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CASE REPORT

Solid type clear cell carcinoma of the pancreas: differential diagnosis of an unusual case and review of the literature

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Abstract Pancreatic neoplasms have been reliably classified on the basis of their histopathology and immunophenotype. In this study, we report on a pancreatic tumor whose phenotype and genotype could not be assigned to any known tumor entity. The tumor was observed in the pancreatic head of a 54-year-old woman. It was found to be a solid infiltrating carcinoma with abundant clear cells. Apart from cytokeratin, the tumor cells expressed vimentin, S100, and MUC-1. DNA microarray analysis revealed a transcription profile clearly differing from that of normal pancreatic tissue and pancreatic ductal adenocarcinoma. Despite metastatic behavior, the tumor displayed a more favorable course than conventional pancreatic ductal adenocarcinoma. We suggest that this tumor be called solid type clear cell carcinoma of the pancreas.

Keywords Pancreatic neoplasm · Microarray · Expression profiling

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Introduction

The pancreas gives rise to a wide spectrum of neoplasms with diverse differentiation and biological behavior [33]. Systematic analyses of pancreatic tumors, advances in immunohistochemistry, and the application of additional molecular diagnostic tools such as mutation analyses or transcriptional profiling make it possible not only to classify and subclassify pancreatic tumors better but also to identify yet undescribed pancreatic tumor entities [11, 15].

We report the case of a 54-year-old woman suffering from a primary pancreatic tumor. Despite extensive morphological, immunohistochemical, and molecular analyses, this tumor could not be assigned to any known pancreatic tumor entity to date [9, 33].

Case report

A 54-year-old woman of Arabic origin presented with obstructive jaundice, a short history of abdominal discomfort, and weight loss of 5 kg within 4 weeks. She denied fever, chills, nausea, or vomiting. No exocrine or endocrine pancreatic insufficiency was noted. Her prior medical history revealed hypertension. Eighteen years ago, she had undergone open cholecystectomy for symptomatic cholecystolithiasis. The family history was negative for malignant diseases.

At the initial diagnostic workup, endoscopic retrograde cholangiopancreatography (ERCP) showed a double duct sign with dilatation of the common bile duct and the main pancreatic duct. A helical CT scan of the abdomen revealed a hypodense lesion in the pancreatic head, measuring 5 cm in largest diameter. There was no evidence of liver metastases or other primary or secondary tumors outside the pancreas. Tumor markers CEA and CA19-9 were within normal limits.

The tumor was completely resected via a partial pancreaticoduodenectomy (classical Whipple procedure). Histopathologically, the resected tumor was staged pT3 pN0. The postoperative course was uneventful, and the patient was discharged from the hospital without adjuvant treatment. After an asymptomatic period of 1 year, routine follow-up CT scan detected three new masses located in segment 5 of the liver (1.2 and 3.5 cm in largest diameter; Fig. 1) and in the right lower lobe of the lung (1.1 cm). After an explorative laparotomy and confirmation of metastases of the primary pancreatic tumor by frozen section, the masses were resected performing an extended right hemihepatectomy and a wedge resection of the right lower lobe of the lung. After another disease-free period of 2 years, further routine follow-up revealed a 5-cm abdominal mass. Again, the patient underwent an explorative laparotomy, now showing a mass adhering to the right colon flexure and the small bowel. A complete surgical resection of the tumor was achieved by performing a right hemicolectomy and segmental resection of the ileum. After another disease-free interval of 2 years, the patient presented with weight loss and abdominal discomfort. A CT scan of the abdomen revealed diffuse liver metastases and local recurrence in the right abdomen with infiltration of the right renal vein. Currently, 4 years after the initial diagnosis, the patient is still alive, although with disease.

Materials and methods

Histology and immunohistochemistry

For histological examination, sections obtained from formalin-fixed, paraffin-embedded tumor tissue were stained with hematoxylin and eosin (H and E) and periodic acid-Schiff (PAS). Immunohistochemical analyses were carried out with primary antibodies directed against pancytokeratins (KL-1; 1:20; Immunotech), cytokeratins 5/6 (1:25; Dako, Carpenteria, CA), cytokeratin 7 (1:50; Dako), cytokeratin 8 (1:100; Dako), cytokeratin 18 (1:10; Dako), cytokeratin 19 (1:50; Dako), cytokeratin 20 (1:20; Dako), p53 (1:100; Dako), DPC/SMAD4 (1:50; Santa Cruz Biotechnology, Santa Cruz, CA), β-catenin (1:200; BD Transduction Laboratories, Lexington, KY), epidermal growth factor receptor (EGFR; 1:50; Zymed Laboratories, Invitrogen, Carlsbad, CA), estrogen receptor (1:50; Dako), progesterone receptor (1:50; Dako), synaptophysin (1:2; BioGenex, San Ramon, CA), chromogranin A (1:2; Histoprime), neuron specific enolase (1:5; Histoprime), vimentin (1:1,000; Dako), actin (1:2; Enzo Diagnostics), desmin (1:2; Linaris), HMB-45 (undiluted, Enzo Diagnostics), LCA (1:5; Immunotech, Beckman Coulter, Fullerton, CA), melan A (1:25; Dako), alpha-1-fetoprotein (1:100; Dako), OCH1E5 (1:50; Dako), CD56 (1:50; Novocastra Laboratories, Newcastle upon Tyne, UK), S100 protein (1:300; Dako), MUC-1 (1:100; Novocastra, Newcastle, UK), CD99 (1:20; WAK-Chemie), trypsin (1:500; Ventrex Laboratories, Portland, OR), alpha-amylase (1:150; Gene Tex, San Antonio, TX), and WT1 (1:50; Dako), using the avidin–biotin–complex method. If necessary, antigen retrieval was achieved by microwave pretreatment in citrate buffer (p53, Smad4, β-catenin, estrogen and progesterone receptors, cytokeratin 20, OCH1E5) or in ethylenediaminetetraacetic acid (EDTA) buffer (cytokeratin 5/6) or by pronase digestion (EGFR, S100) of the slides.

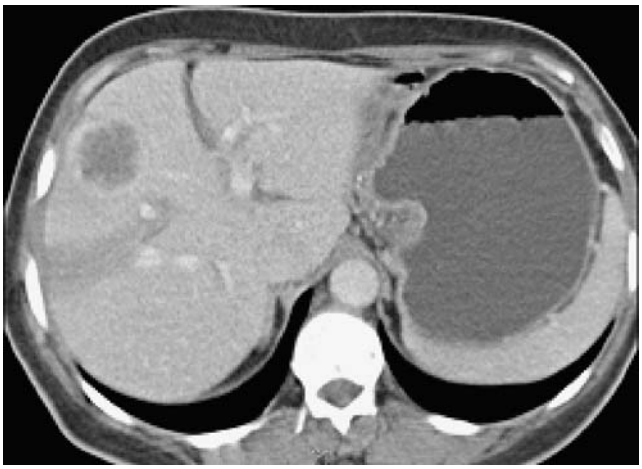

Fig. 1 Helical CT scan of the abdomen showing a metastasis in segment 5 of the liver. The tumor displayed in this figure was resected performing a right hemihepatectomy

Molecular analyses

For mutation analyses of exon 1 of *K-ras* and exon 3 of *β-catenin*, genomic DNA was extracted and amplified by polymerase chain reaction (PCR), using standard protocols. The following primers were used: *K-ras* 1F: 5′-GTG TGA CAT GTT CTA ATA TAG TCA-3′; *K-ras* 1R: 5′-GAA TGG TCC TGC ACC AGT AA-3′;*β-cat* 3 F: 5′-GGA GTT GGA CAT GGC CAT GG-3′; *β-cat* 3R: 5′-CCT GTT CCC ACT CAT ACA GG-3′. After purification, the PCR products were bidirectionally sequenced on an ABIPrism 377 DNA sequencer (Applied Biosystems, Foster City, CA, USA), using the BigDye Termination kit (Applied Biosystems).

For analysis of the SYT-SSX1/2 fusion transcript, total RNA was extracted using standard protocols. Reverse transcriptase PCR was performed using the following primers: FP (SYT) 5′-CCAGCGAGGCCTTATGGATA-3′ and RP (SSX): 5′-TTTGTGGGCCAGATGCTTC-3′.

DNA microarrays

In total, 3,872 human complementary DNAs (cDNAs) representing genes that are of relevance to pancreatic cancer were selected [7, 14]. Amino-modified PCR products were arrayed onto slides with an epoxy surface (Epoxy Slides,

Quantifoil Micro Tools, Jena, Germany) with a Micro-Arrayer from Engineering Services (Virtek's arrayer system, BioRad, Munich, Germany).

Transcriptional profiling

Total RNA was extracted with guanidine isothiocyanate from snap-frozen pancreatic tissues, including ten normal pancreas samples and five pancreatic ductal adenocarcinomas. 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. To prevent bias caused by preferential label incorporation into particular sequences, the dyes were swapped between hybridizations. Hybridization was done under glass coverslips at 62°C overnight. After washing in 0.1× sodium saline citrate, fluorescence signals were detected on a confocal ScanArray 5000 scanner (Packard BioChip Technologies, Billerica, MA). Quantification of the signal intensities was performed with the GenePix Pro 4.1 software (Axon Instruments, Union City, CA).

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 7,800 hybridization experiments are currently stored (http://www.mchips.org) [12, 13]. 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 [8]. Correspondence analysis [12] is an explorative computational method for the study of associations between variables, such as genes and hybridizations, in a multidimensional space. It simultaneously displays data for two or more variables in a low-dimensional projection, thus revealing associations between them. The closer the positional location in the blot, the higher is the degree of correspondence, enabling better data interpretation.

Results

Pathomorphological, immunohistochemical, and molecular findings

At gross examination, the primary pancreatic tumor, measuring 5 cm in largest diameter, displayed a well-circumscribed, firm, homogeneously white to yellowish cut surface without cystic changes. Microscopically, the tumor consisted of round to oval cells with large nuclei and eosinophilic or clear cytoplasm (Fig. 2), the latter being found in approximately 70 to 80% of the cells. The tumor cells were predominantly arranged in solid sheets, intermingled with abundant fibrovascular stalks. Focally, the tumor both displayed trabecular and acinar-like growth patterns. PAS staining did not reveal any cytoplasmatic granules.

Microscopically, the tumor had poorly defined margins and infiltrated the peri-pancreatic fatty tissue and the duodenal wall. Invasion of blood vessels was not seen. There were no regional lymph node metastases.

Immunohistochemically, the tumor cells displayed strong and diffuse staining reactions for pancytokeratin (KL1), cytokeratin 18, β-catenin (membrane bound), and EGFR (in 80% of the tumor cells). Staining for DPC4/SMAD4 was positive but rather weak in comparison with non-neoplastic tissue, the latter displaying strong and diffuse positivity. Focal positive staining reactions were observed for cytokeratin 7, cytokeratin 8, S100, MUC-1, and vimentin, whereas no staining was detected for cytokeratins 5/6, 19, and 20, trypsin, alpha-amylase, actin, desmin, progesterone receptor, estrogen receptor, lymphocytic common antigen, melan A, HMB-45, alpha-1-fetoprotein, CD99, OCH1E5, WT1, and the neuroendocrine markers synaptophysin, chromogranin A, CD56, and neuron-specific enolase. There was no nuclear accumulation of p53 (Table 1).

Molecular analyses revealed wild-type copies of exon 1 of *K-ras* and of exon 3 of *β-catenin*. A SYT-SSX1/2 fusion transcript was not detected.

The resected metastases (liver, lung, and abdominal cavity) showed comparable gross, microscopic, and immunohistochemical characteristics as the primary pancreatic tumor. The resection specimen of the primary tumor as well as the resection specimens of the metastases displayed resection margins free of tumor.

Based on these findings, the working diagnosis of a well-differentiated clear cell carcinoma with unusual expression of vimentin, S100, and MUC-1 was established.

Microarray analysis

Gene expression profiles were generated using high-density DNA microarrays with 3,872 human genes that had been identified to be tumor-associated [7]. The samples obtained from pancreatic ductal adenocarcinomas and normal pancreatic tissues, labeled with either Cy3 or Cy5, were analyzed in competitive hybridizations.

After scanning and quantification of the spot intensities, data were normalized and filtered. In total, 168 PCR fragments contained sequences that were significantly

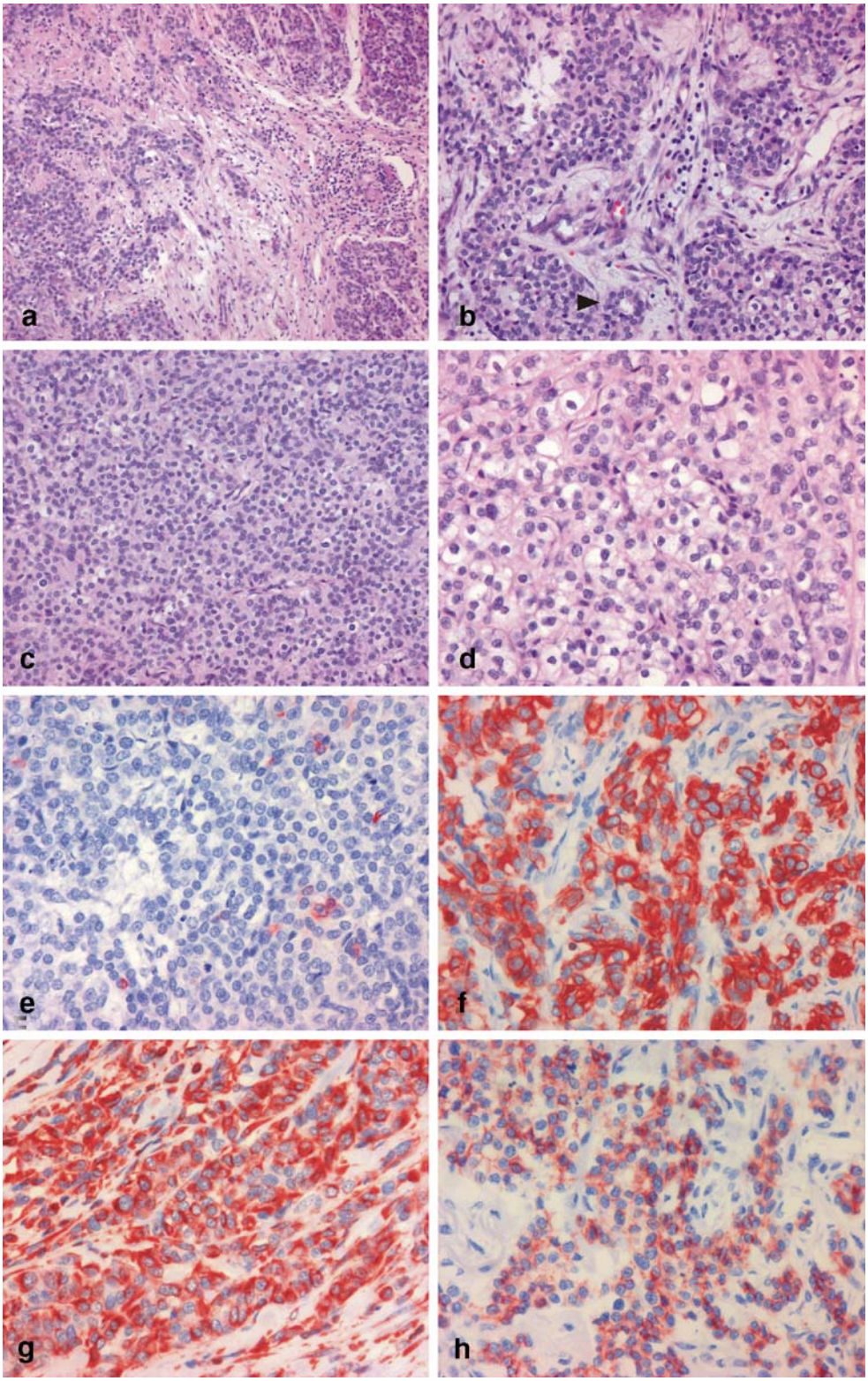

Fig. 2 Histomorphological and immunohistochemical findings. Microscopically, the tumor displayed round to oval cells (**a**–**c**; H and E) that frequently displayed clear cytoplasm (**d**). The tumor cells were predominantly arranged in solid sheets, intermingled by fibrovascular stalks (**b**). Focally, acinar-like formations were seen (**b**, *arrowhead*). The tumor borders were microscopically ill defined (**a**). Immunohistochemically, the tumor cells showed focal positivity for cytokeratin 7 (*staining red*; **e**), diffuse positivity for cytokeratin 18 (**f**), membranous positivity for β-catenin (**g**), and diffuse positivity for vimentin (**h**). Original magnifications: ×32 (**a**), ×64 (**b** and **c**), ×102 (**d**–**h**)

differentially transcribed in at least one of the samples analyzed. The results were subjected to correspondence cluster analysis [4], which is an explorative computational method for the investigation of associations between variables, such as genes and hybridizations, in a multidimensional space. It simultaneously displays data for two (or more) variables in a low-dimensional projection, thus revealing associations between them.

In Fig. 3, not only the differentially transcribed genes (gray dots) but also the results of clustering of the

Table 1 Tested immunohistochemical markers

Immunohistochemical marker	Result
Actin	−
Alpha-amylase	−
Alpha-1-fetoprotein	−
β-catenin	+[a]
CD56	−
CD99	−
CEA	−
Chromogranin A	−
CK5/6	−
CK7	+[b]
CK8	+[b]
CK18	+
CK19	−
CK20	−
c-Kit	−
Desmin	−
EGFR	+[a]
Estrogen receptor	−
HMB-45	−
Lymphocytic common antigen	−
Melan A	−
MUC-1	+[b]
Neuron-specific enolase	−
OCH1E5	−
Pancytokeratin (KL1)	+
Progesterone receptor	−
p53	−
Synaptophysin	−
S-100	+[b]
Trypsin	−
Vimentin	+[b]
WT1	−

(*Plus sign*) positive staining, (*minus sign*) no staining
[a] Membrane positivity
[b] Focal positivity

individual hybridizations—and, thus, the individual tissue samples (colored squares)—are shown. Co-localization of genes and individual experiments are indicative of a strong association between them.

As is apparent from Fig. 3, the transcript profiles permitted an accurate classification of normal pancreatic tissue (cluster I, red circle) and pancreatic ductal adenocarcinoma (cluster II, blue squares). Profiling the RNA of the patient's tumors described here produced a novel distinct blot position (cluster III, green squares; cluster IV, turquoise squares; cluster V, pink squares). Cluster III represents the patient's primary pancreatic tumor, cluster IV the liver metastasis, and cluster V the abdominal metastasis. 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 cluster demonstrated that the samples exhibited a significantly different transcriptional profile. The distribution of clusters II–V is highlighted by circles.

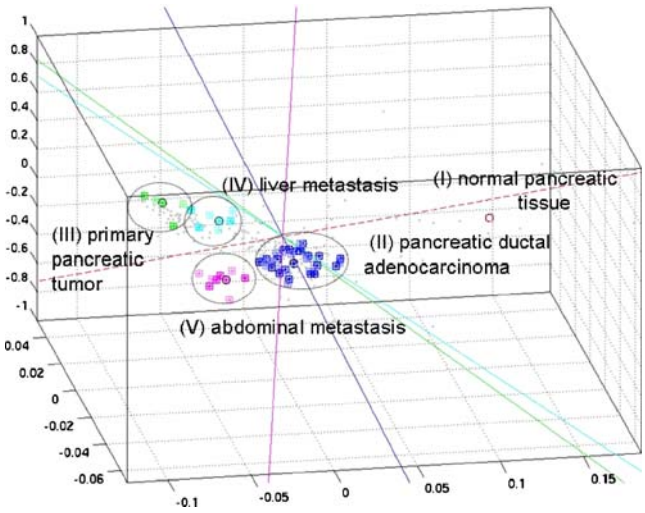

Fig. 3 Cluster analysis. Correspondence cluster analysis of transcript profiles made from normal pancreatic tissue (cluster I, *red circle*), pancreatic ductal adenocarcinomas (cluster II, *blue squares*), and tumors described here (clusters III–V). In the resulting bi-plot, each hybridization of an individual sample is depicted as a *colored square*. Genes that exhibited significantly differential transcription levels are shown as *gray dots*. The closer the co-localization of two spots (both genes and tumors), the higher is the degree of association between them. As a control, normal pancreatic tissue was used (cluster I, *red circle*). As all other experiments were compared to this control, only the center of gravity of all normal tissue samples is shown rather than individual experiments. Cluster II (*blue squares*) is made of pancreatic ductal adenocarcinomas. Cluster III represents the patient's primary pancreatic tumor (*green squares*), cluster IV the liver metastasis (*turquoise squares*), and cluster V the abdominal metastasis (*pink squares*). The distribution of clusters II–V is highlighted by *circles*

Additional immunohistochemical analysis

For verification of the microarray analysis, additional immunohistochemical analysis was carried out for two genes (fibronectin and vitronectin). Transcriptional microarray analysis showed a strong difference in fibronectin expression between the tumor and normal pancreatic tissue. Therefore, we performed immunohistochemical stainings against fibronectin and vitronectin to confirm the results of the microarray analysis. The patient's pancreatic tumors showed a massive increase in the expression of both fibronectin and vitronectin when compared with normal pancreatic tissue. The differences in fibronectin expression of the patient's primary pancreatic tumor in comparison to normal pancreatic tissue are displayed in Fig. 4.

Discussion

We report the clinicopathological, immunohistochemical, and molecular findings of a malignant pancreatic tumor that could

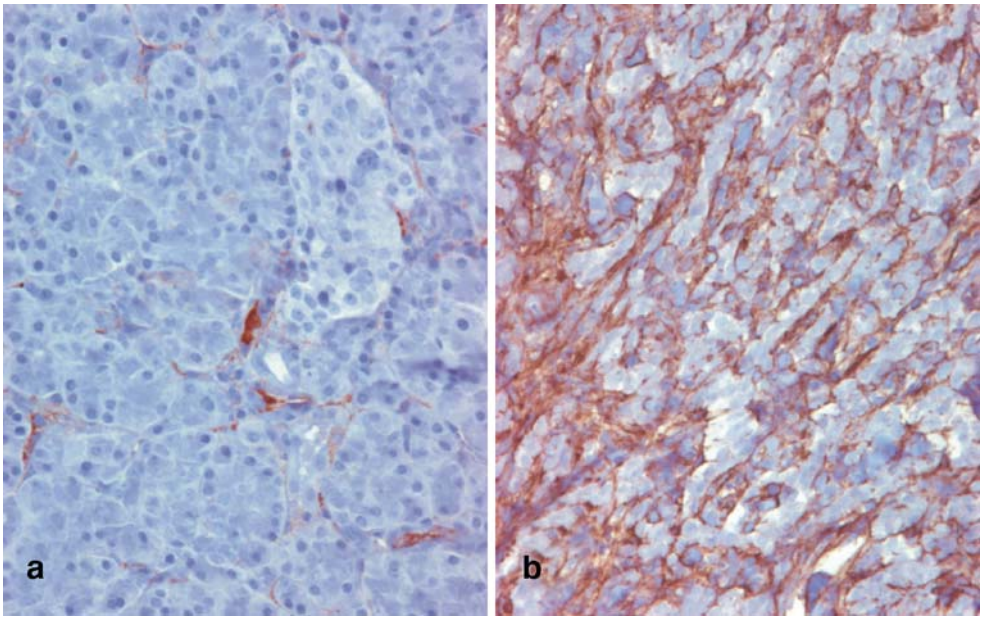

Fig. 4 Verification of gene transcription data by immunohistochemistry: Normal pancreas showed rather weak and focal expression of fibronectin (**a**; *brownish staining*), whereas strong expression was seen in the patient's primary pancreatic tumor (**b**). Original magnification: ×102

not be assigned to any known pancreatic tumor entity [16, 33]. The predominantly solid growth pattern and clear cell features displayed by this tumor are frequent findings in endocrine pancreatic neoplasms. Nevertheless, the present tumor lacked the expression of neuroendocrine markers and, therefore, did not qualify for this diagnosis [10].

Some endocrine neoplasms of the pancreas display a morphologic overlap with acinar cell carcinoma [28]. This might be due to a common cell of origin, which to date has not been identified [28]. Focal acinar-like differentiation and the strong immunohistochemical expression of cytokeratin 18 suggested the diagnosis of an acinar cell carcinoma [2, 18, 19]. However, this diagnosis was rejected because the tumor did not show any expression of the pancreatic enzymes trypsin and amylase.

Due to the relatively young age and female gender of the patient, a solid pseudopapillary neoplasm had to be considered for differential diagnosis [1]. Recently, a clear cell variant of this tumor entity has been described [3]. Although solid pseudopapillary neoplasms usually present a benign clinical course, a few cases of an aggressive variant have been reported [35, 36]. However, the lack of any cystic or pseudopapillary histomorphological features, and the immunohistochemical profile of the tumor, in particular the lack of expression of neuron-specific enolase and the membrane-bound expression of β-catenin, were not in accordance with the diagnosis of solid pseudopapillary neoplasms. Furthermore, the present tumor displayed a wild-type genotype of β-catenin, whereas solid pseudopapillary neoplasms characteristically display point mutations in exon 3 of this gene [1, 21].

Ductal adenocarcinoma is by far the most common primary tumor of the pancreas. As a variant, few cases of a clear cell ductal adenocarcinoma have been described [23, 29]. As in the present case, some of these tumors were found to display solid arrangements of clear cell tumor cells. *K-ras* mutation analyses were obtained in two of these cases, both revealing point mutations in codon 12, a finding that could not be reproduced for the present case. Other frequent alterations include p53 mutations (up to 70%) and DPC4/SMAD4 mutations (approximately 50%) [38], leading to abnormal protein expression. p53 mutations can result in nuclear accumulation of p53 [32]. The DPC4/SMAD4 tumor-suppressor gene can be inactivated either by intragenic mutation in one allele coupled with loss of the other allele (loss of heterozygosity) or deletion of both alleles (homozygous deletion) [20]. In our case, however, there was no evidence for a mutation in the p53 gene or loss of DPC4/SMAD4 expression. Immunohistochemical labeling showed diffuse DPC4/SMAD4 expression but no nuclear accumulation of p53. Because there is a good correlation between immunohistochemical labeling and genetic analysis [28], alterations in the p53 gene and DPC4/SMAD4 gene were deemed very unlikely. Although the present tumor displayed some features of pancreatic ductal adenocarcinoma such as expression of EGFR [22], the immunohistochemical staining pattern for cytokeratins (only scarce positivity for cytokeratins 7 and 8 and negativity for cytokeratin 19) did not match the diagnosis of ductal adenocarcinoma [38]. Furthermore, transcriptional profiling revealed strong evidence for a tumor that significantly differed from ductal adenocarcinoma.

The tumor's clear cell morphology and immunohistochemical positivity for cytokeratin, vimentin, and S100 suggested the possibility of a myoepithelial carcinoma (malignant myoepithelioma). This tumor represents approximately 1% of salivary gland tumors, most frequently affecting the parotid gland [26, 31], and is rarely found to

arise from submucosal bronchial glands [25]. For the present case, the diagnosis of myoepithelial carcinoma became unlikely because it lacked expression of actin, which is seen in up to 80% of myoepithelial carcinomas [26, 31], and because it lacked the expression of the myoepithelial marker cytokeratin 5/6.

On rare occasions, the pancreas gives rise to mesenchymal tumors [5, 24]. Due to the clear cell morphology and the strong expression of vimentin, the differential diagnosis of a synovial sarcoma was taken into account. However, lack of expression of the immunohistochemical marker CD99 and of the SYT/SSX172 fusion transcript made the diagnosis improbable.

Finally, the possibility of a metastasis to the pancreas was taken into account. Metastases in the pancreas have been described for various tumors, including renal cell carcinoma, breast carcinoma, colon carcinoma, malignant melanoma, and sarcoma [37]. Although metastases in the pancreas usually occur as part of disseminated disease, large autopsy series have described the prevalence of solitary pancreatic metastasis to be as high as 6 to 11% [9, 17, 27, 30, 34, 39]. However, clinical investigation failed to detect any extra-pancreatic primary tumor in our patient. In some cases, lack of detection of a primary tumor may be due to spontaneous tumor regression. This phenomenon has been described for malignant melanoma, including few cases of occult primary tumors and solitary pancreatic metastases [6]. However, malignant melanoma was excluded by immunohistochemical analyses.

In summary, the case described in this report represents a primary pancreatic tumor with histomorphological, immunohistochemical, and molecular features that cannot be assigned to any known pancreatic or extra-pancreatic tumor entity. We propose that this tumor be called solid type clear cell carcinoma of the pancreas.

References

1. Abraham SC, Klimstra DS, Wilentz RE, Yeo CJ, Conlon K, Brennan M, Cameron JL, Wu TT, Hruban RH (2002) Solid pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. Am J Pathol 160:1361–1369
2. Abraham SC, Wu TT, Hruban RH, Lee JH, Yeo CJ, Conlon K, Brennan M, Cameron JL, Klimstra DS (2002) Genetic and immunohistochemical analysis of pancreatic acinar cell carcinoma: frequent allelic loss on chromosome 11p and alterations in the APC/beta-catenin pathway. Am J Pathol 160:953–962
3. Albores-Saavedra J, Simpson K, Bilello SJ (2006) The clear cell variant of solid pseudopapillary tumor of the pancreas: a previously unrecognized pancreatic neoplasm. Am J Surg Pathol 30:1237–1242
4. Beissbarth T, Fellenberg K, Brors B, Arribas-Prat R, Boer J, Hauser NC, Scheideler M, Hoheisel JD, Schutz G, Poustka A, Vingron M (2000) Processing and quality control of DNA array hybridization data. Bioinformatics 16:1014–1022
5. Bergmann F, Hackert T, Mechtersheimer G, Penzel R, Bläker H, Berger I, Esposito I, Büchler MW, Otto HF (2004) Differential diagnosis of non-epithelial tumors of the pancreas: malignant non-epithelial pancreatic tumor with focal pigmentation. Virchows Arch 444:190–193
6. Bianca A, Carboni N, Di Carlo V, Falleni M, Ferrero S, Liverani C, Staudacher C, Turra G, Vergani D, Zerbi A (1992) Pancreatic malignant melanoma with occult primary lesion. A case report. Pathologica 84(1092):531–537
7. Brandt R, Grützmann R, Bauer A, Jesnowski R, Ringel J, Löhr M, Pilarsky C, Hoheisel JD (2004) DNA microarray analysis of pancreatic malignancies. Pancreatology 4:587–597
8. Brazma A, Hingamp P, Quackenbush J, Sherlock G, Spellman P, Stoeckert C, Aach J, Ansorge W, Ball CA, Causton HC, Gaasterland T, Glenisson P, Holstege FC, Kim IF, Markowitz V, Matese JC, Parkinson H, Robinson A, Sarkans U, Schulze-Kremer S, Stewart J, Taylor R, Vilo J, Vingron M (2001) Minimum information about a microarray experiment (MIAME)—toward standards for microarray data. Nat Genet 29:365–371
9. Cubilla A, Fitzgerald P (1984) Tumors of the exocrine pancreas. Atlas of tumor pathology. Armed Forces Institute of Pathology, Washington, DC
10. Eriksson B, Oberg K (2000) Neuroendocrine tumors of the pancreas. Br J Surg 87:129–131
11. Esposito I, Bauer A, Hoheisel JD, Kleeff J, Friess H, Bergmann F, Rieker RJ, Otto HF, Klöppel G, Penzel R (2004) Microcystic tubulopapillary carcinoma of the pancreas: a new tumor entity? Virchows Arch 444:447–453
12. Fellenberg K, Hauser NC, Brors B, Neutzner A, Hoheisel JD, Vingron M (2001) Correspondence analysis applied to microarray data. Proc Natl Acad Sci USA 98:10781–10786
13. Fellenberg K, Hauser NC, Brors B, Hoheisel JD, Vingron M (2002) Microarray data warehouse allowing for inclusion of experiment annotations in statistical analysis. Bioinformatics 18:423–433
14. Friess H, Ding J, Kleeff J, Fenkell L, Rosinski JA, Guweidhi A, Reidhaar-Olson JF, Korc M, Hammer J, Büchler MW (2003) Microarray-based identification of differentially expressed growth- and metastasis-associated genes in pancreatic cancer. Cell Mol Life Sci 60:1180–1199
15. Grützmann R, Foerder M, Alldinger I, Staub E, Brummendorf T, Ropcke S, Li X, Kristiansen G, Jesnowski R, Sipos B, Löhr M, Lüttges J, Ockert D, Klöppel G, Saeger HD, Pilarsky C (2003) Gene expression profiles of microdissected pancreatic ductal adenocarcinoma. Virchows Arch 443:508–517
16. Hamilton SR, Aaltonen LA (eds) (2000) World health organization classification of tumours. Pathology and genetics of tumors of the digestive system. IARC, Lyon
17. Hiotis SP, Klimstra DS, Conlon KC, Brennan MF (2002) Results after pancreatic resection for metastatic lesions. Ann Surg Oncol 9:675–679
18. Holen KD, Klimstra DS, Hummer A, Gonen M, Conlon K, Brennan M, Saltz LB (2002) Clinical characteristics and outcomes from an institutional series of acinar cell carcinoma of the pancreas and related tumors. J Clin Oncol 20:4673–4678
19. Hoorens A, Lemoine NR, McLellan E, Morohoshi T, Kamisawa T, Heitz PU, Stamm B, Ruschoff J, Wiedenmann B, Kloppel G (1993) Pancreatic acinar cell carcinoma. An analysis of cell lineage markers, p53 expression, and K-ras mutation. Am J Pathol 143:685–698
20. Hruban RH, Offerhaus GJA, Kern SE, Goggins M, Wilentz RE, Yeo CI (1998) Tumor-suppressor genes in pancreatic cancer. J Hepato Biliary Pancreatic Surgery 5:383–391
21. Kosmahl M, Seada LS, Janig U, Harms D, Klöppel G (2000) Solid-pseudopapillary tumor of the pancreas: its origin revisited. Virchows Arch 436:473–480
22. Lemoine NR, Hughes CM, Barton CM, Poulsom R, Jeffery RE, Klöppel G, Hall PA, Gullick WJ (1992) The epidermal growth factor receptor in human pancreatic cancer. J Pathol 166:7–12

23. Lüttges J, Vogel I, Menke M, Henne-Bruns D, Kremer B, Klöppel G (1998) Clear cell carcinoma of the pancreas: an adenocarcinoma with ductal phenotype. Histopathology 32:444–448
24. Lüttges J, Mentzel T, Hubner G, Klöppel G (1999) Solitary fibrous tumour of the pancreas: a new member of the small group of mesenchymal pancreatic tumours. Virchows Arch 435:37–42
25. Miura K, Harada H, Aiba S, Tsutsui Y (2000) Myoepithelial carcinoma of the lung arising from bronchial submucosa. Am J Surg Pathol 24:1300–1304
26. Nagao T, Sugano I, Ishida Y, Tajima Y, Matsuzaki O, Konno A, Kondo Y, Nagao K (1998) Salivary gland malignant myoepithelioma. A clinicopathologic and immunohistochemical study of ten cases. Cancer 83:1292–1299
27. Nakamura E, Shimizu M, Itoh T, Manabe T (2001) Secondary tumors of the pancreas: clinicopathological study of 103 autopsy cases of Japanese patients. Pathol Int 51:686–690
28. Ohike N, Kosmahl M, Klöppel G (2004) Mixed acinar–endocrine carcinoma of the pancreas. A clinicopathological study and comparison with acinar-cell carcinoma. Virchows Arch 445:231–235
29. Ray S, Lu Z, Rajendiran S (2004) Clear cell ductal adenocarcinoma of pancreas: a case report and review of the literature. Arch Pathol Lab Med 128:693–696
30. Robbins EG II, Franceschi D, Barkin JS (1996) Solitary metastatic tumors to the pancreas: a case report and review of the literature. Am J Gastroenterol 91:2414–2417
31. Savera AT, Sloman A, Huvos AG, Klimstra DS (2000) Myoepithelial carcinoma of the salivary glands: a clinicopathologic study of 25 patients. Am J Surg Pathol 24:761–774
32. Scarpa A, Capelli P, Mukai K, Zamboni G, Oda T, Iacono C, Hirohashi S (1993) Pancreatic adenocarcinomas frequently show p53 gene mutations. Am J Pathol 142:1534–1543
33. Solcia E, Capella C, Klöppel G (1997) Tumors of the pancreas. Atlas of tumor pathology. Armed Forces Institute of Pathology, Washington, DC
34. Stamm BH (1984) Incidence and diagnostic significance of minor pathologic changes in the adult pancreas at autopsy: a systematic study of 112 autopsies in patients without known pancreatic disease. Hum Pathol 15:677–683
35. Takahashi Y, Hiraoka N, Onozato K, Shibata T, Kosuge T, Nimura Y, Kanai Y, Hirohashi S (2006) Solid-pseudopapillary neoplasms of the pancreas in men and women: do they differ? Virchows Arch 448:561–569
36. Tang LH, Aydin H, Brennan MF, Klimstra DS (2005) Clinically aggressive solid pseudopapillary tumors of the pancreas: a report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. Am J Surg Pathol 29:512–519
37. Thompson LD, Heffess CS (2000) Renal cell carcinoma to the pancreas in surgical pathology material. Cancer 89:1076–1088
38. Wilentz RE, Su GH, Dai JL, Sparks AB, Argani P, Sohn TA, Yeo CJ, Kern SE, Hruban RH (2000) Immunohistochemical labeling for dpc4 mirrors genetic status in pancreatic adenocarcinomas: a new marker of DPC4 inactivation. Am J Pathol 156:37–43
39. Z'Graggen K, Fernandez-del Castillo C, Rattner DW, Sigala H, Warshaw AL (1998) Metastases to the pancreas and their surgical extirpation. Arch Surg 133:413–417