Important clues to the diagnosis of pancreatic cancer

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Abstract

The incidence of pancreatic carcinoma is recently increasing but the prognosis remains extremely poor. Widespread awareness of important clues to the diagnosis is particularly important to improve the prognosis. Dilatation of the main pancreatic duct on ultrasonograms and/or CT scans, hyperamylasemia incidentally found during routine blood examinations, and recent onset diabetes mellitus must lead to thorough imaging studies of the pancreas. Death from pancreatic carcinoma occurs in 0.2-1.9% of all diabetic patients, being more than 300 times frequent compared to general population. Diabetes may be the only clinical sign of pancreatic carcinoma in some patients. In our recent study, of 163 diabetic patients selected by several criteria who underwent ERCP screening, 12 patients (7.4%) proved to have pancreatic carcinoma. The prevalence of pancreatic carcinoma was more frequent in those with a recent onset (<3 years) of diabetes (13.7% (8/58)) than in those with a longer history (>3 years, 3.8% (4/105)). Furthermore, intraductal papillary mucinous neoplasm (IPMN) is reported to be associated with pancreatic carcinoma. Concomitant carcinoma was found in 9 of our series of 94 patients (9.5%) who underwent surgical resection of branch duct IPMN. Of particular interest is the fact that two of the 9 patients had carcinoma in situ that could be diagnosed only by cytology of the pancreatic juice. IPMN may be the only clue to the early diagnosis of pancreatic carcinoma presenting with no clinical symptoms or abnormalities on imaging studies.

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Introduction

The incidence of pancreatic carcinoma is increasing probably due to aging of the general population and/or some other reasons, but the early diagnosis remains difficult. There are a few fortunate patients who are incidentally diagnosed as having small pancreatic carcinoma due to the advent of a variety of imaging studies, but most of the patients with pancreatic carcinoma are diagnosed in a far-advanced stage because they do not present with specific symptoms and usual work-up imaging studies do not include the pancreas. The extremely high malignant potential of pancreatic carcinoma and its early extrapancreatic invasion due to the retroperitoneal location readily make it unresectable, keeping the prognosis dismal. A high index of suspicion and awareness of a variety of diagnostic clues are essential to make early diagnosis of pancreatic carcinoma. This is an overview of various important clues to the diagnosis of this disease entity, i.e. 1) dilation of the pancreatic duct and/or hyperamylasemia, 2) diabetes mellitus, and 3) intraductal papillary mucinous neoplasms (IPMN) of the pancreas. In particular, the importance of IPMN as a new hint for the diagnosis is emphasized.

1. Dilation of the pancreatic duct and/or hyperamylasemia

The most frequent key to the diagnosis of pancreatic carcinoma is dilation of the main pancreatic duct detected by US and/or CT. If this dilation is erroneously considered as chronic pancreatitis and further examinations are not conducted, the diagnosis of pancreatic carcinoma would be missed. Diffuse main pancreatic duct dilation tends to be regarded as chronic pancreatitis; however, thorough examinations to negate the

presence of periampullary carcinoma must be performed before any treatment or follow-up as chronic pancreatitis is begun. Hyperamylasemia and/or hyperamylasuria have similar significance and can be the first clue to the diagnosis of pancreatic carcinoma, because these findings can be found by routine blood and urine chemistry. Since the amylase level may vary from day to day, an attitude toward a thorough examination even of one time detection of hyperamylasemia or hyperamylasuria is important.

On the other hand, there has been much controversy as to carcinogenesis in chronic pancreatitis. Chronic inflammation is reported to lead to carcinogenesis in patients with hereditary and nonhereditary chronic pancreatitis. A genetic injury and cell overgrowth caused by chronic persistent inflammation may lead to carcinogenesis by increased cell cycles due to production of inflammatory mediators such as cytokines, superoxide, and NF-κB and cyclooxygenase [1-3]. On the other hand, there were some reports that none of patients with chronic pancreatitis developed pancreatic cancer at long term. Gambill [4] found no single case of pancreatic cancer in their series of 56 patients with chronic pancreatitis followed-up for >20 years. Oguchi et al. [5] also described that none of 53 patients with pancreatolithiasis had pancreatic cancer during observation up to 16 years. A few groups of authors reported that pancreatic cancer occurred in only 1-2% of patients with chronic pancreatitis [6-8]. Therefore, whether persistent inflammation of chronic pancreatitis leads to carcinogenesis or not remains controversial. However, it can be said that diffuse dilation of the main pancreatic duct seemingly due to chronic pancreatitis should prompt thorough examinations of the pancreas to negate the presence of pancreatic cancer.

2. Diabetes mellitus

DiMagno [9] listed recent onset diabetes mellitus as well as chronic pancreatitis, intraductal papillary mucinous neoplasm (IPMN), hereditary pancreatic cancer, hereditary chronic pancreatitis, familial adenomatous polyposis of the colon and hereditary dysplastic nevus syndrome as a high-risk group of pancreatic cancer. He emphasized the importance of recognition of the high-risk population for early diagnosis of pancreatic cancer by reviewing the fact that 15% of all patients with pancreatic cancer had sought medical advice more than 6 months before the diagnosis of cancer but spent that useless period, undergoing various examinations under suspicion of other diseases.

The rate of death from pancreatic cancer reaches 0.2-1.9% in diabetic patients and obviously higher than 0.004-0.008% in ordinary population [10]. Diabetes results from endocrine impairment due to upstream pancreatitis caused by obstruction of the main pancreatic duct, extensive replacement of pancreatic parenchyma by cancer, and/or effects of amylin to raise blood sugar or islet amyloid polypeptide (IAPP), that increases resistance to insulin, produced by pancreatic cancer cells [11,12].

In our previous report, we determined the prevalence of pancreatic cancer in patients with diabetes [13]. We selected a high-risk group in diabetic patients by identifying our original criteria, including: 1) an onset of diabetes after 55 years of age, 2) deterioration of diabetes or body weight loss despite strict medical control, 3) elevation of serum amylase and/or CA19-9 levels, and 4) pancreatobiliary abnormalities such as pancreatic duct dilation, enlargement, and hypoechoic mass on routine ultrasonography, and conducted ERCP screening of pancreatic cancer. We found 6 patients (7.0%) with pancreatic cancer in a consecutive series of 86 such patients with diabetes. When confined to 36 patients with recent-onset diabetes within 3 years, 5 patients (13.9%) were diagnosed as having pancreatic cancer. These prevalence rates remain unchanged even after the number of patients studied has increased to 163, being 7.4% in the whole series and 13.7% in the recent-onset. Pancreatic cancer could be demonstrated by noninvasive imaging modalities such as ultrasonography, computed tomography, and magnetic resonance cholangiopancreatography in all these patients. We should be well aware of the fact that diabetes may be a sign of pancreatic cancer.

3. Intraductal papillary mucinous neoplasm (IPMN)

IPMN is a clinical entity of recent interest, presenting with cystic dilation of either branch or main pancreatic duct or both. Papillary proliferation of mucinous epithelium gradually and slowly grows up and shows malignant transformation. The presence of mural nodules, thickening of the cystic wall, and main pancreatic duct dilation indicates the possibility of malignancy.

In addition to its own malignant transformation the high prevalence of extrapancreatic malignancy is recently drawing attention. Yamaguchi et al. [14] reported that 30% of patients with IPMN resected had synchronous or metachronous extrapancreatic malignancy, i.e. 5 gastric cancers, 3 colon cancers, one cancer each in oral cavity, breast, prostate, and uterine cervix in three of 10 patients with main duct IPMN and 10 of 36 patients with branch duct IPMN. Sugiyama et al. [15] also found extrapancreatic malignant tumors synchronously or metachronously in 15 (32%) of 42 patients with IPMN, including 5 colon cancers, 4 gastric cancers, and one cancer each in the bile duct, lung, breast, bladder, prostate, and uterus. Adsay et al. [16] showed that 8 (28%) of 28 patients with IPMN had a history of extrapancreatic malignancy. Furthermore, even in a large series of 148 patients with IPMN reported by Osanai et al. [17], there was a 24% prevalence of extrapancreatic malignancy.

The exact cause and mechanism of the high prevalence of extrapancreatic malignancy in patients with IPMN are unknown. The fact previously noted that IPMN is more frequent in elderly population may be one of possible explanations. However, the prevalence of extrapancreatic malignant tumors in patients with pancreatic cancer which is similarly more frequent in the aged people is significantly lower than that in those with IPMN, being approximately 7% [14]. This observation indicates that all patients with IPMN including those after surgical resection need to undergo periodic checks of these extrapancreatic organs.

The possibly high prevalence of pancreatic cancer in patients with IPMN is a relatively new finding [18,19]. Benign branch duct IPMN may be associated with synchronous or meta-

Figure 1. **Magnetic resonance cholangiopancreatogram in a 72--year-old man with a 40 years' history of diabetes which showed acute exacerbation two months ago. A branch duct intraductal papillary mucinous neoplasm (arrow) is present in the uncinate process and concomitant cancer in the head of the pancreas (arrow heads). Note marked dilation of the main pancreatic duct proximal to the stenosis due to cancer. This patient has all three important clues to the diagnosis of pancreatic cancer, i.e. exacerbation of diabetes, intraductal papillary mucinous neoplasm, and dilation of the pancreatic duct**

chronous pancreatic cancer in the other portion of the pancreas (*Fig. 1*). In our series of 94 patients who underwent resection of branch duct IPMN for its possibly malignant change or the concomitant presence of pancreatic cancer, 9 patients (9.5%) were found to have pancreatic cancer synchronously or metachronously. In particular, two of the 9 patients were diagnosed as having carcinoma in situ by pancreatic juice cytology during work-up for branch duct IPMN [18]. Although MRCP seems to be replacing ERCP in the diagnosis and evaluation of IPMN, ERCP cytology of the pancreatic juice should not be negated for early detection of pancreatic cancer associated with IPMN.

Main duct IPMN is frequently malignant, the percentage being more than 60-70% [20-28]. Branch duct IPMN is also known to show malignant transformation and Uehara et al. [29] emphasized the important role of pancreatic juice cytology for the diagnosis of the malignant change. Nakaizumi et al. [30] diagnosed carcinoma in situ in patients with pancreatic duct dilation and/or small cystic dilation of branch ducts by enthusiastic use of ERCP cytology. The small cystic dilation of branch pancreatic ducts might have included branch duct IPMN. It seems that pancreatic cancer concomitant with IPMN tends to occur in those with small branch duct IPMN [19]. Therefore, it can be said that small cystic lesions including branch duct IPMN are the only clue to the early diagnosis of pancreatic cancer, especially carcinoma in situ, at the moment. The advances in modern molecular biology are expected to yield more sensitive markers for the diagnosis of pancreatic cancer, either by ERCP aspirates or by blood examinations.

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