Clinicopathological Features of Pancreatic Adenosquamous Carcinoma and Undifferentiated Carcinoma: A case series

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Abstract

Adenosquamous carcinoma(ASqC) and undifferentiated carcinoma(UC) of the pancreas are rare, and thus we do not clearly know their biological characteristics. We therefore conducted a clinicopathological study of 17 patients with ASqC or UC to investigate their clinical features, imaging findings, histopathological findings of resected specimens, and prognostic factors. The subjects were 9 patients (11.1%) with ASqC and 8 (9.9%) with UC among 81 patients with invasive ductal carcinoma. Mean survival time was 16.3 ± 5.0 months in the patients with ASqC and 12.4 ± 5.6 months in those with UC. Analysis of prognostic factors revealed that survival was shorter in the patients with confluent multinodular type than in those with simple nodular type (5.0 ± 2.4 vs. 18.4 ± 4.8 months, $P = 0.039$) in patients with stage IVb rather than stage III or IVa cancer (6.2 ± 2.9 vs. 19.4 ± 5.2 months, $P = 0.026$). Survival tended to be slightly shorter in patients who had recurrence within 6 months. Histopathological findings of immunostaining revealed that all 17 patients were positive with CK7 (a marker for adenocarcinoma) in all 17 patients. ASqC and UC were suggested to be differentiated from adenocarcinoma. They are known to have a poorer outcome than common pancreatic cancer, but may be associated with a relatively good outcome in some patients.

Key words

Pancreatic cancer, pancreatic adenosquamous carcinoma, pancreatic undifferentiated carcinoma

Introduction

Among the epithelial malignancies that occur in the pancreas, adenosquamous carcinoma (ASqC) (incidence, 0.38–4%)^{1–3)} and undifferentiated carcinoma (UC) (incidence, 2–7%)^{4–6)} are relatively rare. Thus we do not clearly know their biological characteristics. To investigate their histogenesis and clinical features, we conducted a clinicopathological study of 17 patients with ASqC or UC treated at the St. Marianna University School of Medicine.

Methods

Eighty-one patients with ductal adenocarcinoma of the pancreas were treated at our hospital between April 2005 and January 2014. Of them, 9 (11.1%) with ASqC and 8 (9.9%) with UC (17 patients in total) were retrospectively studied clinicopathologically (Table 1). These patients were all Japanese, and comprised 12 men and 5 women aged between 37 and 86 years (mean, 66.3 ± 12.5 years; median, 71 years). The mean age of the patients with ASqC was 72 ± 7.1

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Table 1. Basic Characteristics of Patients

Case No.	Pathology	Age/sex	Location	Size (mm)	CA19-9 (U/ml)
1	Adenosquamous carcinoma	74/F	Head	30	483
2		76/M	Head	33	86.5
3		74/M	Head	55	551.2
4		75/F	Head	40	8325.9
5		61/M	Tail	50	947.8
6		59/M	Tail	100	7.7
7		72/M	Tail	53	96.1
8		79/M	Head	18	52.9
9		78/M	Tail	10	38.5
10	Undifferentiated carcinoma	62/M	Tail	50	47.2
11		51/M	Head	25	178
12		54/F	Tail	100	1.6
13		56/F	Body	45	10919.7
14		37/F	Head	40	135
15		71/M	Tail	70	10
16		86/M	Body	50	66.1
17		63/M	Body	45	15

F: female, M: male

years whereas that of the patients with UC was 60 ± 14.5 years, indicating that the patients with UC were younger. The following items investigated: (1) computed tomography (CT) findings (morphological type, contrast enhancement, and presence or absence of cystic component), (2) histopathological findings, (3) clinical course (such as site of recurrence after surgery, and survival.), and (4) survival classified by several factors (histological type, tumor size, preoperative CA19-9 level, morphological type determined by CT, presence or absence of cystic component, infiltration pattern, stage, and timing of recurrence). In relation to tumor size and preoperative CA19-9 level, survival was compared between patients with values of not less than and below the median values of tumor size and CA19-9 level. We obtained approval of the St. Marianna University School of Medicine Ethics Committee (approval number:3156).

CT protocols and findings

Seventeen patients underwent triple-phase CT imaging during the unenhanced, pancreatic and portal venous phase. CT scanning was performed using an Aquilion system (Toshiba Medical Systems Corp., Tokyo, Japan). A section thickness of 2 mm with reconstruction interval of 2 mm, field of view of 300–370 mm, a gantry rotation time of 0.5 s, tube current of 150–200 mA, and peak voltage of 120 kVp were used. For the 64-detector CT scanner, we used detector collimation of 0.75 mm and table speed of 12.0 mm per rotation. For multiphase imaging, 300 mg I/ml of nonionic contrast material (iopromide injection FRI, FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan) was administered. A fixed dose of 1.5 ml iopromide per kilogram body weight was administered at a rate of 2–3 ml/s. The scanning time was early (at 35–45 s) for the unenhanced phase, and delayed (at 70–

Fig. 1. Simple nodular type: a single spherical tumor showing expansive growth.

Fig. 2. Confluent multinodular type: an irregularly shaped tumor comprised of more than one confluent nodule.

80 s) for the pancreatic and portal venous phases, following administration of the contrast material.

To determine the morphological type of tumor from the CT findings, delayed-phase images of the pancreas were examined by two radiologists and one gastrointestinal surgeon specializing in the pancreas, and consensus was reached. Simple nodular type (**Fig. 1**) was defined as a single spherical tumor showing expansive growth. Confluent multinodular type (**Fig. 2**) was defined as a tumor comprised of confluent nodules.

Preparation of histopathological specimens

To prepare histopathological specimens, the tissue was fixed in 10% formalin, embedded in paraffin, and sliced at 5-mm intervals for whole-section analysis. Specimens from all patients were subjected to immunostaining with CK7 and CK14.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation. Survival of patients classified by several factors was compared by log rank test using Kaplan-Meier survival curves. A P -value <0.05 was considered statistically significant.

Results

Imaging findings

On CT images, 13 patients had a simple nodular tumor and 4 patients (2 with ASqC and another 2 with UC) had a confluent multinodular tumor (**Table 2**). In 5 (55.6%) of the 9 patients with ASqC, the tumor was rather strongly enhanced, but it was not strongly enhanced in any of the patients with UC.

Five (55.6%) of the 9 patients with ASqC and 4 (50%) of the 8 patients with UC had a cystic component within the tumor (**Fig. 3**).

Histopathological findings

In patients with ASqC, the squamous carcinoma component accounted for 40% to a maximum of 60% of the tumor (**Table 3**). Of the patients with UC, 5 had the pleomorphic type and 3 had the osteoclast-like giant cell type. The infiltration pattern was β in all patients with UC, whereas it was β in 4 patients and γ in 5 patients with ASqC. In all 17 patients (9 with ASqC and 8 with UC), cells were positive for CK7, a staining marker for adenocarcinoma (**Fig. 4a, b**). CK14 staining was positive in 8 of the 9 patients with ASqC and in 5 of the 8 patients with UC (**Fig. 5a–c**).

Clinical course

All 17 patients had advanced cancers (stage III or higher); 9 cancers were stage III, 3 were stage IVa, and 5 were stage IVb (**Table 4**). Of the 13 patients who underwent surgery, 6 (4 of the 8 patients with ASqC and 2 of the 5 patients with UC) had a recurrence within 6 months of surgery. Recurrence in these 6 patients was in the liver. Two patients with ASqC and one patient with UC survived for 2 years or more.

Comparison of survival according to several factors

Survival was compared between patients classified by histological type, tumor size, preoperative CA19-9 level, morphological type determined by CT, presence or absence of a cystic component, infiltra-

Table 2. CT Findings

Case No.	Pathology	Morphological type	Enhancement pattern/degree	Cystic component
1	Adenosquamous carcinoma	Simple nodular type	Heterogeneous/progressive	Negative
2		Simple nodular type	Heterogeneous/progressive	Positive
3		Simple nodular type	Heterogeneous/progressive	Positive
4		Simple nodular type	Heterogeneous/progressive	Positive
5		Confluent multinodular type	Heterogeneous/moderate	Positive
6		Confluent multinodular type	Heterogeneous/moderate	Positive
7		Simple nodular type	Homogeneous/regressive	Negative
8		Simple nodular type	Homogeneous/regressive	Negative
9		Simple nodular type	Homogeneous/progressive	Negative
10	Undifferentiated carcinoma	Simple nodular type	Homogeneous/regressive	Negative
11		Simple nodular type	Heterogeneous/regressive	Negative
12		Simple nodular type	Heterogeneous/moderate	Positive
13		Simple nodular type	Homogeneous/regressive	Negative
14		Simple nodular type	Heterogeneous/moderate	Positive
15		Confluent multinodular type	Heterogeneous/moderate	Positive
16		Confluent multinodular type	Heterogeneous/moderate	Positive
17		Simple nodular type	Homogeneous/regressive	Negative

Fig. 3. Cystic component inside the tumor (→).

tion pattern, stage, and timing of recurrence (**Table 5**). Mean survival time was 16.3 ± 5.0 months in the patients with ASqC and 12.4 ± 5.6 months in those

with UC ($P = 0.621$). No significant difference in survival was observed with respect to tumor size, preoperative CA19-9 level, or infiltration pattern. However, survival was shorter in patients with a confluent multinodular tumor than in those with a simple nodular tumor (5.0 ± 2.4 vs. 18.4 ± 4.8 months, $P = 0.039$), and in patients in stage IVb rather than stage III or Iva cancer (6.2 ± 2.9 vs. 19.4 ± 5.2 months, $P = 0.026$). Survival tended to be slightly shorter in the patients who had recurrence within 6 months ($P = 0.059$).

Discussion

Invasive ductal carcinoma accounts for the majority of pancreatic malignant neoplasms and has a poor prognosis except in a series of highly selected patients undergoing radical surgical therapy for cure. ASqC and UC are unusual variant of pancreatic neoplasms. Histologically, pancreatic ASqC is distin-

Table 3. Pathologic Findings

Case No.	Pathology	Squamous cells (%)	Classification of undifferentiated carcinoma	INF pattern	CK7 staining	CK14 staining
1	Adenosquamous carcinoma	60	-	γ	Many adenocarcinoma cells were positive	Many squamous cells were positive
2		40	-	β	Many adenocarcinoma cells were positive	Some squamous cells were positive
3		50	-	γ	Many adenocarcinoma cells were positive	Negative
4		40	-	γ	Many adenocarcinoma cells were positive	Many squamous cells were positive
5		40	-	β	Only a few cells were positive	Many squamous cells were positive
6		50	-	β	Many adenocarcinoma cells were positive	Some squamous cells were positive
7		40	-	β	Many adenocarcinoma cells were positive	Many squamous cells were positive
8		40	-	γ	Many adenocarcinoma cells were positive	Many squamous cells were positive
9		40	-	γ	Many adenocarcinoma cells were positive	Many squamous cells were positive
10	Undifferentiated carcinoma	30	Pleomorphic type, spindle cell > adenosquamous > poor	β	Many adenocarcinoma cells were positive	Some squamous cells were positive
11		/	Osteoclast-like giant cell type, spindle cell type	β	Many adenocarcinoma cells were positive	Some cells were positive
12		/	Osteoclast-like giant cell type, spindle cell type	β	Many adenocarcinoma cells were positive	Negative
13		/	Pleomorphic type	β	Many adenocarcinoma cells were positive	Negative
14		/	Osteoclast-like giant cell type	β	Many adenocarcinoma cells were positive	Negative
15		/	Pleomorphic type	β	Diffusely positive	A few cells were positive
16		/	Pleomorphic type	β	Diffusely positive	Some cells were positive
17		/	Pleomorphic type	β	Many cells were positive	A few cells were positive

INF: infiltration, CK7: cytokeratin 7, CK14: cytokeratin 14, poor: poorly differentiated adenocarcinoma

Fig. 4. Hematoxylin and eosin (HE) staining of undifferentiated carcinoma (a). The tumor was positive for CK7, a staining marker for adenocarcinoma (b).

Fig. 5. HE staining of adenosquamous carcinoma (a). The adenocarcinoma component (arrow) and squamous cell carcinoma component (arrow-head) were mixed. The adenocarcinoma component was positive for CK7, whereas the squamous cell carcinoma component was only slightly positive for CK7 (b). The squamous cell carcinoma component was strongly positive for CK14 (c).

guished from ductal adenocarcinoma of the pancreas by the presence of 30% or more malignant squamous cells^{7,8}). ASqC often presents with exophytic growth and has greater vascularity than common ductal carcinoma⁹). In a large tumor of this type of carcinoma, contrast tends to be poorly enhanced in the center due to internal necrosis or cyst formation^{10,11}). In patients with pancreatic ASqC who underwent surgical resection, median survival was reported to be 6 to 14.4 months, indicating a poor prognosis^{12–14}). Boyd *et al.* analyzed 415 patients with ASqC and reported that their 2-year survival was 10.8%¹⁵). Histologically,

ASqC is presumed to arise from malignant transformation of the heterotopic squamous epithelium^{11,12}), direct malignant transformation of adenocarcinoma to squamous carcinoma^{16,17}), or other mechanisms. Presently, direct malignant transformation of adenocarcinoma to squamous carcinoma is considered to be the dominant mechanism.

UC was first reported by Sommers and Meissner in 1954 as pancreatic ductal carcinoma (pleomorphic carcinoma) mixed with a sarcomatoid component¹⁸). As in the case of ASqC, UC is characterized by expansive growth, hypervascularity, and intratumoral

Table 4. Clinical Course

Case No.	Pathology	Stage	Therapy	Adjuvant therapy	Recurrence (months)	Location of metastasis	Survival (months)
1	Adenosquamous carcinoma	IVb	PD	TS-1	1.5	Liver	11
2		IVa	PD	TS-1	7	Liver	28
3		III	PD	None	6	Liver	33
4		III	PD	None	1	Liver	3
5		IVb	Chemo	/	/	/	2
6		III	DP	TS-1	6	Local	12
7		III	DP	TS-1	No recurrence	/	9 (alive)
8		IVa	PD	None	No recurrence	/	5 (alive)
9		III	DP	None	No recurrence	/	1 (alive)
10		III	DP	None	3	Liver	4
11		III	PD	None	1	Liver, lung, lymph node	5
12		III	DP	TS-1	7	Lung	20
13		IVb	DP	TS-1	7	Dissemination	15
14		III	PD	TS-1	36	Remnant pancreas	48
15		IVa	BSC	/	/	/	4
16		IVb	BSC	/	/	/	2
17		IVb	BSC	/	/	/	1

PD: pancreaticoduodenectomy, Chemo: chemotherapy, DP: distal pancreatectomy, BSC: best supportive care

hemorrhage or necrosis¹⁹⁾. Paal *et al.* studied 35 patients with UC and reported a mean postoperative survival time of 3.3 months in patients with spindle cell tumor ($n = 4$) and 6.0 months in those with giant cell tumor ($n = 31$)⁴⁾. WHO classifies giant cell tumor, pleomorphic tumor, and spindle cell tumor as UC and osteoclast-like giant cell tumor as UC with osteoclast-like giant cells, differentiating the former three types from the latter based on their clinical features. The reason is that UC is considered to be of epithelial origin and arises from sarcomatoid metaplasia of invasive ductal carcinoma, whereas UC with osteoclast-like giant cells is considered to be of mesenchymal origin and has a relatively good outcome. However, in a recent study of patients with early

osteoclast-like giant cell tumors, Bergmann *et al.* reported that an initial carcinogenesis of epithelial origin associated with a PanIN3 lesion was found in patients with osteoclast-like giant cell tumors²⁰⁾. Thus, the general conclusion seems to be that osteoclast-like giant cell tumors also originate from epithelial cells²⁰⁾²¹⁾. Maksymov *et al.* discussed the possibility of neoplastic changes in a part of the epithelium, with cells transitionally differentiating into myoepithelial (mesenchymal) cells, and explained the diversity of the epithelial component of osteoclast-like giant cell tumors²²⁾. In the present study, we performed immunostaining of the lesions of 17 patients with two particular types of pancreatic cancer to determine their histogenesis. CK7 staining was positive in all patients

Table 5. Patient Survival Classified by Several Factors

Factor	Comparison	Survival (months)		<i>P</i> value
		(mean ± standard deviation)		
Histological type	Adenosquamous carcinoma (n=9) vs Undifferentiated carcinoma (n=8)	16.3 ± 5.0	vs 12.4 ± 5.6	0.621
Tumor size ^a	≥ 45 mm (n=10) vs < 45 mm (n=7)	11.3 ± 3.6	vs 20.7 ± 8.4	0.294
Preoperative CA19-9 level ^a	≥ 86.5 (n=9) vs < 86.5 (n=8)	17.4 ± 5.5	vs 9.7 ± 3.4	0.381
Morphological type	Confluent multinodular type (n=4) vs Simple nodular type (n=13)	5.0 ± 2.4	vs 18.4 ± 4.8	0.039 ^b
Cystic component	Present (n=9) vs Absent (n=8)	16.9 ± 5.5	vs 9.0 ± 2.2	0.447
Infiltration pattern	γ (n=5) vs β (n=12)	17.2 ± 8.7	vs 13.8 ± 4.5	0.671
Stage	IVb (n=5) vs III or IVa (n=12)	6.2 ± 2.9	vs 19.4 ± 5.2	0.026 ^b
Timing of recurrence	≤ 6 months (n=4) vs > 6 months (n=8)	9.6 ± 3.5	vs 27.8 ± 7.3	0.059

^aThe median value was used as a baseline for comparison.

^b*P* < 0.05

with ASqC and UC, whereas CK14 staining was positive in 8 of the 9 patients with ASqC and in 5 of the 8 patients with UC. It has been reported that CK7 is a staining marker for adenocarcinoma, and CK14 is a staining marker for squamous cell carcinoma. Thus, this finding suggests that carcinomas of these histological types maintain the features of adenocarcinoma while differentiating into ASqC or UC. We experienced a patient who primarily had UC and later had a recurrence of carcinoma in the remaining portion of the pancreas, which was found to be only “common” ductal carcinoma (case no. 14)²⁵. Accordingly, these findings suggests that UC can be differentiated from adenocarcinoma cells.

Mean survival was 16.3 months in the patients with pancreatic ASqC and was 12.4 months in those with UC treated in our hospital. We found that the survival was longer in the patients with stage III and IVa compared to stage IVb cancer, and the survival also tended to be slightly longer in the patients who had recurrence after 6 months. Further more, the patients with a simple-shaped single spherical nodular tumor on imaging survived longer than those with a confluent multinodular type. In our cases, 3 patients (cases 2, 3, and 14) survived for 2 years or more. In all 3 of these patients, the tumor stage was earlier (III and IVa), the recurrence was later, and the tumor revealed a simple-shaped single spherical nodular type. Although definitive staging of the tumor and estimation of the timing of relapse are difficult preoperatively, the finding of a simple-shaped single spherical

nodular tumor is easily defined preoperatively. At present there is no effective chemotherapy for pancreatic cancer, and surgery is the only treatment offering a cure. Thus, aggressive surgery may provide longer survival in patients with such imaging findings.

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