Modern Pathology (2015) 28, 248–260

Pancreatic undifferentiated rhabdoid carcinoma: *KRAS* alterations and SMARCB1 expression status define two subtypes

Abbas Agaimy[1], Florian Haller[1], Judith Frohnauer[1], Inga-Marie Schaefer[2,3], Philipp Ströbel[3], Arndt Hartmann[1], Robert Stoehr[1] and Günter Klöppel[4]

[1]Institute of Pathology, University Hospital of Erlangen, Erlangen, Germany; [2]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Institute of Pathology, University Medical Center, Göttingen, Germany and [4]Department of Pathology, Technical University of München, München, Germany

Pancreatic undifferentiated carcinoma is a heterogeneous group of neoplasms, including pleomorphic giant cell, sarcomatoid, round cell, and rhabdoid carcinomas, the molecular profiles of which have so far been insufficiently characterized. We studied 14 undifferentiated carcinomas with prominent rhabdoid cells, occurring as advanced tumors in seven females and seven males aged 44–96 years (mean: 65 years). Histologically, 10 tumors qualified as pleomorphic giant cell and 4 as monomorphic anaplastic carcinomas. A glandular component, either in the primary or in the metastases, was seen in 5 out of 14 tumors (4 out of 10 pleomorphic giant cell and 1 out of 4 monomorphic anaplastic subtypes, respectively). Osteoclast-like giant cells were absent. Immunohistochemistry revealed coexpression of cytokeratin and vimentin, and loss of membranous β-catenin and E-cadherin staining in the majority of cases. Nuclear SMARCB1 (INI1) expression was lost in 4 out of 14 cases (28%), representing all 4 tumors of the monomorphic anaplastic subtype. FISH and mutation testing of *KRAS* revealed *KRAS* amplification in 5 out of 13 (38%) and exon 2 mutations in 6 out of 11 (54%) successfully analyzed cases. A strong correlation was found between *KRAS* alterations (mutation and/or copy number changes) and intact SMARCB1 expression (7 out of 8; 87%). On the other hand, loss of SMARCB1 expression correlated with the absence of *KRAS* alterations (3 out of 5 cases; 60%). The results suggest that rhabdoid phenotype in pancreatic undifferentiated rhabdoid carcinomas has a heterogeneous genetic background. SMARCB1 loss is restricted to the anaplastic monomorphic subtype and correlates with the absence of *KRAS* alterations, whereas the pleomorphic giant cell subtype is characterized by *KRAS* alterations and intact SMARCB1 expression. Recognition and appropriate subtyping of these rare variants might become necessary for future therapeutic strategies.
Modern Pathology (2015) **28,** 248–260; doi:10.1038/modpathol.2014.100; published online 8 August 2014

Neoplasms with rhabdoid features occur in diverse organs. Their hallmark is 'rhabdoid cells' containing eosinophilic paranuclear cytoplasmic filamentous inclusions of intermediate filaments that displace the nucleus to the cell periphery.[1,2] Usually, these neoplasms, most of which occur in childhood, are also anaplastic, co-express cytokeratin and vimentin and are highly aggressive.[3] In the pancreas, neoplasms with rhabdoid features have been reported under different names (pleomorphic adenocarcinoma, pleomorphic carcinoma, pleomorphic giant cell carcinoma, sarcomatoid carcinoma, anaplastic carcinoma),[4–8] but have generally been included in the category of undifferentiated carcinomas, that are considered to be variants of ductal adenocarcinoma.[9–12] The term 'rhabdoid' was first applied to a pancreatic tumor by Nishihara in 1997.[13] Since then, six other cases using this term have been reported.[14–19] The fact that only some of the undifferentiated carcinomas exhibit rhabdoid cells, and the notion that many reports describe not only neoplasms with anaplastic giant cell features, but also carcinomas with a sarcomatoid spindle cell appearance are strong arguments that the category of undifferentiated carcinomas of the pancreas

Correspondence: Professor A Agaimy, MD, Pathologisches Institut, Universitätsklinikum Erlangen, Krankenhausstrasse 8-10, Erlangen 91054, Germany.
E-mail: abbas.agaimy@uk-erlangen.de
Received 10 April 2014; revised 30 May 2014; accepted 18 June 2014; published online 8 August 2014

includes a spectrum of morphologies that are probably of heterogeneous nature.

SMARCB1 is a member of the chromatin remodeling complex SWI/SNF located at chromosome 22q11.2, which probably functions as a tumor-suppressor gene.[20] Its gene product SMARCB1 (INI-1) is ubiquitously expressed in all normal human tissue types and in all neoplasms with intact *SMARCB1* locus.[20] In several tumor types, rhabdoid cell morphology has been associated with complete loss of nuclear SMARCB1 as a result of deletions/mutations involving the *SMARCB1* locus.[21,22] However, the concept of 'rhabdoid neoplasms' as uniform and specific entities has been challenged by the occurrence of similar cell types in otherwise differentiated neoplasms ('composite rhabdoid tumors'), which only rarely showed chromosome 22q (*SMARCB1*) alterations.[23,24] The increasing availability of more sensitive molecular techniques, and improved immunohistochemical identification of SMARCB1 confirmed the existence of SMARCB1-deficient 'true rhabdoid' variants of different epithelial neoplasms in the pancreas,[17] female genital tract,[25] gastrointestinal tract,[26] upper aerodigestive tract,[27] and other rare sites. Currently, the main entities included under the umbrella of 'SMARCB1-deficient neoplasms' are pediatric atypical teratoid/rhabdoid tumors, malignant rhabdoid tumors of the kidney and of extrarenal soft tissue sites, proximal- and distal-type epithelioid sarcoma, renal medullary carcinoma, epithelioid malignant peripheral nerve sheath tumors, and subsets of extra-skeletal myxoid chondrosarcoma/myoepithelial neoplasms of soft tissue.[28]

Studying a series of undifferentiated carcinomas of the pancreas that were predominantly (>50%) composed of rhabdoid cells, we recognized that their morphology was heterogeneous and allowed the separation of two subtypes: the first with a pleomorphic and the second with a monomorphic anaplastic cell pattern. As it has been recently shown that pancreatic undifferentiated carcinomas frequently show *KRAS* amplifications,[29] we aimed to investigate how the molecular changes in these neoplasms (ie, *KRAS* and *SMARCB1* alterations) relate to their heterogeneous morphology. We herein report our experience with 14 pancreatic undifferentiated rhabdoid carcinomas, which we analyzed for SMARCB1 expression and *KRAS* mutations and/or amplifications. In addition, we performed a comprehensive review of the old and recent literature on comparable neoplasms in order to see how the tumors of our series fit into the clinicopathologic spectrum of this group of pancreatic carcinomas.

Materials and methods

Formalin-fixed and paraffin-embedded tissue blocks from 14 pancreatic tumors were retrieved from our routine surgical pathology files and from the consultation files of two of the authors (GK and AA). Several consultation cases (dating back to 1980) lacked detailed follow-up data. Included were nonendocrine neoplasms predominantly composed (>50%) of highly atypical tumor cells with eosinophilic filamentous paranuclear cytoplasmic ('rhabdoid') inclusions. Five of the fourteen tumors also showed a glandular component. Tumors containing spindle cells and squamoid cells as a dominant component or osteoclastic giant cells were excluded. Tissue sections were stained with hematoxylin and eosin and periodic acid–Schiff. Immunohistochemistry was performed on freshly cut 3-μm paraffin sections using a fully automated slide preparation system 'Benchmark XT System' (Ventana Medical Systems, Tucson, Arizona, USA). All reagents and buffers were retrieved from Ventana Medical Systems. The antibodies used in this study, epitope retrieval conditions, incubation time, secondary antibody information (catalog number, company, and dilution, incubation time) are given in Table 1. Antigen visualization was done using a Ultra View DAB-Kit (Ventana, catalog 05269806001). Positive and negative controls were used throughout. Loss of SMARCB1 expression was recorded, when the tumor nuclei showed 'clean' negative staining as opposed to unequivocal nuclear staining of the adjacent inflammatory, endothelial, stromal, and normal pancreatic cells. If only isolated tumor cells were SMARCB1 negative or showed weak positive staining, SMARCB1 expression was recorded as intact.

Molecular Analysis and Assessment of Microsatellite Status

Mutational analysis of *KRAS* exon 2 was performed at the institutional molecular diagnostics laboratory using standardized protocols. In brief, mutation hotspots in exons 2 (codons 12, 13, 19) and 3 (codon 61) of the *KRAS* gene were analyzed using a single-nucleotide primer extension assay (SNaPshot) as described previously.[30] *KRAS* amplification was assessed using a dual color probe (ZytoLight® SPEC KRAS/CEN12 Dual color Probe, Zytovision, Bremerhaven, Germany) according to the instructions of the manufacturer. A *KRAS*/CEP12 ratio of >2 was considered as amplification. Other alterations (monosomy, polysomy) were recorded too. The expression of the mismatch repair proteins was assessed in all cases using immunohistochemical staining for MLH1, PMS2, MSH2, and MSH6 (see Table 1 for detailed antibody sources and staining conditions). Unequivocal nuclear staining in ≥10% of tumor cells was considered retained (normal) expression. Normal mucosa, endothelial cells, and background inflammatory cells served as internal controls. In addition, microsatellite instability status was evaluated in two of the cases by PCR on tumor DNA

Table 1 Sources of antibodies and conditions of immunohistochemical staining

Antibody	*Source*	*Clone*	*Dilution*	*Pretreatment cook buffer and conditions*	*Incubation time and temperature*
Pancytokeratin	Beckmann-Coulter	KL-1	1:100	Cook buffer CC1, 36 min at 95 °C	RT, 80 min
EMA	DAKO	E29	1:200	Cook buffer CC1, 36 min at 95 °C	37 °C 32 min
Vimentin	DAKO	V9	1:200	Cook buffer CC1, 36 min at 95 °C	37 °C 20 min
Desmin	DAKO	D33	1:50	Cook buffer CC1, 52 min at 95 °C	37 °C 32 min
Protein S100	Zytomed	4C4.9	1:3000	Cook buffer CC1, 36 min at 95 °C	37 °C 32 min
CD34	Immunotech	QBEND-10	1:500	Cook buffer CC1, 52 min at 95 °C	37 °C 48 min
CK7	DCS	OV-TL 12/30	1:1000	Protease 1; 8 min	37 °C 32 min
CK20	DAKO	Ks20.8	1:50	Protease 1; 8 min	37 °C 32 min
E-Cadherin	BD Biosciences	Clone 36	1:2000	Cook buffer CC1, 36 min at 95 °C	37 °C 32 min
β-Catenin	BD Biosciences	14/β-Catenin	1:50	Cook buffer CC1, 64 min at 95 °C	37 °C 32 min
Ki67	DAKO	MIB-1	1:100	Cook buffer CC1, 52 min at 95 °C	37 °C 32 min
SMARCB1	Zytomed	MRQ-27	1:50	Cook buffer CC1, 36 min at 95 °C	37 °C 60 min
MLH1	DAKO	ES05	1:50	Cook buffer CC1, 64 min at 95 °C	RT, 100 min
MSH2	Ventana	G2-19-1129	Prediluted	Cook buffer CC1, 64 min at 95 °C	37 °C 60 min
MSH6	BD Pharmingen	MSH6	1:300	Cook buffer CC1, 76 min at 95 °C	37 °C 32 min
PMS2	DAKO	EP51	1:40	Cook buffer CC1, 64 min at 95 °C	RT, 92 min

Abbreviation: RT, room temperature.

extracted from formalin-fixed paraffin-embedded tissue samples using the methods described previously.[31] One case was analyzed by electron microscopy using paraffin-embedded tissue.

Literature Review

For comparison of clinicopathological, demographic, and prognostic data with those of our tumor series, we performed a review of the MEDLINE literature dating back to 1968 using the keywords 'undifferentiated carcinoma', anaplastic carcinoma,' pleomorphic carcinoma,' 'pleomorphic adenocarcinoma,' 'sarcomatoid carcinoma,' 'giant cell carcinoma,' 'rhabdoid carcinoma,' and 'carcinoma with rhabdoid features'. Included were only those cases whose clinicopathological and demographic data (age, gender, tumor site, size, metastases, treatment and outcome, presence or absence of well-differentiated component, as listed in Table 4) could be traced back to the individual patients and whose tumor histology fits the above-defined criteria. Cases with missing single criteria such as tumor size or site were included as well. Cases with rhabdoid phenotype seen only at metastatic sites were excluded.

Results

Clinical and Demographic Features

The main clinicopathological features of the 14 patients are summarized in Table 2. Patients were seven males and seven females aged 44–96 years (mean age: 65; median: 65 years). Tumors were localized in the pancreas head (9), body (1), tail (3), and unspecified part of pancreas (1). Presenting symptoms included nonspecific abdominal symptoms, weight loss, and deteriorating general condition. One patient presented with leukocytosis (WBC: 37 000/mm^3; granulocytes 97%) and died 2 days after a biopsy was obtained from the tumor. Nine patients underwent radical surgical procedures that varied based on the specific site of the tumor and achieved free surgical resection margins. One extensively necrotic tumor ruptured intraoperatively. Autopsy and biopsy specimens were obtained from three patients and two patients, respectively. Four of twelve patients in whom detailed data were available had positive regional lymph nodes, seven out of ten patients had intra-abdominal and/or liver metastases and one patient had a lung metastasis. Seven patients died of disease within 2 months (four before any therapy and three after surgical resection). One patient (case 2) is currently under palliative chemoradiotherapy 6 months after biopsy.

Pathological Findings

Grossly, the tumors were described as huge masses measuring 3–11 cm (mean size: 6; median: 6 cm), extensively infiltrating into the peripancreatic tissue and often invading adjacent structures, such as stomach, duodenum, and retroperitoneum. Their cut-surfaces were gray-whitish and friable with extensive areas of necrosis and hemorrhage. One tumor was submitted in pieces because of intraoperative rupture. Histological examination revealed two distinctive cytological patterns: pleomorphic giant cell and monomorphic anaplastic subtype. These two subtypes are described separately.

Pleomorphic Giant Cell Subtype

Ten of the fourteen tumors qualified as pleomorphic giant cell subtype. They showed highly pleomorphic neoplastic giant cells with abundant eosinophilic

Table 2 Clinicopathological and molecular features of undifferentiated rhabdoid pancreatic carcinomas, own series ($n=14$)

No	*Pattern*	*Age (years)/sex*	*Site*	*Size (cm)*	*Treatment*	*MTS*	*Outcome*	*Glandular component*	*KRAS mutation status*	*KRAS FISH*	*SMARCB1 IHC*
1	Pleomorphic giant cell	68/F	NS	6	Surgery	Lymph nodes extensive	Abdominal recurrence, DOD 2 mo	PanIN3	p.Gly12Val	Normal	Intact
2	Pleomorphic giant cell	62/M	Body	6.7	Biopsy, palliative CT	Liver	Alive, 6 mo	Focus of WD-ADCA	WT	Normal	Intact
3	Pleomorphic giant cell	58/F	Tail	NS	Biopsy	Liver, peritoneum	DOD, 2 days	No (only biopsy)	p.Gly12Val	Normal	Intact
4	Pleomorphic giant cell	67/M	Head	3	Autopsy	Liver	DOD, initially	ADCA (<5%)	p.Gly12Asp	Amplified	Intact
5	Pleomorphic giant cell, myxoid pseudomucinous	71/M	Head	6	Surgery	No	NA	PanIN1	NR	Normal	Intact
6	Pleomorphic giant cell, melanoma-like	46/M	Head	3	Surgery	Lymph nodes	NA	No	NR	Polysomy (trisomy)	Intact
7	Pleomorphic giant cell, 5% spindle sarcomatous	96/F	Tail	6	Autopsy	Liver	DOD, initially	ADCA <2%	p.Gly12Asp	Amplified	Intact
8	Pleomorphic giant cell	63/F	Head	6	Surgery	Lymph nodes	NA	No	p.Gln61His	Amplified	Intact
9	Pleomorphic giant cell, myxoid stroma	49/F	Head	11	Surgery	Lung	NA	No	NR	Amplified	Intact
10	Pleomorphic giant cell	81/F	Head	10	Autopsy	Peritoneum, liver	DOD, initially	No	WT	NR	Intact
11	Monomorphic anaplastic	76/M	Head	5	Surgery	NS	DOD, 1 mo	No	WT	Normal	Complete loss
12	Monomorphic anaplastic angiosarcoma-like	44/F	Head	6	Surgery	NS	NA	Yes, minimal	p.Gly12Asp	Amplified	Complete loss
13	Monomorphic small cell pseudopapillary	72/M	Head	4	Surgery	Lymph nodes, liver	Died post-operative	No	WT	Normal	Complete loss
14	Monomorphic anaplastic, prominent granulocytes	61/M	Tail	5	Surgery	Intra-abdominal, stomach	NA	No	WT	Normal	Complete loss

Abbreviations: ADCA, adenocarcinoma; CT, chemotherapy; DOD, died of disease; IHC, immunohistochemistry; mo, month; MTS, metastasis; NA, not available; NR, no results due to artifacts or poor preservation; NS, not specified; WD, well differentiated; WT, wild-type.

cytoplasm frequently containing rhabdoid inclusions (Figure 1a–d). The architectural patterns seen in the two subtypes were similar and varied from a 'cytology slide'-like poorly cohesive mononuclear cell arrangement to a nested growth or diffuse sheets of compact tumor cells separated by thin fibrovascular septa lacking dense fibrous stroma and showing occasional acantholytic pseudoalveolar spaces. Cytokeratin immunostaining highlighted the striking variation in the size of the tumor cells (Figure 1e). All cases showed intact nuclear SMARCB1 expression (Figure 1f). In addition to strong and consistent cytoplasmic paranuclear expression of vimentin, all cases expressed pancytokeratin but in highly variable pattern (Figure 1e), usually accompanied by variable CK 7 and EMA staining (Table 3). All anaplastic cells of the tumors lost their membranous E-cadherin staining (Figure 2a), but retained it in the glandular components, especially in the lymph node metastasis (Figure 2b). Membranous β-catenin staining was lost in 10 and focally present in 2 tumors. A variable nuclear staining was seen in a few scattered tumor cells (<1%). The proliferation index (MiB1) exceeded 50% in all cases. Nuclear TP53 labeling was found in four out of seven tumors with assessable staining (Table 3). All other markers (desmin, protein S100, CD34) were not expressed in the tumor cells. The 'rhabdoid' inclusions were found to represent convolutes of intermediate filaments

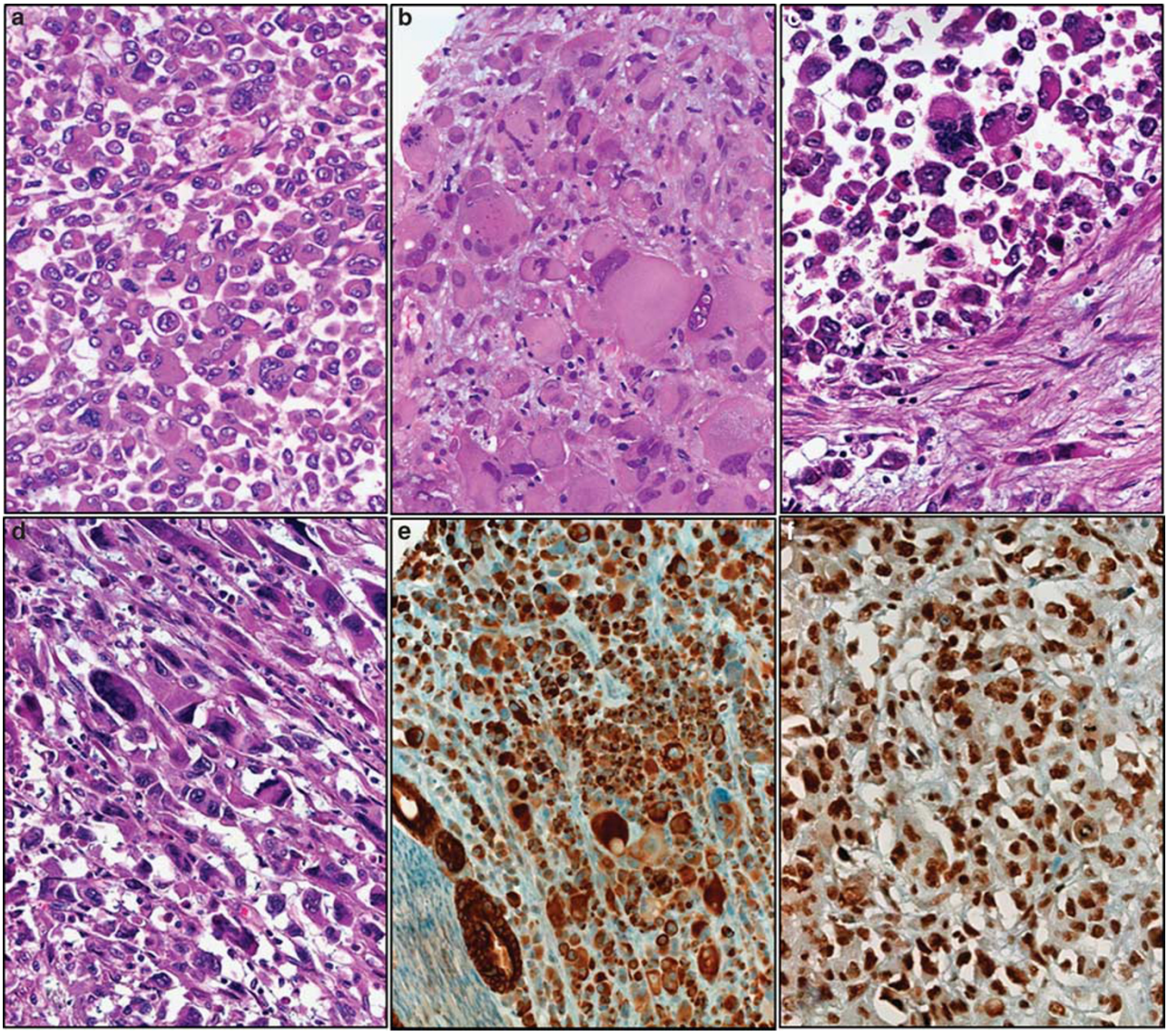

Figure 1 Examples of the pleomorphic giant cell subtype of undifferentiated rhabdoid pancreatic carcinoma. (**a**) Highly pleomorphic tumor cells with variable nuclear sizes and frequent bi- and multinucleation. Note prominent cytoplasmic eosinophilia with rhabdoid inclusions. (**b**) Extreme example of cell size variation and eosinophilic cytoplasm. (**c**) Non-cohesive pseudoalveolar pattern. (**d**) Sarcomatoid spindle cells. (**e**) Cell size variation highlighted by pancytokeratin (note perineural carcinomatous glands lower left). (**f**) Intact nuclear SMARCB1 expression was seen in all cases of this subtype.

Table 3 Immunohistochemical features of undifferentiated rhabdoid pancreatic carcinomas ($n=14$)

No	*Vimentin*	*KL-1*	*CK7*	*EMA*	*E-cadherin*	*β-Catenin*	*TP53*	*SMARCB1 IHC*
1	+ + +	+	−	−	−	−	−	Intact
2	+ + +	+ + +	+ +	+	−	−	NR	Intact
3	+ + +	+ +	+	+ +	−	−	NR	Intact
4	+ +	+ + +	+ + +	+	−	−	−	Intact
5	+ + +	+ +	+	+	−	−	NR	Intact
6	+ + +	+ + +	+ +	+ +	−	+ Membranous	−	Intact
7	+ +	+	+	+	−	−	40%	Intact
8	+ + +	+ + +	+ + +	+ +	−	−	20%	Intact
9	+ + +	+ +	−	−	−	+ Membranous	5%	Intact
10	−	+ + +	+ +	+ +	−	−	10%	Intact
11	+ + +	+ +	−	+	−	−	−	Complete loss
12	+ + +	+ + +	+	+	−	−	NR	Complete loss
13	+ + +	+ +	−	+ +	−	−	NR	Complete loss
14	+ +	+ + +	−	+ + +	−	+ +Cytoplasmic +Membranous	50%	Complete loss

Abbreviations: IHC, immunohistochemistry; NR, no results due to artifacts or poor preservation.

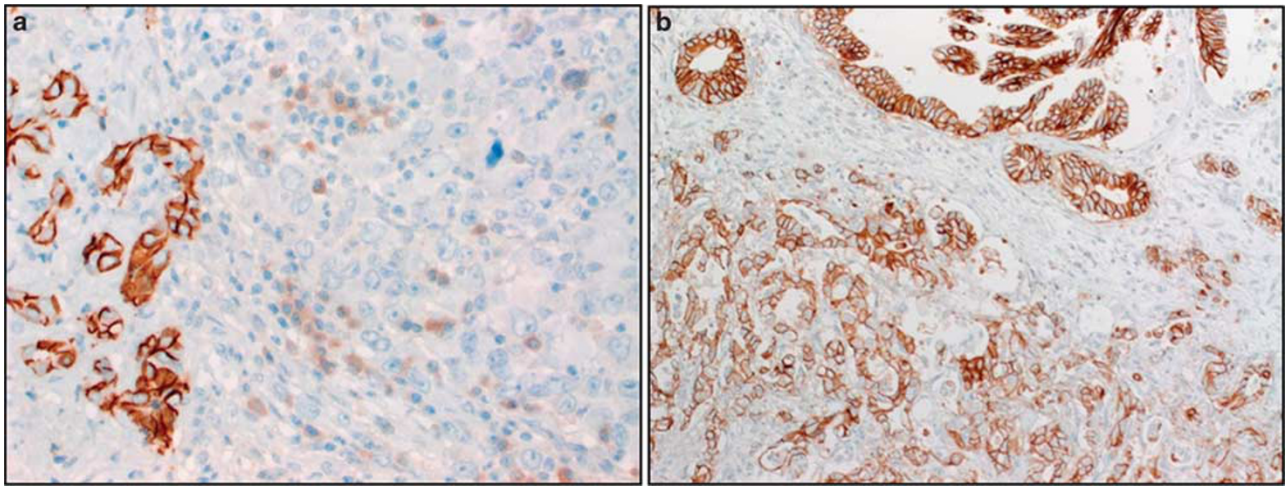

Figure 2 (**a**) Tumor with complete loss of E-cadherin (in contrast to stained normal glands on the left). (**b**) Membranous E-cadherin staining of the glandular tumor component in a lymph node metastasis.

on ultrastructural examination of one case (not shown).

Monomorphic Anaplastic Subtype

Four tumors lacked significant cellular and nuclear pleomorphism and were rather monomorphic, with medium- to large-size vesicular nuclei, prominent nucleoli, and a moderate rim of eosinophilic cytoplasm frequently containing rhabdoid inclusions (Figure 3a). The cells were non-cohesive and loosely arranged without recognizable fibrous stroma. One tumor contained many infiltrating neutrophils (Figure 3b), with occasional cells showing emperipolesis. Another pattern seen in two cases were solid sheets of large epithelioid cells with a variable number of rhabdoid inclusions. This type of growth was frequently associated with prominent vessel-like clefts or hemorrhagic pseudocystic structures closely mimicking epithelioid angiosarcoma (Figure 3c) or proximal-type epithelioid sarcoma (Figure 3d). A mucoid/myxoid stromal pattern was seen focally in one case. Immunohistochemical staining showed similar expression of vimentin and cytokeratin as in the pleomorphic giant cell variant (Figure 3e; Table 3). Nuclear immunostaining for SMARCB1 was completely lost in all four cases (Figure 3f). Other immunohistochemical features were similar to the pleomorphic giant cell subtype. Nuclear TP53 labeling was found in one out of two tumors with evaluable staining (Table 3).

Glandular Differentiation and Other Features

In the pleomorphic giant cell subtype, foci of neoplastic duct-like glandular structures were seen

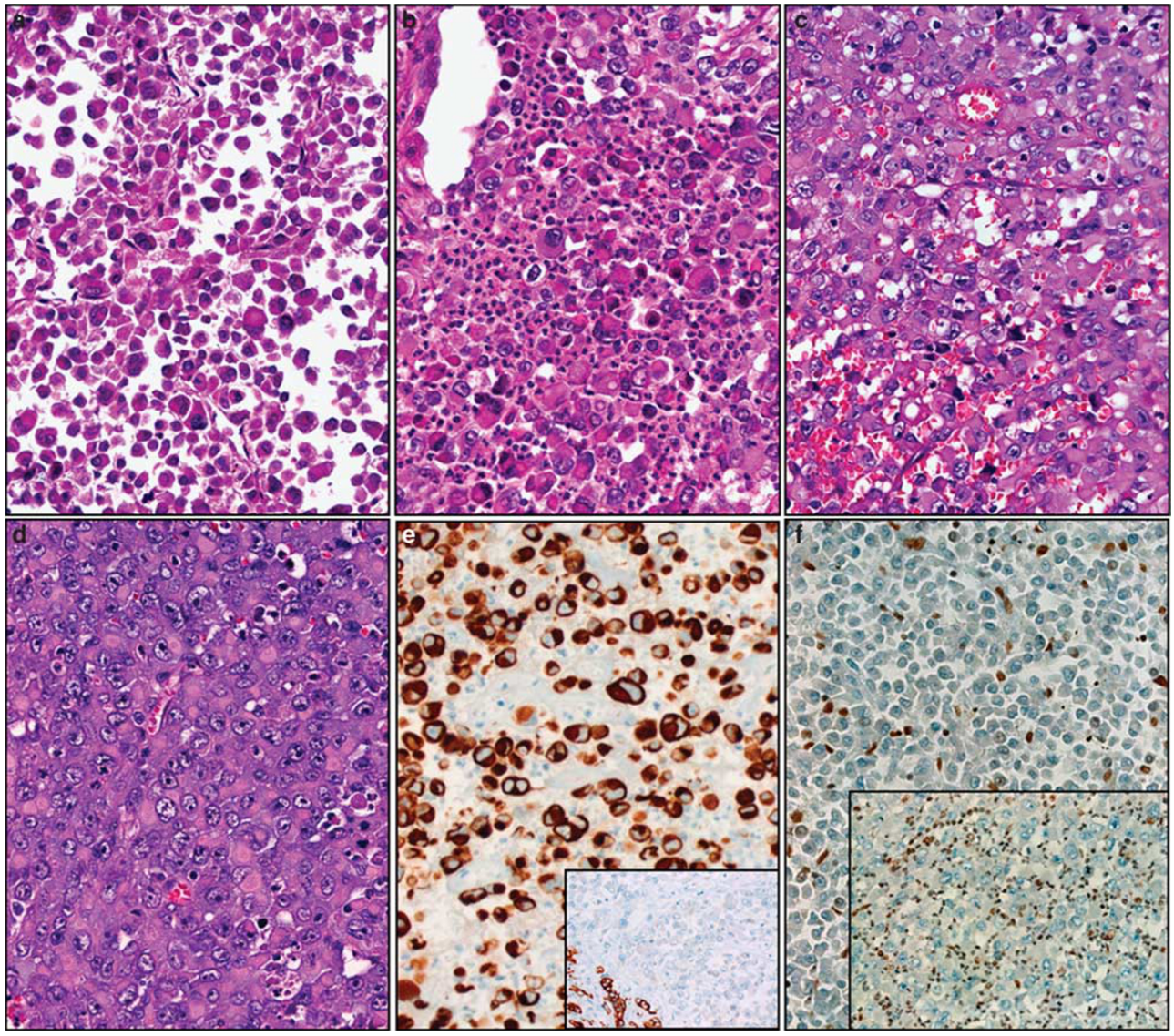

Figure 3 Examples of the SMARCB1-deficient monomorphic subtype. (**a**) Small to medium sized monotonous rhabdoid cells in pseudoalveolar pattern. (**b**) Another case showed prominent neutrophilia and focal gland formation (upper left). (**c**) Epithelioid large cell pattern mimicking angiosarcoma. (**d**) Compact sheets of large cells with frequent rhabdoid inclusions mimicking proximal-type epithelioid sarcoma. (**e**) Characteristic paranuclear cytokeratin expression (KL1). Inset: loss of pancytokeratin in another case with focal expression in gland-like areas. (**f**) Complete loss of nuclear SMARCB1 expression (main image: same case as in **a** with retained expression in endothelial and stromal cells; inset: same case as in **b**, with prominent nuclear staining of neutrophils and stromal cells).

in four cases. One case showed only a focus of severely dysplastic pancreatic intraepithelial neoplasia (PanIN 3), but frankly glandular differentiation in a lymph node metastasis (Figure 2b). One tumor showed a focus of perineural glandular differentiation amid highly pleomorphic tumor giant cells (Figure 1e). In the monomorphic subtype, glandular features (seen in only one case) were very subtle and represented either single-scattered gland-like structures or pseudopapillary acantholytic gland-like spaces. The gland-like structures in the monomorphic variant were all SMARCB1 negative similar to the undifferentiated component. Extensive areas of tumor necrosis usually accompanied by severe hemorrhage, prominent lymphovascular invasion, infiltration of arterial vessels, and diffuse lymphoma-like infiltration of peripancreatic fatty tissue were found in all cases.

Molecular Findings

Molecular analysis revealed *KRAS* mutations in 6 out of 11 (54%) successfully examined tumors. All mutations were point mutations affecting exon 2 (Table 2). *KRAS* amplification was detected in 5 out of 13 (38%) cases successfully analyzed by FISH (Figure 4). One additional case showed polysomy

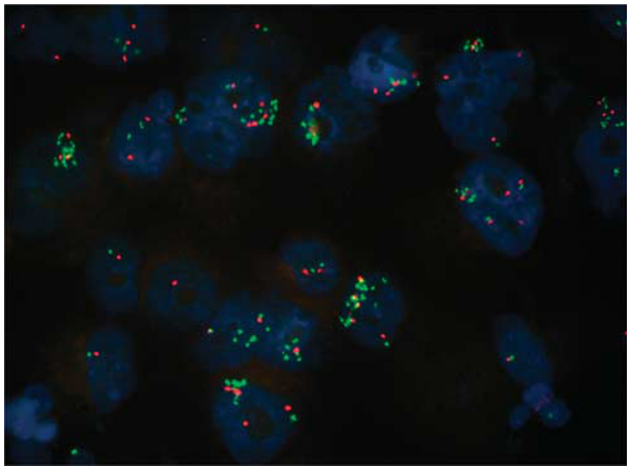

Figure 4 Example of *KRAS* amplification with >6 green signals of *KRAS* (fluorescence *in situ* hybridization dual-color probe).

(most cells displayed three signals for *KRAS* and CEP12). *KRAS* mutations and *KRAS* amplification coexisted in four out of six cases (66%). On the contrary, all four *KRAS* wild-type tumors successfully analyzed by FISH lacked *KRAS* amplification. *KRAS* amplification correlated with intact SMARCB1 expression in four out of five (80%) tumors. Taken together, *KRAS* alterations (mutations and/or copy number changes) highly correlated with intact SMARCB1 expression (7 out of 8 cases; 87%). On the other hand, a strong correlation was found between the absence of *KRAS* alterations and the loss of SMARCB1 expression (three of five *KRAS* wild-type cases were SMARCB1 deficient). All but one of the four SMARCB1-negative cases lacked any *KRAS* alterations.

Literature Review

Our review of the English literature revealed 46 cases of pancreatic carcinoma that were described in details and fulfill the diagnostic criteria of rhabdoid differentiation as defined in this study. These neoplasms have been reported under different names: *pleomorphic adenocarcinoma, pleomorphic carcinoma, pleomorphic giant cell carcinoma, round cell anaplastic carcinoma, sarcomatoid carcinoma, carcinoma with gemistocytes, rhabdoid carcinoma, and carcinoma with rhabdoid phenotype*/features.[5–8,13–19,32,33] Thus, including our cases, a total of 60 rhabdoid carcinomas of the pancreas have been described to date (Tables 2 and 4). Patients were 44 men and 16 women (M/F = 2.8:1) aged 30–96 years (mean age: 65 years). In all, 71.6% of patients were ≥60 years. The tumor originated in the pancreas head (25), body (7), tail (10), diffuse/more than one part (11), and in nonspecified part of pancreas (7).

Most patients presented with locally advanced or widely metastatic disease and received only supportive treatment or palliative surgery with or without chemoradiation. Seventeen patients received surgery as initial and definitive treatment, and three of them also received adjuvant radio/-chemotherapy. Of the remainder, 35 patients underwent biopsy and palliative treatment because of unresectable disease. The tumor was diagnosed at autopsy in five cases. Of four patients who received biopsy followed by radiochemotherapy, three died of disease within 3–13 months and one is alive, currently 6 months under palliative treatment. Lymph node metastases were identified in almost all cases with detailed information (>90% of all). Liver metastases were also seen in the majority of patients, usually shortly after surgical treatment. Follow-up ranging from 1 day to 19 months was available for 49 patients; all but 4 patients (92%) died of disease either postoperatively or within 1–19 months (median: 4 months; mean: 5.4 months). All but three patients died within 1 year (Table 2 and Table 4). The four patients who were reported alive had limited follow-up (≤6 months) or were recent cases.

In the tumor descriptions, rhabdoid cells dominated the tumor histology in most cases. Occasionally, signet ring-like cells with mucicarmine-positive vacuoles were noted. An adenocarcinoma component of varying degree of differentiation or high-grade intraepithelial neoplasia (PanIN3) were detected in 32 out of 41 (78%) of the cases, in which sufficient tissue was examined. In a few cases, mucinous adenocarcinoma, squamous differentiation, and spindle cell areas were reported. Unequivocal glandular differentiation in metastases in association with a primary tumor, which was devoid of such a component, was noted in four cases. The available immunohistochemical findings consistently demonstrated coexpression of vimentin and pancytokeratin, mostly confined to or highlighting the paranuclear rhabdoid cytoplasmic inclusions.

Molecular data were only available in a single case that showed missense mutation of *SMARCB1* in the rhabdoid component.[17] SMARCB1 expression and KRAS mutation were not tested in the 46 previously reported cases.

Discussion

According to the current WHO classification of pancreatic tumors, undifferentiated carcinoma is defined as 'a malignant epithelial neoplasm in which a significant component of the neoplasm does not show a definitive line of differentiation.'[10] Included in this definition are histologic variants, such as anaplastic giant cell carcinoma (composed of pleomorphic mononuclear cells admixed with bizarre-appearing eosinophilic giant cells), sarcomatoid spindle cell carcinoma, and carcinosarcoma with recognizable adenocarcinoma and high-grade spindle cell areas, and undifferentiated carcinoma with osteoclast-like giant cells. The 'rhabdoid

Table 4 Previously reported undifferentiated pancreatic carcinomas with rhabdoid features ($n = 46$)

No	Author/reference	Reported as:	Age (years)/ sex	Site	Size (cm)	Treatment	MTS	Prognosis (mo)	Glandular component	Vimentin	Cytokeratin
1	Guillan[5]	Pleomorphic ADCA	65/M	Head	10	Palliative	Yes	DOD 3 mo	Present	ND	ND
2	Guillan[5]	Pleomorphic ADCA	59/M	Body/tail	6	Palliative	Yes	DOD 3 mo	Present	ND	ND
3	Guillan[5]	Pleomorphic ADCA	72/M	Body/tail	8	Palliative	Yes	DOD 4 mo	Present	ND	ND
4	Guillan[5]	Pleomorphic ADCA	75/M	Body/tail	9	Palliative	Yes	DOD 5 mo	Present	ND	ND
5	Guillan[5]	Pleomorphic ADCA	62/M	Body/tail	15	Palliative	Yes	DOD 3 mo	Present	ND	ND
6	Alguacil-Garcia *et al*[6]	Pleomorphic giant cell ca	78/M	Body	30	Biopsy	Lung, liver	DOD Few days	Present	ND	ND
7	Alguacil-Garcia *et al*[6]	Pleomorphic giant cell ca	74/M	Tail	15	Surgery + CT	None	DOD 4 mo	Present	ND	ND
8	Alguacil-Garcia *et al*[6]	Round cell anaplastic ca	51/F	Head	5	Surgery	Lymph nodes	DOD 1 mo	Absent[a]	ND	ND
9	Alguacil-Garcia *et al*[6]	Round cell anaplastic ca	73/M	Diffuse	11	Biopsy	Lymph nodes, adrenals	DOD few days	Absent[a]	ND	ND
10	Alguacil-Garcia *et al*[6]	Round cell anaplastic ca	30/M	Body	12	Autopsy	Lymph nodes, ileum, kidney, thyroid, lung	Autopsy	Absent[a]	ND	ND
11	Tschang *et al*[7]	Pleomorphic carcinoma	67/M	Tail	3	Biopsy	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
12	Tschang *et al*[7]	Pleomorphic carcinoma	49/M	Tail	NS	Biopsy	Lymph nodes, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
13	Tschang *et al*[7]	Pleomorphic carcinoma	54/M	Body + tail	NS	Biopsy	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
14	Tschang *et al*[7]	Pleomorphic carcinoma	65/M	Tail	NS	Autopsy	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
15	Tschang *et al*[7]	Pleomorphic carcinoma	72/M	Body	NS	Autopsy	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
16	Tschang *et al*[7]	Pleomorphic carcinoma	61/M	Body	NS	Bioposy	Lymph nodes, liver, peritoneum	DOD median 3, mean 6 mo	Present	ND	ND
17	Tschang *et al*[7]	Pleomorphic carcinoma	72/M	Head + body	10	Biopsy	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
18	Tschang *et al*[7]	Pleomorphic carcinoma	65/M	Body + tail	NS	Biopsy + RCT	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
19	Tschang *et al*[7]	Pleomorphic carcinoma	69/M	Head	10	Biopsy + CT	Liver, peritoneum	DOD median 3, mean 6 mo	Present	ND	ND
20	Tschang *et al*[7]	Pleomorphic carcinoma	65/M	Body + tail	NS	Biopsy + RCT	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
21	Tschang *et al*[7]	Pleomorphic carcinoma	72/M	Head	10	Biopsy	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
22	Tschang *et al*[7]	Pleomorphic carcinoma	53/M	Diffuse	10	Biopsy	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
23	Tschang *et al*[7]	Pleomorphic carcinoma	81/F	Body + tail	15	Biopsy	Lymph nodes, liver, extra-abdominal	DOD median 3, mean 6 mo	Present	ND	ND
24	Tschang *et al*[7]	Pleomorphic carcinoma	79/F	Head	10	Biopsy	Lymph nodes	DOD median 3, mean 6 mo	Present	ND	ND
25	Reyes *et al*[8]	Pleomorphic giant cell carcinoma	59/M	Head	Mean 9	Supportive	Lymph nodes, widespread	DOD 1 mo	NA	ND	ND
26	Reyes *et al*[8]	Pleomorphic giant cell carcinoma	37/M	Tail	Mean 9	RCT	Lymph nodes, widespread	DOD 13 mo	NA	ND	ND
27	Reyes *et al*[8]	Pleomorphic giant cell carcinoma	59/M	Head	Mean 9	Supportive	Lymph nodes, widespread	DOD 1 mo	NA	ND	ND
28	Reyes *et al*[8]	Pleomorphic giant cell carcinoma	71/M	Head	Mean 9	Palliative surgery	Lymph nodes, widespread	DOD 2 mo	NA	ND	ND
29	Reyes *et al*[8]	Pleomorphic giant cell carcinoma	70/M	Head	Mean 9	Supportive	Lymph nodes, widespread	DOD 3 mo	NA	ND	ND
30	Reyes *et al*[8]	Pleomorphic giant cell carcinoma	77/M	Head	Mean 9	Supportive	Lymph nodes, widespread	DOD 1 mo	NA	ND	ND
31	Reyes *et al*[8]	Pleomorphic giant cell carcinoma	64/M	Head	Mean 9	Supportive	Lymph nodes, widespread	DOD 2 mo	NA	ND	ND
32	Reyes *et al*[8]	Pleomorphic giant cell carcinoma	62/M	Head	Mean 9	Palliative surgery	Lymph nodes, widespread	DOD 1 mo	NA	ND	ND
33	Reyes *et al*[8]	Pleomorphic giant cell carcinoma	54/M	Body	Mean 9	Supportive	Lymph nodes, widespread	DOD 4 mo	NA	ND	ND
34	Nishihara *et al*[13]	Anaplastic ca + rhabdoid features	52/F	NS	10	Surgery	Initially lymph nodes, 9 mo liver MTS	DOD 19 mo	Mucinous	Diffuse	–
35	Al-Nafussi *et al*[14]	Adenoca + extensive rhabdoid	77/F	NS	NS	No	Soft tissue, liver, lung, kidney, heart, adrenals	DOD initially	PD-ADCA	Diffuse	Diffuse
36	Kuroda *et al*[15]	Anaplastic ca with rhabdoid features	68/F	NS	14	Palliative	Regional + bronchial + iliac nodes	DOD 2 mo	PD-ADCA	Focal	Diffuse
37	Chadha *et al*[16]	Anaplastic pleomorphic carcinoma	74/F	Tail	NS	Palliative	Lymph nodes, liver, adrenal, peritoneum	DOD, 2 wks	Absent in biopsy	NS	Focal
38	Cho *et al*[17]	Mucinous ca + rhabdoid features	65/F	Tail	11	Surgery + RT	Omentum + mesentery, liver + lung	DOD 12 mo	Mucinous 2 cm	Diffuse	Focal
39	Jamali *et al*,[18]	ADSCA + rhabdoid	75/M	NS	3	Surgery	Liver at 6 mo	DOD 6 mo	ADSCA + PanIN1–3	Diffuse	Diffuse
40	Kuroda *et al*[19]	Anaplastic ca with rhabdoid features	59/M	NS	10	Surgery + CT	Liver MTS 2 mo	DOD 2 mo	ADSCA 40%	Focal	Diffuse
41	Layfield *et al*[32]	Pleomorphic giant cell ca	71/M	Head	NS	Surgery	Liver	Alive, 2 mo	NS	NS	NS

Table 4 (Continued)

No	Author/reference	Reported as:	Age (years)/ sex	Site	Size (cm)	Treatment	MTS	Prognosis (mo)	Glandular component	Vimentin	Cytokeratin
42	Layfield *et al*[32]	Pleomorphic giant cell ca	81/F	Head	NS	Palliative	NS	DOD 3 mo	NS	NS	NS
43	Layfield *et al*[32]	Pleomorphic giant cell ca	59/M	Head	NS	Surgery	Lymph nodes, liver	Alive, 3 mo	NS	NS	NS
44	Layfield *et al*[32]	Pleomorphic giant cell ca	81 M	Head	NS	Palliative	NS	NA	NS	NS	NS
45	Layfield *et al*[32]	Pleomorphic giant cell ca	64/M	Body	NS	Palliative	Lymph nodes,	Alive, 4 mo	NS	NS	NS
46	Nakajima *et al*[33]	Anaplastic carcinoma	63/M	NS	10	Liver biopsy, supportive	Synchronous liver metastasis	DOD 11 days	Absent	NS	NS

Abbreviations: Adenoca, adenocarcinoma; ADSCA, adenosquamous carcinoma; ANED, alive with no evidence of disease; aRCT, adjuvant radiochemotherapy; ca, carcinoma; CT, chemotherapy; DOD, died of disease; mo, months; MTS, metastasis; ND, not done; NS, not specified; PD-ADCA, poorly differentiated adenocarcinoma; RT, radiotherapy; wks, weeks.
[a]One case showed adenocarcinoma in the metastasis.

features' that characterize the pancreatic undifferentiated carcinomas of this series and those described in several other reports[5–8,13–19,32,33] have not been included into the descriptive terms of the WHO classification.[10]

Here we show that undifferentiated carcinomas of the pancreas exhibiting rhabdoid features vary greatly in morphology, but may be separated into two subtypes, one with a pleomorphic giant cell and another with a monomorphic anaplastic pattern. When these neoplasms were analyzed for *KRAS* alterations and SMARCB1 expression, a strong correlation was found between histology and molecular findings. *KRAS* mutations and/or amplification, identified by PCR/sequencing and FISH, respectively, and intact immunohistochemical expression of SMARCB1 (as a highly sensitive and specific marker for intact *SMARCB1* locus) were linked to the pleomorphic giant cell subtype, whereas lack of *KRAS* alterations and loss of nuclear SMARCB1 was found in the majority of monomorphic anaplastic carcinomas.

Recently, *KRAS* copy number changes or polysomy of chromosome 12 were identified in 42% of undifferentiated carcinomas of the pancreas but not in ductal adenocarcinomas, and were also found to accompany the intratumoral transition from ductal adenocarcinoma to undifferentiated carcinoma.[29] In addition, a trend toward more frequent *KRAS* amplification was observed among cases with mutant allele-specific imbalances.[29] This study, however, did not focus on tumors with rhabdoid features or the expression of SMARCB1.

Several recent observations support the novel concept of SMARCB1-deficient neoplasms emerging as secondary 'dedifferentiated' clones in the background of a differentiated SMARCB1-positive 'parent' neoplasm (ie, an adenocarcinoma) in different organs including the pancreas.[25,26] Cho *et al*[17] reported on a pancreatic mucinous adenocarcinoma with a 'rhabdoid' component. Molecular analysis revealed a missense *SMARCB1* mutation in the rhabdoid component, but SMARCB1 immunostaining was not performed.

Our results confirm and extend the above-mentioned molecular findings in pancreatic undifferentiated carcinomas. First, they demonstrate that *KRAS* copy number changes on a background of intact SMARCB1 expression are typical for the pleomorphic anaplastic subtype of undifferentiated carcinomas with rhabdoid features. Second, they indicate that SMARCB1-deficient but *KRAS*-intact undifferentiated rhabdoid carcinomas are characterized by a monomorphic anaplastic histological cell pattern. These findings suggest that the molecular pathway leading to a morphological and biological shift of ductal adenocarcinomas to a highly aggressive pleomorphic anaplastic carcinoma with rhabdoid features is heterogeneous, depending, in case of the pleomorphic subtype, either on mutated and amplified *KRAS* on a background of intact

SMARCB1 expression or, in case of the monomorphic subtype, on a loss of SMARCB1 in the presence of wild-type *KRAS*. The molecular mechanisms that follow these two distinct molecular changes and lead to a switch from a differentiated adenocarcinoma to an undifferentiated carcinoma with rhabdoid appearance and aggressive behavior are not known so far. However, it is likely that the concurrent loss of E-cadherin and β-catenin from the surface of the tumor cells, noted in this and other studies,[34,35] is a significant finding contributing to the highly infiltrating growth of the tumors. Concerning the rhabdoid features, which make these tumors so distinct, it can be concluded that their occurrence is not solely caused by loss of SMARCB1 but may also have other causes, as has also been noted in other neoplasms.[26,36] The exact role of SMARCB1 in the single *KRAS* mutated case in our series where its loss is likely to be a secondary event in tumorigenesis (as has been shown also in a subset of microsatellite instable colorectal cancer with secondary SMARCB1 loss[26]) remains therefore to be determined.

Identification of pancreatic undifferentiated carcinomas with rhabdoid cells in previously published reports is often difficult, because many of these tumors were lumped in the category of pleomorphic giant cell carcinoma or anaplastic carcinoma that also included cases without rhabdoid features. It seems that pancreatic undifferentiated carcinomas with rhabdoid features have first been described under the term pleomorphic carcinoma in 1954 by Sommers and Meissner, who found three such tumors among 142 autopsy cases of pancreatic adenocarcinoma (2%).[4] In addition to these cases, we identified 46 other pancreatic tumors with rhabdoid features reported since 1968 (see Table 4). As our review covers a time period of more than 40 years, it is obvious that the relative frequency of these tumors is very low and probably in the range of 1%, particularly, if only surgically treated cases are considered.

The gender distribution and mean age of the patients with pancreatic undifferentiated carcinoma with rhabdoid features as well as the tumor location in the pancreas are similar to the clinicopathological features of pancreatic ductal adenocarcinoma.[10–12] The prognosis, however, whether the tumor contained a glandular component or not, is worse.[5–8] According to our review, almost all patients died of their disease or its complication within a mean of 4 months with >20% dying immediately or within a few weeks after biopsy or surgery. Tschang *et al* summarized the '*usual course of events*' in these patients with the words '*hospitalization, laparotomy and biopsy, and death*.'[7] This seems to be true until today, irrespective of the treatment modality used. The rapid progress of the tumors may be explained by the complete loss of the adhesion molecules E-cadherin and β-catenin from the surface of the cells that probably results in a highly aggressive, non-cohesive (lymphoma-like) tumor cell growth, with easy invasion of adjacent organs, vessels, and the retroperitoneum. Adverse systemic effects caused by cytokines produced by the tumor cells seems to be an adverse prognostic factor in some patients. Nakajima *et al*[33] reported one patient with rhabdoid carcinoma who presented with a peripheral leucocyte count of 91 500/mm^3 (neutrophils: 87.5%) and elevated serum granulocyte colony-stimulating factor. The patient died 11 days after diagnosis and expression of granulocyte colony-stimulating factor could be demonstrated in tumor cells. Similar to that case, one of our patients presented also with elevated leucocyte count of 37 000/mm^3 (neutrophils: 97%) and died 2 days after biopsy. Histologically, prominent granulocytic infiltrates were seen within some tumors.

From a differential diagnostic view point, undifferentiated pancreatic rhabdoid carcinoma needs to be distinguished from proximal-type epithelioid sarcoma of the viscera[37,38] and from microsatellite instable pancreatic medullary carcinoma with DNA replication errors.[39] SMARCB1-deficient undifferentiated rhabdoid carcinoma is indistinguishable from rhabdoid cell-dominated epithelioid sarcoma on morphological ground alone. However, identification of a glandular component in 50% of cases and of a driver *KRAS* mutation in one of our four cases that are SMARCB1 deficient highlights the epithelial derivation of these neoplasms and argues against a visceral variant of epithelioid sarcoma. Pancreatic medullary carcinoma with DNA replication errors is a rare variant of poorly differentiated non-gland-forming carcinoma that is characterized by wild-type *KRAS*.[39] In sharp contrast to our series, this subtype shows expanding borders, syncytial growth of tumor cells, lacks rhabdoid cell features, consistently shows loss of mismatch repair proteins and microsatellite instability, and is characterized by prolonged survival.[39]

In summary, our study highlights the phenotypic and molecular heterogeneity of the pleomorphic/anaplastic variant of pancreatic undifferentiated carcinoma, which has undergone rhabdoid transformation. The clear-cut correlation between tumor histology and molecular findings (*KRAS* alterations and SMARCB1 expression status) highlights the existence of at least two independent molecular pathways, each associated with its own morphological subtype. The rhabdoid phenotype seems to unify these two subtypes. Although the pathogenesis remains in most parts unclear, *KRAS* mutation/amplification on the one side and loss of SMARCB1 on the other side seem to have an essential role for the phenotypic shift from differentiated ductal adenocarcinoma to undifferentiated carcinoma with rhabdoid changes. The results of this study let us therefore assume that the pancreatic undifferentiated carcinomas not only differ in their morphology but also in their molecular profiles. If this assumption is correct, a careful morphological

separation of the variants using a clear terminology is needed. The nomenclature that has been so far used for these neoplasms is often confusing and may impede appropriate future treatments.

Disclosure/conflict of interest

The authors declare no conflict of interest.

References

1 Wick MR, Ritter JH, Dehner LP. Malignant rhabdoid tumors: a clinicopathologic review and conceptual discussion. Semin Diagn Pathol 1995;12:233–248.
2 Fanburg-Smith JC, Hengge M, Hengge UR, *et al.* Extrarenal rhabdoid tumors of soft tissue: a clinicopathologic and immunohistochemical study of 18 cases. Ann Diagn Pathol 1998;2:351–362.
3 Kerl K, Holsten T, Frühwald MC. Rhabdoid tumors: clinical approaches and molecular targets for innovative therapy. Pediatr Hematol Oncol 2013;30:587–604.
4 Sommers SC, Meissner WA. Unusual carcinomas of the pancreas. Arch Path 1954;58:101–111.
5 Guillan RA. Pleomorphic adenocarcinoma of the pancreas. An analysis of five cases. Cancer 1968;21: 1072–1079.
6 Alguacil-Garcia A, Weiland LH. The histologic spectrum, prognosis, and histogenesis of the sarcomatoid carcinoma of the pancreas. Cancer 1977;39:1181–1189.
7 Tschang TP, Garza-Garza R, Kissane JM. Pleomorphic carcinoma of the pancreas: an analysis of 15 cases. Cancer 1977;39:2114–2126.
8 Reyes CV, Crain S, Wang T. Pleomorphic giant cell carcinoma of the pancreas: a review of nine cases. J Surg Oncol 1980;15:345–348.
9 Hoorens A, Prenzel K, Lemoine NR, *et al.* Undifferentiated carcinoma of the pancreas: analysis of intermediate filament profile and Ki-ras mutations provides evidence of a ductal origin. J Pathol 1998;185:53–60.
10 Bosman FT, Carneiro F, Hruban RH, Theise ND (eds). World Health Organization Classification of Tumours of the Digestive System. IARC Press: Lyon, 2010.
11 Solcia E, Capella C, Klöppel G. AFIP Atlas of Tumor Pathology: Tumors of the Pancreas, 3rd edn. Series, Fascicle 20. The American Registry of Pathology: Washington, DC, 1997.
12 Hruban RH, Pitman MB, Klimstra DS. AFIP Atlas of Tumor Pathology: Tumors of the Pancreas, 4th Series. Fascicle 6. The American Registry of Pathology: Washington, DC, 2007.
13 Nishihara K, Katsumoto F, Kurokawa Y, *et al.* Anaplastic carcinoma showing rhabdoid features combined with mucinous cystadenocarcinoma of the pancreas. Arch Pathol Lab Med 1997;121:1104–1107.
14 Al-Nafussi A, O'Donnell M. Poorly differentiated adenocarcinoma with extensive rhabdoid differentiation: clinicopathological features of two cases arising in the gastrointestinal tract. Pathol Int 1999;49:160–163.
15 Kuroda N, Sawada T, Miyazaki E, *et al.* Anaplastic carcinoma of the pancreas with rhabdoid features. Pathol Int 2000;50:57–62.
16 Chadha MK, LeVea C, Javle M, *et al.* Anaplastic pancreatic carcinoma. A case report and review of literature. J Pancreas 2004;5:512–515.
17 Cho YM, Choi J, Lee OJ, *et al.* SMARCB1/INI1 missense mutation in mucinous carcinoma with rhabdoid features. Pathol Int 2006;56:702–706.
18 Jamali M, Serra S, Chetty R. Adenosquamous carcinoma of the pancreas with clear cell and rhabdoid components. A case report. J Pancreas 2007;8:330–334.
19 Kuroda N, Iwamura S, Fujishima N, *et al.* Anaplastic carcinoma of the pancreas with rhabdoid features and hyaline globule-like structures. Med Mol Morphol 2007;40:168–171.
20 Judkins AR. Immunohistochemistry of INI1 expression: a new tool for old challenges in CNS and soft tissue pathology. Adv Anat Pathol 2007;14:335–339.
21 Biegel JA, Zhou JY, Rorke LB, *et al.* Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. Cancer Res 1999;59:74–79.
22 Biegel JA, Tan L, Zhang F, *et al.* Alterations of the hSNF5/INI1 gene in central nervous system atypical teratoid/rhabdoid tumors and renal and extrarenal rhabdoid tumors. Clin Cancer Res 2002;8:3461–3467.
23 Bittesini L, Dei Tos AP, Fletcher CD. Metastatic malignant melanoma showing a rhabdoid phenotype: further evidence of a non-specific histological pattern. Histopathology 1992;20:167–170.
24 Perry A, Fuller CE, Judkins AR, *et al.* INI1 expression is retained in composite rhabdoid tumors, including rhabdoid meningiomas. Mod Pathol 2005;18:951–958.
25 Donner LR, Wainwright LM, Zhang F, *et al.* Mutation of the INI1 gene in composite rhabdoid tumor of the endometrium. Hum Pathol 2007;38:935–939.
26 Agaimy A, Rau TT, Hartmann A, *et al.* SMARCB1 (INI1)-negative rhabdoid carcinomas of the gastrointestinal tract: clinicopathologic and molecular study of a highly aggressive variant with literature review. Am J Surg Pathol 2014;38:910–920.
27 Agaimy A, Koch M, Lell M, *et al.* SMARCB1/INI1-Deficient Sinonasal Basaloid Carcinoma: A Novel Member of the Expanding Family of SMARCB1 Deficient Neoplasms. Am J Surg Pathol; advance online publication, 14 May 2014 (e-pub ahead of print).
28 Hollmann TJ, Hornick JL. INI1-deficient tumors: diagnostic features and molecular genetics. Am J Surg Pathol 2011;35:e47–e63.
29 Krasinskas AM, Moser AJ, Saka B, *et al.* KRAS mutant allele-specific imbalance is associated with worse prognosis in pancreatic cancer and progression to undifferentiated carcinoma of the pancreas. Mod Pathol 2013;26:1346–1354.
30 Lurkin I, Stoehr R, Hurst CD, *et al.* Two multiplex assays that simultaneously identify 22 possible mutation sites in the KRAS, BRAF, NRAS and PIK3CA genes. PLoS One 2010;5:e8802.
31 Nardon E, Glavac D, Benhattar J, *et al.* A multicenter study to validate the reproducibility of MSI testing with a panel of 5 quasimonomorphic mononucleotide repeats. Diagn Mol Pathol 2010;19:236–242.
32 Layfield LJ, Bentz J. Giant-cell containing neoplasms of the pancreas: an aspiration cytology study. Diagn Cytopathol 2008;36:238–244.
33 Nakajima A, Takahashi H, Inamori M, *et al.* Anaplastic carcinoma of the pancreas producing granulocyte-colony stimulating factor: a case report. J Med Case Rep 2008;2:391.
34 Lee HJ, Lee OJ, Jang KT, *et al.* Combined loss of E-cadherin and aberrant *β*-catenin protein expression correlates with a poor prognosis for small intestinal adenocarcinomas. Am J Clin Pathol 2013;139:167–176.

35 Streit M, Schmidt R, Hilgenfeld RU, *et al.* Adhesion receptors in malignant transformation and dissemination of gastrointestinal tumors. Recent Results Cancer Res 1996;142:19–50.
36 Pancione M, Remo A, Sabatino L, *et al.* Right-sided rhabdoid colorectal tumors might be related to the serrated pathway. Diagn Pathol 2013; 8:31.
37 Guillou L, Wadden C, Coindre JM, *et al.* 'Proximal-type' epithelioid sarcoma, a distinctive aggressive neoplasm showing rhabdoid features. Clinicopathologic, immunohistochemical, and ultrastructural study of a series. Am J Surg Pathol 1997;21:130–146.
38 Sullivan LM, Folpe AL, Pawel BR, *et al.* Epithelioid sarcoma is associated with a high percentage of SMARCB1 deletions. Mod Pathol 2013;26:385–392.
39 Goggins M, Offerhaus GJ, Hilgers W, *et al.* Pancreatic adenocarcinomas with DNA replication errors (RER+) are associated with wild-type K-ras and characteristic histopathology. Poor differentiation, a syncytial growth pattern, and pushing borders suggest RER+. Am J Pathol 1998;152:1501–1507.