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A hypoechoic, tumor-like lesion in the pancreatic head and neck on endoscopic ultrasonography may be due to a high-grade pancreatic intraepithelial neoplasia/carcinoma in situ

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ABSTRACT

High-grade pancreatic intraepithelial neoplasia (HG PanIN)/carcinoma in situ (CIS) in the pancreatic body and tail can induce parenchymal atrophy through chronic inflammatory changes presenting as a Hypoechoic area on EUS (Hypocho) or focal pancreatic parenchymal atrophy (FPPA) on computed tomography (CT) and magnetic resonance imaging (MRI). We herein discussed two patients with a hypoechoic area in the pancreatic head and neck on EUS resembling pancreatic ductal adenocarcinoma (PDAC). The lesions consisted of dense fibrosis and fat infiltration with pancreatic parenchymal atrophy around the HG PanIN/CIS in the main pancreatic duct (MPD), which penetrated the lesion and showed mild stenosis and upstream dilation. CT and MRI were unable to visualize the lesions. A specimen was obtained from one lesion by fine-needle aspiration under EUS (EUS-FNA) guidance for histopathological and cytological analysis, but the tests returned negative for adenocarcinoma. However, serial pancreatic-juice aspiration cytologic examination (SPACE) revealed adenocarcinoma in both lesions, prompting surgical resection. Histopathological examination revealed non-invasive HG PanIN/CIS in the MPD surrounded by dense fibrosis and fat deposition in the area of parenchymal atrophy. The CIS was restricted to the area of parenchymal atrophy.These two cases are noteworthy in illustrating a hypoechoic area appearing on EUS as a tumor-like lesion resembling PDAC. EUS-FNA has

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recently been used histopathologically to diagnose a pancreatic lesion. However, in the present and similar cases, EUS-FNA can only reveal secondary changes due to CIS unless the pancreatic duct covered by the CIS is accidentally punctured. We should bear in mind that CIS can appear as a hypoechoic area resembling PDAC on EUS, and that SPACE is the best method for diagnosing CIS in such cases.

Keywords: Carcinoma in situ; endoscopic ultrasonography; focal pancreatic parenchymal atrophy; hypoechoic stricture; serial pancreatic juice aspiration cytological examination

Introduction

Patients with pancreatic ductal cancer (PDAC) generally have a poor prognosis, partly because of delays or difficulties with the diagnosis.[1,2] Kanno et al. reported that patients with stage 0 PDAC showed a good prognosis, 5-year survival rate reached 85%, and stressed that early diagnosis was important for improving the prognosis. [3]

Early diagnosis of PDAC is challenging in the real-world clinical setting because computed tomography (CT) and magnetic resonance imaging (MRI), which are generally used for examining pancreatic disorders, are not very effective in detecting small PDAC. [4] On the other hand, research has shown that endoscopic ultrasonography (EUS) works well for diagnosing small PDAC. [4, 5] However, no matter how small, the tumor, which develops from the pancreatic duct epithelium,is invasive and metastatic. In its early stages, PDAC is limited to the pancreatic duct epithelium where it is described as high grade pancreatic epithelial neoplasia (HG PanIN)/carcinoma in situ (CIS). [6] The difficulty or impossibility of detecting HG PanIN/CIS, even if various endoscopic methods including EUS are used, can lead to delayed diagnosis and a correspondingly poor prognosis.

Recently, some studies have reported so-called secondary findings of HG PanIN/CIS, [7–10] including focal pancreatic parenchymal atrophy (FPPA) on CT or MRI and the presence of a hypoechoic area(Hypoecho) on EUS adjacent to or surrounding the main pancreatic duct (MPD), both of which were limited mainly to the pancreatic body and tail. [11] Previous histopathological analysis has indicated that the pancreatic parenchyma around the CIS atrophies and is replaced by adipose tissue with fibrosis in the area corresponding to the FPPA or hypoechoic area [7–11] although the mechanism underlying this process is not clear. As a more sensitive method of diagnosing pancreatic epithelial lesions, including HG PanIN/CIS, serial pancreatic juice aspiration cytological examination (SPACE) may be used by inserting a nasopancreatic drainage tube during an endoscopic retrograde cholangiopancreatography (ERCP). [8,12] SPACE can enable earlier, more accurate diagnosis and treatment of HG PanIN/CIS with a correspondingly positive impact on the prognosis.

We herein discussed two patients with a hypoechoic area on EUS masquerading as

PDAC in the pancreatic head and neck. SPACE was used to diagnose the cancer and expedited surgery. The hypoechoic area masquerading as PDAC on EUS was a secondary finding of HG PanIN/CIS on histopathological examination.

Case presentations

Case 1

A 65-year-old, male patient was referred to our hospital due to elevated tumor marker levels and a dilated MPD. He had a history of diabetes mellitus as well as a current history of smoking (20 cigarettes per day) and drinking (15 g of alcohol per day) dating back 45 years. A physical examination revealed no abnormalities.

A blood examination found that hemoglobin A1c and cancer antigen 19-9 levels had increased to 8.8% (normal range: 4.9-6.0 %) and 46 U/mL (normal range: 0.0-37.0 U/mL), respectively, while the serum amylase and carcinoembryonic antigen levels were normal. Abdominal ultrasonography and CT demonstrated a dilated MPD but no tumor in the pancreatic head. MRI similarly revealed no tumor while magnetic resonance cholangiopancreatography (MRCP) visualized a MPD stricture in the pancreatic neck (Figure 1a). MRI diffusion-weighted imaging showed no areas of high signal intensity in the pancreatic head. ERCP revealed a mild and irregular stenosis of the MPD from the pancreatic head to neck (Figure 1b). EUS revealed a clearly demarcated, hypoechoic mass with a 20-mm diameter in the pancreatic head to neck (Figure 2a). The MPD showed narrowing where it penetrated the lesion (Figure 2b) but was dilated upstream. Histopathological and cytological analysis of tissue specimens obtained by fine-needle aspiration (FNA) under EUS guidance revealed fibrous tissue but no tumor tissue.

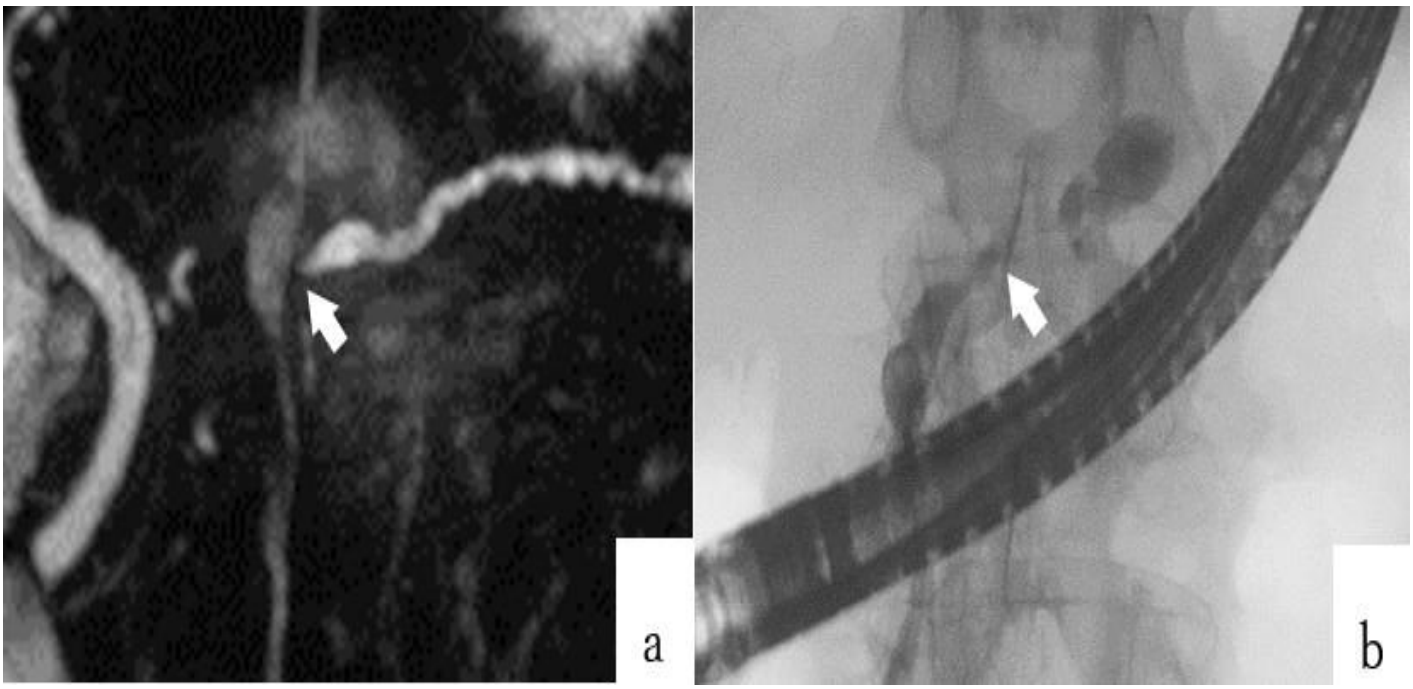

Figure 1. Cholangiopancreatography in Case 1

a. Magnetic resonance cholangiopancreatography revealed a main pancreatic duct (MPD) stricture in the pancreatic neck (arrow).

b. Endoscopic retrograde cholangiopancreatography revealed mild and irregular stenosis in a short segment of the MPD from the pancreatic head to neck (arrow).

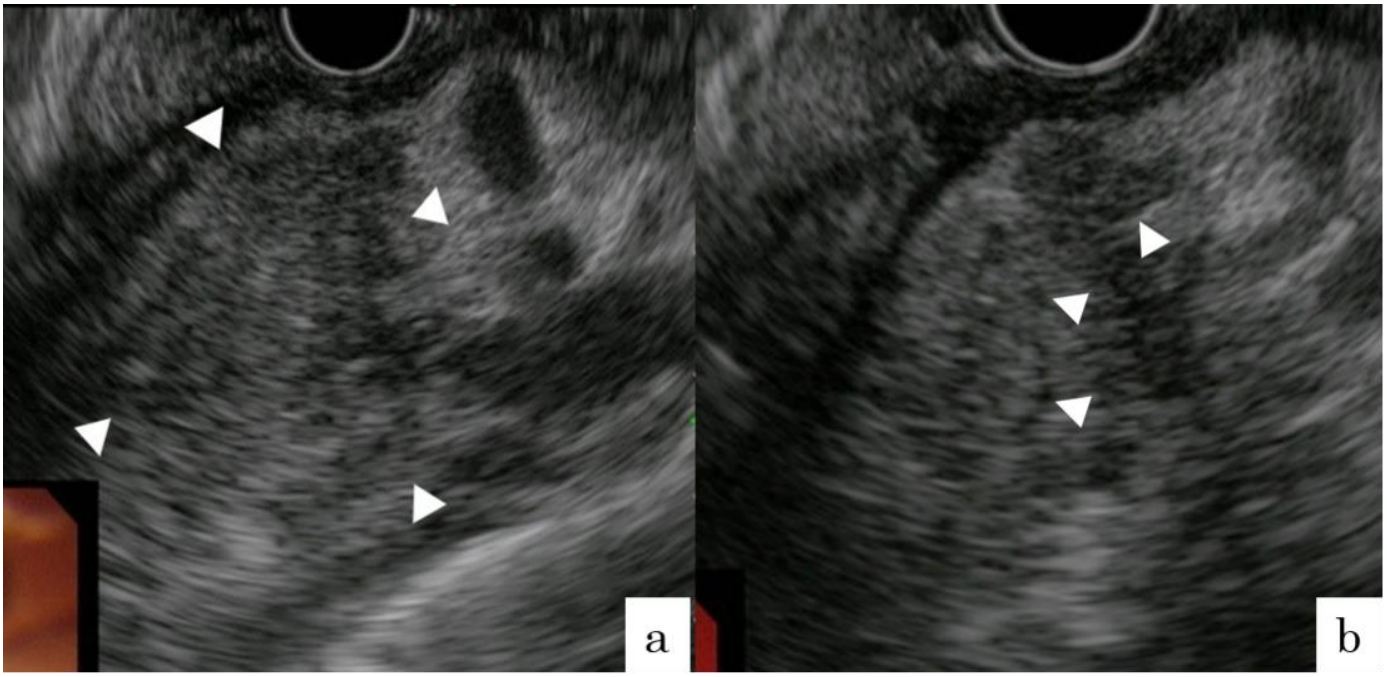

Figure 2. Endoscopic ultrasonographic findings in Case 1

a. A clearly demarcated, hypoechoic mass (arrowheads) can be seen in the pancreatic head.

b. The stenotic main pancreatic duct can be seen penetrating the lesion (arrowheads).

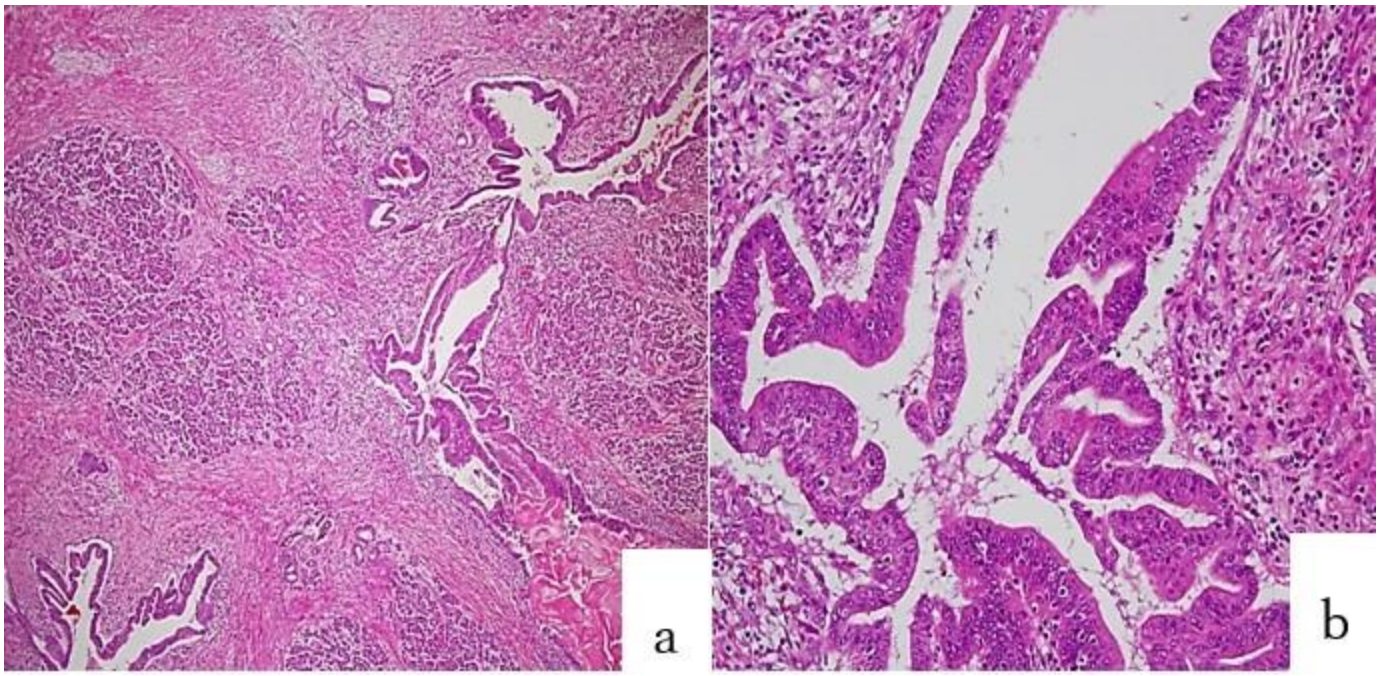

Figure 3. Histopathological findings in Case 1.

a. Hematoxylin and eosin staining demonstrated proliferation of low-grade papillary cells with eosinophilic cytosol in the main pancreatic duct (MPD) epithelium. Dense fibrosis and pancreatic parenchymal atrophy can be seen around the epithelium (magnification × 10).

b. Hematoxylin and eosin staining demonstrated irregularly arranged epithelial cell nuclei with loss of polarity. Based on this finding, atypical epithelium of high grade pancreatic intraepithelial neoplasm/carcinoma in situ was diagnosed. The surrounding fibrous stroma shows infiltration by chronic inflammatory cells (magnification × 200).

SPACE revealed atypical cells suggestive of adenocarcinoma. PDAC of the pancreatic head was suspected, and a pancreatoduodenectomy was performed. Histopathological examination of the resected specimen revealed low papillary growth of cells with eosinophilic cytosol and irregularly arranged nuclei with loss of polarity in the MPD epithelium. Based on these findings, dysplasia in HG PanIN/CIS was diagnosed. Dense fibrosis and pancreatic parenchymal atrophy were observed around the epithelium. The fibrosis was infiltrated by chronic inflammatory cells and adipose tissue (Figure 3).

Case 2

A 60-year-old, male patient with an intraductal papillary mucinous neoplasm (IPMN) presented to our hospital requesting a detailed pancreatic examination. He had a history of diabetes mellitus, renal failure treated with hemodialysis, and acute myocardial infarction, but no notable smoking or drinking habits. He had received the diagnosis of IPMN five years ago and had been undergoing MRI once a year thereafter, but no changes were observed. Physical examination revealed no abdominal abnormalities. Meanwhile, a blood examination demonstrated an increase in hemoglobin A1c, blood urea nitrogen, creatinine, and cancer antigen 19-9 to 7.1%, 40 mg/dL (normal range:8.0-20.0 mg/dL), 10.05 mg/dL (normal range:0.65-1.07 mg/dL), and 46 U/mL, respectively. His carcino-embryonic antigen level was 1.5 ng/dL (normal range: 0.0-5.0 ng/ml). CT imaging revealed a cyst in the pancreatic head but found no tumor. MRCP revealed a mild pancreatic duct stricture in the pancreatic head with a multilocular cyst (Figure 4a). During ERCP, a short, mildly stenotic segment of the MPD was observed in the pancreatic head (Figure 4b). EUS demonstrated a hypoechoic mass with a 10-mm diameter and indistinct margins (Figure 5) adjacent to the cyst and the stenotic MPD segment with upstream dilation within the mass.

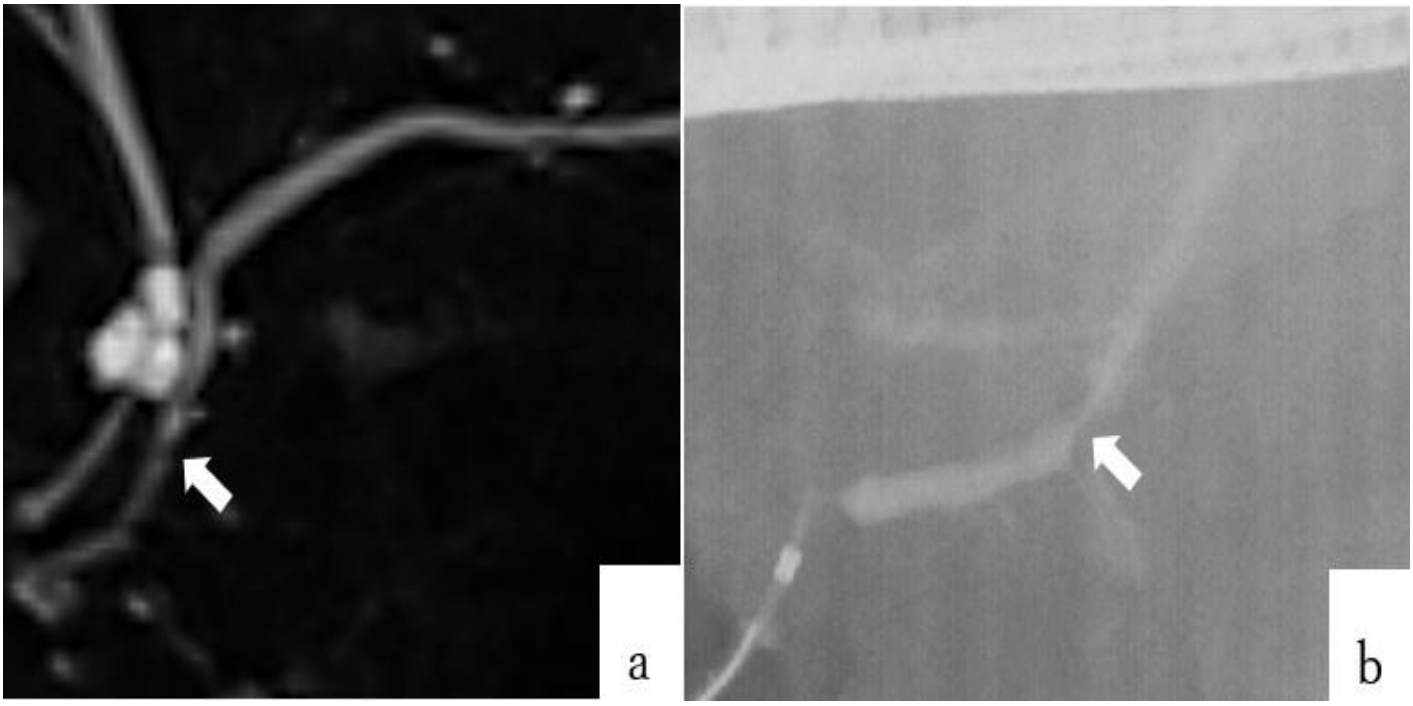

Figure 4. Cholangiopancreatography in Case 2.

a. Magnetic resonance cholangiopancreatography revealed a mild main pancreatic duct (MPD) stricture in the pancreatic head (arrow) with a multilocular cyst.

b. Endoscopic retrograde cholangiopancreatography revealed stenosis in a short segment of the MPD (arrow) without any cystic lesions.

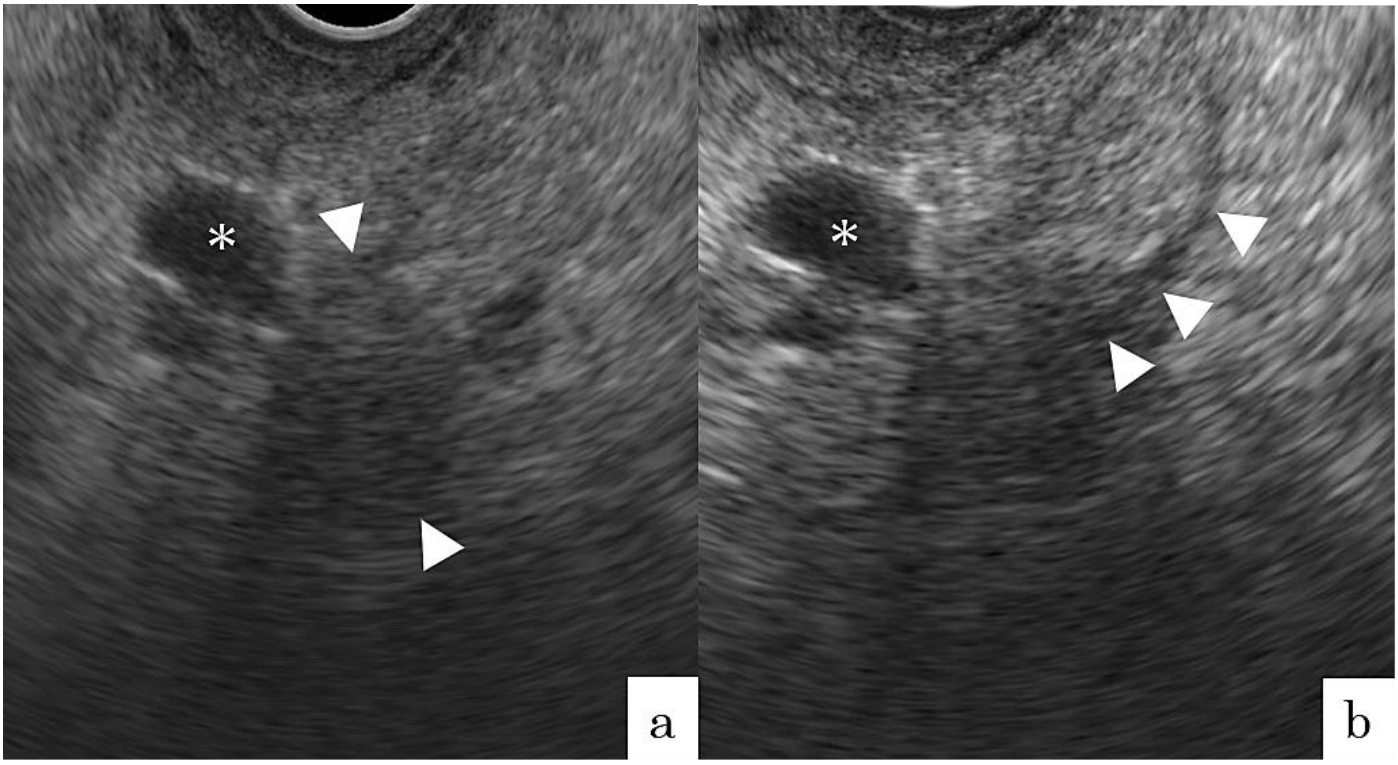

Figure 5. Endoscopic ultrasonography in Case 2.

a. A hypoechoic mass with indistinct margins (arrowheads) can be seen adjacent to a cyst (*).

b. The main pancreatic duct can be seen penetrating the lesion (arrowheads).

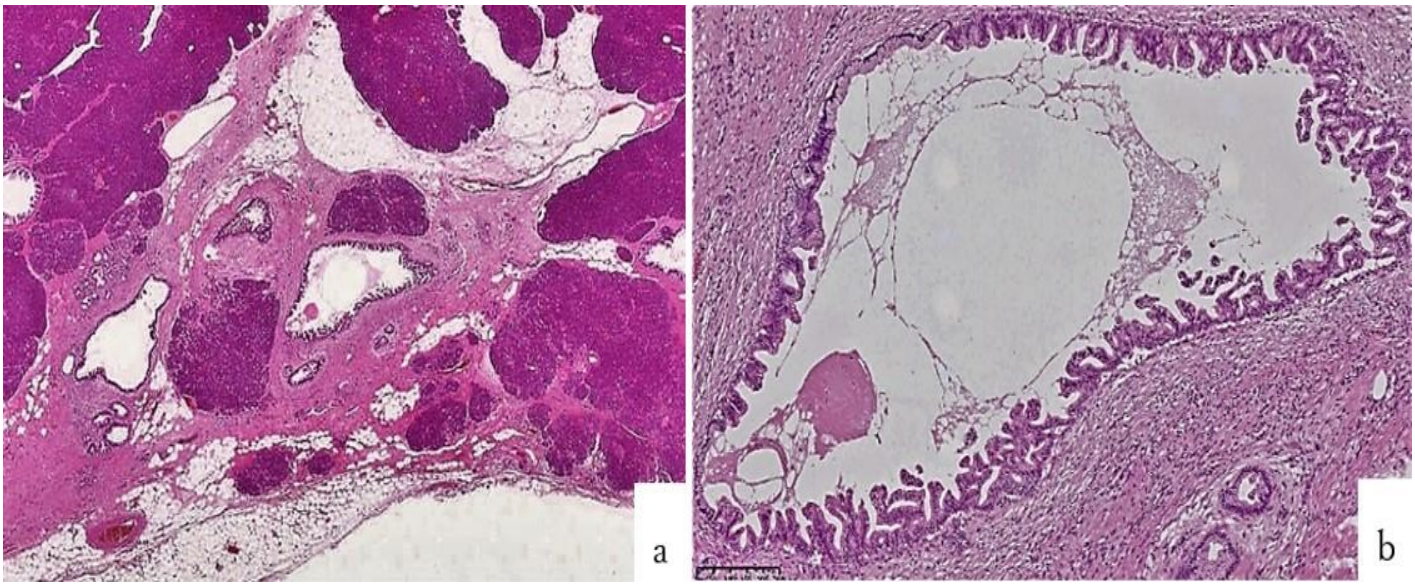

Figure 6. Histopathological findings in Case 2

a. Hematoxylin and eosin staining demonstrated thickening of the walls of the main pancreatic duct and branch duct due to fibrosis and an atrophic pancreatic parenchyma replaced by fibrous stroma and adipose tissue (magnification × 10).

b. Hematoxylin and eosin staining demonstrated dysplastic changes in the epithelial cells, some of which showed nuclear enlargement, loss of polarity, and irregular papillary growth. Based on this finding, high grade pancreatic intraepithelial neoplasm/ carcinoma in situ was diagnosed (magnification × 100).

Based on our experience of using SPACE to diagnose the hypoechoic lesion in *Case 1,* we chose to conduct the same procedure to diagnose the lesion in *Case 2*. SPACE revealed atypical cells suggestive of adenocarcinoma. Non-invasive PDAC of the pancreatic head was suspected, and a pancreatoduodenectomy was performed. Histopathological analysis of the resected specimen confirmed that the epithelial cells of the MPD and branch duct in the pancreatic head had atypical changes (low grade PanIN), and that a portion of the altered epithelium was accompanied by nuclear enlargement, loss of polarity, and irregular papillary growth in the duct wall. Based on these findings, dysplasia in HG PanIN/CIS was diagnosed (Figure 6). The duct wall showed thickening due to fibrosis and was surrounded by adipose tissue, which had replaced the atrophied portion of the pancreatic parenchyma. Cystic dilation of the branch duct showed nondysplastic epithelium, indicating a retention cyst.

Discussion

A cure for PanIN-3/CIS of the pancreas has now become a reality. [3,7–10] CIS can now be more quickly diagnosed on the basis of its secondary signs. For example, the presence of MPD stenosis facilitates the diagnosis of early stage PDAC while the presence of FPPA and a hypoechoic area, which stem from the histopathological changes seen in the deposition of adipose tissue and fiber in the atrophic pancreatic parenchyma, are reportedly reliable secondary signs of HG PanIN/CIS [10].

In recent reports, the hypoechoic area indicative of HG PanIN/CIS was described as presenting an indistinct appearance, [11] mainly in the pancreatic body and tail [13]. However, the lesions in the present cases were located in the pancreatic head and neck and resembled PDAC. They were clearly visible with distinct margins and were penetrated by the MPD on EUS. The findings are specific to these lesions and differed from those in previous reports. It is worth underscoring the fact that the lesions were penetrated by the MPD despite their close resemblance to PDAC. MPD penetration is reportedly characteristic of mass-forming pancreatitis [14]. The final diagnosis of these two lesions was HG PanIN/CIS with the chronic changes of fibrosis and adipose tissue replacing the atrophic pancreatic parenchyma. Although the parenchymal changes might have been induced by the HG PanIN/CIS, they were histopathologically identical with the features of mass-forming pancreatitis. The finding of MPD penetration may serve as means of differentiating the present and similar lesions from PDAC.

EUS-FNA is used histopathologically to diagnose a lesion suspected of being PDAC. However, if the lesion shows evidence of chronic changes, mass-forming pancreatitis rather than cancer may be diagnosed. Although HG PanIN/CIS with a hypoechoic area masquerading as PDAC but showing chronic, histopathological changes in the pancreatic parenchyma, as in the present two cases, may be uncommon, the possibility of HG PanIN/CIS should never be dismissed, and SPACE should be used, if possible, to assess the pancreatic duct.

As described above, FPPA is another sign of HG PanIN/CIS [10] although this feature was absent on CT and MRI in the present two cases. Previous findings of FPPA on CT or MRI suggesting HG PanIN/CIS have been limited mainly to the pancreatic body and tail. The pancreatic body and tail are thin, and the area of FPPA can be visualized on CT and MRI even if it is small. However, the pancreatic head is comparatively large, and the FPPA also needs to be large enough to be detectable on CT or MRI. Thus, a peripheral location makes identifying the deformation of the surface easier. The lesions in the present two cases were small and located in the center of the pancreatic head and neck area, which may account for the negative findings of FPPA on CT or MRI.

In conclusion, HG PanIN/CIS in the pancreatic head and neck may present as a hypoechoic

area and tumor-like lesion masquerading as PDAC. HG PanIN/CIS involves chronic inflammatory changes which may best be diagnosed using SPACE.

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