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Secondary Signs Related to Pancreatic Adenocarcinomas on CT: Are They Really Specific Findings for Malignancies?

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1. Abstract

1.1. Introduction: This study aimed to investigate whether pancreatic secondary signs on contrast-enhanced dynamic CT are really specific for patients with pancreatic adenocarcinomas.

1.2. Methods:

A retrospective review of dynamic CT findings was performed for 93 patients with suspected pancreatic adenocarcinomas and with any secondary CT signs. Among these 93 patients with secondary CT signs, 87 had PA (group A) whereas 6 did not (focal chronic pancreatitis=3, autoimmune pancreatitis=1, others=2) (group B). Two radiologists evaluated the presence and the number of secondary CT signs such as dilated main pancreatic duct, decreased contrast enhancement of distal pancreatic parenchyma, and distal focal atrophic pancreatic parenchyma. These secondary signs were compared between the groups with and without pancreatic adenocarcinomas.

1.3. Results: In the group A, dilated main pancreatic duct, decreased contrast enhancement of distal pancreatic parenchyma, and focal atrophic pancreatic parenchyma were observed in 87 patients (100 %), in 58 patients (67 %), and in 58 patients (67 %) while, in the group B, they were seen in 4 patients (67 %), in 4 patients (67 %), and in 3 patients (50 %), respectively. The incidence of dilated main pancreatic duct was significantly different ($p<0.001$) between the two groups. There was no significant difference in other secondary signs between the two groups.

1.4. Conclusion: It should be noted that secondary CT signs can be present in patients without pancreatic adenocarcinoma although dilatation of the main pancreatic duct will be a secondary sign highly suggestive of pancreatic adenocarcinoma.

2. Introduction

Pancreatic adenocarcinoma is considered to be the fourth leading cause of cancer deaths in the world [1-3], and surgical resection has been shown to be the only curative treatment option [2-9]. Therefore, patients with pancreatic adenocarcinoma require early recognition and an accurate diagnosis. Computed Tomography (CT) has been used for primary investigation in patients clinically suspected with pancreatic adenocarcinoma [4, 5, 9-12]. On dynamic contrast-enhanced CT (DCE-CT), pancreatic adenocarcinoma appears as a hypo-attenuating mass when compared with the pancreatic parenchyma. However, studies have reported the rare appearance of pancreatic adenocarcinoma as an iso-attenuating mass on DCE-CT [2, 3, 6, 7, 10, 11, 13-17]. Iso-attenuating pancreatic adenocarcinomas are difficult to detect, and small tumors may be overlooked. Studies have reported several secondary signs on CT indicative of pancreatic adenocarcinoma, such as a dilated Main Pancreatic Duct (MPD), a contrasting effect between the proximal and distal pancreatic parenchyma, and focal atrophy of the pancreatic parenchyma [5, 10, 15-20]. Especially, some studies showed that all patients with dilatation of the distal main pancreatic duct on dynamic CT had a small pancreatic adenocarcinoma [5, 18]. In clinical practice, however, we have occasionally experienced "secondary CT signs" in individuals without pancreatic adenocarcinoma. Therefore, the aim of this study was

to investigate whether secondary signs on DCE-CT are really specific findings for patients with pancreatic adenocarcinoma.

3. Methods

3.1. Patients

This retrospective study was approved by our institutional ethics committee, and the requirement of informed consent was waived. We retrospectively reviewed the DCE-CT data of 194 patients who were suspected with pancreatic adenocarcinoma between April 2009 and December 2013. Among these patients, 93 with secondary signs in the pancreas were included in the present study. Of the 93 patients, 60 were men and 33 were women, and the median age of the patients was 70.7 years (range, 40–88 years). The following secondary signs were considered: a dilated MPD (diameter >3 mm), decreased contrast enhancement of the distal pancreatic parenchyma, and distal focal atrophic pancreatic parenchyma (Figure 1). Among the 93 patients with secondary signs, 87 patients had pancreatic adenocarcinoma (group A) and 6 patients did not have pancreatic adenocarcinoma (group B). Among the 87 patients with pancreatic adenocarcinoma, cancer was confirmed with pathological examinations in 61 patients, and with clinical findings, biochemical and hematologic blood tests, and radiologic imaging features in the remaining 26 patients. Among the 6 patients without pancreatic adenocarcinoma, the absence of cancer was confirmed with pathological examinations in 2 patients, and with clinical findings, biochemical and hematologic blood tests, and absence of a pancreatic tumor over a follow-up period of ≥1.5 years in the remaining 4 patients. Final diagnosis of these 6 patients were chronic pancreatitis in 3, autoimmune pancreatitis in 1, dissection of the abdominal aorta in 1, and unknown etiology in 1.

3.2. Imaging Technique

All CT scans were performed using a multi-detector row CT system (Light Speed Ultra 16; General Electric Medical Systems, Milwaukee, WI or Asteion 4, Activion 16, or Aquilion 64; Toshiba Medical Systems, Tokyo Japan). All patients received nonionic contrast material (Iopamidol [Iopamiron 370], Bayer Schering Pharma, Osaka, Japan; Iopamidol [Oyparomin 300/370], or iohexol [Iopaque 300]; Fuji Pharma, Tokyo, Japan, or iohexol [Omunipaque 300]; Daiichi Sankyo, Tokyo, Japan) at a rate of 3.3–5.0 mL/s and a volume of 80–150 mL according to body weight, using an automated power injector (Nemoto Kyorindo, Tokyo, Japan). The total dose was fixed at 150 mL for patients weighing >75 kg. A fixed injection duration of 30 s was used; therefore, the injection rate was automatically decided according to the weights of the patients. The contrast medium was injected through a 20-gauge plastic IV catheter placed in an antecubital vein. The section thickness and reconstruction interval were 5 mm and 5mm, respectively. After obtaining pre-contrast CT images, contrast-enhanced dynamic CT images were obtained during the arterial phase, portal venous phase, and late phase with delays of 40, 70, and 210 s, respectively, based on our optimized standard protocol.

4. Data Analysis

All CT examinations were randomized, and CT images were independently reviewed by 2 abdominal radiologists (one with 10 years of experience and the other with 15 years of experience). The radiologists were blinded to the clinical data, CT image interpretations, and the final diagnosis in order to avoid bias. Disagreements between the radiologists were resolved with consensus. All images were visually evaluated for the incidence of pancreatic secondary CT signs, such as a dilated MPD, decreased contrast enhancement of the distal pancreatic parenchyma, and distal focal atrophic pancreatic parenchyma on a clinical Picture Archiving and Communication System (PACS) workstation monitor (Rapideye Core; Toshiba Medical Systems). Then, the number of secondary signs visualized in each patient was recorded. A dilated MPD was defined as upstream ductal dilatation with a maximal diameter of more than 3 mm. Decreased contrast enhancement of the distal pancreatic parenchyma was defined as a visually decreased CT attenuation of the distal pancreatic parenchyma compared to normal parenchyma in the arterial phase. CT attenuation value of pancreatic parenchyma was not measured considering the complexity of region-of-interest placement for atrophied distal pancreatic parenchyma. Distal focal atrophic pancreatic parenchyma was defined as a main pancreatic duct caliber to total pancreatic parenchymal width ratio of less than 0.50 [21].

5. Statistical Analysis

Fisher's exact test was performed to compare each of the secondary signs in the pancreas between group A and group B. The Mann-Whitney U test was performed to compare the number of secondary signs between the 2 groups. All statistical analyses were performed using SPSS version 19.0J for Windows (SPSS, Chicago, IL). A p-value <0.05 was considered to indicate a statistically significant difference. The sensitivity, specificity and accuracy of the secondary sign for the CT differentiation of pancreatic adenocarcinoma were also calculated.

6. Results

Among the 87 patients in group A with pancreatic adenocarcinomas, a dilated MPD was noted in all 87 patients (100%), decreased contrast enhancement of the distal pancreatic parenchyma was noted in 58 patients (67%), and distal focal atrophic pancreatic parenchyma was noted in 58 patients (67%). In contrast, among the 6 patients in group B without pancreatic adenocarcinomas, a dilated MPD was noted in 4 patients (67%), decreased contrast enhancement of the distal pancreatic parenchyma was noted in 4 patients (67%), and distal focal atrophic pancreatic parenchyma was noted in 3 patients (50%) (Table 1). The incidence of a dilated MPD was significantly higher in group A than in group B (100% vs. 67%, $p < 0.001$). For decreased contrast enhancement of the distal pancreatic parenchyma and distal focal atrophic pancreatic parenchyma, no significant differences were noted between group A and group B (67 % vs. 67 %, p =

0.411 and 67% vs. 50%, p = 1, respectively).

Regarding the number of secondary signs detected on CT in group A, 20 patients (23%) had 1 secondary sign, 18 patients (21%) had 2 secondary signs, and 49 patients (56%) had 3 secondary signs. The mean number of secondary signs in group A was 2.3 ± 0.8. Conversely, in group B, 2 patients (33%) had 1 secondary sign, 3 patients (50%) had 2 secondary signs, and 1 patient (17%) had 3 secondary signs (Table 2). The mean number of secondary signs in group B was 1.8 ± 0.8. There was no significant difference in the mean number of secondary signs detected on CT between group A and group B (p = 0.46). Regarding the sensitivity, specificity, and accuracy of 3 secondary signs for the CT differentiation of pancreatic adenocarcinoma, a dilated MPD had 100% sensitivity, 33% specificity and 96% accuracy, decreased contrast enhancement of the distal pancreatic parenchyma had 67% sensitivity, 33% specificity and 65% accuracy, and distal focal atrophic pancreatic parenchyma had 67% sensitivity, 50% specificity and 66% accuracy, respectively.

Table 1: Frequency of pancreatic secondary signs with or without cancer lesion on contrast-enhanced dynamic CT

	Group A n=87	**Group B n=6**	**p value**
Dilated MPD	87	4	0.004
Decreased contrast enhancement of distal pancreatic parenchyma	58	4	1
Focal atrophic change	58	3	0.411

Table 2: Detail of secondary signs of pancreas without cancer lesion on contrast-enhanced dynamic CT

	Secondary signs of pancreas			Cause of secondary signs
Case No.	Dilated MPD	Decreased contrast enhancement of distal pancreatic parenchyma	Focal atrophic change	
1	+	-	+	Unknown
2	-	+	-	Disection
3	+	+	+	Chronic pancreatitis
4	+	-	+	Chronic pancreatitis
5	+	+	-	Chronic pancreatitis
6	-	+	-	AIP

7. Discussion

Previous studies have reported on secondary signs in the pancreas and suggested that these secondary signs might indicate pancreatic adenocarcinoma causing obstructive pancreatitis of the distal pancreatic parenchyma [5, 10, 15-20]. Especially, some studies have reported that all patients with the secondary sign of a dilated MPD had pancreatic adenocarcinoma, and suggested that the secondary sign of upstream dilatation of MPD might be the characteristic sign of early pancreatic adenocarcinoma [5]. However, in the current study, 6 patients without pancreatic adenocarcinoma had pancreatic secondary signs, and specificity of 3 secondary signs for the CT differentiation of pancreatic adenocarcinoma was 33% for a dilated MPD, 33% for decreased contrast enhancement of the distal pancreatic parenchyma, and 50% for distal focal atrophic pancreatic parenchyma, respectively. This fact indicated that pancreatic secondary signs were not necessarily specific signs for the CT diagnosis of pancreatic adenocarcinoma. Therefore, for the correct diagnosis of pancreatic diseases, it would be important to understand that pancreatic secondary signs can be seen even in patients without pancreatic adenocarcinoma.

Conversely, sensitivity of a secondary sign of a dilated MPD for the CT differentiation of pancreatic adenocarcinoma was 100%, and the presence of only this sign was significantly different between patients with pancreatic adenocarcinoma and those without pancreatic adenocarcinoma. This result suggested that the secondary sign of a dilated MPD may be associated with a high risk of pancreatic adenocarcinoma. Kim et al. and Prokesch et al. reported that a dilated MPD was the most common sign of pancreatic adenocarcinoma [10, 15], and their results were similar to those of our study.

Regarding secondary signs seen in 6 patients without pancreatic adenocarcinoma, a dilated MPD was observed in 4 patients (chronic pancreatitis=3, unknown etiology=1). In two of these patients with chronic pancreatitis, a dilated MPD was seen in upstream of ductal obstruction induced by severe fibrosis on histopathology (Figure 2). Chronic pancreatitis caused by ductal obstruction has been shown to be characterized by MPD dilation [22], and a previous study reported that chronic pancreatitis occasionally shows focal or mass formation [23]. Therefore, we should note that the secondary sign of a dilated MPD in patients without pancreatic adenocarcinoma may be seen on CT, possibly caused by focal chronic pancreatitis.

Among 6 patients without pancreatic adenocarcinoma, the secondary sign of decreased contrast enhancement of the distal pancreatic parenchyma was demonstrated in 4 patients; chronic pancreatitis in 1, Autoimmune Pancreatitis (AIP) in 1, aortic dissection in 1, and unknown in 1 patient. Shimizu et al. suggested that a "black and white sign" in the arterial-phase dynamic CT in patients with pancreatic adenocarcinoma, which shows a contrasting effect between areas proximal and distal to the obstruction, is caused by segmental obstruction of the MPD due to pancreatic adenocarcinoma [18]. In two of our patients with chronic or autoimmune pancreatitis showing decreased contrast enhancement of the distal pancreatic parenchyma, this secondary sign is likely to be caused by focal pancreatitis with fibrotic changes inducing segmental obstruction of the MPD. It has been reported that AIP can result in focal or mass formation and that mass-forming AIP accounts for approximately 33-41% of AIP cases [24], possibly causing this type of the secondary sign (Figure 3). In one patient with aortic dissection, a mechanism of decreased contrast enhancement of the distal pancreatic parenchyma was unique, different from a case of focal pancreatitis with segmental obstruc-

tion of the MPD. In this patient with aortic dissection, pancreatic head and a half of body were supplied by rapid arterial flow from true lumen of dissected aorta while pancreatic tail and the other half of body were supplied by slow arterial flow from the false lumen, resulting in relatively decreased contrast enhancement of the distal pancreatic parenchyma.

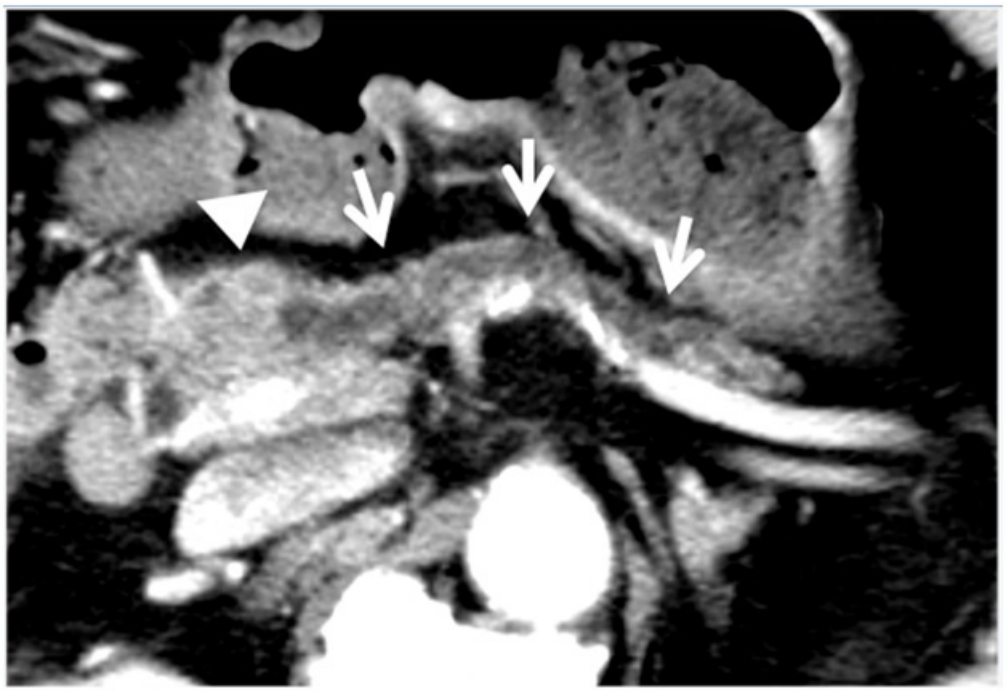

Figure 1: Typical CT appearances of pancreatic secondary signs from two different patients with pancreatic cancer.

Figure 1A: Contrast-enhanced arterial CT images in 82 years old man with cancer of pancreatic head (arrowhead) shows the secondary sign of a dilated MPD and focal atrophic pancreatic parenchyma (arrows).

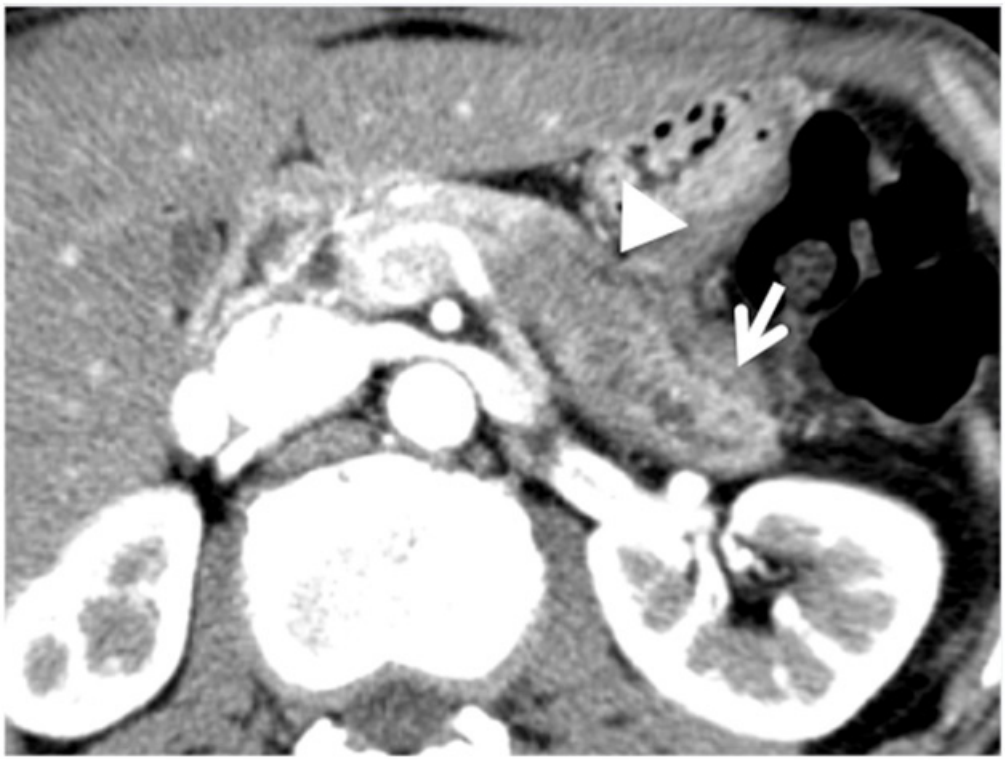

Figure 1B: Contrast-enhanced arterial CT image in 63 years old man with cancer of pancreatic body (arrowhead) shows the secondary sign of a dilated MPD and decreased contrast enhancement of the distal pancreatic parenchyma (arrow).

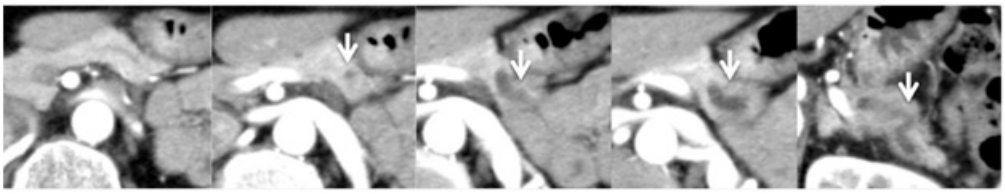

Figure 2: A patient without pancreatic cancer.

Figure 2A: Contrast-enhanced arterial-phase CT images show the secondary sign of a dilated MPD (arrows).

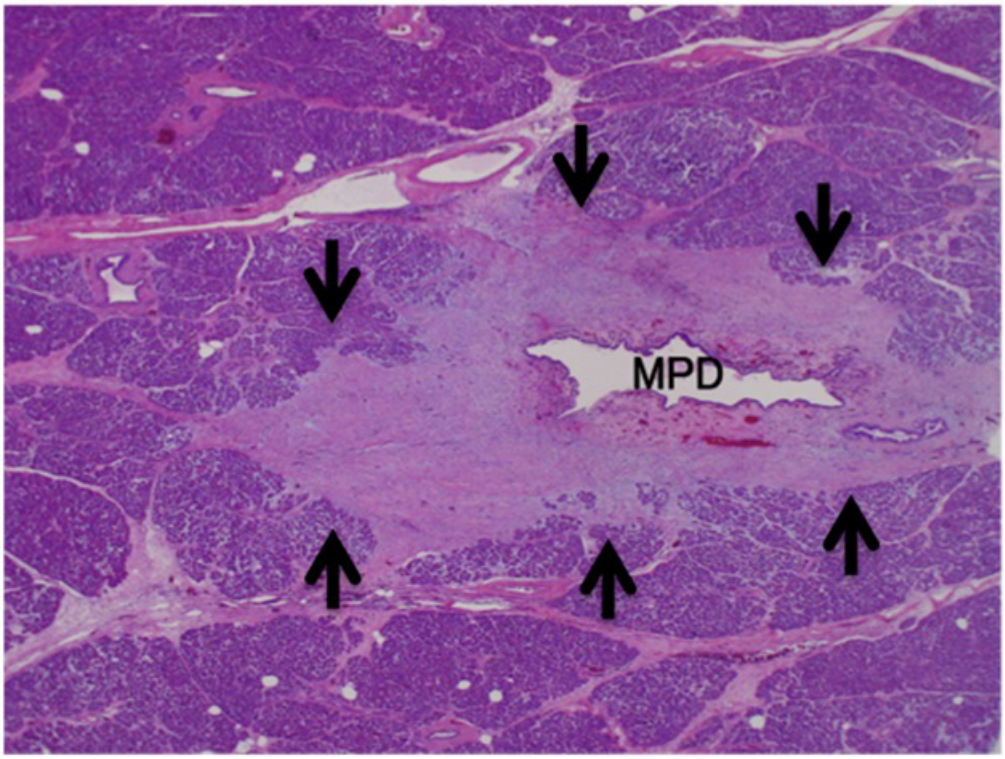

Figure 2B: Severe fibrosis (arrows) corresponding to chronic pancreatitis was observed around the MPD on histopathology (H&E, 2×).

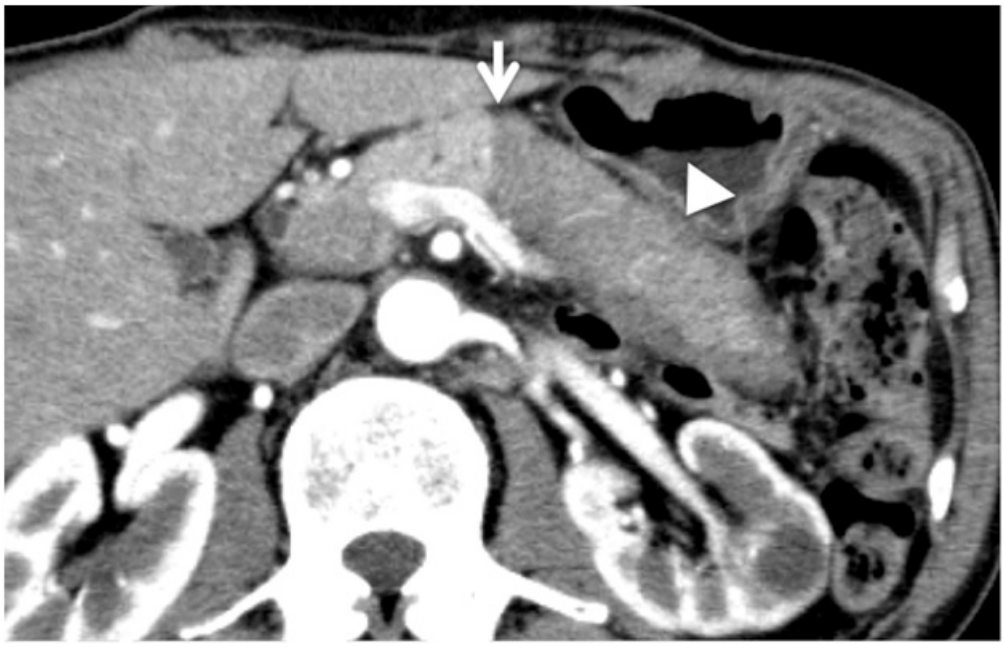

Figure 3: A patient with AIP.

Contrast-enhanced arterial-phase CT image shows decreased contrast enhancement of the distal pancreatic parenchyma (arrowhead) owing to AIP. The boundary (arrow) between the focal AIP lesion and normal pancreatic parenchyma was very clear.

The secondary sign of distal focal atrophic pancreatic parenchyma was seen in 3 of 6 patients without pancreatic adenocarcinoma (chronic pancreatitis=2, unknown etiology=1). Patlas et al. have reported that the lack of pancreatic body or tail atrophy indicated chronic inflammation rather than malignancy [25]. Conversely, Ahn et al. showed that focal atrophic pancreatic parenchyma can be caused by long-term ductal obstruction in patients with chronic pancreatitis [3], similar to our results. Therefore, we should note that a secondary sign of distal focal atrophic pancreatic parenchyma can be seen in patients with chronic pancreatitis although there was no significant difference in the incidence of this sign between patients with and without pancreatic adenocarcinoma.

The present study had some limitations. First, this was a retrospective study; thus, different CT protocols were used for diagnosis. Future studies should be performed with a single CT protocol, preferably using a same CT scanner and contrast materials. Second, the total number of participants without pancreatic adenocarcinoma, who had secondary signs in the pancreas was small, and this was because the absence of pancreatic adenocarcinoma in individuals with secondary signs in the pancreas was rare. Future studies should accumulate more cases involving secondary signs in the pancreas without the presence of pancreatic adenocarcinoma from multiple institutions. Finally, some individuals with secondary signs were not evaluated pathologically. Therefore, the causes of the secondary signs were speculative or unknown in some cases. However, we believe that our results have clinical implications, although pathological evaluations were not performed in some cases. Additionally, this limitation did not influence the primary results of this study.

In conclusion, it should be noted that secondary CT signs can be present in patients without pancreatic adenocarcinoma although a dilated MPD will be a secondary sign highly suggestive of pancreatic adenocarcinoma.

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