

CASE REPORT

A Minute Pancreatic Ductal Adenocarcinoma with Lipomatous Pseudohypertrophy of the Pancreas

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ABSTRACT

Context This report describes a minute pancreatic ductal adenocarcinoma which appeared to be in early stage tumor progression based on the study of its molecular abnormalities. In addition, it was associated with lipomatous pseudohypertrophy, a rare disease. **Case report** A 78-year-old male presented to our department with an incidental pancreatic tumor. Abdominal dynamic computed tomography showed an enlarged pancreas, and diffuse fat density in the entire pancreas was demonstrated. In the pancreatic body, a slightly enhanced early phase 10 mm mass was detected. He underwent a distal pancreatectomy. The histological features of the tumor revealed abundant fibrosis and duct lesions with various atypia. Duct lesions equivalent to well-differentiated adenocarcinoma were shown sparsely, but no vessel or lymphatic permeation nor perineural invasion were observed. In the background of the pancreas, diffuse fatty infiltrations which were composed of abundant normal adipose tissue and scattered pancreatic parenchyma were observed. The results of immunolabeling for MUC1, p16, p53 and Smad4 demonstrated that there is the possibility of coexistence of precancerous duct lesions and cancerous lesions in the genetic progression of pancreatic cancer. **Conclusion** The above results suggested that this pancreatic ductal adenocarcinoma with lipomatous pseudohypertrophy might be an example of very early stage tumor progression.

INTRODUCTION

With regard to the carcinogenesis of pancreatic ductal adenocarcinoma, the multiple progression model of pancreatic intraepithelial neoplasms (PanINs), is widely known [1]. However, the features of the transitional stage during the progression from a high-grade PanIN to an invasive pancreatic ductal adenocarcinoma are still indistinct [2]. We studied a patient with a minute pancreatic ductal adenocarcinoma which appeared to be in early stage tumor progression based on a study of the molecular abnormalities. Moreover, the presence of a rare histological feature, lipomatous pseudohypertrophy in the background of the pancreatic parenchyma, was shown in association. We herein describe the extremely rare and interesting case of a minute pancreatic ductal adenocarcinoma with lipomatous pseudohypertrophy.

CASE REPORT

A 78-year-old male presented to our department with incidental pancreatic tumor. He had no significant

symptoms and no history of alcoholic abuse or diabetes mellitus, but had a history of smoking and an arrhythmia for which he was on medication. His laboratory data on admission were almost within the normal limits. His hepatitis B and C virus markers were negative, while his serum CA 19-9 level was slightly elevated at 37 U/mL (reference range: 0-24 U/mL). Chest computed tomography showed pulmonary emphysematous changes and slight bronchiectasis at the right pulmonary hilum. Abdominal dynamic computed tomography showed multiple hepatic, pancreatic, and renal cysts. Moreover, an enlarged pancreas, diffuse fat density, and net-like shadow in the entire pancreas were demonstrated (Figure 1a). In the pancreatic body near the main pancreatic duct, a slightly enhanced 10 mm mass in the early phase, and delayed enhancement in the late phase, were shown. Magnetic resonance cholangio-pancreatography demonstrated no anomalous arrangement of the pancreatobiliary ducts. Moreover, obstruction, or narrowing or dilatation of the main pancreatic duct were not observed (Figure 1b). Upon performing endoscopic retrograde cholangiopancreatography, pancreatic juice was obtained from the main pancreatic duct near the tumor, and cytology revealed class IV cells. Positron emission tomography plus computed tomography showed no significant accumulations at the tumor. A minute pancreatic body cancer with diffuse fatty infiltration of the pancreas was diagnosed.

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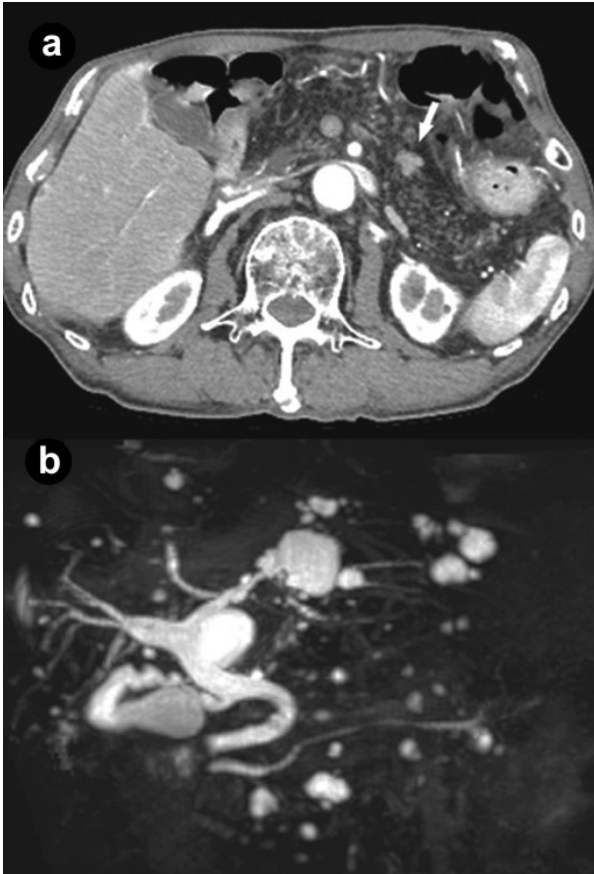


Figure 1. a. Abdominal dynamic computed tomography showed a slightly enhanced early phase 10 mm mass (arrow) in the pancreatic body, diffuse fat density, and net-like shadow in the entire pancreas. b. Magnetic resonance cholangiopancreatography demonstrated no abnormal findings, such as obstruction, narrowing or dilatation in the main pancreatic duct or multiple hepatic and pancreatic cysts.

In 2010, a distal pancreatectomy with lymphadenectomy and splenectomy was performed. The yellowish pancreatic specimen was elastic, soft and enlarged. The cut surface demonstrated diffuse fatty-infiltration and contained a well-demarcated white to grayish tumor, which was 10 mm in diameter (Figure 2).

The histological features of the tumor revealed abundant fibrosis and duct lesions with various atypia (Figure 3a). Apparent irregular duct lesions with moderate to severe

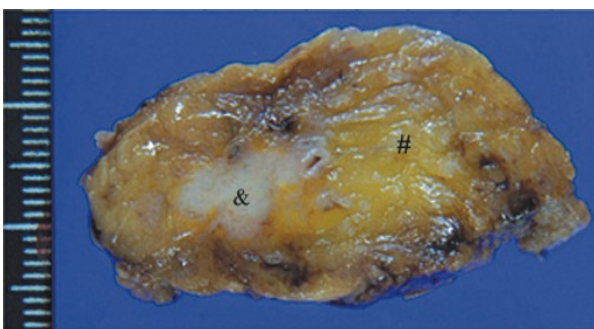


Figure 2. The cut surface demonstrated diffuse fatty infiltration (#) and contained a well-demarcated white to grayish tumor (&).

atypia which were equivalent to well-differentiated adenocarcinoma were sparsely observed in the vicinity of the center of the tumor, but no vessel or lymphatic permeation nor perineural invasion or lymph node metastases were observed. In the periphery of the tumor, normal duct-like lesions, mucinous metaplasia, and acinar atrophy were seen (Figure 3b). We defined mucinous metaplasia as lesions which were not present in the small pancreatic duct because, when the lesions are in the duct, they are equivalent to PanINs [3]. In the background of the pancreas, diffuse fatty infiltrations which were composed of abundant normal adipose tissue and scattered pancreatic parenchyma were observed (Figure 4a). In the scattered pancreatic parenchyma, dilated ducts or acinar atrophy with fibrosis were recognized with considerably high frequency, and low-grade PanINs or mucinous metaplastic lesions were seen in spots (Figure 4b). On the whole, lymphocytic infiltration was notably present in the residual pancreatic parenchyma, but fibrosis was minimal. On the other hand, the scattered islets of Langerhans and the duct systems were notably well-preserved in the entire pancreas. As a result, the patient was finally diagnosed as having a minute pancreatic ductal adenocarcinoma with lipomatous

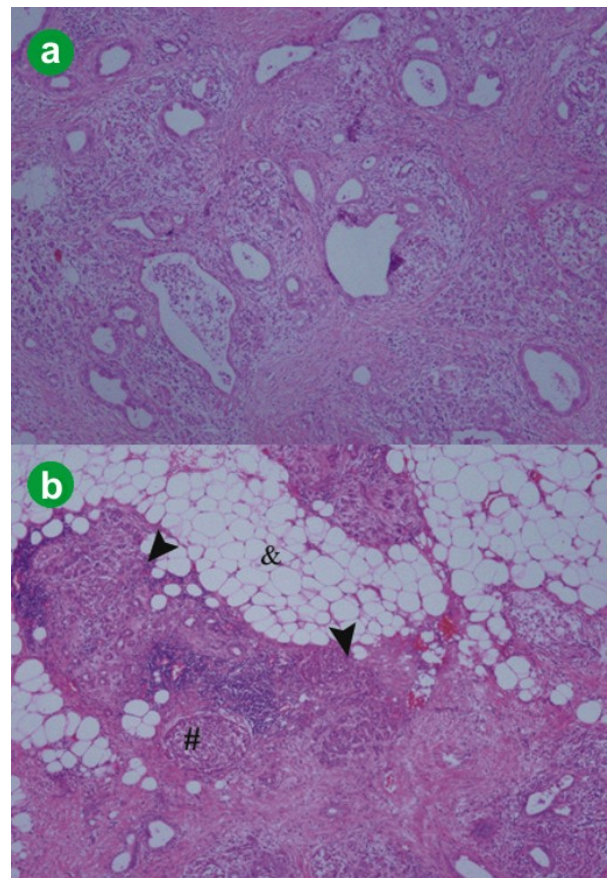


Figure 3. a. Histological features of the tumor revealed abundant fibrosis and duct lesions with various atypia (x100). b. In the periphery of the tumor, normal duct-like lesions, islets of Langerhans (#) and acinar atrophy (arrow heads) were observed and, around the tumor, abundant normal adipose tissue (&) was seen (x100).

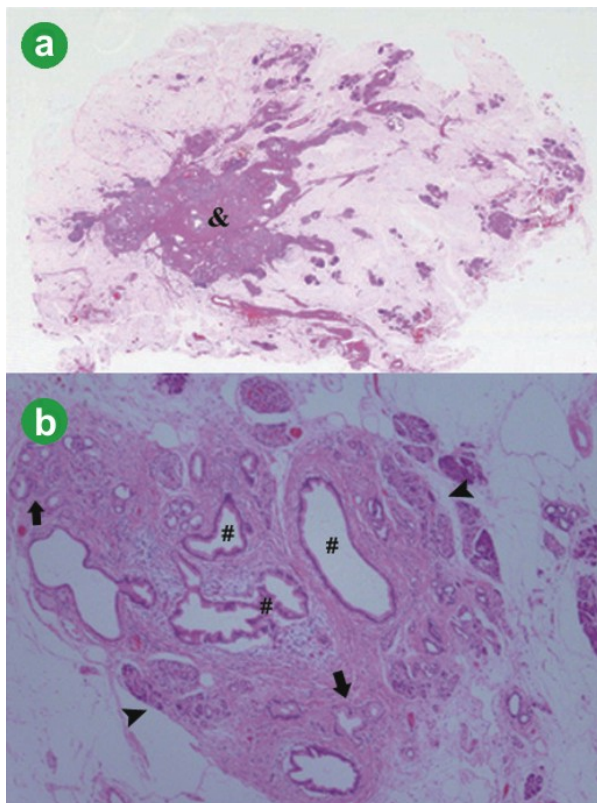


Figure 4. a. In the back ground pancreas, abundant normal adipose tissue and scattered pancreatic parenchyma were seen around the tumor (&) (x20). b. In the scattered pancreatic parenchyma, small or dilated ducts, mucinous metaplasia (arrows) including low-grade PanIN (#), and acinar atrophy (arrow heads) were observed (x40).

pseudohypertrophy.

The immunolabeling for Muc1, p16, p53, and Smad4 was carried out by using the EnVision+ Dual Link System-HRP (DAB+) system (Dako Cytomation, Glostrup, Denmark) on 3 µm tissue sections of the pancreatic tumor. The primary antibodies used were a mouse monoclonal (DF3) for Muc1 (Gene Tex, Irvine, CA, USA), E6H4 for p16 (CINtec, Heidelberg, Germany), DO-7 for P53 (Dako Cytomation, Glostrup, Denmark) and L43 for Smad4 (Bioworld Technology, St. Louis Park, MN, USA). The site of the labeling by each antibody was mainly the cell surface and partially the cytoplasm by anti-MUC1, the nucleus by anti-p53, and the nucleus and cytoplasm by anti-p16 and anti-Smad4. The assessment of immunolabeling was as follows: immunolabeling in less than 5% of the cells within a lesion was considered negative, immunolabeling in 5-25% was considered focal positive, and immunolabeling in more than 25% was considered diffuse positive [4]. The intensity was expressed as negative, weak, moderate and strong. In particular, a complete absence of cytoplasmic and nuclear labeling for p16 and Smad4 in the lesion was considered negative as described in the literature [5, 6, 7], and the results were also evaluated for genetic abnormalities. Positive and negative controls were confirmed using each type of immunolabeling [4, 5, 6, 7].

The results of the immunolabeling were as follows: various duct lesions (irregularly shaped or normal, small or dilated, with or without atypia) within the tumor area showed focal positive-labeling with moderate to weak-intensity for MUC1 (Figure 5a), diffuse positive-labeling with weak to moderate-intensity for Smad4 (Figure 5b), and negative-labeling for p16 and p53. Hence, it was thought that genetic abnormalities in p16 were observed within the tumor area. Moreover, genetic abnormalities in Smad4 and p53 were not observed in the tumor. In the periphery of the tumor, some duct lesions showed negative expression for Muc1, p53, and p16, and showed intact expression for Smad4.

One year after surgery, the patient had no evident recurrence, and continued to receive S-1.

DISCUSSION

In order to define the early stage of an invasive pancreatic ductal adenocarcinoma, it is important to clarify not only the histological features but also the molecular abnormalities associated with genetic progression.

Another important point is to identify the tumor border. In most pancreatic ductal adenocarcinomas, the border is indistinct because of infiltrative growth. However, in

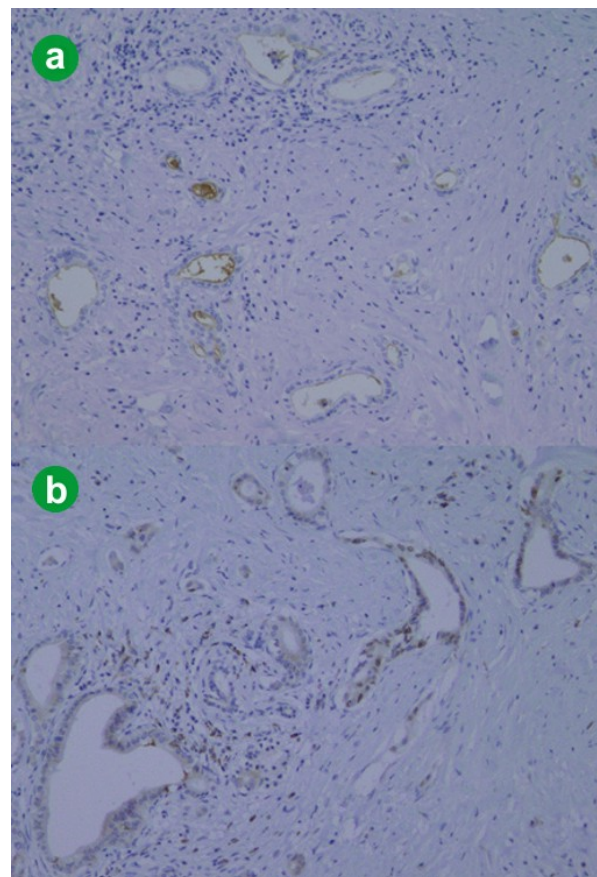


Figure 5. a. Immunolabeled features of the tumor showed focal positive-labeling for MUC1/DF3 mainly at the cell membrane (x100). b. Diffuse positive labeling for Smad4 mainly at the cytoplasm and focally nucleus are also seen (x100).

the present case, the presence of lipomatous pseudohypertrophy made the tumor border distinct because the pancreatic parenchyma around the tumor had been almost completely replaced by normal adipose tissue. Hence, we were able to easily and precisely identify whether immunolabeled duct lesions existed within the tumor area or not.

The characteristic histological features of this minute pancreatic ductal adenocarcinoma were as follows. First, the pancreatic ductal adenocarcinoma was composed of abundant fibrosis, called the desmoplastic reaction, and various duct lesions. However, such duct lesions as could be distinctly diagnosed as adenocarcinoma were present sparsely in the vicinity of the center of the tumor. The desmoplastic reaction is one of the characteristic features of an invasive pancreatic ductal adenocarcinoma [3, 8], and it has been hypothesized that cancer cells within the desmoplastic reaction area grow as the result of a mechanism, such as tumor-stroma interaction [9]. Hence, the evident presence of the desmoplastic reaction, in spite of a minute pancreatic ductal adenocarcinoma and the sparse presence of cancer cells within the desmoplastic reaction area, appeared to be valid for the very early features of a pancreatic ductal adenocarcinoma. Second, normal duct-like lesions, mucinous metaplasia and acinar atrophy were observed only in the periphery of the tumor. It is thought that these components may have originally been present in the scattered acini in which this pancreatic ductal adenocarcinoma occurred and they were later included in the tumor with progression of the pancreatic ductal adenocarcinoma. In addition, the features of no vessel and lymphatic permeation and no neural invasion support the fact that this case was likely to be the early stage of an invasive pancreatic ductal adenocarcinoma.

In this study, we carried out immunolabeling for p16, p53, Smad4, and MUC1 to clarify the stage of genetic progression of this minute pancreatic ductal adenocarcinoma. Inactivation of the p16 function in pancreatic ducts is considered to be an early event in the genetic progression of carcinogenesis [7]. On the other hand, inactivation of p53 and Smad4 are considered to be late events [4, 5, 6]. Maitra *et al.* reported that loss of the p16 function is found in low-grade PanINs with a frequency of up to approximately 95% in invasive pancreatic ductal adenocarcinoma [4]. Nuclear overexpression of p53 protein and loss of DPC4 expression are found only in PanIN-3 (with frequencies of 57% and 28%, respectively) and invasive pancreatic ductal adenocarcinoma (50-75% and 55%, respectively) [4]. On the other hand, MUC1 is one of the representative surface markers of a pancreatic ductal adenocarcinoma [10], and Ueda *et al.* reported that MUC1 is the most sensitive and specific marker for invasive pancreatic carcinoma [11].

In light of these immunohistochemistry results, focal positive labeling for MUC1 in various duct lesions suggested that all duct lesions within the tumor area did not have sufficient malignant potential. On the other

hand, no expression of p16, p53 and Smad4 suggested that the genetic abnormalities of early events, such as p16 inactivation, had occurred, but that late events, such as p53 or Smad4 inactivation, had not occurred sufficiently. In other words, these duct lesions within the tumor area might be a state where precancerous lesions and cancerous lesions coexist.

Lipomatous pseudohypertrophy was first described in 1931 [12] but it is a rare disease and the specific etiology of lipomatous pseudohypertrophy remains unknown. At CT imaging, this patient demonstrated typical features [13]. Histologically, the pancreatic acini showed marked atrophy and loss, but the islets of Langerhans were relatively preserved; hence, it was thought that glucose tolerance was preserved. In the residual scattered acini, low-grade PanINs, mucinous metaplasia, acinar atrophy, dilated ducts and slight lymphocytic infiltration were shown with a considerably high frequency. Altinel *et al.* reported that scattered acini do not show signs of injury, such as cellular attenuation, inspissated secretions or tubular complex formation [14]. However, it is unknown whether the above features of the acini in this patient occurred in association with diffuse fatty infiltrations or a minute pancreatic ductal adenocarcinoma because there have only been a handful of case reports about lipomatous pseudohypertrophy. In the literature, there are only three reports of pancreatic carcinomas associated with lipomatous pseudohypertrophy: one squamous cell carcinoma and two adenocarcinomas [14]. To date, 30 cases of lipomatous pseudohypertrophy have been reported [14], but the study of carcinogenesis in lipomatous pseudohypertrophy patients has been extremely limited. In this patient, two risk factors, advanced age and smoking, might be involved in the possible occurrence of pancreatic cancer. Until now, it has been unclear whether lipomatous pseudohypertrophy should be considered as a risk factor for pancreatic ductal adenocarcinoma. However, if lipomatous pseudohypertrophy of the pancreas is observed, careful attention should be paid to the risk of carcinogenesis.

Conflict of interest The authors have no potential conflict of interest

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