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Sarcomatous Component in Pancreatic Adenosquamous Carcinoma: A Clinicopathological Series of 7 Cases

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Abstract. *Background/Aim: The aim of this study was to examine the clinicopathological features of pancreatic adenosquamous carcinoma (PASC). Patients and Methods: Our study included seven patients who underwent resection of PASC. Results: PASC is characterized by large tumors and strong infiltration into the major blood vessels and other organs, forcing many patients to undergo extended resections. In addition, all patients experienced liver metastasis recurrence following surgery, with a very poor prognosis. Histopathologically, a poorly differentiated sarcomatous component existed in all patients in addition to an adenocarcinoma component and squamous carcinoma component. Although P40 staining for the sarcomatous component was positive along with squamous carcinoma, E-cadherin expression disappeared while vimentin was expressed. It has been suggested that it is highly likely that these sarcomatous components are derived from squamous carcinoma and have an impact on prognosis. Conclusion: The sarcomatous component may be related to the biological malignancy of PASC.*

Pancreatic cancer is a very aggressive malignancy with a very poor prognosis a 5-year survival rate of only 1-9.2%, and more than half of patients already have distant metastases at diagnosis (1-4). Among the pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC) is the most common, accounting for about 85%, and pancreatic adenosquamous cell carcinoma (PASC) is a rare type, accounting for only 1-4% (1, 2, 5). It is clearly known that the prognosis of PASC is much worse than PDAC, and even in resected patients the median survival is only 5-14.8 months (1, 2, 5-11). Moreover, in other cancers [esophageal cancer (12), gastric cancer (13), colon cancer (14), gallbladder cancer (15), bile duct cancer (16, 17), lung cancer (18), and brest cancer (19)], adenosquamous carcinoma is also a poor prognostic type. PASC is defined as a cancer in which a squamous cell carcinoma component is present at 30% or more (1, 20). It has been reported that PASC is frequently associated with tumor growth, vascular and perineural invasion, and poor tumor cell differentiation (2, 6, 7, 9). Recently, it was reported that a very poorly differentiated sarcomatous component exists in PASC to a varying degree which may potentially have a strong impact on prognosis (2, 10, 21). The higher biological malignancy of PASC and its very poor prognosis may be related to the sarcomatous component. Evaluating the sarcomatous component in PASC is expected to clarify the biological malignancy of PASC. Therefore, we evaluated the sarcomatous component in PASC and studied the relation with clinicopathological factors and prognosis.

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Patients and Methods

This clinicopathological study was conducted on seven patients with PASC among 118 patients with pancreas cancer who underwent resections at Kurume University Hospital from 2012 to 2017. The excised specimens were fixed in 10% neutral buffered formalin solution and cut into 5 μm sections which were stained with hematoxylin-eosin (HE). Microscopic evaluation of immunostaining was performed as described below. PASC diagnosis was made based on the WHO classification (1) and staging was classified using the TNM classification (22).

Immunohistochemistry. Paraffin-embedded tissues were sectioned to 4 μm and examined on a coated glass slide. Sections with a sarcomatous component were selected per patient and assessed. These were labeled with the following antibodies: E-cadherin (100×; NCH-38, Dako cytomation, Carpinteria, CA, USA), vimentin (10×; V9, Dako cytomation) and Zinc finger E-box binding homeobox

1(ZEB1) (200×; IHC419, Bethyl Laboratories, Montgomery, TX, USA). Immunostaining with all antibodies was performed for 30 min on the fully automated Bond-Max system (Leica Microsystems, Newcastle, UK) using onboard heat-induced antigen retrieval with Epitope Retrieval Solution 1 for Vimentin and Retrieval Solution 2 for E-cadherin and ZEB1, followed by a Refine polymer detection system (Leica Microsystems). p40 (BC28, Ventana medical systems, Tucson, AZ, USA) staining was performed using BenchMark ULTRA fully automated immunostaining platform (Ventana medical systems). The slides were heat-treated using Ventana's CC1 retrieval solution for 36 minutes, and then were incubated with antibody for 32 min. This automated system used the streptavidin-biotin complex method with 3,3'diaminobenzidine as the chromogen (Ventana iVIEW DAB detection kit).

Statistical analysis. Clinical characteristics were evaluated using Student's *t*-test and Chi-square test. Survival curves of both groups were made using the Kaplan–Meier method, and Log-rank test was performed. Significant difference was set at p-value<0.05. JMP Pro 13.0.0 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Patient characteristics. The patients included five males and two females, aged from 49 to 75 years old. Compared with PDAC, PASC had no difference in age, gender, tumor site, and serum CA19-9, but tumor size was significantly larger (p=0.001).

Pancreatoduodenectomy (PD) was performed in four patients and distal pancreatectomy (DP) in three patients. Three patients who received PD (75%) also underwent combined resection of portal vein (PV) and/or superior mesenteric vein (SMV), one of which included combined resection of the right hepatic artery suspected of being infiltrated. Two patients (67%) who underwent DP also underwent combined resection of the left adrenal gland, one of which included combined resection of the celiac artery suspected of being invaded. Combined resection rate of the major arteries (*e.g.*, celiac artery, common hepatic artery, right hepatic artery) and other organs (*e.g.*, left adrenal gland) were significantly higher in PASC compared with PDAC.

Pathological diagnosis revealed that there were three T2 patients and four T3 patients, which were significantly more advanced than PDAC. Infiltration into the portal vein system such as PV, SMV, and splenic vein (SV) was found in five patients (71%), which was significantly higher than PDAC. Infiltration into other organs was found in three patients (two in the left adrenal gland, one in the spleen), which was significantly higher than PDAC. Regional lymph node metastases were found in all patients, while distant metastases were found in three patients, which was significantly higher than PDAC (Table I).

All patients developed recurrence due to liver metastasis and PASC had a very poor prognosis compared to PDAC (Figure 1).

Table I. *Clinicopathological findings in the PASC and PDAC.*

	PASC (n=7)	PDAC (n=111)	p-Value
Age (y), mean±SD	62.4±9.3	67.8±8.2	0.10
Gender (%)			0.32
Male	5 (71.4)	58 (52.3)	
Female	2 (28.6)	53 (47.7)	
CA19-9, mean±SD	167.5±173.0	247.0±530.7	0.69
Location (%)			0.50
Head	4 (57.1)	77 (69.4)	
Body/tail	3 (42.9)	34 (30.6)	
Tumor size, mean±SD	45.1±16.9	27.2±12.7	0.001
Neoadjuvant therapy (%)	2 (28.6)	35 (31.5)	0.87
Surgery type (%)			0.73
PD	4 (57.1)	76 (68)	
DP	3 (42.9)	33 (30)	
TP	0	2 (2)	
Combined resection (%)			
PV and/or SMV	3 (42.9)	32 (28.8)	0.43
Major artery *	2 (28.6)	4 (3.6)	0.004
Other organs **	2 (28.6)	5 (4.5)	0.009
T category (%)			
Tis	0	1 (0.9)	0.008
T1	0	35 (31.5)	
T2	3 (42.9)	62 (55.9)	
T3	4 (57.1)	13 (11.7)	
Local invasion (%)			
Portal venous system	5 (71.4)	20 (18.0)	0.001
Arterial system	0	2 (1.8)	0.72
Nerve plexus	1 (14.3)	19 (17.1)	0.85
Other organ	3 (42.9)	3 (2.7)	<0.0001
N category (%)			0.002
N0	0	63 (56.8)	
N1	3 (42.9)	33 (29.7)	
N2	4 (57.1)	15 (13.5)	
M category (%)			<0.0001
M0	4 (57.1)	106 (95.5)	
M1	3 (42.9)	5 (4.5)	
Staging (%)			0.004
0	0	1 (0.9)	
IA	0	25 (22.5)	
IB	0	30 (27.0)	
IIA	0	4 (3.6)	
IIB	2 (28.6)	31 (27.9)	
III	2 (28.6)	15 (13.5)	
IV	3 (42.9)	5 (4.5)	
Residual tumor (%)	2 (28.6)	11 (9.9)	0.13
Histological findings (%)			
Lymphatic invasion	6 (85.7)	74 (67)	0.30
Venous invasion	7 (100)	95 (86)	0.28
Nerve invasion	7 (100)	95 (86)	0.28
Sarcomatous component	7 (100)	2 (1.8)	<0.0001

PASC: Pancreatic adenosquamous carcinoma; PDAC: pancreatic ductal adenocarcinoma; PD: pancreatoduodenectomy; DP: distal pancreatectomy; TP: total pancreatectomy; PV: portal vein; SMV: superior mesenteric vein.; *Including celiac artery, common hepatic artery, and/or right hepatic artery; **Including left adrenal gland, kidney, colon, and/or stomach.

Table II. *Immunohistochemistry of sarcomatous component.*

Case	E-cadherin	Vimentin	P40	ZEB1
1	–	+	+	+
2	–	+	+	-
3	–	+	+	+
4	–	+	+	-
5	–	+	+	+
6	–	+	+	–
7	–	+	+	–

ZEB1: Zinc finger E-box binding homeobox 1.

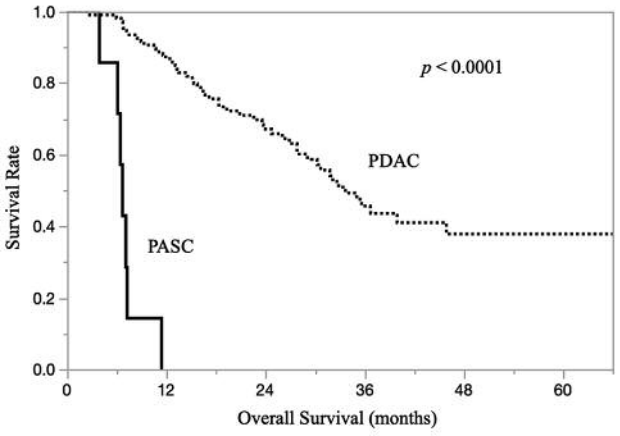

Figure 1. *Overall survival curves of patients with resected pancreatic adenosquamous carcinoma (PASC) (n=7) and pancreatic ductal adenocarcinoma (PDAC) (n=111). Median survival for PASC is 6.4 months and PDAC is 33.5 months.*

Pathological features. Macroscopically, the resected tumors were white and solid, with hemorrhage and necrosis inside. Histologically, the proliferation of bizarre tumor cells besides the adenocarcinoma component and squamous cell carcinoma component we confirmed (Figure 2A). The tumor cells lacked cell adhesion and exhibited morphologies from round to spindle-shaped. We defined them as a sarcomatous component (Figure 2B).

The frequency of occurrence of sarcomatous component was clearly significant compared to PDAC (Table I). The sarcomatous component was sometimes observed as an independent component and sometimes as a continuation of the squamous carcinoma component. We focused on this component and conducted immunological studies. E-cadherin expression was observed in adenocarcinoma and squamous cell carcinoma but not in the sarcomatous component (Figure 3A). On the other hand, Vimentin expression was not observed in adenocarcinoma and squamous cell carcinoma but in the sarcomatous component (Figure 3B). Moreover, P40 expression was not observed in adenocarcinoma but in squamous cell carcinoma and sarcomatous component (Figure 3C). ZEB1 expression was observed in sarcomatous component of three patients (Figure 3D) (Table II).

Discussion

It is difficult to detect pancreatic cancer early and is often found progressed (4). PASC is also found to be in progress, but its characteristics have become clear. PASC is characterized by its expansive growth and large tumor size. Squamous cell carcinoma is known to proliferate twice as fast as adenocarcinoma (11, 23). Hashimoto *et al*. have reported that Ki-67 labeling index is higher in squamous cell carcinoma than adenocarcinoma (24). In support of this, contrast-enhanced CT examinations often show large tumor size and internal cystic changes formed by hemorrhage and necrosis, in particular, the ring-shaped contrast effect around the tumor is a characteristic of ASC that can be a predictive factor for diagnosis (25, 26).

The most effective treatment for PASC and PDAC to prolong overall survival is surgery (2, 6, 7). In this study, all cases were resected, but there were many cases invading tissues outside the pancreas. Therefore, they underwent combined resections of the portal vein, the arteries, and other organs. If the tumor is large and combined resection is expected, the presence of PASC should be assumed.

Histopathologically, vascular infiltration and nerve infiltration were observed in all patients, and histological infiltration into surrounding organs (portal organs and other organs) was confirmed. Moreover, there were significantly more lymph node metastases and distant metastases compared to PDAC, suggesting that biological malignancy was strong. Although it is not clear why PASC is so poor, a sarcomatous component was observed in all seven patients to varying degrees. There are very few case reports on the sarcomatous component of PASC, and all report very poor prognoses (27). So, sarcomatous components were considered to be associated with poor prognosis, and we performed immunostaining to define these sarcomatous components. As a result, P40 expression which has been shown in squamous cell carcinoma was also observed in the sarcomatous component (28). Therefore, there is a high possibility that the sarcomatous component is derived from squamous cell carcinoma. In the transition from squamous cell carcinoma to sarcomatous component, it is possible that the expression of E-cadherin decreased and the expression of vimentin increased. Moreover, the expression of ZEB1 was confirmed in approximately half of the patients. Therefore, we hypothesized that epithelial–mesenchymal transition (EMT) was induced by certain factors. ZEB1, as well as snail and twist, *etc*. are known as transcription factors driving EMT (29, 30). It is considered

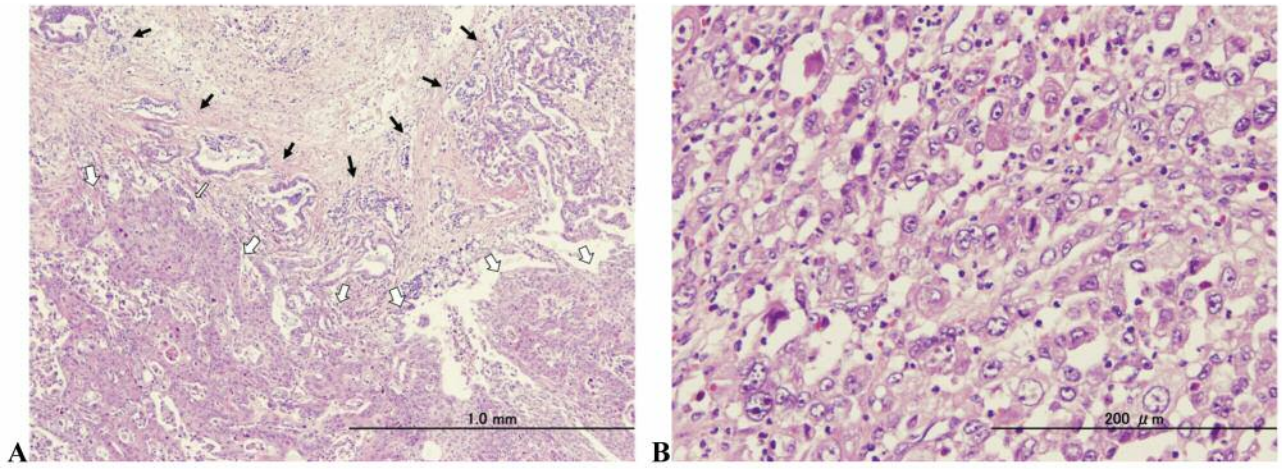

Figure 2. *Microscopic features in pancreatic adenosquamous carcinoma. (A) Adenocarcinoma component (black arrow) and squamous cell carcinoma component (white arrow) (HE staining, ×40). (B) A sarcomatous component was present in all cases, which is the lack of adhesion between cells, and the proliferation of bizarre tumor cells that exhibit morphologies from round to spindle-shaped (HE staining, ×200).*

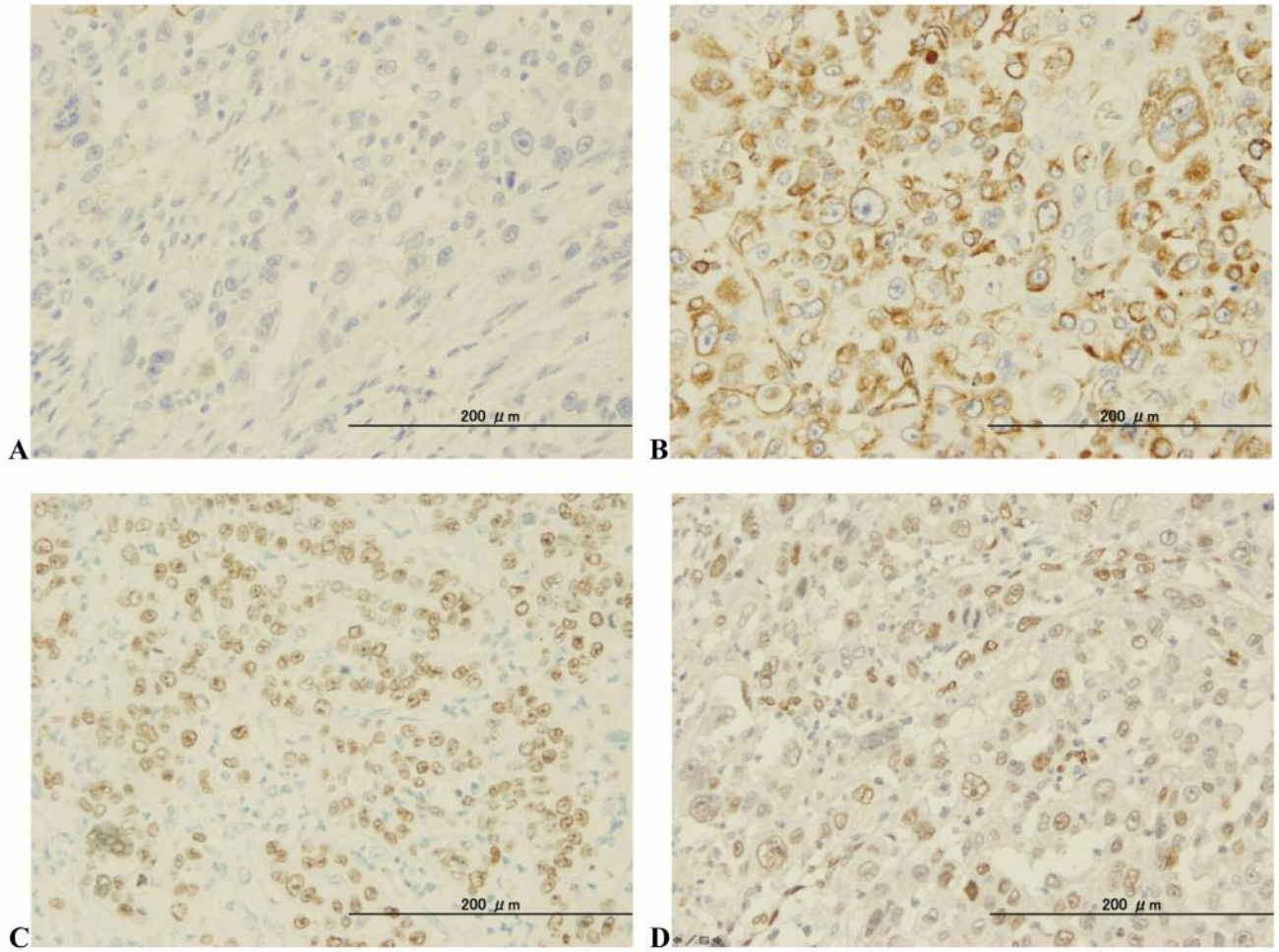

Figure 3. *Microscopic features and immunohistochemical characteristics of sarcomatous components (×200). (A) E-cadherin expression was not identified. (B) Vimentin expression was observed. (C) P40 expression was observed, similar to squamous cell carcinoma. (D) Zinc finger E-box binding homeobox 1 (ZEB1) expression was observed in three patients.*

that such a mechanism may have acted in some cases of sarcomatous component.

In this study, the survival time of all patients who underwent PASC resection was less than one year and the prognosis was very poor. The presence of squamous cell carcinoma is known to deteriorate the prognosis of pancreatic tumors (31); moreover, it is known that in cholangiocarcinoma, the prognosis is worse as the squamous cell carcinoma component is higher (16). Therefore, it is imperative to develop more effective treatments.

Recently, it has been found that PD-L1 appears at a certain percentage (15-83%) in PASC (32, 33), and development of new therapeutics including immune checkpoint inhibitors is expected. Furthermore, miR-509-5p and miR-1243 have been identified as EMT inhibitory miRNA and it has been revealed that they inhibit the expression of ZEB1 and Snail (34, 35). These are expected not only as biomarkers but also as targets of novel treatments of PDAC. Since ZEB1 expression was also confirmed in PASC in this study, they may function in the same way in some patients.

In conclusion, the biological malignancy of PASC was higher than PDAC and sarcomatous components were confirmed in all patients with PASC to varying degrees. It has been suggested that it is highly likely that these sarcomatous components are derived from squamous cell carcinoma and have an impact on prognosis. Emergence and proliferation of PASC need to be further examined for the development of future treatment strategies.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

Shinichi Taniwaki designed the study, and wrote the initial draft of the manuscript. Shinichi Taniwaki and Toru Hisaka contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All Authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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