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CLINICAL CASE

A case of exocrine-endocrine neoplasm of the pancreas in a patient with ulcerative colitis with literature review

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Summary

Until now only Japanese authors have reported 4 cases of pancreatic neoplasm associated with ulcerative colitis (UC). We report on a case of a 44-year-old woman who was operated on for complicated UC and an exocrine-endocrine neoplasm of the pancreas, where the endocrine component was presented by pancreatic polypeptide (PP)-producing cells. By means of molecular genetics methods we found microsatellite instability (MSI) in the markers D18S35, FGA and p53 in the colonic lining, and loss of heterozygosity (LOH) in the p53 marker in the pancreatic tumor. A literature review concerning the coexistence of these two conditions showed that PP is involved in the pathogenesis of the UC and that UC increases the risk of development of extracolonic neoplasms.

Key words: microsatellite instability, pancreatic neoplasm, pancreatic polypeptide, ulcerative colitis

Introduction

According to literature data 0.8-3.9% of patients with UC develop extracolonic neoplasms, the most common being leukemia, lymphoma and carcinoma of the uterus, stomach, breast, skin and bile ducts [1-3]. Only Japanese authors have reported association of pancreatic neoplasms with UC in 4 patients -3 with carcinoma of the pancreas and 1 with pancreatic intraductal papillary adenoma and adenocarcinoma of the stomach, but also with Hansen's disease [3].

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Case presentation

UC was diagnosed in a 44-year-old woman 3 years ago. The patient had 2 mild relapses of the disease during that period. In May 2000 she was admitted to another hospital for severe US relapse. After 10 days of ineffective conservative treatment including hydrocortisone, an emergency subtotal colectomy with a modified Hartmann operation was performed for toxic megacolon. During the operation cholecystolithiasis was diagnosed as well, but cholecystectomy was not performed. During the postoperative period the patient developed acute pancreatitis.

On admission to our department 3 months later she was complaining of a constant feeling of encumbrance, had scanty purulent and bloody bowel movements and was still underweight -13 kg below her normal body weight of 63 kg (being 170 cm tall). A painless formation was palpable in the lower part of her epigastrium.

Preoperative diagnostic workup

Ultrasonography showed evidence of an enlarged

gallbladder with a calculus in the isthmus, common bile duct 12 mm in diameter, and an encapsulated area in the head of the pancreas of non-homogeneous structure, 5 cm in diameter. In computed tomography of the upper abdomen this finding in the pancreas was assessed as pseudocyst in a phase of forming (Figure 1). The patient refused endoscopic retrograde cholangiopancreatography. Rectoscopy showed ulcerative proctitis in active phase. Full blood count showed hemoglobin (Hb) 11 g/L; erythrocytes 3.19×10^6/mm^3; white blood cells 6,700/mm^3; platelets 125,000/mm^3. Erythrocyte sedimentation rate (ESR) 80 mm/h; total serum protein 66 g/L; serum albumin 29 g/L; serum amylase 51 U/L (normal range 40-300 U/L); serum alkaline phosphatase 152 (normal range 50-170 U/L). The rest of serum biochemistry (FBS, BUN, creatinine, LFTs, electrolytes) was within normal limits.

Pancreato-duodenal resection was performed and the intraoperative frozen sections showed an endocrine tumor of the pancreas, predominantly trabecular in appearance.

Operative specimens

1. Gallbladder 10 cm long with thickened wall and harsh mucosa. 2. Encapsulated tumor of the pancreas 6 cm in diameter, with motley colour (different in size gray-pink, gray-red and gray-brownish zones) with different consistence (in some areas dense or dense-elastic and in others soft-elastic or soft with cyst-like zones).

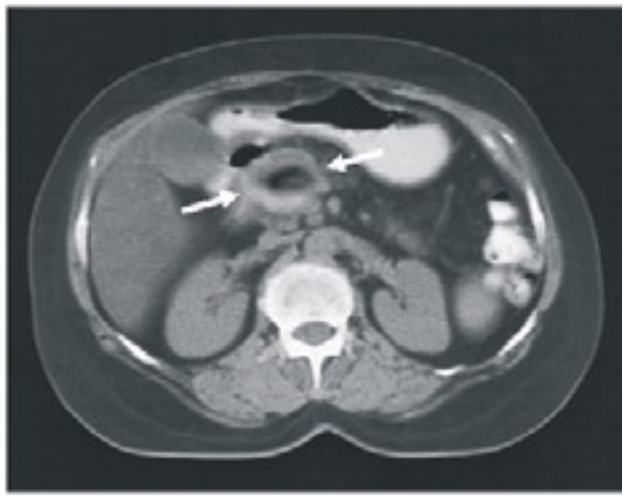

Figure 1. CT demonstrating a formation in the area of head-body of the pancreas (arrows) with mixed structure-cystic central part and hydrops of the gallbladder.

Histological details

The following findings were determined histomorphologically: 1. Chronic fibrosing ("pseudoglandular") cholecystitis. 2. Solid-cystic papillary epithelial neoplasm of the pancreas of mixed exocrine-endocrine type (Figure 2 a-c). We asked for the colonic histological preparations from the previous colectomy, which showed chronic UC with severe activity (Figure 3 a, b).

The pancreatic tumor was tested immunohistochemically for the presence of the basic Langerhans islets hormones insulin, glucagone, somatostatin, and PP. The following antibodies were used: Guinea Pig Anti-Insulin Biogenex Lab.–Lot No RH 029123; Rabbit Anti-Glucagone-Lot No RH 039063; Rabbit Antisomatostatin–Lot. No RH 042112; Rabbit AntiHuman Pancreatic Polypeptide (DAKO) Lot No 00111. The procedure was performed with the stan-

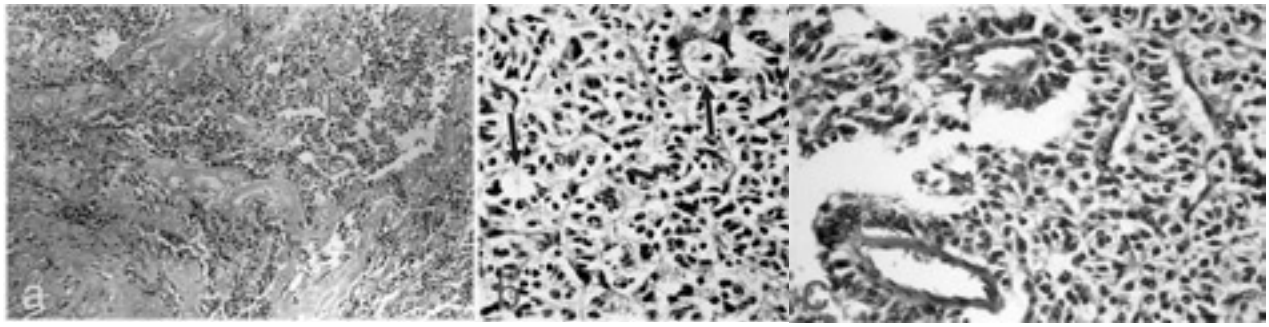

Figure 2. ***a:*** A zone of the tumor with irregular, fissure-like (light) spaces and bands (homogenous) of hyalinized and collagenized stroma (H&E ×25). ***b:*** Solid zone of the pancreatic tumor-small elongated or polygonal (of endocrine type) cells, arranged around thin-walled small caliber blood vessels (arrows); single bigger irregularly-shaped cells (H&E ×100). ***c:*** Pancreatic tumor-zones with endocrine characteristic (lower right) and fissure-like spaces with formation of pseudopapillary structures of exocrine type (left) (H&E×100).

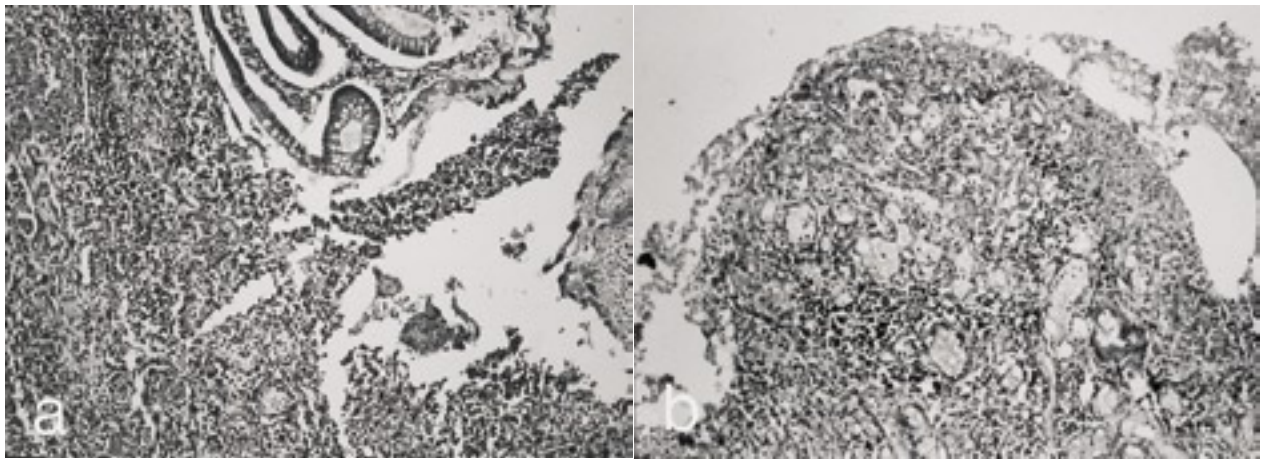

Figure 3. ***a:*** Large bowel mucosa with edema and abundant inflammatory infiltrate in the mucosa (rich in neutrophils), acute ulcerative defects and thromboses of blood vessels with fibrinoid necrosis in their walls, ulcerative defects with scarring and inflammatory pseudopolyps and abundant inflammatory infiltrate in lamina propria, thromboses of blood vessels with fibrinoid necrosis in their walls and ulcerative defect with pseudopolypous growth of the mucosa at the edges (H&E ×25). ***b:*** Inflammatory pseudopolyp at the bottom of an ulcerative defect (H&E ×25).

dard Biotin-Streptavidin-HRP test (DAKO LSAB2 system–KO673). The presence of MSX Nestin (human specific) (Chemicon-International) was examined. Negative (with primary antibody release) and positive controls were used. Positive results were obtained only for PP both in single tumor cells and in clusters of tumor cells. The intensity of the immunohistochemical staining varied both among different areas of the neoplasm and among different tumor cells (Figure 4).

DNA was derived from fresh blood, from colonic mucosa (paraffin-embedded tissues from the colectomy) and from the pancreatic tumor, using standard protocols, and was tested for MSI and LOH.

For this purpose 6 microsatellite markers were used: 1 mono- BAT26, 4 di- D2S123, D5S346, D18S35, p53 and 1 tetranucleotide- FGA. The repeat markers were amplified from both normal and tumor DNA samples and were resolved by 6% denatured polyacrylamide gel electrophoresis and detected by automated fluorescence sequencer ALFExpress (Pharmacia Biotech, Uppsala, Sweden). MSI was defined by the appearance of different alleles in the colonic and tumor DNA, compared to the corresponding normal DNA. LOH was defined by at least 50% reduction in the relative intensity of one allele in the tumor compared to the normal DNA.

In the DNA from the colon tissue MSI was detected in D18S35, FGA and p53 markers (Figure 5 a). In the DNA from the pancreatic tumor LOH was found in p53 marker (Figure 5 b).

Three years after surgery the patient is doing well. Ultrasonography and computed tomography show no pathologic changes. CEA and CA 19-9 are within normal limits (they were not measured preoperatively).

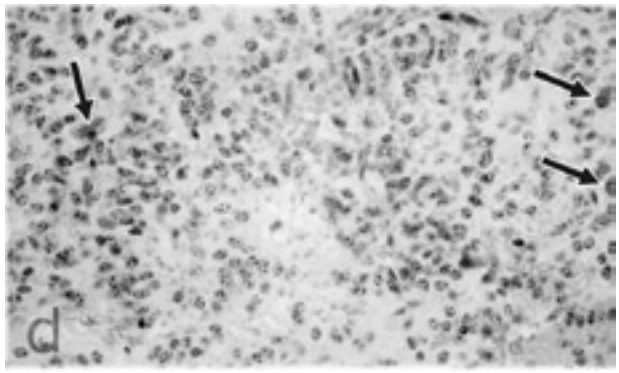

Figure 4. Demonstration of positive immunohistochemical reaction for the presence of PP in some groups or in single tumor cells (arrows) (×100).

Discussion

The cholecystolithiasis, the postoperative acute pancreatitis, the palpable formation 3 months later, the findings from the imaging procedures and the lack of data for the pancreatic formation during the emergency operation gave grounds for the diagnosis of a pancreatic pseudocyst. The operation for complicated UC soon after that and the unsolved bile-pancreatic problem explained the lack to gain weight, the increase of ESR

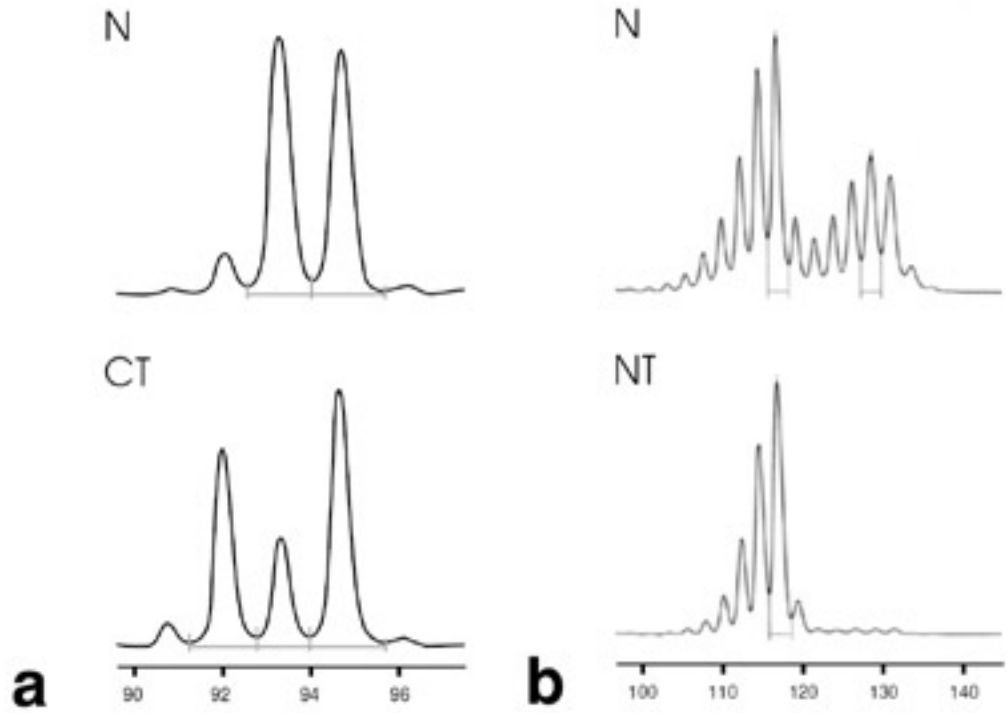

Figure 5. ***a:*** Demonstration of microsatellite instability in FGA marker. PCR- amplified alleles from normal DNA (N) and from the corresponding colon tissue (CT). ***b*****:** Demonstration of loss of heterozygosity in p53 marker. PCR-amplified alleles from normal DNA (N) and from the corresponding pancreatic neoplasm tissue (NT).

and the low values of Hb, erythrocytes, platelets and serum albumin. However, the lack of pain and fever, the normal values of serum amylase, and the fact that 3 months after the pancreatitis the formation showed considerable solid part, made the diagnosis of pseudocyst quite dubious. The indications for surgery were not only the cholecystolithiasis, but also the unclear biological characteristics of the pancreatic formation.

Lack of metastases intraoperatively, no evidence of infiltration histomorphologically and Nestin-positive test immunohistochemically, all led to the conclusion that the pancreatic tumor was not malignant. However, many studies connect the loss of p53 genetic material and its overexpression as an important step in the carcinogenetic process [4].

From the relevant literature 2 main problems arise concerning the association of a pancreatic neoplasm with PP-cell component and UC, as well as the presence of an extracolonic neoplasm in a patient with UC: the participation of PP in the pathogenesis of inflammatory bowel disease (IBD) and the hypothesis that UC increases the risk of development of extracolonic neoplasms.

The gastrointestinal neuroendocrine peptides, among which PP is included, are known to play a role in the regulation of the intestinal motility, absorption and secretion [5]; many of them have immunomodulatory function [6] and take part in the intestinal immune response [5]. Disturbances in these functions are typical for IBD; that's why the neuroendocrine regulatory system in these patients is an area of investigation [5, 6].

According to Bordi et al. [7] PP-producing pancreatic tumors can be divided into 3 types: pure PP-omas, mixed tumors with minor PP-cell population, and PP-cell hyperplasia. According to Strodel et al. [8] PP have limited biological activity. But even when hypersecreted, PP can not be related to certain clinical syndromes [8, 9], although few patients have been described with diarrhoea, abdominal pain, gastrointestinal bleeding and wasting [8-10].

Reassessment of the clinical features of our patient (bloody diarrhea, wasting at the last relapse complicated with toxic megacolon), pointed again towards chronic-recurring UC. Yet, without preoperative serum value of PP we cannot discuss these manifestations in the context of the supposed participation of PP in the pathogenesis of UC.

There have been only few reports analyzing the frequency of extra-colonic malignancies in patients with UC [1]. Prior et al. [11] in their study of the respiratory, reproductive, urinary and the reticuloen-

dothelial and the integumentary systems did not find higher than expected incidence. Greenstein et al. [1] found greater incidence of lymphoma, leukemia and certain squamous cell carcinomas in patients with IBD. The analysis by Mir-Madjlessi et al. [2] showed significant increase of the relative risk for bile duct carcinoma, leukemia, bone and endometrial tumors in patients with UC, as well as significantly lower relative risk for lung cancer.

The reason for this correlation is unclear. However, it is well known that in UC immune regulation is disturbed, so, theoretically, such an association can be related to changes in immunity. In reticuloendothelial tumors Greenstein et al. [1] explain this correlation by attributing it to primary immune suppression associated with IBD, secondary immune suppression related to drug therapy, and the long-term effects of low-dose irradiation. Still, these hypotheses do not explain clearly the pathogenetic mechanism of such a correlation. The same authors point out that there are many speculations in the literature about the oncogenic potential of these factors [1].

The commonly accepted risk factors for development of malignancy in UC patients are disease duration for more than 10 years, severe disease, pancolitis and prolonged cortisone treatment. Analysis of these factors with regard to our patient showed:

1. Mild US of 3 years duration, without steroid treatment. Cortisone was administered only during the last relapse, which was severe and complicated.

2. The retrospective review of the bioptic material from the first operation showed pancolitis and presence of pseudopolyps, which are markers predictive of severe disease relapse.

3. MSI in 3 loci. In patients with UC without colorectal carcinoma (CRC), Ishisuka et al. [12] found difference in the degree of MSI in the colonic mucosa according to the duration of the disease: up to 2 loci if the duration was up to 4 years and more than 2 loci if the duration was more than 5 years. Still, the question remains if these genomic changes are transient or it is just a matter of time the changes in p53 overexpression to lead to the development of CRC in the future [12].

In summary, pancolitis, pseudopolyps, toxic megacolon and MSI in more than 3 loci, among which p53, are markers of UC with longer duration than the patient's personal medical history implies, bearing also a more severe prognosis. This fact can be explained with a latent process outside clinically obvious relapses. These data can be taken as predisposing factors for future development of CRC, partially prevented by colectomy, but cannot be related to a pancreatic neoplasm. We can accept that the lack of MSI in the pancreatic neoplasm shows that a possible future CRC would develop through different carcinogenetic mechanisms than the one in the pancreas.

The research results do not lend support for linking the two diseases pathogenetically. We only present the facts of this case, which may be useful for comparison with other similar ones.

Acknowledgements

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