Unusual early-stage pancreatic sarcomatoid carcinoma

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Abstract

Sarcomatoid carcinoma of the pancreas (SCP) is a very rare pathological type of carcinoma that usually has a poor prognosis. Its pathogenesis has not been elucidated. We herein report a case of an early-stage SCP involving successful treatment and a good prognosis. The patient was a 48-year-old Chinese man with a 5-mo history of vague abdominal pain. Ultrasonography revealed a 93 mm × 94 mm × 75 mm mass of mixed echogenicity in the tail of the pancreas. Laboratory test results were within the normal range, with the exception of an obviously increased pretreatment neuron-specific enolase level. The plasma transforming growth factor (TGF)$\beta_1$ and interleukin-11 levels were obviously increased according to enzyme-linked immunosorbent assay. Microscopically, the excised tumor tissue comprised cancer cells and mesenchymal cells. Immunohistochemical analysis was positive for $\alpha$-1-antichymotrypsin, pan-cytokeratin, cytokeratin 19, cytokeratin 8/18, and vimentin and negative for CD68 and lysozyme. The pathogenetic mechanism of this case shows that TGF$\beta_1$ may regulate the epithelial-to-mesenchymal transition in SCP. With early eradication of the tumor and systemic therapy, this patient has been alive for more than 3 years without tumor recurrence or distant metastasis. This case is also the first to show that TGF$\beta_1$ may regulate the epithelial-to-mesenchymal transition in early-stage SCP.
mesenchymal transition in SCP. This case is also the first to show that TGFβ1 may regulate the epithelial-to-mesenchymal transition in early-stage SCP.

### INTRODUCTION

Microscopically, sarcomatoid carcinoma of the pancreas (SCP) comprises mostly anaplastic cells and is strikingly sarcoma-like in appearance. SCP may originate from many different organs, such as the pancreas, lung, liver, and esophagus. Confirmation of this disease is often based on the pathological diagnosis. Advanced radiographic studies are also good tools with which to support the diagnosis of sarcomatoid carcinoma. Early diagnosis and eradication of the tumor is important for a better prognosis of malignant sarcomatoid carcinomas.

It has been proposed that during malignant progression, carcinoma cells undergo an epithelial-to-mesenchymal transition (EMT), which is a vital step in the formation of pancreatic ductal adenocarcinoma (PDAC). The etiology of SCP is unknown. The EML4-ALK fusion gene was reportedly involved in the development of a sarcomatoid carcinoma of the lung. ALK gene amplification is a nonrandom and clonally related event in a subset of pulmonary sarcomatoid carcinomas, but its biologic rationale deserves further investigation.

The mechanism of the formation of SCP and its metastasis remains unknown.

### CASE REPORT

A 48-year-old Chinese man suffered from vague abdominal pain for 5 mo. He had no evidence of jaundice, hematuria, vomiting, or fever, but abdominal swelling and chest distress were present. He had no smoking or drinking habits, and no history of malignant or other diseases. Ultrasonography revealed a 95 mm × 94 mm × 75 mm mass of mixed echogenicity in the tail of the pancreas (Figure 1). Computed tomography (CT) showed displacement of the retroperitoneal organs by the mass (Figure not shown).

Laboratory test results, including a blood count, serum biochemistry, and urinalysis, were within the normal ranges. The levels of 11 common serum tumor markers, including CA19-9, CEA, and CA242, were normal, except that NSE was obviously increased before any treatment (Table 1). The plasma transforming growth factor (TGFβ)1 and Interleukin (IL)-11 levels were higher than those of the healthy controls, patients with PDAC, and patients with pancreatic intraepithelial neoplasias (PanINs) (Table 2).

Surgery was performed, and the tumor was completely resected. The mass measured 10 cm × 8 cm × 3.5 cm and had cystic features after the excision. The section containing the solid tumorous tissue was pale in color. Microscopically, the excised tumor tissue comprised cancer cells and mesenchymal cells, with dispersion of atypical cells and obvious karyokinesis. Some were fusiform in shape and some were multinucleated giant cells (Figure 1A and B). Therefore, SCP was pathologically diagnosed. The neighboring lymph nodes and incisal margin were free of tumor cells. Immunohistochemical study results showed that the tumor cells were positive for vimentin, α-1-antichymotrypsin (AACT), cytokeratin (Figure 1A), and pan-cytokeratin (Figure 1D) and negative for CD68 and lysozyme (data not shown). Thus, an early-stage SCP was diagnosed.

The preoperative diagnosis was cystadenoma in the tail of the pancreas. Seven months after surgical excision, there was no evidence of tumor recurrence or metastasis. Digital subtraction angiography interventional chemotherapy was then implemented. Gemcitabine (1.4 g), oxaliplatin (150 mg), and floxuridine (1.0 g) were intravenously injected via the superior mesenteric artery and celiac trunk artery. After 28 mo of follow-up, a

### Table 1  Pretreatment serum tumor markers

| Tumor markers | Index | Normal range |
|---------------|-------|--------------|
| CA19-9 (KU/L) | 1.21  | < 35.00      |
| CA242 (KU/L) | 1.14  | < 20.00      |
| CA125 (KU/L) | 11.71 | < 35.00      |
| CA15-3 (KU/L) | 2.32  | < 35.00      |
| NSE (ng/mL)  | 23.42 | < 13.00      |
| CEA (ng/mL)  | 0.24  | 5            |
| Ferritin (ng/mL) | 16.17 | < 32.00 |
| p-HCG (MIU/mL) | 0.12 | < 3.00 |
| AFP (ng/mL)  | 1.07  | 20.00        |
| Free-PSA (ng/mL) | 0.32 | < 1.00 |
| PSA (ng/mL)  | 1.53  | < 5.00       |
| HGH (ng/mL)  | 0.36  | < 7.50       |

CA: Cancer antigen; NSE: Neuron-specific enolase; CEA: Carcinoembryonic antigen; p-HCG: β-human chorionic gonadotropin; AFP: α-fetoprotein; PSA: Prostate-specific antigen; HGH: Human growth hormone.

### Table 2  Plasma transforming growth factorβ1 and interleukin-11 in sarcomatoid carcinoma before any treatment

| Tumor (pg/mL) | Index (median) | n |
|---------------|----------------|---|
| TGFβ1         | 35688          | 1 |
| PDAC          | 10475 (5142-50865) | 20 |
| PanINs        | 7949 (6655-11404) | 10 |
| HC            | 6865 (3272-22463) | 11 |
| IL-11         | 58             | 1 |
| HC            | 22 (10-42)     | 11 |

SCP: Sarcomatoid carcinoma of the pancreas; HC: Healthy control; PDAC: Pancreatic ductal adenocarcinoma; PanINs: Pancreatic intraepithelial neoplasias; TGF: Transforming growth factor; IL-11: Interleukin-11.
routine check-up and CT scan revealed that the patient was in good condition and free of tumor recurrence and metastasis. Because the patient had the opportunity to be treated in the early stage of the disease, he is in good condition and has been alive for more than 3 years without tumor recurrence or metastasis.

**DISCUSSION**

Sarcomatoid carcinoma is a rare and very aggressive malignant tumor comprising a mixture of carcinomatous and sarcomatous elements\(^1\). Areas of spindle cells arranged in a storiform pattern were present\(^2\). The tumor demonstrated cellular patterns similar to those present in tumors of mesenchymal origin in the case. In the present case, many cells undergoing heterotypic division were seen in the tissue specimen, and karyokinesis was frequent. Some cells were fusiform in shape, and some were pleomorphic giant cells. This change into pleomorphic giant cells was the most frequent sarcomatoid transformation encountered\(^3\). Compared with ordinary pancreatic carcinomas, malignant giant cell tumors of the pancreas appear to have a distinctive behavior characterized by local invasiveness, a reluctance to metastasize, and a more favorable prognosis when resected\(^4\). Immunohistochemical study results showed that the tumor cells were positive for vimentin, AACT, pan-cytokeratin, cytokeratin 19, and cytokeratin 8/18 and negative for CD68 and lysozyme. Some authors reported that the tumor cells in sarcomatoid carcinoma were positive for

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Figure 1 Hematoxylin and eosin stained sections, immunohistochemical test and ultrasonography diagnosis. A: Histologic findings of the tumor; the morphology of sarcomatoid carcinoma of the pancreas (SCP) is shown (hematoxylin and eosin, × 100); B: Microscopically, the excised tumor tissue comprised cancer cells and mesenchymal cells, with dispersion of atypical cells and obvious karyokinesis (hematoxylin and eosin, × 200); C: Widely diffuse immunohistochemical staining for the epithelial marker cytokeratin 18 (× 100); D: Heterogeneous immunohistochemical staining for the epithelial marker pan-cytokeratin (Pan-CK) (× 100); E: Widely diffuse immunohistochemical staining for the mesenchymal marker vimentin (× 100); F: Ultrasonography revealed a 93 mm × 94 mm × 75 mm mass of mixed echogenicity in the tail of the pancreas.
Mesenchymal cells in sarcomatoid carcinoma

TGFβ1 ↑

EMT

Panc-CK; Vimentin

Pathological diagnosis; Promote metastasis

CK, S-100 protein, α1-antitrypsin, α1-chymotrypsin, anti-CAL-9-9, and SMA. No cells were positive for vimentin or desmin.[16] Vimentin-positive tumor cells are of mesenchymal origin in sarcomatoid carcinoma and are also seen in inflammatory myofibroblastic tumor of the prostate, another rare malignant disease.[17,18] In the present case, both epithelial and mesenchymal markers were positive. The process of EMT may play an important role in the formation of SCP. TGFβ signaling plays a dual role in oncogenesis. TGFβ can sometimes function as a tumor suppressor gene that inhibits the proliferation of normal epithelial cells, while in other tumor types it functions as an oncogenic gene. This dual function implies that the activity of TGFβ is highly dependent on the cellular context, pathological type, and specific environment.[19-21]. In this case, the TGFβ1 level was markedly higher than those in patients with PDAC and PanINs and in HCs. TGFβ1 may regulate the EMT pathway in pancreas cells and promote the formation of SCP. The plasma IL-11 level in the present patient was obviously higher than that of the healthy controls. IL-11 is a TGFβ target gene. IL-11 stimulates the production of the osteoclastogenic factors RANKL and granulocyte macrophage-colony stimulating factor in osteoblasts. Induction of IL-11 and CTGF expression by TGFβ is mediated by the SMAD pathway.[22] TGFβ1 could be an important driving force during the sarcomatoid transdifferentiation of clear cell renal cell carcinoma.[23] The combination of early diagnosis of sarcomatoid carcinoma, eradication of the tumor, and systemic therapy may provide a chance of a good prognosis. Whether postoperative patients in the early tumor stage require chemotherapy may be controversial. High levels of NSE, TGFβ1, and IL-11 in the serum or plasma may help in the early diagnosis of SCP. TGFβ1 may play an important role in tumor metastasis (Figure 2) and some papers support our hypothesis.[24,25] In view of the complex biologic behavior of SCP, continued real-time monitoring of the clinical course of the disease is strongly recommended.

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