Pancreatic Anomaly With Multiple Endocrine Neoplasia Type 1
A Case of Pancreas Divisum and Hemosuccus Pancreaticus (Santorinirrhage)

To the Editor:

Hemosuccus pancreaticus, or bleeding from the ampulla of Vater, is an uncommon cause of gastrointestinal hemorrhage and can occur in the setting of pancreas divisum[1] as well as pancreatic tumors.[2] It has never previously been reported in association with multiple endocrine neoplasia (MEN) syndrome. We describe a case of hemosuccus pancreaticus within pancreas divisum, in a patient with MEN type 1 (MEN-1), which highlights specific diagnostic and management issues that this condition presents.

CASE REPORT

A 60-year-old woman with a parathyroid adenoma and a previously excised growth hormone–secreting pituitary tumor presented with weakness, lethargy, and melena. Laboratory investigations revealed significant anemia: hemoglobin, 80 g/L (reference range, 120–150 g/L). She was admitted to Bankstown Hospital for blood transfusion and further investigation.

Frank bleeding from the minor ampulla was visible at endoscopy. At endoscopic retrograde cholangiopancreatography, cannulation of the major ampulla demonstrated a small ventral duct suggesting pancreas divisum. Attempts to cannulate the minor ampulla were aborted because of vigorous bleeding. An endoscopic ultrasound and computed tomographic scan of the abdomen yielded no further information. Magnetic resonance imaging confirmed pancreas divisum and no other abnormalities (Figs. 1A and B).

Due to persistent transfusion-dependent hemorrhage and concern for an occult pancreatic malignancy, surgical exploration and a Whipple pancreaticoduodenectomy were performed. Macroscopic examination of the resected specimen showed pancreas divisum, a dilated pancreatic duct with blood clot adherent to the wall of the dilated minor papilla. There were no other abnormalities. Histological examination of the pancreas showed no evidence of significant pancreatitis (Fig. 1C), neoplasia, or pseudoaneurysms, revealing only low-grade pancreatic intraepithelial neoplasia (PanIN-1A/1B). (Fig. 1D). Following surgical intervention, the patient's melena and transfusion requirements ceased. She made a complete recovery after surgery.

DISCUSSION

Hemosuccus pancreaticus is associated with chronic pancreatitis,[3] visceral pseudoaneurysms,[4] and pancreatic microcystic adenoma.[2] Chronic pancreatitis in the setting of pancreas divisum has been known rarely to present with hemosuccus pancreaticus.[1] Our case illustrates the occurrence of ampullary bleeding (or santorinirrhage: bleeding from the duct of Santorini) in association with pancreas divisum; however, extensive investigations, including computed tomography, endoscopic ultrasound, and magnetic resonance cholangiopancreatography, revealed no pancreatitis or potential site of hemorrhage such as pseudoaneurysm. In the absence of pancreatitis, the ongoing bleeding led us to surgical exploration for a suspected pancreatic

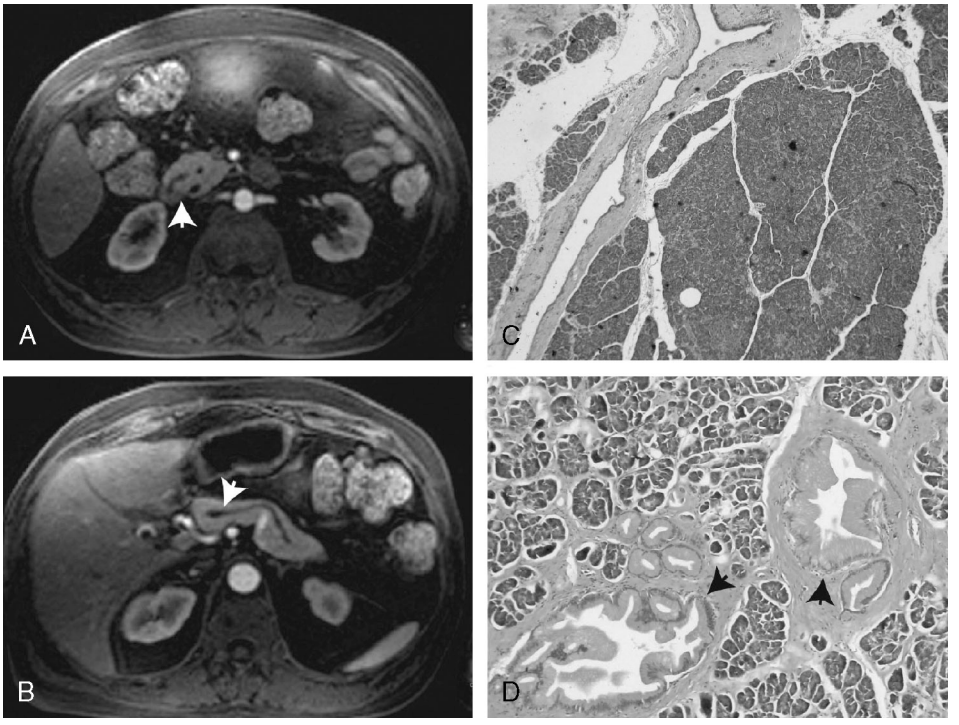

FIGURE 1. A, Magnetic resonance imaging for investigation of persistent santorinirrhage reveals a dorsal pancreatic duct draining through the minor papilla, and a separate ventral duct, indicating pancreas divisum, indicated by the arrow. B, Magnetic resonance image of a large dorsal duct of Santorini, with no communication with ventral duct or major papilla, confirming pancreas divisum, indicated by the arrow. C, Hematoxylin-eosin stain of representative region of pancreas showing no evidence of significant pancreatitis. D, Pancreatic intraepithelial neoplasia 1A and 1B lesions (arrows) were the only significant histological findings.

tumor without identification of a causative factor or bleeding site.

The incidence of pancreatic tumors in pancreas divisum has been documented as 12.5%,[5] which is higher than the incidence in the normal population. No tumors were present in the resected specimen, with the only abnormality being PanIN-1A/1B, which is a common finding, likely incidental and not related to the hemorrhage.[6]

The presence of a parathyroid adenoma and a prior pituitary tumor in our patient confirms a clinical diagnosis of MEN-1.[7] As pancreatic microadenomatosis has been well described in MEN-1,[8] it was anticipated that this may be a possible histological finding in the absence of pancreatitis or pseudoaneurysms, but the only histological abnormality identified in the resected specimen was PanIN-1A, despite examination of the complete specimen. PanIN has not been previously described in patients with MEN; however, such low-grade lesions are prevalent in all pancreata, with aging.[6,9]

Obscure gastrointestinal hemorrhage can present a diagnostic challenge, and the pancreas should be considered as a potential source for sporadic bleeding.[10] Hemorrhage from the ampulla can present with transfusion-dependent anemia, and patients with pancreas divisum or cancer-susceptible states such as MEN-1 pose a therapeutic dilemma due to the increased risk of occult malignancy.[5,7] In the absence of an identifiable cause, surgical management should be directed at cases of refractory anemia and/or if there is significant risk of malignancy.

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Vitamin D_3 in Operable Periampullary and Pancreatic Cancer
Perioperative Outcomes in a Pilot Study Assessing Safety

To the Editor:

Periampullary carcinomas constitute 30% of all malignant tumors arising from the pancreatic head. In 2001, the prevalence of periampullary cancers in India was estimated to be 14,230.[1] Periampullary cancers are a heterogeneous group of tumors, both in terms of their biological and clinical courses. With the absence of established efficacy of chemoradiotherapeutic agents in periampullary cancers in the adjuvant or neoadjuvant setting, there remains a persistent need to explore the possibility of agents like vitamin D_3 as antineoplastic agents. Before studies on any drug can be undertaken for therapeutic purposes, it is essential to prove the safety of such an agent in human subjects. Calcitriol is already being investigated extensively.[2,3] The safety of intramuscular vitamin D_3 in human subjects has been proven safety (for vitamin D deficiency).[4–6] It is easy to administer and has a sufficiently long half-life (7–10 days). Because its safety in patients with operable periampullary and pancreatic cancers has never been tested, we decided to evaluate the safety of the drug in such patients undergoing pancreaticoduodenectomy (PD) in the perioperative setting so as to assess its influence on surgical outcomes (if any). Considering that PD is associated with high morbidity, it is important that any agent used before this procedure must not negatively influence outcomes.

We conducted a prospective open-label study in the Department of Gastrointestinal Surgery of the Tata Memorial Hospital to assess the safety and efficacy of a single therapeutic intramuscular injection of 200,000 IU (5 mg) cholecalciferol (vitamin D_3 [Arachitol]; Solvay Pharma India Ltd) in patients with periampullary and pancreatic head cancers undergoing curative PD. The study was carried out between August 1, 2006, and April 30, 2007.

The inclusion criteria were the following:

1. all patients undergoing surgery for histologically or cytologically confirmed or suspected periampullary cancer,
2. serum calcium levels of 1.75 to 2.65 mmol/L,
3. adequate hepatic functions (bilirubin level of 1.5 times the upper limit of normal or lesser),
4. adequate renal functions (serum creatinine of 2 times the upper limit of normal or lesser), and

5. normal findings for hemoglobin level (11–14 g/dL)/white blood cell count (4000–11,000 per microliter)/ platelet count (1.5–4.5 × 10^5 per microliter).

The exclusion criteria were the following:

1. patients with history of hypercalcemia (serum calcium, >2.75 mmol/L),
2. patients with disordered calcium metabolism (primary hyperparathyroidism [hypercalcemia with inappropriately elevated serum parathyroid hormone levels], thyrotoxicosis, Paget disease, significant renal impairment [serum creatinine, >0.15 mmol/L], significantly elevated early-morning 2-hour urine calcium/creatinine excretion index [>0.8]),
3. history of any calcium-lowering therapy in the previous 2 weeks (current treatment with calcitriol or high-dosage oral calcium supplements [1200 mg/d of elemental calcium]), and
4. patients with any other contraindications for vitamin D treatment (liver disease [alanine aminotransferase or aspartate aminotransferase level of greater than 2 times the upper limit of the reference range]).

A single intramuscular injection of 200,000 units of vitamin D_3 was administered on the day before surgery.

Definitions of Postpancreatectomy Complications

We use the following definitions for identification of complications after PD:

Pancreatic Fistula was defined according to International Study Group on Pancreatic Fistula.[7]

Biliary leak was defined as persistent biliary drainage from the drain placed in the right upper quadrant and confirmed by hydroxy iminodiacetic acid scan.

Chyle leak was defined as persistent discharge of white "chylelike" fluid in the postoperative period in the presence of no associated clinical symptoms with normal drain fluid amylase on postoperative days 3 and 7.

Assessment of Toxicity and Response

Before starting therapy, all patients underwent a clinical assessment and measurement of complete blood cell count, renal function tests including blood urea and serum creatinine, serum electrolytes, liver function tests, and blood glucose levels.

Serum calcium levels were performed before administering the injection and on the third and seventh postoperative days (elevations in the levels to >2.75 mmol/L were looked into). Serum electrolytes and renal functions were routinely performed postoperatively. Liver function tests were performed postoperatively in all operable cases, and if indicated, in inoperable patients.

We routinely placed a nasojejunal tube (intraoperatively) in all patients undergoing PD. We thus began enteral feeds from the first postoperative day, thereby overcoming the confounding effects that total parenteral nutrition may have on the measurements of serum calcium.

Twenty-nine patients were preoperatively given intramuscular vitamin D_3, of which, 19 (12 men and 7 women) were ultimately resectable. The mean age was 54.2 ± 8.6 years (range, 36–71 years). No local or systemic toxicity as a result of the injection was noted in any of the patients. The mean serum calcium levels recorded are provided in Table 1.

The histological patterns encountered included 11 cases of ampullary adenocarcinomas, 4 cases of duodenal adenocarcinomas, and 2 cases each of pancreatic head adenocarcinoma and lower common bile duct cholangiocarcinomas.

The morbidity rate was 15.7% (3/19). There was 1 case each of pancreatic fistula, biliary fistula, and chyle leak. All these were managed conservatively. There were no adverse events as defined by the National Cancer Institute–Common Toxicity Criteria 1999. There were no mortalities recorded. The average hospital stay was 17.7 ± 9.4 days (range, 9–39 days).

TABLE 1. Mean Serum Calcium Levels Recorded

Day	Mean ± SD, mmol/L	Range, mmol/L
Preoperative	2.17 ± 0.160	1.9–2.5
Postoperative day 3	1.97 ± 0.132	1.75–2.25
Postoperative day 7	1.97 ± 0.156	1.75–2.32

Exocrine pancreatic cancer is characterized by infiltration of surrounding blood vessels and perineural tissues, spread to regional lymph nodes, and early vascular dissemination. Subclinical metastases are present in most patients at the time of diagnosis, even when findings from imaging studies are normal. Therefore, disease recurrence occurs in 80% to 90% of patients after potentially curative surgery.[8] These findings indicate that treatment regimens that are effective against systemic metastasis are needed. Furthermore, if one is to believe the theory of malignant cell dissemination during curative surgery, then an agent that can reduce hematogenous tumor cell shedding at the time of surgery would play an important role in tumor control.

Although postoperative gemcitabine significantly delayed the development of recurrent disease after complete resection of pancreatic cancer when compared with observation alone,[9] randomized trials using neoadjuvant chemotherapy (gemcitabine—alone and in combination with cisplatin) have yet to show convincing results.

The antineoplastic properties of vitamin D_3 include the following: antiproliferation activity by inducing cell cycle arrest in G1 phase, induction of differentiation, reduction in invasion and angiogenesis, growth inhibition, and antiapoptosis.

Furthermore, vitamin D receptors (VDRs), and enzymes involved in the synthesis and degradation of vitamin D, have now been identified in many nonneoplastic peripheral tissues, including colon, pancreas, brain, lymph nodes, and keratinocytes, suggesting a role for vitamin D in the regulation of normal cellular growth at a local level.

1, 25-Dihydroxyvitamin D (calcitriol), the most active metabolite of vitamin D, has significant antineoplastic activity in preclinical models. Vitamin D induces cell cycle arrest at the G1/S checkpoint.[10] By its action on the levels of E-cadherin, vitamin D_3 exerts its antiinvasive role in tumor tissues expressing VDRs.[11]

Albrechtsson et al[12] have clearly demonstrated the expression of VDR in pancreatic cancer cell lines using reverse transcriptase polymerase chain reaction and Northern blotting. They deduced that vitamin D analogues caused a reduction in cell numbers in pancreatic cell lines, although they believed that in vivo studies were needed to confirm these findings.

So far, Evans et al[3] reported a phase 2 trial of the vitamin D analogue Secocalcitol (EB 1089) in patients with inoperable pancreatic cancer. They noted that this analogue was well tolerated in pancreatic cancer, and there was a degree of the anticipated dose-dependent hypercalcemia, with most patients tolerating the maintenance treatment. Thirty percent of patients had stable disease over a median of 168 days. The time to treatment failure ranged from 22 to 847 days, with a median survival of approximately 100 days. The authors concluded that further studies were necessary to determine if this agent would have any benefit in minimal disease states of pancreatic cancer. Furthermore, Evans et al[3] also noted that calcitriol requires close monitoring of a number of parameters and a long duration of treatment. Moreover, dose escalation is fraught with the risks of hypercalcemia (a known precipitant of acute pancreatitis).

The morbidity rate of 15.7% encountered in our series was well within the accepted rates for morbidity (20%–30%) after PD.[13] There was no deviation from the normal course, either intraoperatively or postoperatively, that would suggest that the vitamin D_3 administration had any adverse effect on outcome.

The ability of a vitamin D_3 supplement to maintain sustained levels of vitamin D_3 in the body provides the benefits of vitamin D_3 not only in the perioperative period but also in the postoperative period. The levels of vitamin D_3 reach a nadir at 4 to 6 months, negating the need for repeated administration. All these point to the fact that we are potentially looking at an agent lacking the side effects of conventional chemotherapy and yet having the desired antineoplastic action against periampullary and pancreatic cancers.

Our study confirms the safety of intramuscular vitamin D_3 in patients with operable periampullary and pancreatic head cancers. These safe outcomes can now provide fresh impetus to further evaluate the antineoplastic efficacy of intramuscular cholecalciferol in trials dealing with patients with operable periampullary and pancreatic head cancers.

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A Loss of Function Polymorphism (G191R) of Anionic Trypsinogen (PRSS2) Confers Protection Against Chronic Pancreatitis

To the Editor:

Chronic pancreatitis (CP) is a condition characterized by a progressive and irreversible destruction and fibrosis of the exocrine parenchyma, resulting in exocrine pancreatic insufficiency with maldigestion and endocrine failure leading to diabetes.[1] Cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), and mesotrypsinogen (PRSS3) are the 3 different trypsinogen isoforms described in human pancreatic secretions. Alterations in the genes encoding cationic trypsinogen (PRSS1)[2] and serine protease inhibitor Kazal type 1 (SPINK1) have been associated with various forms of chronic pancreatitis.[3,4]

Autosomal dominant hereditary chronic pancreatitis is associated with PRSS1 variants, namely, R122H and N29I, which are particularly prevalent among families with inherited chronic pancreatitis. Both R122H and N29I cause increased autoactivation of trypsinogen, whereas the R122H mutation also results in increased trypsin stability.[5]

Serine protease inhibitor Kazal type 1 acts as a specific trypsin inhibitor, and a single–amino acid substitution, p.N34S, appears to be a risk factor for various sporadic forms of chronic pancreatitis. Indeed, N34S is enriched in patients with idiopathic chronic pancreatitis[3] and in those with alcoholic chronic pancreatitis.[6] In addition to SPINK1,

recent evidence points to a possible involvement of PRSS2 gene variants in chronic pancreatitis. PRSS2 maps to chromosome 7q35 and consists of 5 exons.[7] In a search for disease-associated alleles, a PRSS2 variant that appeared to be protective against chronic pancreatitis has been recently identified. The particular substitution arose from a c.571G>A transition in exon 4 and leading to a glycine by arginine exchange at codon 191 (p.G191R).[7] The G191R variant was present in 220 (3.4%) of 6459 controls but in only 32 (1.3%) of 2466 affected individuals (odds ratio [OR], 0.37). Although association studies are a potentially powerful approach to identifying disease-associated variants for common multifactorial diseases such as chronic pancreatitis, results are not always consistently reproducible. Ideally, the most robust way to assess a relatively rare protective allele is to test the thesis in a population with a high disease frequency. The prevalence of chronic pancreatitis in Hungary is particularly high and is with 40 to 60 cases per 100,000 inhabitants among the highest worldwide.[8] To this end, we analyzed whether G191R is a protective variant against chronic pancreatitis in this population.

The study was approved by the local medical ethical review committee, and all subjects gave their written informed consent. Patient recruitment took place from January 2002 to July 2002 in the MÁV Hospital, Budapest, Hungary. All subjects studied were of Hungarian origin. The group of patients with chronic pancreatitis (CP) consisted of 140 adult patients (97 males and 43 females), with a mean age of 52.6 years (SD, 13.4 years; range, 7.3–80.1 years). Three patients (2%) had a family history of CP, 70 patients (50%) had an alcohol-induced CP, 43 patients (31%) were classified as having idiopathic CP, whereas in 24 patients (17%), other causes were identified. The clinical diagnosis of CP was based on standard criteria outlined elsewhere.[9] The ethnically matched control group of this study was obtained from 2 different sources. All 350 controls were unrelated, healthy individuals of Hungarian origin who do not have pancreatic disease. A total of 220 controls (128 females and 92 males) were sampled at the Semmelweis University and lived in Budapest and suburban area. A second, separate, control population of 130 samples (66 females and 64 males) was obtained from the University of Szeged in southern Hungary.

Discrimination between heterozygotes and wild-type G191R variant was performed using 2 independent methods. The use of molecular beacons on the iCycler (Bio-Rad Laboratories) afforded a fine discrimination between wild type and heterozygotes as shown in Figure 1.

Method A (Nijmegen). A dual-color, allele-specific discrimination assay using molecular beacons and the iCycler iQ Multicolour Real-Time Detection System (Bio-Rad Laboratories) was applied. Polymerase chain reaction (PCR) was performed using primers as described previously[7] in the presence of the developed molecular beacons. 6-carboxy-fluorescein-labeled wild-type beacon (5′-CGC GTC ATC CTT GCC TCC CTC GAG GAA GCC GAC GCG-3′) and the hexachloro-6-carboxy-fluorescein-labeled mutant beacon (5′-CGC GTC ATC CTT GCC TCT CTC GAG GAA GCC GAC GCG-3′). The 25-μL reaction mixture contained 200 ng of genomic DNA, 10 mmol/L Tris/HCl (pH 9.0), 50 mmol/L KCl, 0.1% Triton X-100, 4 mmol/L MgCl2, 0.25 mmol/L dNTPs, 5 pmol of each primer, 200 nmol/L of each beacon, and 2.5 U Taq polymerase. The PCR conditions were 3 minutes at 95°C, then 40 cycles of 30 seconds at 95°C, 30 seconds at 59°C, and 30 seconds at 72°C. Fluorescent signals were measured at 59°C. Genotypes were assigned using the iCycler iQ Optical System Software version 3.1 (Fig. 1).

Method B (Berlin). *Melting curve analysis*. We performed melting curve analysis for the G191R alteration using a pair of fluorescence resonance energy transfer probes and the LightCycler (Roche Diagnostics) as described previously. We used similar primers for the PCR of exon 4 as described above.[7]

Data were analyzed using GraphPad InStat version 3.05 for MSWindows (GraphPad Software, San Diego, Calif).

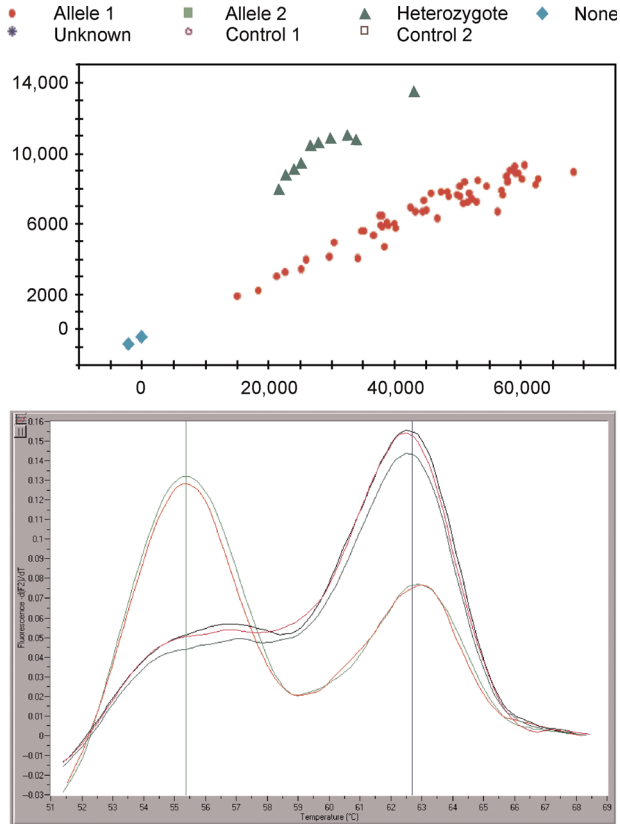

FIGURE 1. Identification of the G191R allele. The upper panel shows discrimination of the G191R variant from the wild-type allele on the iCycler, whereas the lower panel shows discrimination of G191R from the wild-type allele on the LightCycler.

Fisher exact test was used to estimate differences in the presence of genotype frequencies of G191R among the study groups. Odds ratios with 95% confidence interval (95% CI) were calculated by using logistic regression analysis for the G191R genotype frequency. The distribution of the G191R genotype frequency of the control population was tested for the Hardy-Weinberg equilibrium. The Cochran-Armitage test was used to test for trends in the proportions of genotypes between the patients and controls. With the present sample size, we had a power of 80% at a significance level of 0.05 to detect an OR of less than 0.7.

We detected one G191R heterozygote in the CP population (1/140, 0.7%) but 19 heterozygotes among 350 controls (19/350, 5.4%). The difference was statistically significant ($P = 0.0096$; OR, 0.13; 95% CI, 0.017–0.945). The robustness of this finding was confirmed using the Cochran-Armitage test for trends which yield a significant difference ($P = 0.02$). The G191R genotype frequency of 5.4% in the Hungarian controls in our study was significantly higher than that of 3.4% found in the previously studied European populations originating from Austria, Czech Republic, France, Germany, Italy, The Netherlands, Romania, Spain, and Switzerland ($P = 0.0319$; OR, 1.6; 95% CI, 1.006–2.6). We did not find patients or controls that were homozygous for the variant. The frequency of the G191R genotypes in the control population was consistent with the Hardy-Weinberg equilibrium. ($P = 0.87$)

This study confirmed that the PRSS2 G191R gene alteration protects against CP. This variant was present in 0.7% of CP patients but in 5.4% in unaffected individuals (OR, 0.13). The frequency of the G191R allele in the Hungarian control population is appreciably higher compared with other European populations. This is the first genetic study analyzing the PRSS2 gene variant in a Hungarian population and the first to confirm the initial European study published in 2006.[7] We selected a Hungarian population because the lifetime risk to develop CP is among the highest in Europe, in part due to the high level of alcohol abuse.[10] The strengths of the present study on CP risk are based on a large sample size and a homogeneous study cohort of a single ethnic group.

In contrast to many other genetic association studies, we were able to replicate the findings from the pioneer study. It appears rather the rule that a genetic variant is associated with a disorder in some populations but not in others. Such interstudy heterogeneity has been reported for many complex common diseases, and a significant heterogeneity between studies on the same topic has been shown. This is certainly true for studies in pancreatic disorders. For example, one study in 115 patients linked the UGT1A7*3 allele to pancreatic cancer and alcoholic CP,[11] but these data were refuted by a much larger study analyzing almost 1000 patients.[9]

Our data suggest that the concept of the PRSS2 G191R allele as a protective factor in CP holds for various populations and that it enjoys wider applicability.

One important aspect is that functional data support the role of the G191R variant in causing CP.[7] Recombinant R191 protein has no trypsin activity owing to the introduction of a new tryptic cleavage site that renders the enzyme hypersensitive to autocatalytic proteolysis. This led to the speculation that the G191R PRSS2 variant mitigates intrapancreatic trypsin activity and thereby protects against CP.

This study reiterates the importance of trypsinogen in the pathophysiology of CP. PRSS1 mutations lead to increased autoactivation of trypsin and disease susceptibility, whereas a specific PRSS2 variant that lacks trypsin activity apparently protects against CP.

ACKNOWLEDGMENT

J.P.H.D. is a recipient of a ZON-MW VIDI research grant. The study was supported by Deutsche Forschungsgemeinschaft (DFG) (Wi 2036/2–1) and by the Sonnenfeld-Stiftung (Berlin, Germany).

The authors thank the study participants for their contribution to their study.

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A Peculiar Variant of Pancreatoblastoma in an Adult

To the Editor:

Among pancreatic solid tumors, acinar cell carcinoma (ACC), pancreatoblastoma, solid pseudopapillary neoplasm (SPN), and endocrine tumor are grouped together as nonductal tumors. Such nonductal tumors overlap morphologically and immunophenotypically, and the prognoses are usually favorable in comparison with the prognosis of ductal adenocarcinoma. We report a case of nonductal solid tumor of the pancreas with an extremely rare histology and a favorable outcome. Although squamoid corpuscles were not seen, the morphological features raise the possibility that this tumor may be related to pancreatoblastoma. On the other hand, the immunophenotypic features may make an argument for a neoplasm of mixed endocrine and solid pseudopapillary differentiation.

CASE REPORT

The patient was a 74-year-old woman in whom a 3-cm tumor was discovered during a routine check-up 3 years previously. The tumor was located between the pancreas and the inferior vena cava (Fig. 1A). The patient was followed up with periodic computed tomographic scanning, but the tumor enlarged to 4.5 cm, and she underwent surgical excision. Biochemistry tests did not show any abnormalities, and levels of tumor markers (carcinoembryonic antigen [CEA], carbohydrate antigen 19-9 [CA19-9]) were normal. At surgery, the tumor was found to adhere to the pancreas, but it was easily enucleated. It was also easily peeled from the inferior vena cava.

Grossly, the tumor was covered by a thick fibrous capsule and measured 3 × 4 × 5 cm. The cut surface revealed a solid mass with some bleeding and degeneration probably secondary to a circulatory disorder. Tumor necrosis was not seen.

Histologically, various patterns of tumor cell proliferation were seen, but we were able to divide them into 2 components (biphasic appearance) on low-power view (Fig. 1B). One was an "organoid" or differentiated component, comprising trabeculae and nests (Fig. 1C), in which cell density was comparatively high; mitotic figures were observed with a frequency of 6 per 50 high-power fields. Nuclei of the tumor cells were round or oval with a "salt-and-pepper" chromatin pattern. Some cells had prominent nucleoli, and the cytoplasms were weakly eosinophilic. The second was an "enigmatic" or dedifferentiated or undifferentiated component, showing solid, reticular, and cystic structures (Fig. 1D) associated with bleeding, edema, and hyaline degeneration. Mitotic figures were observed with a frequency of 3 per 50 high-power fields. Nuclear features were approximately similar to those of the organoid component. Tumor cells in the degenerated areas had clear or vacuolated cytoplasms. In addition to these 2 components, some small ductules were intermingled throughout the tumor. Squamoid corpuscles were not seen.

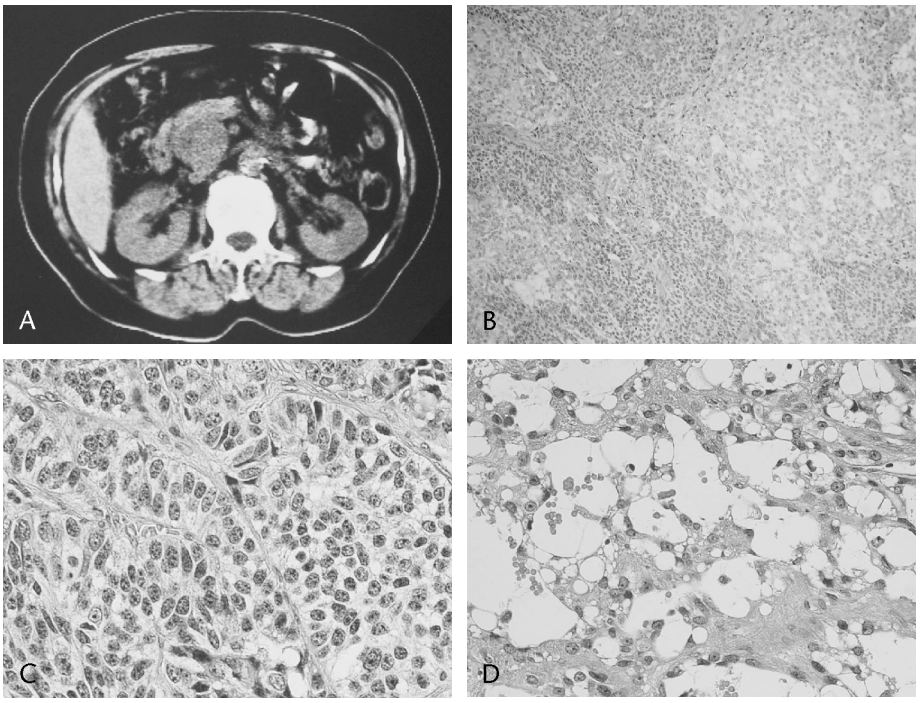

FIGURE 1. A, Computed tomographic finding. The tumor is located between the pancreas and the inferior vena cava. B, Histological finding of the tumor (hematoxylin-eosin staining, original magnification ×200). On low-power view, the tumor shows a biphasic appearance; an organoid component (left) and an enigmatic component (right). C, Histological finding of the organoid component (HE staining, original magnification ×400). Cellular trabeculae or nests are seen. Nuclei of the tumor cells are round or oval with a salt-and-pepper chromatin pattern. D, Histological finding of the enigmatic component (HE staining, original magnification ×400). Degenerated reticular structure with bleeding is seen.

The stroma was fibrous, and intracapsular invasion and microvascular invasion were found in the marginal areas of the tumor. A small amount of pancreatic tissue and a small lymph node were found close to the fibrous capsule, but neither invasion nor metastasis was observed.

Immunohistochemically, both the organoid and enigmatic components were positive for AE1/3 (pan-cytokeratin [CK]), but the enigmatic component showed stronger expression of vimentin than that of AE1/3 (Table 1). Both components were diffusely positive for CK8 and CK18, but negative for CK7 and CK19. Markers of squamous epithelium and basal cells, CK5/6, CK10/13, 34βE12, and p63, were all negative. Regarding pancreatic endocrine and exocrine markers, widespread expression of endocrine markers, such as chromogranin A (CgA), synaptophysin, and CD56, was found in the organoid component, whereas patchy expression of trypsin, an exocrine acinar cell marker, was found. In the enigmatic component, expression of CD56 was also widespread, but expression of CgA and trypsin was poor. Expression of amylase and α-1-antichymotrypsin was weak in either component. Regarding hormones, a few pancreatic polypeptide–positive cells were observed in the organoid component. Expressions of CA19-9 and CEA were minimal. Regarding cell proliferation–related markers, Ki-67– and topoisomerase II–positive cells were more frequently scattered in the organoid component than in the enigmatic component, but the number of positive cells was extremely low in both components. Expression of cyclin D1 was more widespread in the organoid component, and aberrant nuclear expression of β-catenin was widespread in the enigmatic component. Of other markers, nestin, a stem cell marker, was widely expressed in the enigmatic component, but c-kit, another stem cell marker, was not expressed in either component. There were a few cells that stained positively for progesterone receptors in the enigmatic component. CD10 was widely expressed in both components.

TABLE 1. Results of Immunohistochemical Staining

Antigen	Organoid Component	Enigmatic Component
CK AE1/3	+	±
CK8, CK18	+	+
CK7, CK19, CK20	−	−
CK5/6, CK10/13, CK 34βE12	−	−
p63, maspin	−	−
Vimentin	−	+
Trypsin	+	−
Amylase	±	±
α-1-Antichymotrypsin	±	±
CgA	+	−
Synaptophysin	+	±
CD56	+	+
Insulin, glucagon, somatostatin	−	−
Pancreatic polypeptide	±	−
CA19-9	±	±
CEA	±	−
α-Fetoprotein	−	−
MUC1, MUC2	−	−
Ki-67	0.13%	0.01%
Topoisomelase IIα	1.92%	0.03%
Cyclin D1	+	±
p53, bcl-2	−	−
β-catenin	±	+
Nestin	−	+
c-kit	−	−
PgR	−	±
CD10	+	+

Staining was classified as widespread or scattered (+), extending across the whole tumor; partial or singular (single cell) (±); or negative (−). For Ki-67 and topoisomelase IIá, a minimum of 1000 tumor cells were counted in areas in which positive cells were concentrated, and labeling indices were calculated as the number of positive cells per 100 tumor cells and expressed as percentages.

MUC indicates mucin core protein.

Since this tumor was removed, there has been no recurrence and/or metastasis for 9 years.

DISCUSSION

We consider the tumor described herein to be a solid tumor occurring primarily in the pancreas because it was close to the pancreas and because it expressed specific markers for the pancreas, such as trypsin. In addition, we consider that the tumor is a nonductal tumor from both the morphology and the keratin expression pattern of CK7−, CK19−, CK8+, and CK18+. It can be distinguished from high-grade malignant carcinoma because the patient has such a good outcome and because the tumor did not have features suggestive of high-grade malignancy, such as tumor necrosis, a high number of mitotic figures, or high proliferative activity. However, it is difficult to place this tumor into any of the current World Health Organization classifications of pancreatic exocrine or endocrine neoplasms because the tumor had the enigmatic component.

The tumor had a biphasic (or multiphasic, if the small ductular component is included) appearance. Among pancreatic neoplasms, this appearance is often seen in pancreatoblastoma, which has various degrees of differentiation to acinar, ductal, and endocrine cells.[1–3] Generally, pancreatoblastoma is seen in children, but adult cases have been reported.[4–9] However, the tumor we describe here did not have several of the histological characteristics of pancreatoblastoma. For example, a major component of pancreatoblastoma is generally the presence of tumor cells with acinar differentiation, and morphologically, an acinar arrangement is seen throughout the tumor.[1] In the tumor we describe, acinar differentiation (trypsin-positive cells) was found only in the organoid component, and it was less prominent than endocrine differentiation. Thus, acinar differentiation was a minor component of the tumor. In addition, squamoid corpuscles, regarded as essential to the diagnosis of pancreatoblastoma,[1,8] were not found, and the expression of squamous epithelium markers was also poor. Nevertheless, the possibility of being a peculiar variant of pancreatoblastoma

cannot be definitively excluded because the enigmatic component appears to be similar to the undifferentiated solid areas that are sometimes seen in pancreatoblastomas, and the expression of β-catenin raises the possibility that this tumor may be related to pancreatoblastomas.[10] In adult patients with pancreatoblastomas, the outcome is usually fatal, the mean survival time is 10 months[8] to 2 years,[4] but prolonged survival times were reported even in the presence of multiple hepatic metastases.[6,10] Encapsulated, as seen in our tumor, tumors have a better prognosis.[8]

A biphasic or multiphasic appearance is sometimes observed in ACCs. However, ACC was not considered as a diagnosis in this case because the tumor did not consist mainly of acinar differentiated cells. The organoid component in this case showed expression of both endocrine markers and acinar markers, such that if considering only this component, we might diagnose the tumor as an endocrine tumor with focal acinar differentiation. It has been reported that some endocrine tumors show acinar differentiation. Alternatively, we might be able to regard this component as a mixed acinar-endocrine carcinoma, although such carcinoma is considered a variant of high-grade ACC in the World Health Organization classification system. However, in neither case have there been reports of these tumors occurring in association with an enigmatic component. Regarding the enigmatic component, we noticed that the histological and immunohistologic features resemble those of SPN. For example, the enigmatic component consisted of small, round or oval cells forming solid, reticular, and cystic structures; widespread expression of vimentin, distinct expression of endocrine markers (CgA−, CD56+); expression of PgR, CD10, and nestin; and abnormal nuclear expression of β-catenin. These are all characteristics of SPN. Thus, this unique neoplasm may expand the category of mixed pancreatic neoplasms to include a mixture of endocrine and solid pseudopapillary cell types. We could not clearly identify tumor cells of the enigmatic component as tumor cells of SPN in this case alone, but additional reports of similar cases may clarify the identification.

Finally, pancreatic nonductal solid tumors, such as ACC, pancreatoblastoma, SPN, and endocrine tumor, often show overlapping pathomorphology, and the tumor described herein is thought to be such a tumor. Predicting outcome on the basis of histology is difficult; at the very least, differential diagnosis from high-grade malignant carcinoma is recommended.

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Plasma Glutamine Levels Are Negatively Correlated With the Severity of Acute Pancreatitis

To the Editor:

Glutamine infusions are frequently given in severe acute pancreatitis, but to date, there is little evidence to justify this treatment. We set out to assess the prognostic value of plasma glutamine levels and to establish a rationale for glutamine substitution in acute pancreatitis.

In acute experimental pancreatitis, glutamine has been shown to stabilize intestinal barriers and reduce pancreatic infection.[1,2] On this basis, it seems mandatory to ensure that intravenous glutamine (dipeptide) is infused into the patients who are critically ill with severe acute pancreatitis. Unfortunately, there is no routine parameter available for assessing the individual glutamine status.

Therefore, our aim was to evaluate whether plasma glutamine levels in acute pancreatitis can be used routinely as a valid biomarker to justify glutamine-enriched nutritional support.

Free amino acid concentrations in plasma were assessed on admission and after 72 hours in a prospective single-center study involving 26 fasted patients (17 men and 9 women; median age, 58 years [range, 31–86 years]), using reversed-phase high-performance liquid chromatography. Free amino acids were initially obtained using orthophthaldialdehyde and 3-mercapto-propionic acid, which were subsequently separated in an RP-C18 column by gradient elution. A fluorometric method was used for detection (Ex λ, 330 nm; Em λ, 450 nm). Quantitative evaluations were based on repeated analyses of amino acid standard mixtures, using norvaline as an internal standard (coefficient variation, 4.2%–6.8%).[3]

Acute pancreatitis was diagnosed on the basis of characteristic signs and symptoms (upper abdominal pain with

TABLE 1. Association Between the Change in Plasma Glutamine Levels From Admission to 72 Hours and Patients' Characteristics*

Strata	No. Patients	Blood Glutamine Levels			
		On Admission	After 72 h	Change (U/mL)	*P*†
All subjects	26	405.8 ± 131.4	378.8 ± 126.1	−27.0 ± 109.6	0.22
Age, yrs					
<60	12	416.4 ± 170.1	435.5 ± 124.7	19.1 ± 106.6	0.57
≥60	14	396.8 ± 92.5	330.2 ± 109.1	−66.5 ± 99.2	0.04
Etiology					
Alcoholic	9	389.5 ± 156.7	408.1 ± 163.1	18.5 ± 102.5	0.65
Biliary	13	427.6 ± 110.8	359.3 ± 111.1	−68.2 ± 97.1	0.04
Idiopathic	4	371.9 ± 158.1	376.3 ± 89.0	4.4 ± 139.2	1.00
Pain intensity					
−5	5	520.2 ± 165.6	530.3 ± 126.7	10.1 ± 142.6	1.00
6–7	9	409.3 ± 151.6	407.3 ± 88.5	−2.0 ± 115.9	1.00
8+	11	360.9 ± 62.2	298.7 ± 77.6	−62.2 ± 92.0	0.07
Ranson score (48 h)					
0–1	12	382.7 ± 130.6	401.3 ± 97.1	18.6 ± 11.7	0.68
2–3	9	456.3 ± 145.4	415.2 ± 146.3	−41.1 ± 106.5	0.30
4+	5	370.3 ± 99.3	259.2 ± 90.7	−111.1 ± 49.8	0.062
Imrie score (48 h)					
0–1	13	379.7 ± 127.3	400.7 ± 91.1	21.0 ± 14.9	0.45
2+	13	431.9 ± 135.3	356.9 ± 154.2	−75.0 ± 95.0	0.027
Balthazar score (72 h)					
A–D (0–3)	8	397.5 ± 107.6	427.5 ± 83.3	30.0 ± 122.6	0.55
E (≥4)	18	409.5 ± 143.5	357.1 ± 137.5	−52.4 ± 96.2	0.043

Statistical analysis was performed using paired *t* test (signed rank paired test) to assess significance of the change in plasma glutamine levels between admission and 72 hours. All *P* values are 2-sided.

*The numbers may not add up to the total because of missing data.

†Based on nonparametric test.

or without guarding and/or rebound tenderness, nausea with or without vomiting), elevated serum enzymes, and abnormal contrast-enhanced computed tomography findings, scored according to Balthazar et al.[4] The etiology of acute pancreatitis was biliary disease in 13 (stones in gallbladder and/or common bile duct), alcohol abuse in 9 (>60 g pure alcohol/day), and unknown in 4 patients. Plasma glutamine levels were then considered in the context of all relevant parameters for the severity of the disease.[5]

The study was approved by the ethics committee of the Georg-August University of Göttingen (January 24, 2003).

Overall, plasma glutamine levels were significantly lower in our group of patients who had been diagnosed with severe acute pancreatitis (mean ± SD, 405.8 ± 131.4 μmol/L) compared with those reported in a healthy control group (655 ± 84 μmol/L, $P < 0.0001$).[6] Only 5 patients had a "normal" plasma glutamine level on admission (reference range, 487–823 μmol/L, defined as mean ± 2 SD) and only 3 after 72 hours. We therefore decided to use the median glutamine level recorded on admission (384 μmol/L) as the cutoff value.

Lower plasma glutamine levels on admission were associated with increasing pain ($P = 0.026$). After 72 hours, low levels were associated with old age (≥60 years, $P = 0.016$), increasing pain ($P = 0.016$), rebound tenderness on admission ($P = 0.005$), and a Ranson

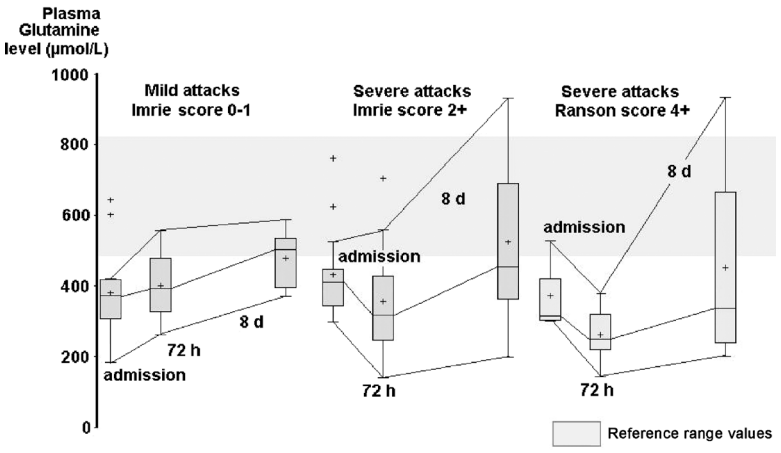

FIGURE 1. Plasma glutamine levels on admission, after 72 hours, and after 8 days in patients with a mild attack (Imrie score 0–1) or a severe attack (Imrie score ≥2 or Ranson score ≥4) of acute pancreatitis. The shaded area shows the range of concentrations of glutamine obtained in 27 healthy individuals; mean age, 39 years; 655 ± 84 μmol/L.[6]

score of 4 points or higher (48 hours, $P = 0.016$). In multivariate analysis, only rebound tenderness on admission ($P = 0.029$) and increasing pain ($P = 0.080$) remained associated with low glutamine levels after 72 hours.

A significant decrease in plasma glutamine levels between admission and day 3 was observed in those patients with biliary pancreatitis ($P = 0.026$) and associated with several parameters indicating severe disease, such as old age (≥60 years, $P = 0.026$), intense pain on admission ($P = 0.049$), high prognostic scores (48 hours: Ranson score ≥4, $P = 0.0076$; Imrie score ≥2, $P = 0.0147$; Table 1, Fig. 1), or high Balthazar score (72 hours: ≥E4 (the most severe form of interstitial pancreatitis ± pancreatic necrosis), $P = 0.034$; Table 1).

All patients showed far lower plasma glutamine concentrations on admission and after 3 days (Fig. 1). This observation suggests that in these critically ill patients, glutamine demand may exceed endogenous production. A relative deficiency of glutamine could compromise recovery, resulting in prolonged illness and an increase in late mortality, morbidity, and, consequently, hospital costs.

To our knowledge, there are no published data reporting plasma glutamine levels correlated with the severity of acute pancreatitis, evaluated using prognostic parameters and contrast-enhanced computed tomography. Gupta et al[7] reported no change in the plasma glutamine levels over 7 days in patients with acute pancreatitis who were receiving total enteral (n = 8) and total parenteral (n = 9) nutritional support. However, the patients in these groups were not severely ill and had few complications. Ockenga et al[8] studied 28 patients with acute pancreatitis who received either a standard total parenteral nutrition with 1.5 g/kg protein or an isonitrogen, isocaloric total enteral nutrition that contained 0.3 g/kg L-alanyl-L-glutamine. The baseline of follow-up plasma concentrations of total amino acids and glutamine was the same for both groups. Nevertheless, analysis of a small subgroup showed that in patients with a marked systemic inflammatory response, indicated by a serum C-reactive protein of more than 100 mg/dL, the baseline glutamine concentrations were significantly reduced compared with patients with a lower C-reactive protein level. Earlier, Roth et al[9] found that amino acid concentrations in plasma and muscle were considerably lower than the reference range in 19 patients with acute hemorrhagic pancreatitis, nowadays called necrotizing pancreatitis. The findings of their study are in line with our observations, but at that time, the authors did not correlate plasma concentrations with clinical signs and symptoms.

This preliminary exploratory study shows that plasma glutamine levels are decreased in severe pancreatitis. This justifies a randomized trial to study the effect of glutamine substitution in such patients.

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Resectable Carcinoma Developing in the Remnant Pancreas 3 Years After Pylorus-Preserving Pancreaticoduodenectomy for Invasive Ductal Carcinoma of the Pancreas

To the Editor:

Despite recent advances in diagnostic modalities and surgical techniques, the postoperative clinical course of patients with invasive ductal carcinoma of the pancreas remains dismal because of the frequent recurrence of the disease, even in patients who have undergone a curative resection. The local spread of cancer cells to the pancreatic bed, metastasis to the liver, and peritoneal dissemination are the major patterns of recurrence of pancreatic carcinoma after resection, which limit the possibility of a second resection, and only a few cases have a chance for resection of pancreatic carcinoma recurrence. We describe a rare case of a patient presenting with a resectable carcinoma of the remnant pancreas 3 years after undergoing a pylorus-preserving pancreaticoduodenectomy for invasive ductal carcinoma of the head of the pancreas.

CASE REPORT

A 58-year-old man with a 3-year history of non–insulin-dependent diabetes treated with oral antidiabetic agents and dietary modifications was admitted to Goto Chuo Hospital in January 2001, with a complaint of a deterioration in the control of diabetes. At that time, the patient was found to have a raised serum concentration of carbohydrate antigen 19-9 (CA 19–9) of 129 U/mL (reference range, <37 U/mL). Abdominal computed tomography (CT) depicted a mass lesion in the head of the pancreas along with a dilation of the distal pancreatic duct and an atrophy of the pancreatic parenchyma. Endoscopic retrograde cholangiopancreatography demonstrated a stricture of the main pancreatic duct in the head of the pancreas and a markedly dilated distal pancreatic duct. The pancreatic juice cytology specimens tested positive for cancer cells. These findings were consistent with a diagnosis of carcinoma of the head of the pancreas. The patient underwent a pylorus-preserving pancreaticoduodenectomy (PPPD), followed by Child modified procedure for the reconstruction of the digestive tract in February 2001. The pancreatic tumor was 2.5 cm in diameter and histologically diagnosed as an invasive ductal carcinoma composed of a papillary and well-differentiated tubular adenocarcinoma with infiltration to the microvessels. There was no invasion to the retropancreatic soft tissue, and the surgical margins of the resected specimen, including the stump of the pancreas, were free of atypical or cancer cells. Regional lymph node metastasis was not observed; pStage IB (pT2, pN0, pM0) and R0 according to the International Union Against Cancer (UICC) TNM classification for malignant tumor.[1] The postoperative course was uneventful, and the serum concentration of CA 19-9 declined to a normal level.

After October 2003, the CA 19-9 value gradually rose to 256 U/mL. A follow-up abdominal CT examination detected a low-density mass in the tail of the remnant pancreas, measuring 3.0 cm in diameter, in December 2003. During an additional 3-month follow-up, no other recurrence was observed to develop. The patient was thus referred to our department in expectation of a second surgery for the remnant pancreatic tumor. A reevaluation with abdominal ultrasonography, contrast-enhanced CT scan, magnetic resonance imaging, and positron emission tomography confirmed a solitary tumor within the remnant pancreas, but no distant metastasis or nodal involvement. The patient thereafter underwent a second operation in March 2004. The tumor was confined to the remnant pancreas, and invasion into the surrounding soft tissue, lymph node involvement, liver metastasis, or peritoneal dissemination was not observed. A complete resection of the tumor was accomplished by performing a removal of the remnant pancreas including the pancreaticojejunostomy, lymph nodes around the pancreas, and the spleen. Histologically, the second tumor was an invasive ductal carcinoma of the pancreas consisting of a papillary adenocarcinoma, showing similar histopathological findings as the first pancreatic tumor. There were no microscopic lymph node metastases; pStage IB (pT2, pN0, pM0) and R0 according to the UICC TNM classification.[1] In addition, a histological examination of the remnant pancreas confirmed that the pancreatic exocrine parenchyma in the body of the remnant pancreas had fully regenerated, along with a decrease in the degree of pancreatic fibrosis, in comparison with the findings recognized in the body of the pancreas distal to the initial pancreatic tumor at the first operation, presenting with abundant fibrosis and severe acinar atrophy (Fig. 1). The postoperative course was uneventful, and the CA 19–9 value was again normalized after the second surgery. The patient returned to his normal lifestyle without any trouble, except for the need to continue injecting himself with insulin.

Twenty-three months after the second operation, the patient underwent a partial hepatectomy because of a solitary metastatic tumor in the medial segment of the liver, followed by systemic chemotherapy with gemcitabine. The patient is still alive at 6 years and 3 months after the first operation and 3 years and 2 months after the second operation at the time of this writing, although a recent CT scan revealed a recurrence of cancer around the hepatic hilum.

DISCUSSION

A surgical resection provides the chance for a cure for patients with a malignant pancreatic tumor, although pancreatic ductal carcinoma remains a lethal disease. The reported 5-year survival rates after a surgical resection for pancreatic ductal carcinoma are still less than 20%, and most of the patients develop a recurrence of the same cancer within 1 or 2 years after removal of the tumor.

In the present case, the relapse of carcinoma was recognized in the remnant pancreas 2 years and 10 months after the PPPD for an invasive ductal carcinoma of the head of the pancreas, and the remnant pancreatic tumor was successfully

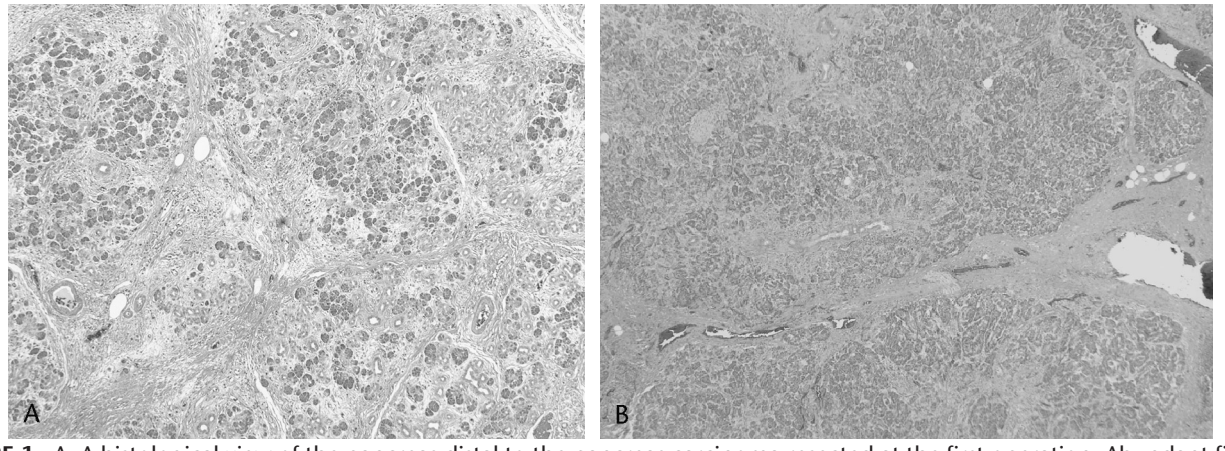

FIGURE 1. A, A histological view of the pancreas distal to the pancreas carcinoma resected at the first operation. Abundant fibrosis and the disappearance of lobules with severe acinar atrophy are seen. B, A histological view of the body of the remnant pancreas resected at the second operation demonstrates a reduction of pancreatic fibrosis and a regeneration of atrophied pancreatic exocrine parenchyma, in comparison with the findings in Figure 1A.

TABLE 1. Reported Cases of Resectable Carcinoma Developing in the Remnant Pancreas After Pancreatectomy for Invasive Ductal Carcinoma of the Pancreas

Patient No.	Author	Age/Sex	Interval*	First Operation	UICC TNM Classification for the Initial Pancreatic Cancer			Second Operation	UICC TNM Classification for the Second Pancreatic Cancer	Follow-Up After the Second Operation
1	Eriguchi et al[2]	67/F	7 yrs 4 mo	DP	pStage I	(T1N0M0)	R0 (5th ed)	TP	pStage III (T1N1M0)	8 mo (alive)
2	Wada et al[3]	52/F	1 yr 8 mo	PPPD	pStage III	(T3N1M0)	R0 (5th ed)	TP	TxN0M0	44 mo (dead)
3	D'Amato et al[4]	44/M	3 yrs 4 mo	PPPD	pStage III	(T2N1Mx)	R0 (5th ed)	TP	T2NxM0, R0	22 mo (alive)
4	Doi et al[5]	60/M	2 yrs 2 mo	DP	pStage IIA	(T3N0M0)	R0 (6th ed)	TP	pStage IB (T2N0M0), R0	7 mo (dead)
5	Takamatsu et al[6]	63/M	3 yrs 7 mo	PD	pStage II	(T3N0M0)	R0 (5th ed)	TP	pStage II (T3N0M0), R0	10 mo (alive)
6	Dalla Valle et al[7]	63/M	12 mo	PD	pStage IIA	(T3N0Mx)	R0 (6th ed)	TP	pStage IIA (T3N0M0), R0	24 mo (alive)
7	Miura et al[8]	72/F	2 yrs 5 mo	PPPD	pStage IV	(T3N0M0)	R0 (6th ed)	DP	TxNxM1 (liver metastases)	5 mo (dead)
8	Present case	58/M	2 yrs 10 mo	PPPD	pStage IB	(T2N0M0)	R0 (6th ed)	TP	pStage IB (T2N0M0), R0	38 mo (alive)

*Interval between operation for initial pancreatic carcinoma and diagnosis of remnant pancreatic carcinoma.
DP indicates distal pancreatectomy; PD, pancreaticoduodenectomy; TP: total pancreatectomy.

removed, thus resulting in long-term survival. The indication for the second operation in our case was that the relapse of carcinoma was limited to the remnant pancreas without any local recurrence, nodal involvement, distant metastasis, or peritoneal dissemination, even after an additional follow-up interval of 3 months from the detection of the tumor in the remnant pancreas. There have been few reports of a resectable remnant pancreatic carcinoma after a pancreatectomy for invasive ductal carcinoma of the pancreas (Table 1).[2–8] The previously reported cases and our patient had common clinical features, that is, the R0 resection for the first pancreatic tumor, including the negative surgical margin at the pancreatic stump, and the relapse of carcinoma limiting to the remnant pancreas, except for 1 case with liver metastases in the left lateral segment of the liver.[8] Regarding the surgical procedures used in the second operation, a complete removal of the remnant pancreas was performed in all cases, except for one who underwent a resection of the tail of the remnant pancreas after a PPPD. The efficacy of repeated pancreatectomies for remnant pancreatic carcinoma is obscure because of the lack of sufficient accumulation of such cases. However, we believe that repeated pancreatectomies can offer good results for select cases.

It is difficult to define whether a pancreatic carcinoma developing in the remnant pancreas after a pancreatectomy for a malignant pancreatic tumor is a local recurrence or a second primary cancer. In our case, the first pancreatic tumor was an invasive ductal carcinoma of ordinary type, and the surgical margins of the resected specimen, including the stump of the pancreas, were free of atypical or cancer cells. The second pancreatic tumor developed in the remnant pancreas with a long-term interval of about 3 years after the pancreaticoduodenectomy for the first pancreatic tumor. Meanwhile, the first and second pancreatic tumors were histologically similar (ie, both tumors consisted of a papillary adenocarcinoma). Launois et al[9] observed an incidence of 32% of multifocal carcinoma of the pancreas in a series of 47 total pancreatectomies for patients with pancreatic ductal adenocarcinoma. Likewise, a considerably high incidence of multicentric precancerous foci in the pancreas has been documented in patients with pancreatic ductal carcinoma. We therefore presumed that a minute cancerous focus had most likely existed in the remnant pancreas at the initial surgery in our patient.

The present case raised another interesting issue in terms of pancreatic fibrosis and pancreatic parenchymal regeneration. Occlusion of the major pancreatic ductal system leads to pancreatic duct dilatation, parenchymal atrophy, and finally, disappearance of the acinar cells replaced by fibrosis, as seen in our patient at the first operation. Meanwhile, the histopathologic evaluation of the remnant pancreas demonstrated a reduction of pancreatic fibrosis and a regeneration of atrophied pancreatic exocrine parenchyma after the first operation, suggesting that pancreatic fibrosis and pancreatic acinar atrophy due to obstructive pancreatitis could be reversed after pancreaticoduodenectomy by releasing the pancreatic ductal obstruction. These findings are consistent with the results of experimental studies.[10]

In conclusion, our patient demonstrated that repeated pancreatectomies can provide a chance for long-term survival for patients with a relapse of carcinoma in the remnant pancreas even after a pancreatectomy for an invasive pancreatic ductal carcinoma if the recurrence of the carcinoma is limited to the remnant pancreas. This case may also support the concept of multicentric carcinogenesis in the pancreas.

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Clinical Outcome of Gemcitabine/S-1 Combination Therapy for Advanced Pancreatic Cancer

To the Editor:

The previous phase II study of gemcitabine/S-1 combination therapy demonstrated promising results for metastatic pancreatic cancer, which remains one of the most lethal malignancies in the world.[1–3] According to the previous report by Nakamura et al,[3] gemcitabine/S-1 combination therapy showed 48% response rate and 12.5 months of median survival time with tolerable adverse events. To verify the previous report, we retrospectively evaluated the efficacy and safety of gemcitabine/S-1 combination therapy for advanced pancreatic cancer patients in our hospital. Between June 2003 and June 2006, 87 advanced pancreatic cancer patients received chemotherapy at an outpatient oncology unit in Kyoto University Hospital. Among them, a total of 32 patients who received gemcitabine/S-1 combination therapy were evaluated. Combination therapy consisted of intravenous administration of gemcitabine 600 to 1000 mg/m^2 on days 8 and 15 and 60 to 80 mg/m^2 of S-1 orally for 14 consecutive days. The cycle was repeated every 3 weeks. All toxicities, response to treatment, and survival data were retrieved from a computer-assisted database system (Cyber-Oncology, Cyber Laboratory Inc, Tokyo, Japan), which enables us to analyze these data in a real-time manner with more accuracy. Toxicities were graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0). Measurable target lesions were assessed by Response Evaluation Criteria in Solid Tumors.[4]

When this article was submitted, 22 out of 32 patients had died. In our current study, gemcitabine/S-1 combination therapy demonstrated no complete response, partial response in 9 out of 32 patients (28%), 12 months of median survival time (95% confidence interval [CI], 9.3–19.1 months), and 50.4% of 1-year survival rate (95% CI, 32–68%) (Table 1). Notably, 5 patients got potentially resectable on CT scans after several cycles of this combination therapy and underwent surgery. These patients have achieved a good survival except 1 patient. Because surgery remains the only modality to potentially cure this disease, a future study with a large sample size will be warranted to confirm the efficacy and feasibility of gemcitabine/S-1 combination therapy followed by surgery.

The toxicity observed in this combination therapy was similar to the previous report and well tolerated at an outpatient setting (Table 1). The most common, but reversible, toxicity of this combination therapy was neutropenia. Grade 3 and 4 neutropenia was observed in 9 and 5 patients, respectively. Febrile neutropenia was observed in 1 patient. Grade 3 and 4 anemia and thrombocytopenia was observed in 1 and 3 patients, respectively. Anorexia, nausea, and diarrhea were common nonhematological toxicities (14 cases of grade 1–2 anorexia, 13 cases of grade 1–2 nausea and grade 1–2 diarrhea); however, severe nonhematological adverse events (grades 3–4) were rare. No treatment-related deaths were observed in this study.

Patients in our study were not limited to metastatic disease but locally advanced disease (n = 3) as well as recurrent disease (n = 4) after potentially curative resection was included (Table 1). Thus, our current results represent the outcome of advanced pancreatic cancer patients treated with gemcitabine/S-1 combination therapy in daily practice in a high-volume hospital. In summary, gemcitabine/S-1 combination therapy demonstrated favorable clinical outcome with tolerable toxicity in advanced pancreatic cancer, which strongly supported

TABLE 1. Results of Gemcitabine/S-1 Combination Therapy for Advanced Pancreatic Cancer

	Our Report	Nakamura et al[3]
No. patients	32	33
Locally advanced	3	0
Recurrent	4	0
Metastatic	25	33
First line/second line	13/19	33/0
Response rate (CR/PR)	28% (0/9)	48% (1/15)
MST, mo (95% CI)	12.0 (9.3–19.1)	12.5 (5.9–19.1)
1-year survival rate (95% CI)	50.4% (32–68)	54% (36–72)
Grade 3–4 leukopenia	8/32 (25%)	11/33 (33%)
Grade 3–4 neutropenia	14/32 (44%)	18/33 (55%)
Grade 3–4 anemia	1/32 (3%)	3/33 (9%)
Grade 3–4 thrombocytopenia	3/32 (9%)	5/33 (15%)
Febrile neutropenia	1/32 (3%)	2/33 (6%)
Interstitial pneumonia	0/32 (0%)	2/32 (6%)

CR indicates complete response, PR, partial response; MST, median survival time.

a result of previous phase II trial. A future prospective trial with a larger sample size will be warranted to confirm the efficacy and survival benefit of this combination regimen over gemcitabine monotherapy for advanced pancreatic cancer.

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ARTICLE AMENDMENT

ERRATUM: Safe Induction of Diabetes by High-Dose Streptozotocin in Pigs

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Original citation: *Pancreas* 2008 January 36(1):31–38.

Citation for this erratum: *Pancreas* 2008 April 36(3):328.

The authors apologize for the misspelling of co-author A.N. Balamurugan's name. It should read A.N. Balamurugan, instead of A.N. Balamarugan.