

## Case Report

# A Case of Ductal Dysplasia of the Pancreas

## — A Possible Prerequisite for Pancreatic Cancer —

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The precise pathobiology of precursor lesions, which develop into pancreatic adenocarcinoma, remains controversial. Recently, we encountered a patient with dysplastic lesion of the pancreas; a case in which a precursor lesion of the pancreatic carcinoma may have been documented. The patient was a 73-year-old female with epigastric discomfort. As part of a general check-up, she underwent abdominal ultrasound, which revealed the pancreatic duct in the pancreatic body to be slightly indented. Computed tomography (CT) scan revealed mild dilatation of the main pancreatic duct and a small low-density area (less than 1 cm in diameter). Endoscopic retrograde cholangiopancreatography (ERCP) showed the irregularity in the body of the main pancreatic duct. Under general anesthesia, resection of the distal portion of the pancreas was performed with splenic conservation. Pathological examination revealed focal hyperplastic epithelium of the pancreatic duct with moderate dysplasia. Expression of the proliferating cell nuclear antigen (PCNA) in the lesion was observed, indicating a slightly proliferative nature. Mutant p53 protein was slightly expressed in the lesion. As is seen in this case, ductal hyperplasia of the pancreas might represent precursor lesions, and constitute part of a continuous development spectrum evolving into ductal adenocarcinoma of the pancreas with accumulation of genetic alterations.

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**Key Words:** ductal hyperplasia of the pancreas, precursor lesion of the pancreatic cancer

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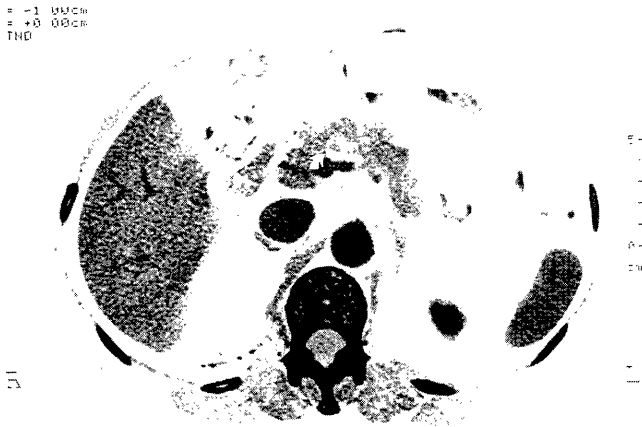
## Introduction

Although the precise pathobiology of precursor lesions that develop into pancreatic adenocarcinoma remains controversial, elucidation of the mechanisms of tumorigenesis might possibly provide for earlier detection, prevention, and treatment. Thus far, infiltrating adenocarcinoma of the pancreas has been characterized at the molecular level, though little is currently known about the early events in the development of this neoplasm or about the role of precursor lesions in tumor development<sup>1, 2)</sup>. The identification of the precursor lesions to infiltrating adenocarcinoma of the pancreas is especially important because most infiltrating cancers of the pancreas already have spread beyond the pancreas by the time the lesions are detected clinically. Recently, we encountered a patient with pancreatic hyperplasia for whom partial resection of the pancreas was performed. Here we describe the case and discuss an hypothesis regarding tumorigenesis.

## Case report

The patient was a 73-year-old female with epigastric discomfort, who was referred to our hospital in 1998 due to hyperglycemia. As a part of general check up, she underwent abdominal ultrasound, which revealed the pancreatic duct in the pancreatic body, having an appearance similar to a string of beads. No particular family history existed. She had no history of alcohol abuse nor was she a heavy smoker. On admission, the patient's physical examination revealed no particular abnormal findings. In addition, count of blood ball cells, biochemistry (Amylase 105 IU/l), and tumor markers (CA19-9 27U/ml, Span-I 50U/ml) except for Dupan-2 (190 U/ml) all showed normal data. Both her pancreatic exocrine (PFD test: 43.5%) and endocrine (75g oral glucose tolerance test was diabetes mellitus pattern)

function were poor. CT scan revealed mild dilatation of the main pancreatic duct and a small low-density area (less than 1 cm in diameter; Fig. 1). Preoperative ERCP showed the irregularity in the body of the main pancreatic duct (Fig. 2). Magnetic resonance imaging

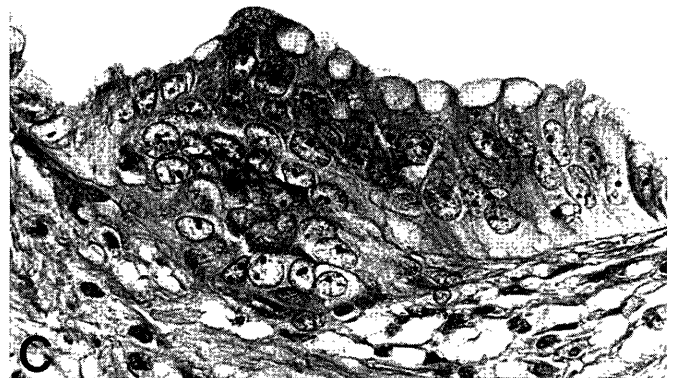
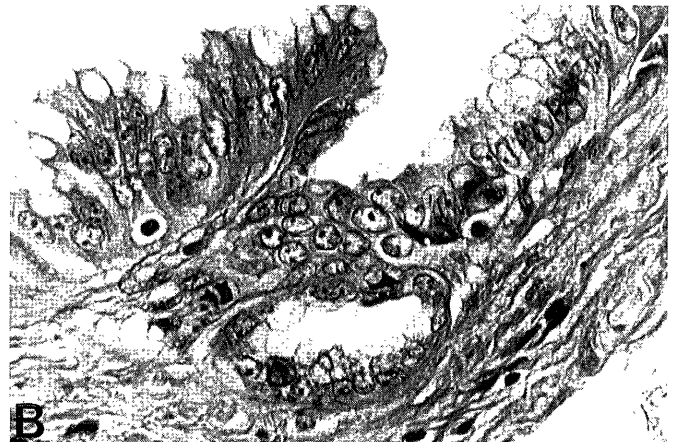
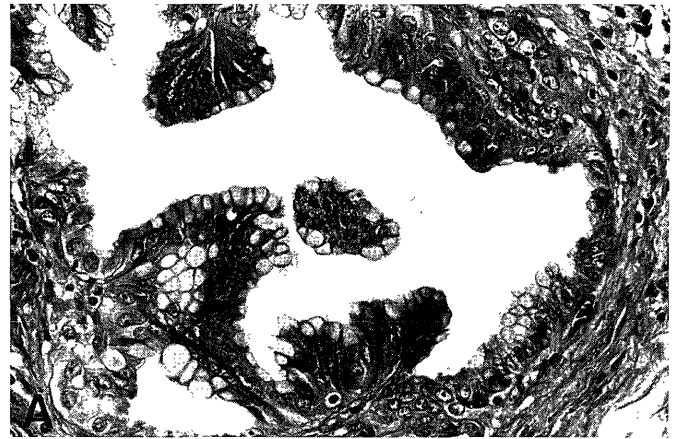


**Fig 1.** CT scan revealed mild dilatation of the main pancreatic duct and a small low-density area less than 1 cm in diameter (arrow).



**Fig 2.** Preoperative ERCP showed the irregularity in the body of the main pancreatic duct.

showed slight dilatation of the main pancreatic duct and a small mass lesion in the body. Angiography revealed no abnormalities. Due to a preoperative diagnosis of possible pancreatic cancer, under general anesthesia, resection of the distal portion of the pancreas was performed with splenic conservation. Pathological examination revealed focal hyperplastic epithelium of the pancreatic duct with dysplasia (Fig. 3 A, B, C). In



**Fig 3.** Pathological examination revealed focal hyperplastic epithelium of the pancreatic duct with some degree of dysplasia. (A:100x, B:200x, C:400x)

addition, pyloric gland hyperplasia in the lesion was seen and slight inflammation was present in the whole resected specimen. The final histological diagnosis was ductal hyperplasia with moderate dysplasia of the pancreas. Expression for proliferating nuclear antigen (PCNA) was observed in the nucleus of the lesion (Fig. 4). Immunohistochemically, mutant p53 protein was expressed in the lesion. Also, both CA19-9 and Carcinoembryonic antigen (CEA) protein were slightly expressed in the lesion. Post operative course was uneventful and the patient was discharged home. There has been no evidence of recurrence of the disease and she has been symptom-free for 1 year at this writing.

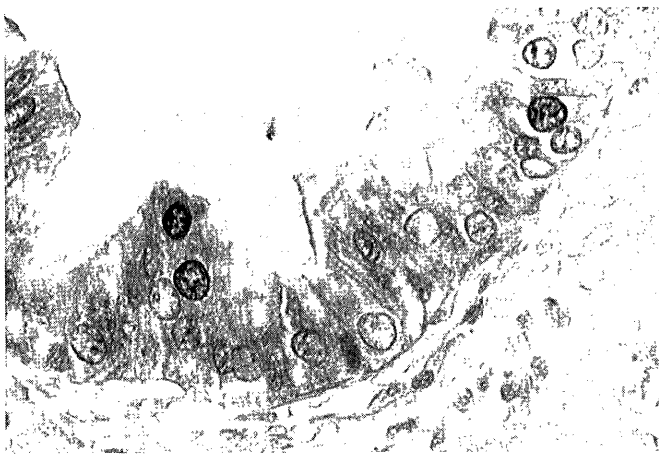


Fig 4. Slight expression of the proliferating nuclear antigen (PCNA) was observed in the lesion. (200x)

## Discussion

In the present case, we may have detected a precursor lesion of pancreatic carcinoma, which can be hardly detected clinically. In the resected specimen, slight expression of PCNA was observed in the lesion, indicating a slightly proliferative nature. Generally, aside from de novo development, it has been presumed that the development spectrum of hyperplasia - dysplasia - carcinoma in situ exists, although it is relatively difficult to prove in vivo<sup>3,4</sup>. Thus far, several reports have been published stressing the involvement of ductal hyperplasia in infiltrating adenocarcinoma of the pancreas, although the papillary hyperplasia - atypical hyperplasia (dysplasia) - to papillary adenocarcinoma sequence has been relatively well investigated with regard to mucin producing adenocarcinoma<sup>5,6</sup>. Thus, although a putative development spectrum evolving into ductal adenocarcinoma of the pancreas was advocated, hyper or dysplastic lesions of the pancreas are barely detected, though this may have been accomplished in the present

case.

Mutant p53 protein was slightly expressed in the lesion. In a previous report, it was shown that mutant p53 protein was expressed at 0% in normal duct, 55% in hyperplastic lesions, 67% in dysplastic lesions and 80% in adenocarcinomas<sup>7</sup>. It has also been reported that K-ras mutation was highly related to carcinogenesis of pancreatic cancer, although it was not investigated in our case<sup>7,8</sup>. This finding implies a putative development spectrum evolving into ductal adenocarcinoma of the pancreas with accumulation of genetic alteration. Ductal hyperplasia and dysplasia of the pancreas might represent precursor lesions, in a fashion similar to that seen in colorectal tumorigenesis with accumulating progressive genetic alterations such as p53 and K-ras<sup>9</sup>.

From a different perspective, it is presumed that pancreatic hyperplasia might be a different entity from hyperplasia of other organs such as gastrointestinal tract. Brat et al. stressed that the term "pancreatic hyperplasia" should be replaced by the more specific term "pancreatic intraepithelial neoplasia" since pancreatic hyperplasia can develop into infiltrating adenocarcinoma just as adenoma in the colorectum<sup>10</sup>. In their cases, adenocarcinoma developed long-term after detection of the atypical papillary hyperplasia. The difference of meaning of "hyperplasia" should be elucidated, in time, by further investigation with more detailed genetic clarification.

As seen in our case, chronic inflammation and/or ductal epithelial papillary hyperplasia may play a role in the pathogenesis of the tumor. However, thus far, the relationship between chronic pancreatitis and ductal neoplasia of the pancreas is still under discussion<sup>11,12</sup>. In any event, the identification of the precursor lesions to infiltrating adenocarcinoma of the pancreas is especially important because most infiltrating cancers of the pancreas already have spread beyond the pancreas by the time the lesions are detected clinically. Our patient may have been fortunate since the lesion was resected prior to the development of infiltrating adenocarcinoma, which usually provides a poor prognosis.

In summary, we experienced a case with hyperplasia of the pancreas with a somewhat dysplastic (morphological and genetic) lesion. This type of lesion is rarely detected, and this case may thereby provide information regarding carcinogenesis of infiltrating adenocarcinoma of the pancreas, the development of which likely includes this step.

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