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CASE REPORT

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Microcystic tubulopapillary carcinoma of the pancreas: a new tumor entity?

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Abstract An unusual pancreatic tumor with microcystic and tubulopapillary features was observed in a 53-year-old woman. The tumor presented as a large, focally cystic mass in the head of the pancreas, which compressed the surrounding structures. The histological and immunohistochemical analysis revealed a neoplasm that could not be assigned to any of the known pancreatic tumor types. At the molecular level, the tumor showed inactivation of the DPC4/SMAD4 gene, deletion of exon 1 of the $p16^{INK4A}$ gene and a point mutation at codon 34 (GGA>AGA) of *β-catenin*. Transcriptional profiling analyses and subsequent correspondence cluster analysis demonstrated that the transcriptional profile of the tumor differed distinctly from that of ductal adenocarcinomas, pancreatic cystic tumors and normal pancreatic tissues. These data suggest that the neoplasm most likely represents a new pancreatic tumor entity, which we would like to refer to as microcystic tubulopapillary tumor.

Keywords Pancreas · Microarray analysis · DPC4/SMAD4 · β-Catenin · $p16^{INK4A}$

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Introduction

Pancreatic neoplasms with cystic and papillary features mainly belong to the category of intraductal papillary mucinous cystic tumors. These tumors cause a dilatation of the pancreatic duct and/or of its branches that, especially when focal, may produce a cystic-like gross appearance [26]. Another pancreatic tumor with papillary (or more precisely, pseudopapillary) structures is the solid pseudopapillary neoplasm, a low-grade malignant tumor that occurs predominantly in young women and often displays a cystic gross appearance due to extensive hemorrhage and necrosis [16]. In rare cases, papillary and micropapillary structures can also be found in ductal adenocarcinomas, especially if they are well differentiated [24]. Here, we report the case of an unusual pancreatic tumor with tubulopapillary and microcystic features, which could not be assigned to any of the known pancreatic tumor types. The histological and immunohistochemical data and the results of a molecular analysis, which included the use of the increasingly employed microarray technology [11], all suggest that this tumor represents a new entity, not previously described in the pancreas.

Case report

A 53-year-old woman presented with a short history of discomfort and swelling in the right upper abdomen. Relevant data in her prior history included alcohol intake, interrupted 10 years ago, and episodes of pancreatitis. Moreover, the patient suffered from diabetes mellitus and liver cirrhosis (child A). A computed tomography scan revealed a 10- to 15-cm tumor mass in the pancreatic head; therefore, an exploration and a subsequent pylorus-preserving pancreaticoduodenectomy were performed.

Materials and methods

Formalin-fixed, paraffin-embedded sections obtained from the tumor mass were stained routinely with hematoxylin and eosin and periodic acid-Schiff (PAS). Immunohistochemical analysis was performed on consecutive slides with the streptavidin-biotin meth-

Table 1 Immunohistochemical profile of the reported tumor

Immunohistochemical marker	Result
CK7	+
CK8	+
CK18	+
CK20	+
CEA	–
Vimentin	–
Chromogranin	–
Neuron-specific enolase	–
Synaptophysin	+*
Trypsin	–
Inhibin	–
Thyroglobulin	–
TTF-1	–
Estrogen/progesterone receptors	–
MUC1	–
MUC2	–
MUC6	+
p53	(+)
p16	–
DPC4	–
β-Catenin	+°

* Focal cytoplasmic positivity
° Cytoplasmic and nuclear positivity

od, using diaminobenzidine as the chromogen. A large panel of antibodies (all supplied by Dako, Carpenteria, CA, USA, with the exception of the anti-trypsin antibody, provided by Prof. Klöppel's laboratory) was used (Table 1).

Immunohistochemistry for p16, p53, Dpc4 and β-catenin

The following primary antibodies were used: mouse monoclonal anti-p16 (clone E6H4; mtm laboratories AG-Dako), mouse monoclonal anti-p53 (clone DO7; Dako); mouse monoclonal anti-DPC4/SMAD4 (clone B8; Santa Cruz Biotechnology, Santa Cruz, CA, USA) and mouse monoclonal anti-β-catenin (BD Transduction Laboratories, Lexington, KY, USA). Microwave antigen retrieval in citrate buffer was used with all three antibodies.

Electron microscopy

Small tissue samples were fixed in 3% glutaraldehyde and processed for ultrastructural investigation. Semi-thin sections were stained with 1% toluidine blue and examined using light microscopy to find appropriate areas for ultramicrotomy. Ultra-thin sections were contrasted with lead and examined under an electron microscope (Carl Zeiss, Jena GmbH, Jena, Germany).

DNA isolation

Tumor cells were manually microdissected from formalin-fixed, paraffin-embedded, 5-µm-thick tissue sections. Genomic DNA was isolated using the QIAamp DNA Mini Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's protocol.

Deletion analysis of the $p16^{INK4A}$ gene

Tumor DNA and DNA from the corresponding normal tissue were subjected to Duplex polymerase chain reaction (PCR) analysis using *p16* exon 1 (Ex1F: 5′-CTC AGA GCC GTT CCG AGA T-3′; Ex1R: 5′-TTT TCG AGG GCC TTT CCT AC-3′) or exon 2-specific primers (Ex2F: 5′-ACC CTG GCT CTG ACC ATT C-3′; Ex2R: 5′-TGG AAG CTC TCA GGG TAC AAA-3′), each combined with primers for the β-globin gene [22] as a control. Duplex PCRs were carried out as one-tube reactions under the following conditions: initial denaturation at 96°C for 3 min, 35 cycles of denaturation at 96°C for 1 min, annealing at 60°C for 1 min, extension at 72°C for 1 min and final extension at 72°C for 5 min. Duplex PCR products were electrophoretically separated on an ethidium bromide-stained 2% agarose gel and documented by digitalization (Gel documentation system, Herolab GmbH, Wiesloch, Germany).

Sequencing analysis

Exon 1 of the k-ras gene, which contains the codons 12 and 13, was amplified using the primers k-ras 1F (5′-GTG TGA CAT GTT CTA ATA TAG TCA-3′) and k-ras 1R (5′-GAA TGG TCC TGC ACC AGT AA-3′). The primer pairs β-Cat 2F (5′- GGA GTT GGA CAT GGC CAT GG-3′) and β-Cat 2R (5′-CCT GTT CCC ACT CAT ACA GG-3′) were used to amplify exon 3 of the β-catenin gene, which contains four threonine/serine phosphorylation sites essential for APC/GSK-3β-mediated degradation of β-catenin. PCR reactions were performed under standard conditions, and the purified PCR products were sequenced directly in the forward and reverse directions on an ABIPrism 377 DNA sequencer (Applied Biosystems, Foster City, CA, USA), using the BigDye Termination Kit (Applied Biosystems, USA).

DNA microarrays

Human cDNAs representing 3500 different human genes, which had been selected because they are informative with respect to pancreas tumors, were PCR-amplified using amino-modified M13 universal primers. PCR products were purified with PCR multi-screen columns (Millipore GmbH, Schwalbach, Germany), suspended in spotting solution (TeleChem International Inc., Sunnyvale, CA, USA) and arrayed onto slides with an epoxy surface (Epoxy Slides, Quantifoil Micro Tools GmbH, Jena, Germany). DNA spotting was performed with a Micro-Arrayer from Engineering Services Inc. (Virtek's arrayer system, BioRad, Munich, Germany) using SMP3 pins (TeleChem, USA). Each microarray presents 3872 spots divided into 16 blocks, containing each spot in duplicate.

Transcriptional profiling

Total RNA was extracted with guanidine isothiocyanate from snap-frozen pancreatic tissues, including seven normal pancreas samples, five ductal adenocarcinomas and seven cystic tumors (mucinous cystic adenomas, mucinous cystic adenocarcinomas, serous cystic adenomas, intraductal papillary-mucinous tumors). Fluorescence-labeled cDNA samples were prepared from 10 µg total RNA and incorporation of Cy3- or Cy5-labeled dCTP during first-strand synthesis. The labeling reaction was performed at least three times in total. Hybridization was done in SlideHyb-Buffer 1 (Ambion Inc., Austin, TX, USA) under glass coverslips at 62°C overnight. To prevent bias caused by preferential label incorporation into particular sequences, the dyes were swapped between hybridizations. After washing in 0.1× sodium saline citrate for 3 min and drying using nitrogen, fluorescence signals were detected on a confocal ScanArray 5000 scanner (Packard BioChip Technologies, Billerica, MA, USA). Quantification of the signal intensities was performed with the GenePix Pro 4.1 software (Axon Instruments, Inc., Union City, CA, USA).

Data analysis

Data quality assessment, normalization and correspondence cluster analysis were performed with the analysis and data warehouse software package M-CHiPS (Multi-Conditional Hybridization Intensity Processing System), in which more than 5800 hybridization experiments are currently stored (http://www.mchips.org) [8, 9, 10]. Normalization was performed as described in detail by Beissbart et al. [4]. For further analysis, only genes that exhibited significant changes between at least one sample and the control material of the normal pancreas were selected. Data analysis and

also the compilation of experimental and sample-specific annotations met the criteria for MIAME2 compliance [6].

Correspondence analysis [8, 10] is an explorative computational method for the study of associations between variables. Much like principle component analysis, it displays a low-dimensional projection of the data onto a plane. Data are projected simultaneously for two variables, such as genes and patient samples, thus revealing associations between them. The closer the data points are located on the blot, the higher the degree of correspondence, thereby enabling a superior data interpretation.

Results

Morphology

Macroscopic examination of the surgical specimen revealed a 15×9×8-cm tumor with extensive necrotic areas, resulting in a focally cystic appearance. The tumor was surrounded by a thin pseudo-capsule and displayed expansive margins of growth. The duodenum and the distal bile duct were compressed and dislocated, but not infiltrated. Lymph node metastases were not found. Histologically, the tumor was composed of cubic to cylindrical cells, containing elongated, mostly basally located and frequently stratified nuclei, which showed moderate pleomorphism and granular chromatin. The cytoplasm was eosinophilic. The tumor cells formed well-developed tubular and papillary structures, which were often cystically dilated and contained amorphous eosinophilic PAS-positive material (Fig. 1A, B, C). Focally, there were necrotic areas. Extensive sampling failed to reveal solid areas. It was not possible to determine whether the tumor had an intraductal component, since very little pancreatic parenchyma was included in the surgical specimen. Ultrastructurally, the nuclei displayed shallow cytoplasmic invaginations and contained irregular masses of heterochromatin. In the cytoplasm, swollen

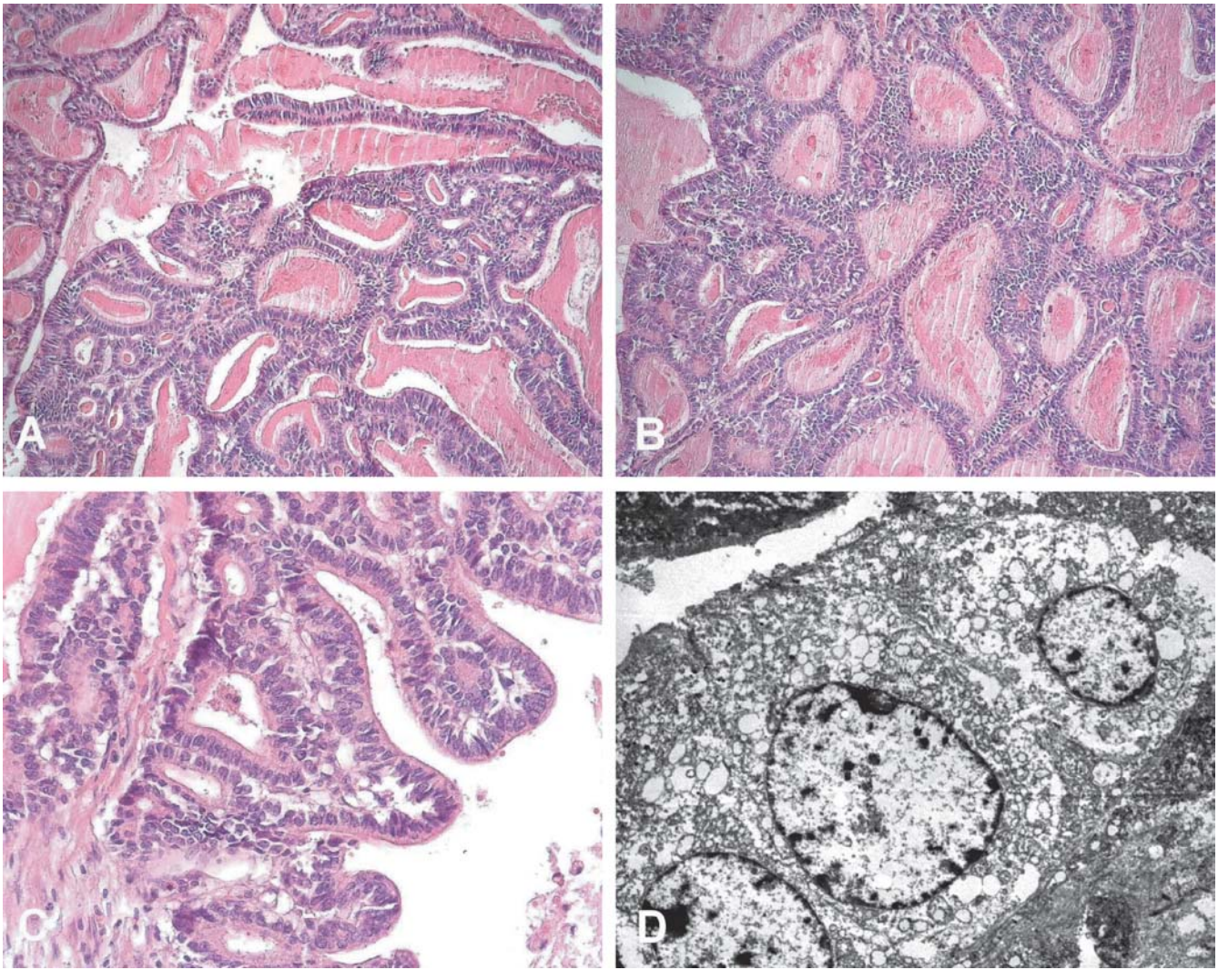

Fig. 1 **A**, **B**, **C** Microscopic appearance of the tumor, consisting of cubic to cylindrical cells with elongated nuclei, arranged to form small glandular or papillary structures, often projecting into cystically dilated lumina (**A**, **B**, ×100; **C**, ×200). **D** Electron microscopy revealed the presence of tight junctions between adjacent cells, which displayed nuclei with shallow invaginations and absence of secretory products in the cytoplasm (×2000)

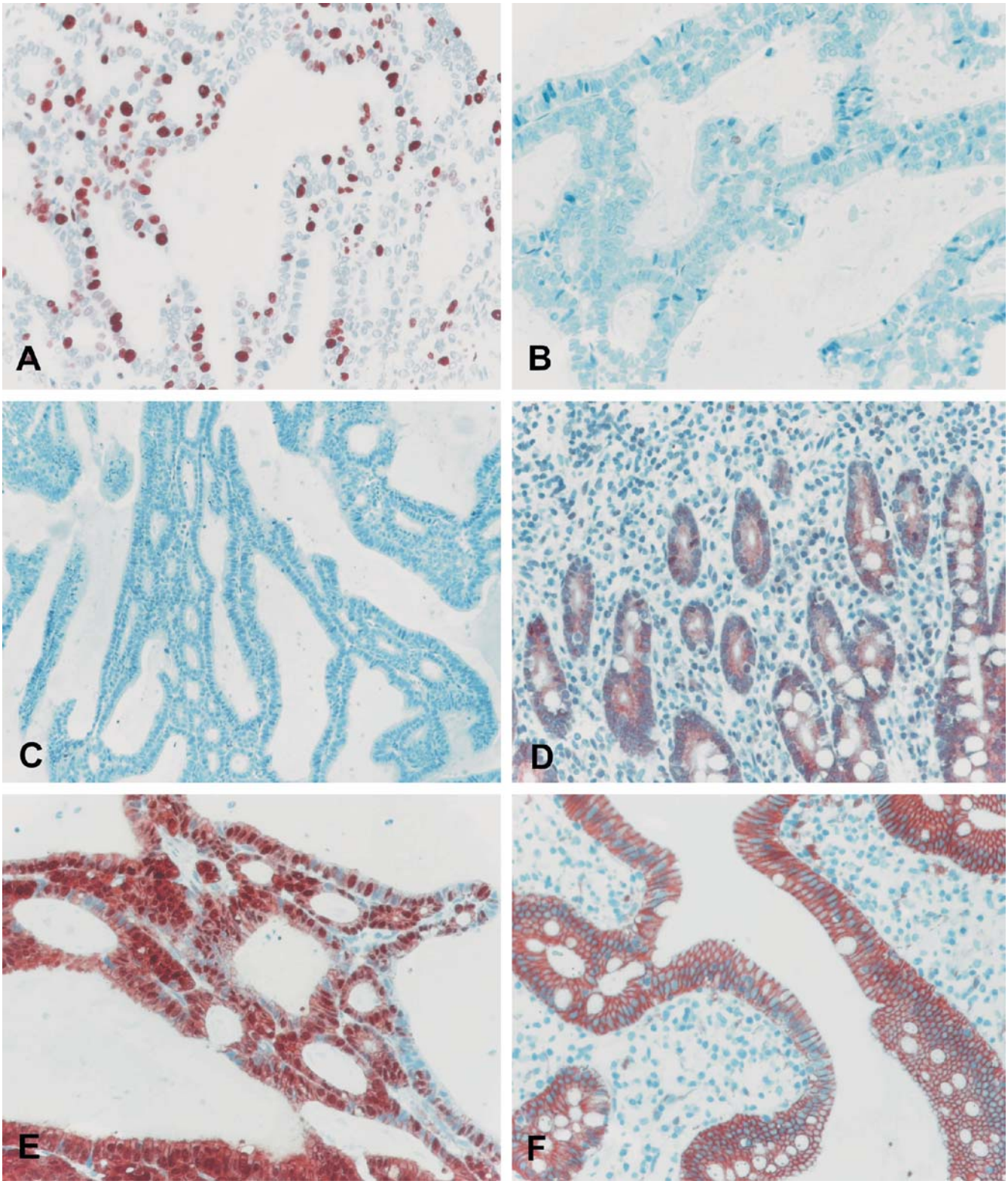

Fig. 2 **A** Immunostaining with MIB1 antibody revealed a proliferation index of about 15% (×200). **B** p53 accumulation was detected only in a small percentage (<2%) of the tumor cells (×200). **C** DPC4/SMAD4 expression was not detectable in the tumor cells (×100). **D** Cytoplasmic and nuclear staining of DPC4/SMAD4 in the surrounding normal duodenal tissue (×200). **E** β-catenin was present at the membranous, cytoplasmic and nuclear levels in the tumor cells (×200). **F** In the normal duodenal tissue, only membranous immunoreactivity of β-catenin was detected (×200)

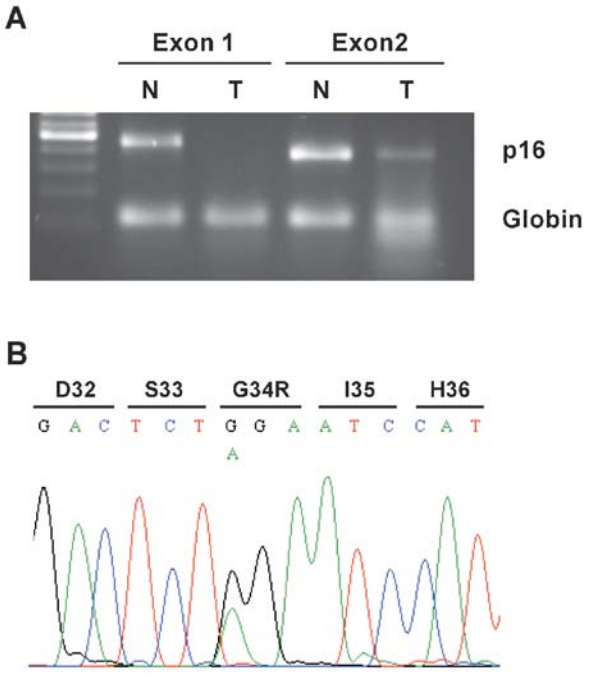

Fig. 3 **A** Deletion analysis of *p16*^{INK4A} using duplex polymerase chain reaction revealed a complete lack of exon 1 in the tumor sample (*T*), whereas the corresponding control (*N*) showed no alteration. Exon 2 was detectable in tumor and control samples. **B** Partial sequence of exon 3 of *β-catenin*, displaying a heterozygous point mutation (GGA>AGA) in codon 34, causing the amino acid substitution glycine to arginine

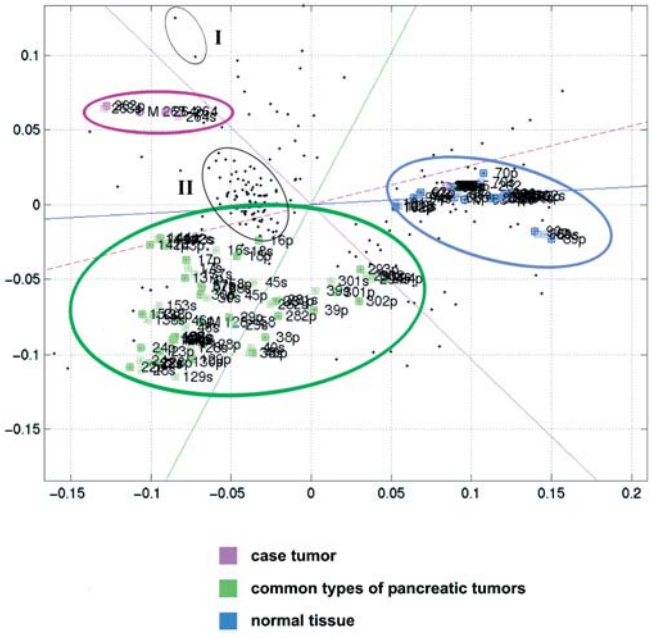

Fig. 4 Correspondence cluster analysis. In the resulting biplot, each hybridization of the RNA from an individual tissue sample is depicted as a *colored square*. Each significantly differentially transcribed gene is shown as a *black dot*. Also, several guiding lines are displayed in the diagram. They correspond to the position of virtual genes, whose transcription profiles would exhibit a signal in one condition only. Genes with insignificant changes would be positioned close to the centroid of these lines, but are not shown in the blot. The samples from the most common types of pancreatic tumors (ductal adenocarcinoma and cystic tumors) and from normal tissues form distinct clusters. The individual case reported here is clearly different from all other analyzed tissues. Two genes (group I) are the most specific ones for discriminating it from the other tumors. Alternatively, group II indicates genes that distinguish tumors from normal tissue, but do not discriminate between the tumor samples

mitochondria, prominent lysosomes and secondary lysosomes were detected. Tight junctions were seen at the border between two adjacent cells (Fig. 1D). The proliferative activity, evaluated using Ki-67 immunostaining, was moderate (15%) (Fig. 2A). Table 1 depicts the results of the immunohistochemical analysis. On the basis of the histological and immunohistochemical data, the descriptive diagnosis of a microcystic tubulopapillary carcinoma was made; however the tumor could not be assigned to any of the known types of pancreatic tumors.

Immunohistochemical and molecular profile

Only a few tumor cells (<1%) displayed positive nuclear staining for p53 (Fig. 2B). p16^{INK4A} and DPC4/SMAD4 were not expressed in the tumor cells, whereas they were normally present in the cytoplasm and nuclei of surrounding non-neoplastic duodenal tissue (Fig. 2C, D). *β*-Catenin was expressed at the membranous and cytoplasmic level in the great majority of the tumor cells; strong *β*-catenin nuclear expression was detected in about 50% of the tumor cells (Fig. 2E). In the epithelial cells of the duodenum, only membranous expression of *β*-catenin was detected (Fig. 2F).

Deletion analysis by duplex PCR revealed a complete lack of exon1 of *p16*^{INK4A} in the tumor sample (Fig. 3A). Sequencing of exon 3 of *β-catenin* showed a point mutation at codon 34 (GGA>AGA), which caused amino acid substitution of glycine with arginine (Fig. 3B). In contrast, no mutations were found in exon 1 of *k-ras*.

Microarray analysis

Transcriptional profiling analyses were performed with material obtained from ductal adenocarcinomas, pancreatic cystic tumors and normal pancreatic tissues. The samples, labeled with either Cy3 or Cy5, were analyzed in competitive hybridizations. Unspecific hybridization to non-homologous sequences did not occur, as could be seen on spots generated with unrelated control DNA fragments. After scanning and quantification of the spot intensities, data were normalized and filtered. In total, 269 PCR fragments contained a sequence that was significantly differentially transcribed in at least one of the samples analyzed. The results were subjected to correspondence cluster analysis [8]. One major advantage of this process is its ability to present the results of cluster analyses on different but corresponding factors in one plot. In Fig. 4, not only the genes (black dots), but also the

results of clustering of the individual hybridizations—and, thus, the individual tissue samples (colored squares)—are shown. Co-localization in the blot of genes and experiments/conditions is indicative of a strong association between them. In addition, virtual transcription profiles were calculated on the basis of the results and projected onto the plot. Classification by correspondence analysis resulted in the formation of two distinct clusters for common types of pancreatic tumors (ductal adenocarcinoma and cystic tumors) and normal tissues (Fig. 4). Profiling the RNA of the tumor described here, however, produced a distinct blot position. All repetitions of the analysis produced the same result, actually forming a cluster of their own in the correspondence analysis. Distances to the other tumor clusters demonstrated that the sample exhibited a significantly different transcriptional profile.

Discussion

In this report, we describe an unusual microcystic tumor of the pancreas, whose histology was characterized by a tubulopapillary architecture. The histological, immunohistochemical and molecular features of this neoplasm were found to differ from all known pancreatic tumors.

The differential diagnosis of this tumor particularly includes other cystic tumors, such as solid-pseudopapillary neoplasm, the cystic variant of acinar cell carcinoma and metastatic tumors.

According to the gross appearance of the tumor (large mass, necrotic–hemorrhagic areas, well-defined demarcation) and its occurrence in a female patient, the possibility of a solid-pseudopapillary tumor had to first be discussed. Points favoring this diagnosis included the immunohistochemical expression of β-catenin, which was found to be accompanied by a point mutation in exon 3 of the β-catenin gene [1]. However, the histological features, in particular the tubulopapillary pattern, the cytology and immunohistochemical data (such as positivity for cytokeratins and negativity for neuron-specific enolase and vimentin) were not in accordance with such a diagnosis [17].

The tubulopapillary and microcystic pattern of the carcinoma partially resembled the cystic variant of acinar cell carcinoma. This rare tumor affects men more frequently than women [14], usually reaches great dimensions and can be encapsulated [15, 25]. It contains macrocysts and microcysts with a cuboidal or cylindrical epithelial cell lining. The tumor cells express pancreatic enzymes, such as trypsin, lipase, chymotrypsin and phospholipase A2, which are useful immunohistochemical markers of acinar cell carcinoma [15]. Moreover, *β-catenin* mutations have also been reported in a small percentage of acinar cell carcinomas [2]. However, the absence of trypsin expression in our case and the absence of secretory granules, as revealed by the ultrastructural analysis, made the diagnosis of acinar cell carcinoma unlikely. In addition, the loss of DPC4/SMAD4 protein expression in the tumor cells is not a common finding in acinar cell carcinomas [2].

Other pancreatic cystic tumors (serous and mucinous tumors) as well as intraductal papillary mucinous tumors were excluded on the basis of the histopathological appearance.

Although unlikely, the possibility of a metastatic tumor was also taken into account. Secondary tumors of the pancreas are a rare event in the absence of widespread disease and can be the consequence of direct infiltration of the organ or, more frequently, of hematogenous metastasis [7]. Colon, gastric and bile duct carcinomas are the most common sources of direct infiltration of the pancreas [7, 19], whereas lung, kidney and breast cancers and melanomas are the most frequent primary tumors in cases of blood-borne metastases to the pancreas [7, 12, 28]. Metastases of renal cell carcinomas often occur as solitary lesions and are subjected to surgical resection [13, 21]. Rarely, symptoms related to the pancreatic metastases, such as jaundice or pancreatitis due to duct obstruction, have been the first clinical manifestations of an otherwise unknown primary tumor [18, 20]. In our case, there was no evidence of a neoplastic disease in the patient's history or in the results of physical, laboratory and imaging tests. Therefore, it was considered very unlikely that the pancreatic tumor mass was a metastasis. However, some additional immunostainings were performed (thyroglobulin, TTF-1, estrogen and progesterone receptors), all with negative results.

The molecular profile of pancreatic adenocarcinomas is characterized by K-*ras* mutations in codon 12. Other frequent alterations include $p16^{INK4A}$ mutations (up to 80% of the cases), p53 mutations (up to 70%) and loss of DPC4/SMAD4 expression (approximately 50%) [3]. The last two alterations lead to abnormal protein expression, so that there is a good correlation between immunohistochemical results and genetic analyses. In particular, the absence of DPC4/SMAD4 immunostaining reflects the inactivation of the corresponding gene [27]; p53 mutations often lead to nuclear accumulation of the protein, which can consequently be visualized using immunohistochemical labeling [5, 23]. The immunohistochemical and molecular analysis of this tumor revealed an unusual pattern, characterized by wild-type K-*ras*, absence of p53 overexpression, loss of DPC4/SMAD4 and deletion of exon 1 of $p16^{INK4A}$.

Transcriptional microarray analysis demonstrated that the tumor had a distinct profile when compared with other pancreatic tumor entities. Although the diagnostic utility of gene profiling techniques has already been emphasized, this is the first report demonstrating the use of microarrays in the field of diagnostic molecular pathology. In addition to the morphological, immunohistochemical and genetic results, the array data helped to define a new type of pancreatic tumor. Larger series are needed to confirm and validate the data presented here.

A last issue that needs to be discussed is the malignant potential of this tumor. The presence of nuclear pleomorphism and atypical mitotic figures, together with the

moderate proliferation index, would indicate malignancy. The extensive areas of necrosis could indicate rapid growth in the absence of suitable vascular supply, although there are no reliable data in the patient's history that could confirm this assumption. However, the expansive growth, the absence of infiltration of surrounding structures and, ultimately, the absence of lymph-node and/or distant metastases would indicate low aggressiveness and a good prognosis.

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