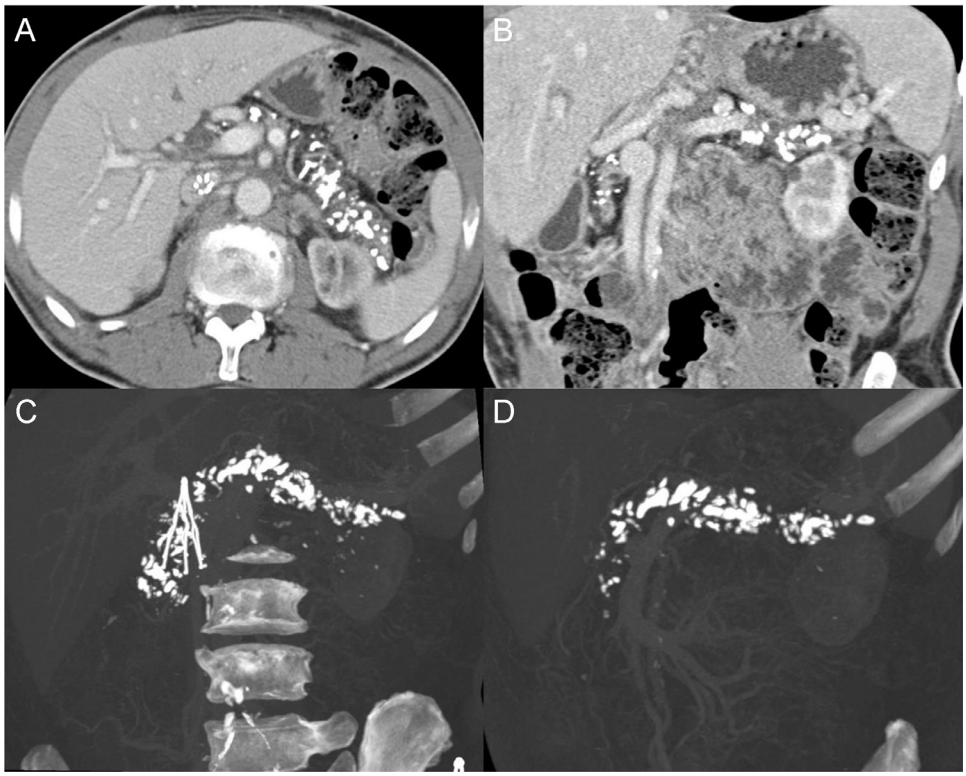

Fig. 1 – Contrast enhanced (A) axial and (B) oblique coronal reformatted CT images show severely atrophic pancreas with diffuse calcifications, compatible with chronic pancreatitis. (C) Coronal and (D) oblique coronal maximal intensity projection images show diffuse calcifications throughout the pancreas. Inferior vena cava filter overlapping the pancreatic head on (C) coronal image.

of pancreatic cancer. It has been shown that patients with chronic pancreatitis (CP) have a life-time risk of 1.5% – 4% of developing PDAC within 10 or more years of diagnosis [4,5].

Radiological imaging, particularly computed tomography (CT) is a noninvasive and widely utilized modality that plays a key role in detecting pancreatic masses and malignancy. CP itself has a range of presentations, including diffuse involvement, mass-forming chronic pancreatitis (MFCP), and focal autoimmune pancreatitis (AIP). Furthermore, imaging features overlap between PDAC and CP, which add to the diagnostic complexity [6]. Accurately distinguishing these pathologies is thus of paramount importance with a direct consequence on patient management. It has been shown that changes in radiological features of the pancreatic gland in patients with CP may be associated with the development of PDAC. Here, we report a case of patient with CP with calcifications who subsequently developed PDAC arising in association with an IPMN with high-grade dysplasia with a peculiar associated finding of diminished calcifications at the time of PDAC diagnosis.

Case presentation

A 61-year-old male with a past medical history significant for hypertension, insulin dependent type 2 diabetes mellitus, mild untreated chronic hepatitis C, and end-stage renal disease requiring dialysis presented to our hospital for an evaluation as a candidate for a kidney transplant. He also had a remote history of smoking, intravenous drug use, and alcohol dependence. As part of his workup, a CT abdomen with contrast was performed, which demonstrated numerous calcifications in an atrophic pancreas compatible with CP (Fig. 1). Three-dimensional rendering and minimal intensity projection images also showed calcifications throughout the atrophic pancreas, intermittent mild dilatation of the main pancreatic duct, and no discrete pseudocyst or mass (Fig. 1). No urgent intervention was deemed necessary for chronic pancreatitis and watchful waiting was recommended. The patient continued care at outside hospitals and clinics over the following years.

Eight years later, the patient presented to an outside institution and underwent workup for gastrointestinal bleeding. Endoscopy was performed and showed a gastric ulcer and a submucosal gastric mass, although biopsy was negative. CT of the abdomen showed severe atrophy of the pancreatic head with multiple parenchymal calcifications and enlargement of body and tail of the pancreas with heterogeneous soft tissue with loss of normal contours and lobulations. There were multiple cystic areas in the body and tail that were difficult to distinguish from the pancreatic duct (PD), and these findings were overall consistent with pancreatitis, however, also concerning for an underlying mass in the body and tail region. The

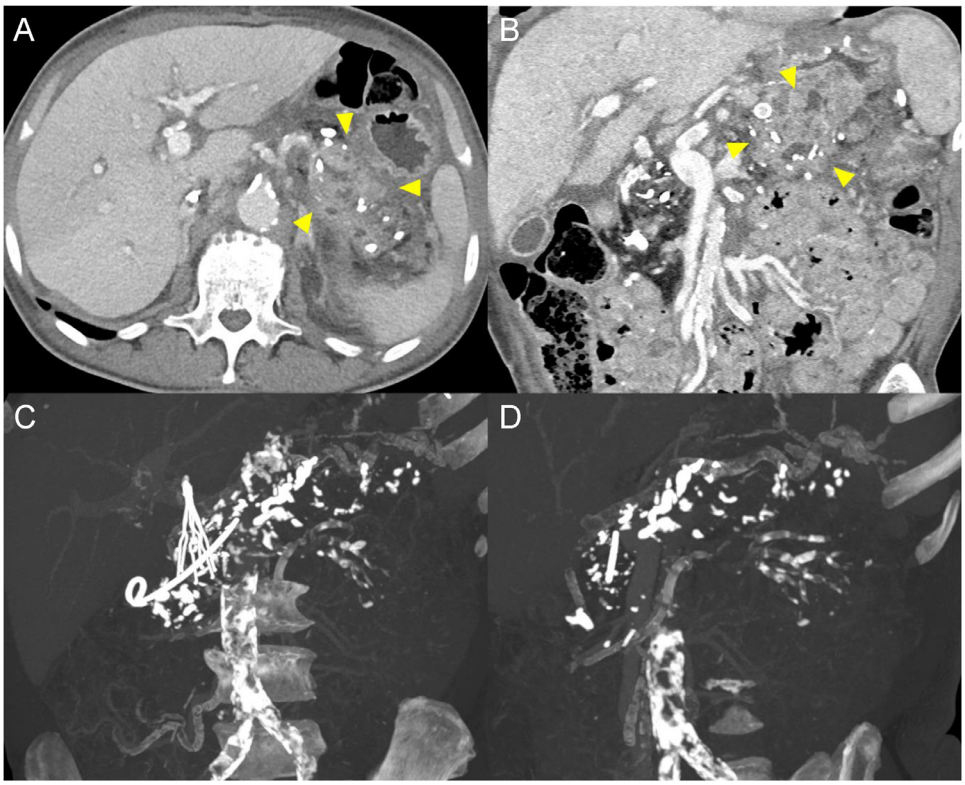

Fig. 2 – Contrast enhanced (A) axial and (B) oblique coronal reformatted CT images show interval development of ill-defined heterogeneous hypodense enlargement of body and tail of the pancreas (yellow arrowheads) with scattered cystic lesions. Loss of fat plane between the enlarged pancreas and stomach is well appreciated on oblique coronal image. Calcifications in body and tail are decreased compared to Figure 1. (C) Coronal and (D) oblique coronal maximal intensity projection images show diffuse calcifications throughout the pancreas, but body and tail calcifications in the area of enlargement are decreased compared to Figure 1. Diffuse vascular calcifications involving aorta, iliac artery, splenic and renal arteries developed secondary to end stage renal disease. Pancreatic duct stent and inferior vena cava filter are seen overlapping with the pancreatic head.

patient underwent exploratory laparotomy and partial gastric resection, and a cystic pancreatic mass was seen adherent to the stomach for which biopsy was obtained. While pathology returned negative for neoplasm in the stomach, the pancreatic biopsy was positive for an invasive, well-differentiated adenocarcinoma arising from an intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia. An EUS was obtained after the surgery and demonstrated a hypoechoic mass in the body of the pancreas with malignant-appearing lymph nodes. CA19-9 was also elevated at 1846 U/mL. He was deemed unresectable at the outside institute due to locally advanced disease and was recommended chemoradiation therapy.

When the patient presented for a second opinion at our institute, biopsy specimens were reviewed and confirmed an invasive well-differentiative pancreatic adenocarcinoma arising in association with an IPMN with high-grade dysplasia. A CT abdomen with contrast demonstrated a severely atrophic and calcified pancreas. Interval enlargement and heterogeneity of the body and tail were noted with a lobulated outline and multiple cystic lesions difficult to distinguish from the PD (Fig. 2). No fat plane separating the pancreas from the posterior gastric body could be appreciated. There was significant peripancreatic stranding and bands of fluid owing to inflammatory changes. While a discrete mass could not be well visualized, the findings were consistent with the known infiltrative carcinoma. 3D postprocessing better delineated the soft tissue mass infiltrating the body and tail of the pancreas with and encasement of the splenic artery, as well as the involvement of the gastric body. Interestingly, while calcifications were appreciable, there was a marked decrease compared to the prior CT in the regions of the body and tail where the infiltrating cancer developed. To corroborate these findings, we also quantified the distribution of pancreatic calcifications in both scans (Fig. 3) after segmenting the pancreas and associated structures and using a 160 Hounsfield units (HU) threshold. A decrease in calcification volume (from 11.8 cc to 8.6 cc) was appreciated despite an increase in pancreas volume owing to the infiltrative tumor.

The case was reviewed and discussed in the tumor board before coming to a consensus and owing to the high risk of a pancreatectomy due to medical comorbidities, chemotherapy was recommended. The patient was lost to follow-up, and he passed away 8 months later.

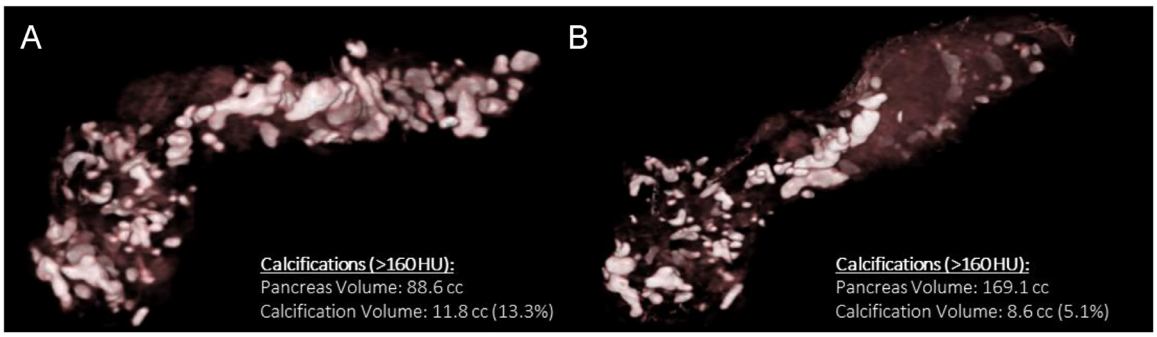

Fig. 3 – Volumetric representation showing the distribution of pancreatic calcifications in the original CT scan (A) and the follow-up scan (B). Calcification volume was quantified by counting voxels within the pancreatic parenchyma with a HU value above 160 in the arterial phase. The percentage was calculated based on the total voxel count within the pancreatic parenchyma. CT: computed tomography; cc: cubic centimeters; HU: Hounsfield units.

Discussion

We report a case of chronic pancreatitis who developed an invasive adenocarcinoma arising in association with IPMN with a concurrent finding of diminishing parenchymal classifications at the time of PDAC diagnosis. There have been very few reports describing a similar regression of calcifications. A paper by Tucker and Moore in 1963 is one of the earliest to describe a patient who had CP for 8 years prior to the diagnosis of PDAC. Compared to a study performed 4 years prior to the diagnosis of PDAC, a plain film of the abdomen showed a drastic decrease in calcification in the pancreatic body. A postmortem examination and histopathological analysis performed 1 week later confirmed a large pancreatic adenocarcinoma and the "vanishing calcium" at the same location [7]. Contrastingly, disappearance of calcifications due to chronic pancreatitis from other reasons has also reported. Baltaxe and Leslie reported in 1967 a case of diminishing calcifications that were not associated with PDAC but instead were associated with a 4-year long period of remission of CP after cessation of alcohol consumption and sphincterotomy. Decreased calcifications completely vanished by the time of the patient's death, with no signs of malignancy on postmortem examination [8]. Similarly, in 1974, Donowitz et al. reported the case of a patient with CP who also demonstrated a marked decrease in pancreatic calcifications as seen on abdominal plain film over the period of 4 years. Surgical exploration and histopathological examination and postmortem studies revealed no signs of malignancy. In their case, it was thought that hemorrhaging into a pseudocyst was responsible for displacing the calcifications [9]. A more recent publication by Friedberg et al. in 2018 also described a case of CP calcifications, both parenchymal and intraductal, that disappeared over a ten-year period and a clear cause could not be determined, although whether they developed malignancy or not had yet to be seen [10].

A number of explanations have been suggested in the aforementioned cases. These include diminution of calcifications following surgical drainage and/or extracorporeal shock wave lithotripsy (ESWL), the absence of cross-sectional imaging that may have led to missed intraductal calcifications that were previously assumed to be parenchymal, drainage through fistulae, and spontaneous dissolution due to pH changes related to CP and developing PDAC [7–10]. To our knowledge, since Tucker and Moore's report, ours is the only other report describing diminishing calcifications that appear to signal developing PDAC. However, our case is more complex because PDAC arose in association with IPMN. On the initial CT, there was intermittent mild dilatation of the main pancreatic duct which is thought to be secondary to calculi obstructing the PD. No other findings to suggest underlying IPMN were noted on the initial CT. At the time of PDAC diagnosis, diminished calcifications were seen in the region of enlarged body and tail with heterogeneous soft tissue, therefore, diminished calcifications are thought to be secondary to development of invasive adenocarcinoma. However, diagnosis of invasive adenocarcinoma with IPMN was made by biopsy, and exact extent of invasive adenocarcinoma and underlying IPMN is unable to determine.

PDAC remains a challenging diagnosis, more so in the background of CP as the chronic inflammation distorts the normal pancreatic parenchyma and typical attenuation patterns. Irregular pancreatic duct dilatation is commonly seen in CP, which can be obstructed by calculus in the pancreatic duct or stricture from pancreatic parenchymal scarring. This is complicated by overlapping clinical presentations such as weight loss and diarrhea and overlapping risk factors including alcohol use and smoking, as seen in our case, as well as common radiographic findings such as duct dilatation, fibrosis, atrophy, and inflammation [12,13]. Secondary imaging features that have been correlated with impending or coexisting PDAC include a new soft tissue mass, double duct sign (dilation of both the CBD and PD), a duct-to-parenchyma ratio greater than 0.34, deformity and encasement of vessels, and an SMA-to-SMV ratio greater than 1 [11]. Displacement of chronic calcifications has been described where a focal hypoattenuating lesion pushes them to the periphery, unlike in our and other similar cases where the calcifications seem to diminish instead [11]. EUS-FNA may not always be predictive either, and specificity for detection of solid masses can drop from over 90% in a normal pancreas to as low 71% in the background of CP [14]. Thus, a complete clinical picture and meticulous

workup including imaging and laboratory markers is necessary for an early diagnosis.

Vanishing or spontaneously diminishing calcifications in CP might be an indicator of PDAC or a sign that an insidious process is ongoing with chronic inflammation. This interesting observation provides merit to further study this phenomenon. In the future, it will be interesting to further elucidate the underlying mechanisms of calcifying CP and PDAC, as well as the incorporation of findings such as disappearing calcifications in the development of predictive models for early diagnosis. These could include tools based on deep learning and radiomics, which detect subtle yet significant changes in the pancreatic gland that are otherwise considered inconspicuous or are missed [15,16].

Conclusion

Our interesting observation of diminishing calcification in a patient with CP at the time of diagnosis of PDAC warrant further investigation. We believe that this finding could be an early indicator of a PDAC in CP patients and could hold value in early diagnosis of malignancy.

Patient consent

The patient reported in the manuscript signed the informed consent/authorization for participation in research, which includes the permission to use data collected in future research projects such as the presented case details and images used in this manuscript.

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