Sarcomatoid carcinoma of the pancreas (Review)

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Abstract. Sarcomatoid carcinoma of the pancreas (SCP) is a rare and aggressive subtype of undifferentiated pancreatic ductal adenocarcinoma, with a generally poor prognosis and only sporadic cases reported worldwide. Histologically, the most notable feature of SCP is the presence of abundant of mesenchymatoid spindle tumor cells in the tumor, which lack glandular differentiation. Immunohistochemically, SCP is characterized by the expression of both mesenchymal and epithelial markers. With only a few reported cases, there is limited knowledge about its molecular and clinicopathological characteristics. Therefore, the present study performed a literature search to identify all relevant published studies. The present review provides an overview of the histogenesis, diagnosis, genetic features, prognosis and treatment of SCP, specifically focusing on the molecular alterations. Furthermore, a single-center experience is reported, which adds to the limited evidence available in the literature.

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Abbreviations: SC, sarcomatoid carcinoma; SCP, sarcomatoid carcinoma of the pancreas; PC, pancreatic cancer; CSP, carcinosarcoma of the pancreas; PDAC, pancreatic ductal adenocarcinoma; USC, undifferentiated SC; WHO, World Health Organization; UCP, undifferentiated carcinoma of the pancreas; RCP, rhabdoid carcinoma of the pancreas; TGF-β, transforming growth factor-β; EMT, epithelial-mesenchymal transition; IL, interleukin; IHC, immunohistochemistry; PARP, poly ADP-ribose polymerase; OCGCS, osteoclast-like giant cells; CK, cytokeratin; MUC1, transmembrane glycoprotein mucin 1; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1; CPS, combined positive score

Key words: PC, SC, tumors, precision oncology

Contents

1. Introduction

Pancreatic cancer (PC) is the seventh leading cause of cancer-related death globally (1). Pancreatic ductal adenocarcinoma (PDAC) accounts for >90% of PC cases and is the most typical type of PC. Despite advances in treatment, PDAC has a low survival rate, as the 5-year overall survival rate is <10% (2). Sarcomatoid (spindle cell) carcinoma (SC) is an aggressive form of carcinoma composed of malignant spindle cells, with or without a coexisting epithelial cell component. Though it can occur in all organs of the body, it mainly affects the respiratory tract, lungs, breasts and kidneys, and in extremely rare cases, the pancreas (3). Undifferentiated SC of the pancreas (SCP) is an aggressive malignant neoplasm originating in the pancreas with a poor prognosis. Following the World Health Organization (WHO) classification (Fifth edition, 2019), SCP represents a histologically undifferentiated PDAC subtype, accounting for 2-3% of all PDACs and its variants (4-6); however, the histogenesis of this carcinoma type remains debatable. Currently, the clinicopathological features, molecular landscape and therapeutic strategies for SCP are poorly understood due to its low incidence. The present review aimed to describe the histogenesis, diagnosis, genetic characteristics, prognosis and treatment of SCP, specifically focusing on the molecular alterations to elucidate potential targets for precision therapy. The eligible cases of SCP from the Affiliated Lihuili Hospital of Ningbo University (Ningbo, China) were retrospectively collated to summarize the single-center experience and a literature review was performed by searching PubMed (https://pubmed.ncbi.nlm.nih.gov) and the China Science Periodical Database (wanfangdata.com.cn) from January 1, 1990 up to August 31, 2023 with a combination of the following keywords: 'sarcomatoid carcinoma'; 'undifferentiated carcinoma'; and 'pancreatic cancer'. Studies that reported an explicit histopathological diagnosis of SCP with

follow-up data were considered eligible for inclusion in the present review. The present review excluded certain articles where terminologies such as 'carcinosarcoma', 'sarcoma-like' or 'carcinosarcomatous histology' were used, and collected and analyzed data from 38 patients with SCP (Table SI) (7-28).

2. Histological ontogeny

Histologically, SCP predominantly comprises mesenchymatoid spindle-shaped tumor cells originating from pancreatic ducts and acinus, but it does not exhibit glandular differentiation. The tumor displays a distinct biphasic component of carcinoma and sarcoma. Carcinosarcoma of the pancreas (CSP) also originates in the pancreas and has similar biphasic features (29). Previously published studies often use the terms 'carcinosarcoma' and 'sarcomatoid carcinoma' interchangeably and the definitions of these terms vary in the literature (30,31). According to the fifth edition of the WHO classification of exocrine pancreatic tumors from 2019, SCP and CSP are classified as undifferentiated carcinoma of the pancreas (UCP) (32). UCP, a subtype of PDAC, represents a group of rare tumors that account for ~5% of PC (30). The primary difference between UCP and PDAC is that UCP is a hypercellular tumor with minimal stroma and scant desmoplastic reaction, whereas conventional PDAC has a considerable amount of desmoplastic stroma with few neoplastic cells/glands. Based on the aforementioned WHO classification of exocrine pancreatic tumors, SCP consists of spindle-shaped cells that may contain allogenic components, such as bone and cartilage. The microscopic description is a critical indicator for differentiating SCP from CSP. SCP is defined as a neoplasm composed of >80% atypical spindle cells, with or without heterogenic differentiation. Pathologically, CSP is defined as a UCP subtype composed of a combination of round epithelioid cells and spindle sarcoma cells, with each component constituting ~30% of the tumor (Table I) (32). In addition, there is a transitional zone between the epithelioid and sarcomatoid cells in SCs, whilst in carcinosarcomas, these two portions are separated without such a transitional zone (Table I) (16,31). The sarcomatous tissues of the SCs exhibit biphasic expression of mesenchymal markers and epithelial markers, and ultrastructures of epithelial cells (11,16). Sarcomatoid components in carcinosarcomas do not have this feature; they express only mesenchymal markers and are negative for epithelial-derived markers (Table I) (13,32). However, the pathogenesis of SC remains unclear. Researchers have presented the following hypotheses to explain the phenomenon that a particular tumor exhibits both epithelial and sarcomatous traits biphasically: i) Conversion: The sarcomatous components are transformed from cancerous components by metaplasia; ii) collision: The sarcoma and carcinoma grow independently adjacent to each other; and iii) combination: Bidirectional differentiation of primitive totipotent stem cells into epithelium and sarcoma tissue (33-36). The genetic alterations in sarcoma and epithelial components have been reported to be nearly identical in pancreatic mucinous cystic neoplasms and sarcomatous stroma, which is consistent with the 'combination theory' that the two components of the neoplasms have the same clonal origin and subsequently differentiate into the epithelial and sarcomatous components of the carcinosarcomas (37). Since the emergence of the epithelial-mesenchymal transition (EMT) theory in cancerous tissues in the 1990s, EMT has been reported by certain researchers to explain the histogenesis mechanism of carcinosarcoma. They have pointed out that the complete transformation of epithelial cells into mesenchymal cells is a continuous process driven by the EMT program, generating cells that exhibit a series of intermediate phenotypic states. This process is regulated by contextual signals and the intracellular gene circuitry of the cells. Therefore, cells in intermediate states may exhibit the characteristics of mesenchymal cells but can retain certain epithelial markers (38). In certain instances, transforming growth factor-β (*TGF-β*) can act as an oncogene to promote the proliferation of normal epithelial cells. Therefore, *TGF-β* is considered to induce EMT in pancreatic cells and to promote the formation of SCP (Fig. 1) (39). In other tumor types, *TGF-β* is also a powerful tumor suppressor inhibiting the multiplication of pre-malignant cells by triggering apoptosis. This dual effect of *TGF-β* is mainly mediated by the Smad pathway (40). Furthermore, the pathological type, cellular context and specific environment determine the tumor responsiveness to *TGF-β* (41-43). Ren *et al* (10) reported that the plasma interleukin (IL)-11 and *TGF-β* levels were notably higher in patients with SCP compared with those in healthy controls and patients with PDAC. IL-11 is a *TGF-β* target gene and *TGF-β* induces IL-11 production in several cell types. The Smad tumor suppressor pathway mediates the expression of IL-11 and connective tissue growth factor via *TGF-β* (44). Furthermore, *TGF-β* may be a critical driver of sarcomatoid transdifferentiation in renal clear cell carcinoma (45). Kimura *et al* (26,27) assessed the expression of fibronectin, Snail and phosphorylated (p)Smad2/3 in the sarcomatoid tissues of 3 patients with SCP. Fibronectin is an extracellular marker of spindle metaplasia during EMT (46). Snail is a zinc-finger transcription factor that represses the transcription of *E-cadherin*, which is involved in the regulation of EMT during embryonic development. pSmad2 and pSmad3 are regarded as critical intracellular transduction molecules that transmit *TGF-β* signals from the cell surface into the nucleus (47,48). The aforementioned studies reported that sarcomatoid components may be converted from cancerous components via EMT mediated by TGF-β. However, further studies are required to elucidate the molecular mechanisms underlying the processes of cellular differentiation leading to SCP.

3. Diagnosis

According to the aforementioned WHO guidelines, the diagnosis of SCP is highly dependent on pathology and immunohistochemistry (IHC); however, it is challenging to distinguish SCP from other pancreatic tumors preoperatively. Potential preoperative diagnosis includes PDAC, mucinous cystic neoplasm, pseudocyst and solid pseudopapillary tumor (18). Several studies have also reported certain specific imaging features of SCP, such as large irregular cystic-solid masses, which were prone to invading adjacent organs (9,12,14,17,26). Furthermore, biopsy is crucial for the preoperative diagnosis of SCP and fine needle aspiration guided by endoscopic ultrasound has relatively high sensitivity and specificity for the diagnosis of solid pancreatic masses. The final diagnosis requires histological examination and immunohistochemical analysis. Due to the poor prognosis

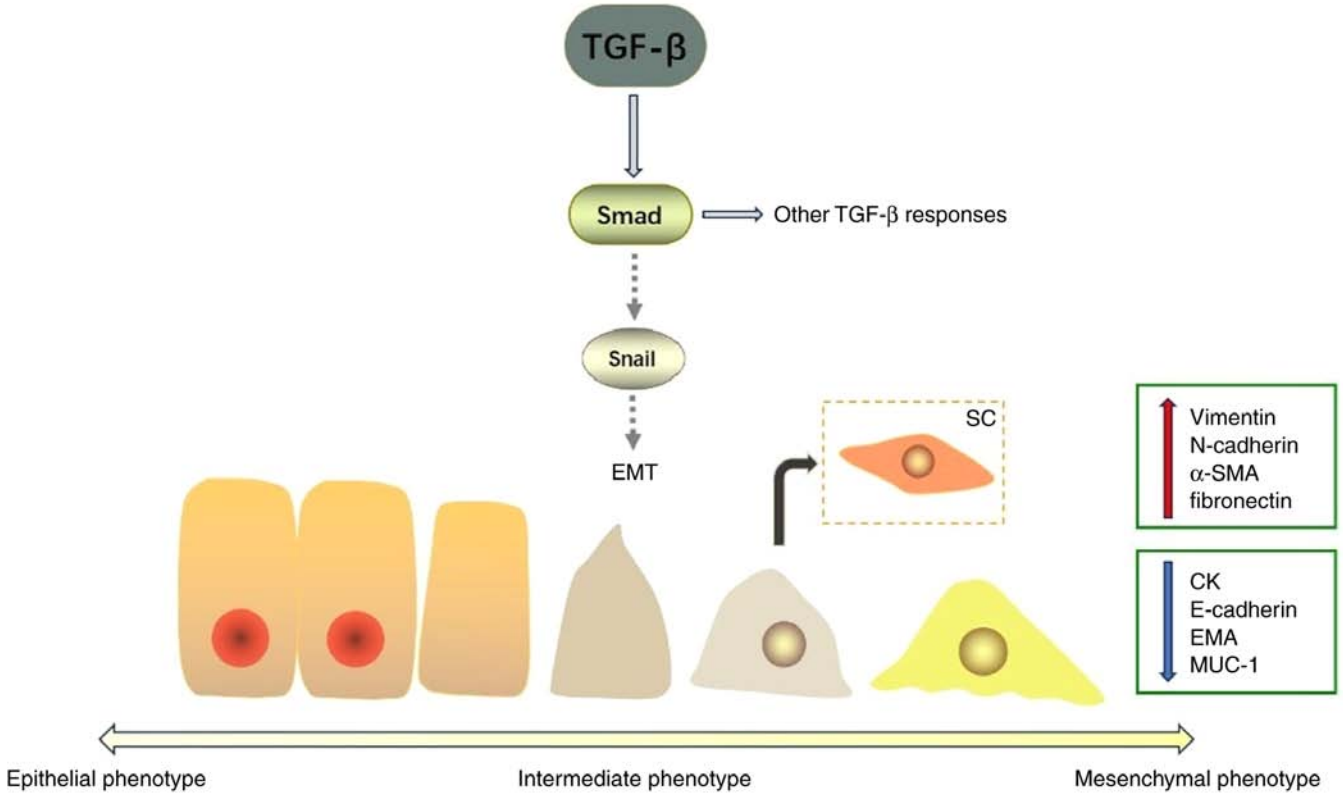

Figure 1. TGF-β-mediated EMT pathway. The EMT pathway converts epithelial cells to mesenchymal cells, which express mesenchymal markers such as vimentin, N-cadherin and α-SMA, and these mesenchymal cells lost the expression of epithelial markers at the same time. This pathway is reversible and generates a spectrum of different intermediate cells. Individual cells with certain states may biphasically exhibit both epithelial and sarcomatous features and gradually evolve into spindle cells in the SC. TGF-β regulates the EMT pathway via the Smad-Snail pathway. EMT, epithelial-mesenchymal transition; SMA, smooth muscle actin; SC, sarcomatoid carcinoma; CK, cytokeratin; EMA, epithelial membrane antigen; MUC-1, transmembrane glycoprotein mucin 1.

and aggressive clinical behavior, the early diagnosis of SCP is critical (15,20,29).

Clinical manifestation and laboratory examination. Based on the 38 patients with SCP in the present study (Table SI), the incidence of SCP was higher in middle-aged and elderly individuals, with the age of onset ranging between 48-88 years. The average age of onset was 65 years. SCP was more common in male patients than in female patients (12:7). Patients with SCP typically presented with abdominal symptoms (73.7%), weight loss (18.4%), loss of appetite, fatigue, vomiting and emaciation. Jaundice (18.4%) occurred when tumors involved the head of the pancreas blocking the biliary tract, similar to the symptoms observed with PDAC; however, 2 patients mainly complained of back pain and 4 patients were asymptomatic during the initial pre-operative visit but had tumors that were found incidentally. Abdominal palpation revealed tenderness in the upper abdomen and an abdominal mass was detected in certain cases. The analysis of serum tumor markers in 18 patients revealed elevated levels of carbohydrate antigen (CA)19-9 (61.1%) and CA 12-5 (33.3%), whilst in the remaining cases, the levels were within the normal range. Elevated liver enzyme or bilirubin levels were observed when tumors were located in the pancreatic head block bile ducts (7,8,14-16).

Imaging features. Most cases of SCP were reported based on pathological examinations; however, in 28 cases, distinct imaging features were reported. According to the data of the 28 cases (Table SI), SCP primarily occurred in the pancreatic head and pancreatic tail (head, n=13; body, n=6; and tail, n=9). The tumors were quite large, ranging between 2.4-20 cm, with a mean maximum diameter of 6.47 cm. Generally, SCPs exhibited the following features: i) Rapid growth with the presence of non-uniformly enhanced large irregular cystic-solid and cystic masses; ii) enhanced computed tomography (CT) revealed moderate tumor enhancement, with the lowest CT value in the arterial phase and the most significant in the portal phase; iii) SCPs were highly aggressive and prone to invading adjacent organs; iv) the tail of the pancreas did not atrophy in general, and SCP at the head of the pancreas frequently pressed the pancreatic duct and bile duct, causing dilation of the pancreatic duct and bile duct; and v) necrosis was common, which may be related to the rapid growth and insufficient vessels of the tumor, and the mixed cystic-solid structure (49). Nevertheless, distinguishing the undifferentiated sarcomatoid carcinoma (USC) subtype from PDAC with cystic changes is challenging. Compared with the latter, extrapancreatic vascular and perineural invasion, peripheral organ infiltration and parenchymal atrophy of the pancreas are more common in UCP (50).

Pathological features. Among the data we collected from the literature, histological examination revealed that SCP is primarily characterized by a dominance of spindle cells (15-28). These cells are heteromorphic, active in terms of nuclear division and arranged in a disorganized or interleaved

pattern. They account for >80% of the tumor cells (4,51) and are occasionally accompanied by multinucleated giant cells (52). The epithelial components, accounting for <20%, can be adenocarcinomas or squamous cell carcinomas. As demonstrated in Table SI, adenocarcinoma was the most common epithelial component, which was mainly poorly differentiated (n=8) and moderately differentiated (n=5), whilst no highly differentiated adenocarcinoma was found (n=0). A certain case exhibited an epithelial component of a mucinous cystic neoplasm (18), and another exhibited two different epithelial components, including adenocarcinoma and squamous carcinoma (12). Furthermore, one case exhibited an area of calcification/ossification with scattered large, atypical cells adjacent to malignant polymorphic spindle cell hyperplasia; the final diagnosis was SCP with heterologous elements (osteosarcomatous differentiation) (20).

IHC serves an indispensable role in the pathological diagnosis of SCP. The most notable feature of SCP is the expression of both epithelial and mesenchymal markers by its sarcomatoid components, as observed by immunohistochemical staining; however, CSP does not express the former. Vimentin is one of the most typically expressed mesenchymal markers with the highest positivity rate (7). Notably, other mesenchymal markers such as myogenic markers, including smooth muscle actin, myoglobin and desmin, neurogenic markers and osteogenic markers may be expressed in the corresponding components. Conversely, commonly used epithelial markers include cytokeratin (CK)7, CK19, CK (pan), CAM5.2 and epithelial membrane antigen, which are expressed in the epithelial and sarcomatoid areas (9,12-15). In addition, the transmembrane glycoprotein mucin 1 (MUC1) has been reported to be present in several adenocarcinomas. In one case, its expression was observed in the sarcomatoid region of SCP (7). The expression of MUC1 is also associated with tumor metastasis and recurrence (7). Furthermore, an additional two cases exhibited the loss of membranous E-cadherin expression in tumor cells of the sarcomatoid lesion (12,24). The loss of E-cadherin is also a sign of EMT (48). According to data in the present study (Table SI), the average Ki-67 index of sarcomatoid cells in SCP was 38.5%, ranging between 11-90%.

4. Genetic features

At present, there are numerous reports of the relationship between PDAC carcinogenesis and several gene alterations, including mutations in genes such as *KRAS*, *TP53*, *SMAD4* and *CDKN2A* (29,53). Due to the rarity of SCP, only a few individual cases have been reported (20,54,55), without any large prospective studies, and its genetic characterization has not been fully described. As a subtype of PDCA, SCP has a genetical landscape mimicking PDAC (29). Recently, Ding *et al* (54) assessed the clinicopathological and genetic characterization of 71 patients with USC, which included five USCs of the pancreas. This study reported the presence of highly frequent *TP53*, *RB1*, *TER0054* and *KRAS* alterations. In particular, mutations in *TP53* and *KRAS* were identified in all cases and the *KRAS* mutation was reported to be associated with a poor prognosis (54). Furthermore, a next-generation sequencing (NGS) analysis of 10 SCP samples revealed that SCP was genetically similar to PDAC. It was also reported that 100% of these samples exhibited *KRAS* mutations, 90% exhibited *TP53* mutations and 60% exhibited *CDKN2A* mutations. However, SCP also exhibited several critical genetic characteristics that were distinct from PDAC. *SMAD4*, a tumor suppressor gene that is altered in 50-60% of conventional PDAC cases (56,57), was mutated in only 1 SCP case (10%). This type of mutation may indicate early metastasis of the tumor (56). Furthermore, tumor cells in PDAC rarely revealed recurrent *KRAS* amplification, whilst it was present in 3/10 cases. Similarly, rhabdoid carcinoma of the pancreas (RCP) is a subtype of UCP. A cohort study on RCP revealed this amplification in 5/13 (38%) patients (58). Moreover, in at least a subset of patients with PDAC, *KRAS* amplification may be a genetic driver for the acquisition of undifferentiated morphology. Finally, two potential molecular therapeutic targets such as the *POLQ* mutation and *MCL1* amplification that did not belong to the typical PDAC molecular landscape were detected in 2 cases (55).

PDAC is occasionally associated with germline *BRCA* mutations. The *BRCA* genes, including *BRCA1* and *BRCA2*, encode proteins involved in repairing the broken DNA double strands via the homologous recombination pathway (20,59). A previous large prospective study reported that patients with pathogenic *BRCA1/2* variants may benefit from poly-ADP ribose polymerase (PARP) inhibitor treatment, an emerging therapy targeting the genes involved in DNA maintenance (59). A study reported mutations in *TP53* and *KRAS*, as well as *BRCA2* (20). The molecular profiles of the SCP cases we collected are summarized in Table II. Overall, these genomic profiling results indicate encouraging outcomes for precise targeted therapy in SCP.

At present, validated predictive biomarkers for immunotherapy include programmed death ligand 1 (PD-L1), as well as microsatellite instability and tumor mutation load. As presented in Table II, all previously mentioned cases exhibited low levels of tumor mutation burden with microsatellite-stable states, indicating poor outcomes of immunotherapy. Notably, Lehrke *et al* (60) reported that patients with UCP with osteoclast-like giant cells (OCGCs) expressed PD-L1 significantly more frequently than patients with PDAC (63 vs. 15%; $P<0.01$). Another study retrospectively evaluated PD-L1 and Notch expression in 6 cases of SCP (61). The combined positive score (CPS) is an index that can be used to evaluate PD-L1 expression in tumor's and is obtained by dividing the number of PD-L1-stained cells, namely tumor cells, macrophages and lymphocytes, by the total number of viable tumor cells multiplied by 100 (61). A CPS ≥1 was typical in 5 cases of SCP (83%) and 3 of the subjects (50%) had a CPS ≥50. This finding indicates an improved effectiveness in SCP compared with conventional PDAC. However, high expression levels of Notch1 and Notch3 were also reported in all cases. Further immunofluorescence analysis revealed that, when the expression levels of PD-L1 and Notch3 were upregulated within the cytoplasmic or membranous compartments of the sarcomatoid cells, both proteins were co-localized in the same cells, providing a rationale for future research in anticipation of evaluating the potential crosstalk between the PD-L1/programmed cell death protein 1 axis and the Notch3 pathway (61). Therefore, further studies on the significance of immunotherapy are required.

The research into molecular classifications and genetic signatures has long spurred the development of novel therapeutic strategies, enabling medical practitioners to make accurate and personalized decisions. Table III summarizes

Table I. Histopathological characteristics of undifferentiated carcinoma of the pancreas.

Characteristic	Sarcomatoid carcinoma	Carcinosarcoma
Spindle cells, %	>80	>30
Epithelioid cells, %	<20	>30
Presence of transitional zone	Yes	No
Markers expressed	Mesenchymal and epithelial	Only mesenchymal

Table II. Summary of genomic alterations in the cohort of sarcomatoid carcinoma of the pancreas.

				Gene alteration				
First author/s, year	Case	TMB, muations/mb	MSI	Gene	Variation	Mutation type	Frequency	(Refs.)
Zhang *et al*, 2023	11	6.2	No	KRAS	p.G12V	NA	55	(20)
				NTRK3	p.T261A	NA	48	
				BRCA2	p.L698P	NA	21	
Gkountakos *et al*, 2022	1	7.6	No	KRAS	p.G12V	Substitution: Missense	68	(55)
				TP53	p.M237I	Substitution: Missense	29	
				SMAD4	p.Q28fs*17	Deletion: Frameshift	36	
	2	8.6	No	KRAS	p.G12V	Substitution: Missense	62	
				TP53	p.G245S	Substitution: Missense	41	
	3	6.7	No	KRAS	p.Q61H	Substitution: Missense	40	
				TP53	p.Y220C	Substitution: Missense	37	
	4	5.4	No	KRAS	p.Q61H	Substitution: Missense	57	
				TP53	p.C176Y	Substitution: Missense	26	
	5	5.4	No	KRAS	p.G12D	Substitution: Missense	13	
	6	4.9	No	KRAS	p.G12D	Substitution: Missense	51	
				TP53	p.R248Q	Substitution: Missense	38	
				PHF6	p.F19_G29del	Deletion: In frame	17	
	7	11.9	No	KRAS	p.G12C	Substitution: Missense	25	
				TP53	p.P177_C182del	Deletion: In frame	20	
	8	10.8	No	KRAS	p.G12D	Substitution: Missense	48	
				TP53	p.K101*	Substitution: Nonsense	35	
				CDKN2	p.H83Y	Substitution: Missense	37	
	9	7.0	No	KRAS	p.G12D	Substitution: Missense	57	
				TP53	p.R175H	Substitution: Missense	92	
				CDKN2	p.P81L	Substitution: Missense	82	
	10	5.4	No	KRAS	p.G12D	Substitution: Missense	77	
				TP53	p.R273C	Substitution: Missense	50	
				POLQ	c.7389þ1G>A	Substitution: Splice site	44	
Present study	12	4.0	No	BRCA1	p.I1824fs	Deletion: Frameshift	53	-
				Tp53	p.Y234C	Substitution: Missense	14	
				KRAS	p.Q61H	Substitution: Missense	9	

TMB, tumor mutation burden; MSI, microsatellite instability; KRAS, Kirsten rat sarcomaviral oncogene homolog; NTRK, neurotrophin receptor kinase; BRCA, breast cancer susceptibility gene; SMAD4, SMAD family member 4; POLQ, DNA polymerase θ; TP53, tumor protein p53; PHF6, plant homeodomain-like finger protein 6; CDKN2, cyclin dependent kinase inhibitor 2A.

gene alterations in SCP compared with in PDAC. Nevertheless, due to the low incidence of SCP, there are limited genomic profiling data available. Thus, further studies based on larger cohorts of patients with SCP are warranted to explore the genetic features of SCP.

5. Prognosis and treatment

Due to its rarity, the surgical protocols, postoperative adjuvant treatments and overall prognosis of SCP are insufficiently described in the literature. Notably, no direct

Table III. Gene alterations of sarcomatoid carcinoma of the pancreas.

First author/s, year	Key gene	Mutation rate	Alteration	(Refs.)
Gkountakos *et al*, 2022	*SMAD4*	1/10	Downregulation	(55)
	POLQ	2/10	Upregulation	
	KRAS amplification	3/10	Upregulation	
	MCL1 amplification	2/10	Upregulation	
Agaimy *et al*, 2015	*KRAS* amplification	5/13	Upregulation	(58)
Silvestris *et al*, 2021	*PD-L1* CPS ≥1	5/6	Upregulation	(61)
	Notch2	0/6	Downregulation	
	Notch3	6/6	Upregulation	

SMAD4, SMAD family member 4; POLQ, DNA polymerase θ; KRAS, Kirsten rat sarcomaviral oncogene homolog; MCL1, myeloid cell leukemia-1; PD-L1, programmed death-ligand 1; CPS, combined positive score.

Table IV. Serological alterations in cases of sarcomatoid carcinoma of the pancreas at the Affiliated Lihuili Hospital of Ningbo University (Ningbo, China).

	Case							
Parameter	1	2	3	4	5	6	7	Normal range
TB, mmol/l	9	8.5	149.6	192.6	13	17.2	135.3	0-23.0
DB, mmol/l	2.7	2.1	127.4	165.2	4.5	6.2	116.8	0-8.0
ALT, U/l	11	11	233	164	25	22	195	7-40
AST, U/l	19	14	116	81	26	28	133	13-35
CA19-9, U/ml	38	13.1	56.9	39.3	109.2	1986	22	0-37.0
CA12-5, U/ml	101.7	4.6	83.2	6.2	6.6	134.7	5.5	0-30.2

TB, total bilirubin; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CA, carbohydrate antigen.

comparisons between SCP and PDAC have been made; however, patients with SCP tend to have worse survival rates than those with PDAC (11,28). Generally, most patients present with an advanced, unresectable state of the disease, with only ~12% of the patients surviving >5 years (62). For patients presenting with resectable disease (10-15%), surgery followed by adjuvant chemotherapy is the standard therapeutic approach, with an anticipated median overall survival of 54.4 months (53).

The poor prognosis of SCP makes identifying effective treatments a top priority. Notably, total R0 surgical extirpation is the sole opportunity for a radical cure (28,63) and it has been reported that patients who did not undergo complete R0 tumor extirpation had an early recurrence, leading to mortality in <3 months. Surgical procedures mainly include pancreaticoduodenectomy and distal pancreatectomy. Occasionally it is necessary to remove the surrounding invaded organs to ensure the complete removal of the tumor. In addition to surgery, patients can benefit from postoperative adjuvant treatments, especially chemotherapy (29). A study analyzing the prognoses of 261 patients with UCP indicated that surgery was the first choice for resectable UCP and that adjuvant therapies needed to be introduced immediately (64). Generally, patients with UCP were administered the same regimens as those with more common PDACs. Albumin paclitaxel and gemcitabine, and fluorouracil, irinotecan, leucovorin and oxaliplatin, the first-line chemotherapy regimens for PDAC, are also the preferred choices of adjuvant therapy for SCP (53,65). Furthermore, gemcitabine has been reported to be effective in patients with tumor recurrence or portal vein thrombosis (65). A multicenter cohort study retrospectively analyzed the outcomes of 50 patients with unresectable UCP and assessed the efficacy of several chemotherapies. It was reported that the median overall survival of these patients was 4.08 months and a paclitaxel-containing regimen was associated with a relatively longer survival (65). Gkountakos *et al* (29) also reported that complete surgical resection followed by PDAC-standardized adjuvant chemotherapy was the only tangible possibility for long-term survival in patients with SCP. Another retrospective study reported 8 patients with SCP in a single center. 2/8 cases underwent R0 resection and received adjuvant therapy with the tumors located in the body/tail of the pancreas, surviving >5 years. Furthermore, one of the aforementioned cases had a survival of ~16 years in spite of lymph node metastasis, representing the longest survival time of patients with SCP in the literature, to the best of our

knowledge (28). Additionally, immune checkpoint inhibitors are increasingly being administered in several types of cancer; however, PDAC has shown a limited response to immunotherapy compared with other tumor types. It has been reported that PD-L1 expression is more frequent in SCP and UCP. Therefore, immunotherapy has become a promising treatment option (29,59); however, its effectiveness in SCP needs to be confirmed in large prospective studies.

Molecular alterations may serve as targets for precise therapy. These abnormal genetic events can be detected by NGS and can be used to find approaches to selectively kill tumor cells (66). SCP is genetically similar to PDAC (29,55). In general, the main stages of tumorigenesis include oncogene activation and tumor suppressor inactivation. Notably, numerous researchers are working to develop strategies to target oncogenes such as *KRAS*; however, no KRAS inhibitor has reached the clinical application stage at present (67). Advances have been made in clinical and preclinical trials of treatments targeting *TP53*, *CDKN2A* and *SMAD4*, the three major tumor suppressors of PDAC (53), and further studies are warranted to assess whether the reactivators clinically improve the prognosis of patients. Moreover, the genes involved in chromatin stabilization and remodeling, such as *BRCA* and *KDM6A*, have been reported to be deficient in patients with PDAC and SCP (66). It is encouraging that administering PARP inhibitors to block base-excision repair leaves both double- and single-stranded DNA breaks unrepaired, leading to death of the cells with *BRCA* dysfunction (68). Furthermore, a phase III trial reported that, among patients with germline *BRCA* mutations and metastatic PC, the progression-free survival was longer in patients with maintenance olaparib administration than in those with placebo administration (69). Therefore, precise therapy based on molecular alterations is a promising approach.

In PDAC, several histopathological factors have been reported as prognostic factors, including tumor grade, R0 resection margin, lymph node status and adjuvant therapy (28,70). In SCP, a comparison analysis of these factors is not adequate. Notably, evidence has suggested a possible association between cellular senescence induced by TGF-β and long-term survival could be interpreted as a promising finding. The study reported positive staining for fibronectin, Snail and pSmad2/3 at the IHC level in the tumor cells of 3 patients with SCP. γ-H2AX, p53 and p21, typically used as markers of cellular senescence, were observed in the sarcomatoid component of a case with long-term survival but not in the others. Consistent with this finding, the Ki-67 labelling index of the long-term survivor was the lowest compared with that of the other 2 patients (26,27). The Ki-67 labelling index is a strong prognostic factor in pancreatic neuroendocrine tumor (71); however, its clinical significance in PDAC has not been thoroughly evaluated. Therefore, TGF-β-mediated senescence and a low Ki-67 labelling index may be critical in reducing the proliferation and metastasis of sarcomatous cells. Furthermore, OCGCs, the multinucleated giant cells with abundant cytoplasm resembling giant cell tumors of the bone, have previously been reported to protect against anaplastic carcinoma, with long-term survival reported in ~50% of patients in a previous study (30,72).

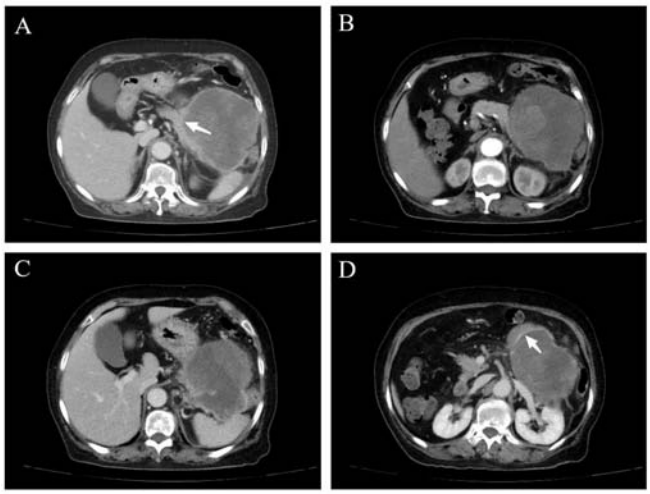

Figure 2. Representative CT images of sarcomatoid carcinoma of the pancreas from the single-center experience in the present study. The patient was a 76-year-old female. CT revealed the following: (A) A 10.1-cm mass in the left upper abdomen, closely related to the tail of the pancreas (arrow). The boundary between the lesion and the adjacent small intestine, stomach and left kidney was blurred; (B) in the arterial phase, the retroperitoneal tumor showed partial solid component enhancement; (C) in the portal phase, the posterior peritoneal tumor showed clear peripheral enhancement; and (D) the adjacent small intestine was displaced by this mass and the serositis was obviously enhanced (arrow). CT, computed tomography.

6. A single-center experience

We included cases with histological diagnosis of PDAC and excluded cases with a previous history of malignant tumors. Between August 2015 and August 2023, 603 cases of PDAC, including 7 cases of SCP, were pathologically confirmed at the Affiliated Lihuili Hospital of Ningbo University (Ningbo, China) and the prevalence of SCP in all PDACs was 1.16%, which is lower than that previously reported in the literature (1,2). Of the 7 cases (Table SI), 3 exhibited abdominal pain, 3 exhibited jaundice and 1 was asymptomatic. Serum bilirubin, mainly direct bilirubin, alanine aminotransferase and aspartate aminotransferase increased in all 3 cases with jaundice. CA 19-9 was increased in 5 cases, and CA 12-5 was increased in 3 cases (Table IV). All the patients underwent contrast-enhanced CT. CT revealed that the pancreatic mass was cystic-solid or cystic, with inhomogeneous or mild enhancement, and the boundary was mostly unclear (data not shown). Fig. 2 presents the imaging features of a typical case.

As indicated in Table SI, 6 patients underwent radical surgery and histological examination (Fig. 3), and all had lymphovascular and perineural invasion. The tumor invaded adjacent organs (duodenum, n=2; stomach, n=1; and colon, n=1) in 4 patients (57.1%). A total of 2 patients (28.6%) had no lymph node metastases, whereas the remaining patients had ≥1 positive lymph node metastasis. All samples examined by immunohistochemical staining were positive for vimentin and CK (Fig. 4). The protocol was as follows: Samples of all cases were fixed with 3.7% neutral formaldehyde solution, dehydrated, embedded in paraffin and slices were subjected to H&E staining according to routine procedures to prepare slides observed under a light microscope. All paraffin blocks containing tumors were stained with 34BE12+P540s double labelling.

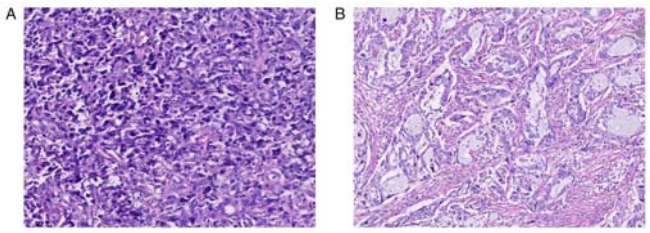

Figure 3. Histopathological images of sarcomatoid carcinoma of the pancreas from the single-center experience. (A) The tumor is characterized by a predominance of sarcoma-like appearance and spindle-shaped cells (H&E stain; magnification, x100). (B) The epithelial component that accounts for a minority of tumors is adenocarcinoma (H&E stain; magnification, x40).

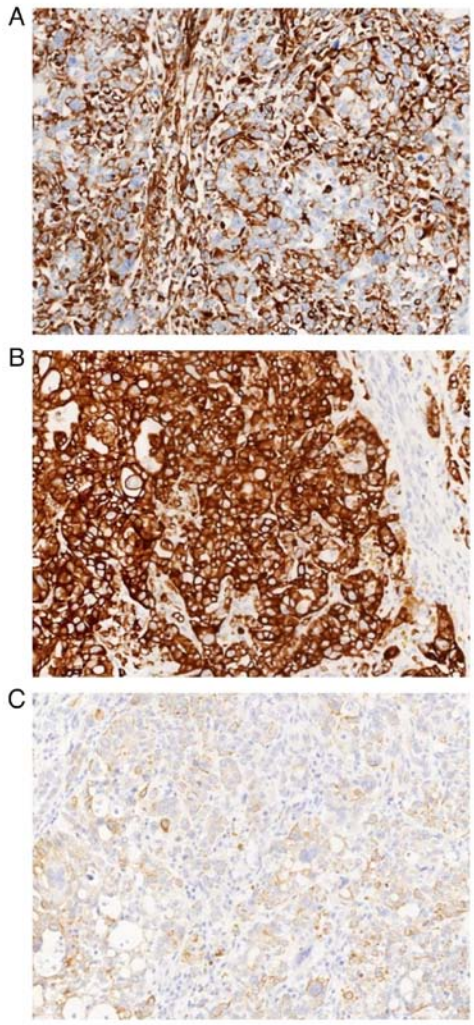

Figure 4. Immunohistochemical assessment of sarcomatoid carcinoma of the pancreas from the single-center experience. Tumor cells demonstrate positive expression of (A) vimentin, (B) CK7 and (C) CK19 (magnification, x100). CK, cytokeratin.

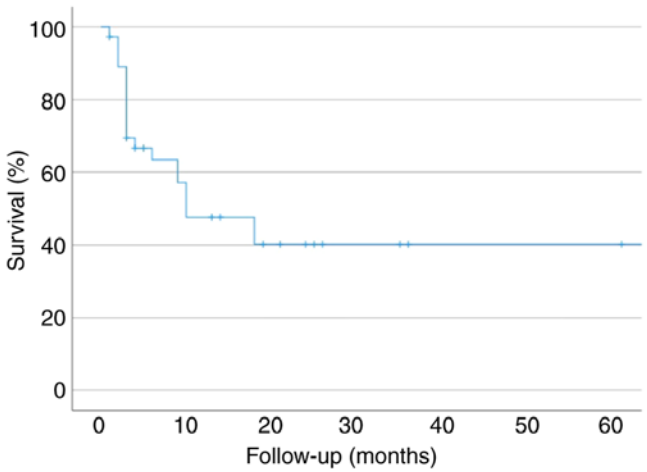

Figure 5. Kaplan-Meier curve of the 38 patients with sarcomatoid carcinoma of the pancreas.

Immunohistochemical staining for certain markers in the cases was performed at the time of diagnosis. Immunohistochemical analysis was performed at the clinical laboratory of our institution using the Roche BenchMark automated system (Roche Diagostics) with appropriate controls. The following primary antibodies were applied: CK7 [cat. no. ZM-0071; 1:200 dilution; Zhongshang Goldenbridge (ZSGB)-Bio], CK19 (cat. no. l1006; pre-diluted antibody; Biolynx), CK20 (cat. no. ZA-0574; 1:100 dilution; ZSGB-Bio), CK8/18 (cat. no. ZM-0315; pre-diluted antibody; ZSGB-Bio), MUC1 (cat. no. CMM-0251; pre-diluted antibody; Celnovte), smooth muscle actin (cat. no. CAM-0191; pre-diluted antibody; Celnovte), human melanoma black 45 (cat. no. ZM-0187; 1:1 dilution; ZSGB-Bio), vimentin (cat. no. ZM-0260; 1:200 dilution; ZSGB-Bio) and Ki-67 (cat. no. ZM-0166; 1:800 dilution; ZSGB-Bio). All antibodies were incubated for 30 min at room temperature. Next, a conjugated secondary antibody was added (cat. no. DS0003; pre-diluted antibody; ZSGB-Bio) and incubated at room temperature for 30 min. Subsequently, visualization was performed by applying 0.1% 3,3'-di-aminobenzidine tetrahydrochloride solution for 5 min at room temperature. The sections were finally counter-stained with Mayer's hematoxylin for 1 min at room temperature, dehydrated and mounted with coverslips after being embedded in mounting medium. The slides were stored at room temperature. The sections were viewed under a light microscope by two independent pathologists blinded to the patients' clinical data. Immunoreactivity was evaluated in a semiquantitative manner to assess the percentage of immunopositive tumor cells: Negative (-), 0%; focal, <25%; moderate, 25-75%; and diffuse, >75%.

In all 3 surviving patients, the tumor was located in the distal pancreas rather than in the pancreatic head, without distant metastases. Among them, 1 patient underwent a gene test. The NGS revealed *TP53* and *KRAS* mutations, and a pathogenic variant of the germline *BRCA1* gene. Therefore, the patient received a PARP inhibitor because of their poor tolerance to chemotherapy; to the best of our knowledge, this is the first report of this drug administration to a patient with SCP in the literature. It was encouraging that a good result was obtained after administering olaparib to the patient with a germline *BRCA* mutation and this prompted continuation of the genetic testing of patients with rare tumors.

Accordingly, as presented in Table SI, the 3-month and 1-year mortality rates of the patients with SCP exceeded 23.3 and 46.7%, respectively, despite aggressive surgical management, with many succumbing to early metastasis. Subsequently, Kaplan-Meier curves of the survival outcomes

of all patients with SCP were plotted (Fig. 5), and the median overall survival time was 10 months. Despite the small sample size and incomplete follow-up data, the data indicates that SCP is associated with a worse prognosis.

7. Conclusions

SCP is a rare subtype of PDAC and is generally considered to be an aggressive neoplasm with a poor prognosis. Nevertheless, the low incidence and the incomplete understanding of its clinical course hinder the possibility of performing large-scale studies on patients with SCP. At present, the treatment strategy for SCP is empirical therapy based on medical research of PDAC. Similarly, surgical resection followed by PDAC-standardized adjuvant chemotherapy is the most likely treatment option for achieving long-term survival. A considerable portion of patients with SCP may benefit from emerging immunotherapy-based strategies in the near future. Notably, patients with SCP frequently exhibit *TP53* and *KRAS* mutations, highlighting the hereditary homogeneities with PDAC; however, there are also certain crucial distinctions. Particularly, certain molecular alterations in SCP, including *BRCA* mutation, *MCL1* amplification and *POLQ* mutation, uncover more genetic features and provide novel therapeutic targets. For example, PARP inhibitors aim to selectively kill carcinoma cells with *BRCA* mutation. Lately, several clinical trials have confirmed the partial efficacy of olaparib, prompting further investigation to achieve synthetic lethality in PC. For this reason, there is an urgent need for genomic and transcriptomic studies based on larger cohorts of patients with SCP to explore its molecular profile in greater depth and to identify its histogenesis.

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Availability of data and materials

The data generated in the present study may be found in the CNGB Sequence Archive of China National GeneBank DataBase under accession number CNP0005730 or the following URL: https://db.cngb.org/search/project/CNP0005730/. All other data generated in the present study may be requested from the corresponding author.

Authors' contributions

SM, CL, YM and KW conceived and designed the study. HZ performed the pathological examination of the patients in our center. YM, HZ and KW collected and analyzed the data from our single center. YM, YY, YH, SW, HZ and JM performed the literature searches and drafted the manuscript. All authors have read and approved the final manuscript. YM and KW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by The Ethics Committee of The Affiliated Lihuili Hospital of Ningbo University (Ningbo, China; approval no. KY2021PJ263) and was performed in accordance with the Declaration of Helsinki.

Patient consent for publication

Written informed consent for publication (case 32) was obtained from the patient and their relative.

Competing interests

The authors declare that they have no competing interests.

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