

Pancreatic carcinoma metastasis to a lung carcinoma lesion and pulmonary fibrotic regions, overtaking the stromal microenvironment

A case report

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Abstract

Rationale: Suppression and of cancer metastasis is one of the most important issues in cancer care. Considering the typical clinical course of metastases, cancer cells might prefer certain environments or conditions. However, favorable environments for cancer metastasis have not been clearly identified. We had previously described a case of dual, yet separate, pancreatic and colon cancer, in which the metastatic pancreatic cancer was localized at the invasive portion of the colon cancer. We hypothesized that metastatic pancreatic cancer took over the colon cancer microenvironment.

Patient concerns: We experienced an another case of double cancer in a 65-year-old man who had lung squamous cell carcinoma and an independent pancreatic adenocarcinoma that metastasized to the liver as well as to the lung cancer lesion and pulmonary fibrotic regions associated with pneumothorax and bronchiolization.

Interventions: The pneumothorax could not be controlled by conservative treatment. Thus, an emergency surgery with partial resection of the lower lobe of right lung was performed.

Diagnoses: We found multiple pancreatic cancer metastases in the lung cancer and fibrotic lesions in the surgical specimen. However, we detected no metastasis in normal lung tissues except inside small arteries, although the lung cancer and fibrotic tissue areas were smaller than the normal lung tissue areas in the surgical specimen.

Outcomes: The patient died 50 days after the surgery.

Lessons: This case may thus provide evidence to strengthen our hypothesis that pancreatic cancer prefers to metastasize to other independent cancer lesions, overtaking the cancer microenvironment constructed by other independent cancers. The lung cancer microenvironment, rich in myofibroblasts and/or cancer-associated fibroblasts, might be suitable for pancreatic carcinoma metastasis. In addition, we propose the hypothesis that compared with normal tissues, noncancerous fibrotic lesions are preferable destinations for cancer metastasis. Furthermore, metastasis of pancreatic carcinoma to lung cancer and fibrotic tissues might be more common, although such cases have not been previously reported.

Abbreviations: CK = cytokeratin, MUC = mucin, α SMA = α -smooth muscle actin.

Keywords: cancer metastasis, double cancer, lung cancer, metastatic pancreatic cancer, myofibroblasts, pulmonary fibrosis, tumor microenvironment

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1. Introduction

Suppression and control of cancer metastasis is one of the most important issues in cancer care.^[1–4] In particular, among many types of cancer, pancreatic cancer has a poor prognosis, and it is critical to identify the mechanisms of cancer metastasis and invasion. To metastasize, cancer cells must overcome various difficult steps, namely, release from primary lesion, colonization and engraftment at different tissues, and survival and proliferation at the secondary sites. Considering the typical clinical course of most metastases, cancer cells might prefer certain environments or conditions.^[5] However, favorable environments for cancer metastasis have not been clearly identified yet.

We had previously described a case of dual, yet separate, pancreatic and colon cancer, in which the metastatic pancreatic cancer was localized at the most invasive portion of the colon cancer, namely, the serosal and subserosal layers.^[6] We hypothesized that metastatic pancreatic cancer took over the colon cancer microenvironment.

In this report, we describe a case of metastatic pancreatic cancer in an independent primary lung squamous cell carcinoma

and fibrotic regions associated with pneumothorax and bronchiolization. The phenomenon was similar to that our previous case.^[6] This case may thus provide evidence to strengthen our hypothesis that pancreatic cancer prefers to metastasize to other independent cancer lesions, overtaking the cancer microenvironment constructed by other independent cancers. In addition, we propose the hypothesis that compared with normal tissues, noncancerous fibrotic lesions are preferable destinations for cancer metastasis.

2. Case presentation

2.1. Clinical history

Here, we present a case of double cancer in a 65-year-old male patient. The patient was diagnosed with 3 cancerous lesions: pancreatic cancer, a cancerous lesion in the liver, and an independent tumor with pneumothorax in the lower lobe of the right lung.

Doctors performed biopsies of the pancreatic and liver tumors. Biopsy of the pancreas revealed that the pancreatic tumor was primary adenocarcinoma (Fig. 2E–G). The liver lesion was metastatic adenocarcinoma from the pancreatic cancer.

As for the lung tumor, doctors first speculated that it was metastatic pancreatic carcinoma. However, there was no histological evidence on the tumor before surgery.

Additionally, doctors could not control the pneumothorax by conservative treatment without performing surgery. Thus, an emergency surgery with partial resection of the lower lobe of right lung was performed, and the surgical specimen was subjected to histopathological examination. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

The patient died 50 days after the surgery.

2.2. Pathological findings

The surgical specimen of the right lung was subjected to histopathological examination. The specimen was $105 \times 43 \times 20$ mm in size and had a tumor of $45 \times 27 \times 15$ mm in size.

The main tumor was invasive squamous cell carcinoma of the nonkeratinizing type, and it was diagnosed as primary lung cancer (Fig. 1A). The primary lung cancer displayed no evidence of pleural dissemination and was classified as pT2b.

The background lung tissue included bronchiolization and fibrotic lesions with mucinous metaplasia and emphysematous changes.

Small adenocarcinomatous lesions were detected in the lung lesion. Metastatic adenocarcinoma lesions were located in the primary lung cancer lesion, outside the pleural elastic fibers (Fig. 1A–D). We also found metastatic adenocarcinoma in the fibrotic regions associated with pneumothorax and bronchiolization, adjacent to the lung cancer (Fig. 1E–H).

In addition, adenocarcinoma was detected in the intima of small arteries in the lung (Fig. 2A–D).

The metastatic adenocarcinoma in the lung displayed similar histopathological characteristics, based on hematoxylin-eosin staining, as the primary pancreatic adenocarcinoma and metastatic pancreatic adenocarcinoma in the liver (Figs. 1A, E and 2E).

The lung adenocarcinoma was positive for cytokeratin (CK)-7, mucin (MUC)-5AC and MUC1 and negative for CK20, D2-40, MUC2, MUC6 and Napsin A, and its immunohistopathological

features were the same as those of the pancreatic cancer lesion (Table 1, Figs. 1B–D, F–H and 2B–D, F). Comparison of the immunohistopathological staining patterns of the cancer lesions demonstrated that the adenocarcinoma lesions in the lung and lung small arteries were not primary lung adenocarcinomas but metastatic pancreatic carcinoma (Table 1).

We detected no metastatic adenocarcinoma in the normal lung tissues except inside the small arteries, although the tumor and fibrotic areas were smaller than the normal lung tissue areas in the lung surgical specimen.

The stromal tissues of the lung cancer and fibrotic regions, to which the pancreatic cancer had metastasized, included abundant α -smooth muscle actin (α SMA)-positive myofibroblasts (Fig. 3A–C), but the normal lung tissues did not (Fig. 3D, E).

3. Discussion

Metastasis of pancreatic cancer to an independent lung cancer lesion and pulmonary fibrotic areas associated with pneumothorax and bronchiolization is very interesting phenomenon.

Based on pancreatic cancer metastasis to an independent colon cancer lesion, we hypothesized that the cancer stromal microenvironment, abundant in cancer-associated fibroblasts, might be suitable for the metastasis and engraftment of other independent metastatic cancer cells.^[6] Pancreatic cancer metastasis to an independent lung cancer lesion in this case might support our hypothesis.

We identified some metastatic pancreatic carcinoma lesions in small arteries of the lung cancer specimen (Fig. 2A–D). Thus, the main metastatic route of this pancreatic cancer to the lung was likely hematogenous.

If cancer metastasis and engraftment had occurred at random, metastatic pancreatic carcinoma may have been found in normal lung tissues whose area was larger than that of the primary lung cancer lesion and pulmonary fibrotic tissues in the examined specimen. However, the metastatic carcinoma lesions were restricted to the lung cancer and fibrotic regions associated with pneumothorax and bronchiolization in the surgical specimen (Fig. 1). The present case thus strongly supports the hypothesis that metastatic carcinoma prefers the microenvironment established by an independent cancer or fibrotic tissues.^[6]

Controversial results at the experiment level exist regarding whether pancreatic cancer-associated fibroblasts promote cancer growth or restrain it.^[7–10] The 2 cases of pancreatic cancer metastasis to other independent cancer lesions identified by us suggest that the cancer microenvironment, with abundant cancer-associated fibroblasts and/or myofibroblasts, supports the metastasis and engraftment of cancer cells, even when the cancer-associated fibroblasts and microenvironments are derived from an independent primary carcinoma lesion.^[6]

Interestingly, the pulmonary fibrotic regions associated with pneumothorax and bronchiolization also included metastatic lesions (Fig. 1E–H). Additionally, the fibrotic regions associated with pneumothorax and bronchiolization included abundant α SMA-positive myofibroblasts, similar to the cancer stroma (Fig. 3A, B).

Cancer-associated fibroblasts comprise large populations of myofibroblasts.^[2,11,12] Fibrotic tissues associated with pneumothorax or bronchiolization might include myofibroblasts that resemble myofibroblasts in the cancer microenvironment.

Fibrosis is often caused by tissue remodeling, including pneumothorax formation and bronchiolization, following

inflammation.^[13,14] The cancer microenvironment resembles remodeled tissue during inflammation and includes abundant myofibroblasts.

The metastatic pancreatic cancer cells colonized both the independent adenocarcinoma lesion and the independent

squamous cell carcinoma lesion,^[6] indicating that a common biological mechanism may be at play to help the metastasis of other independent cancers to both adenocarcinoma and squamous cell carcinoma lesions, irrespective of the histopathological type of cancer.

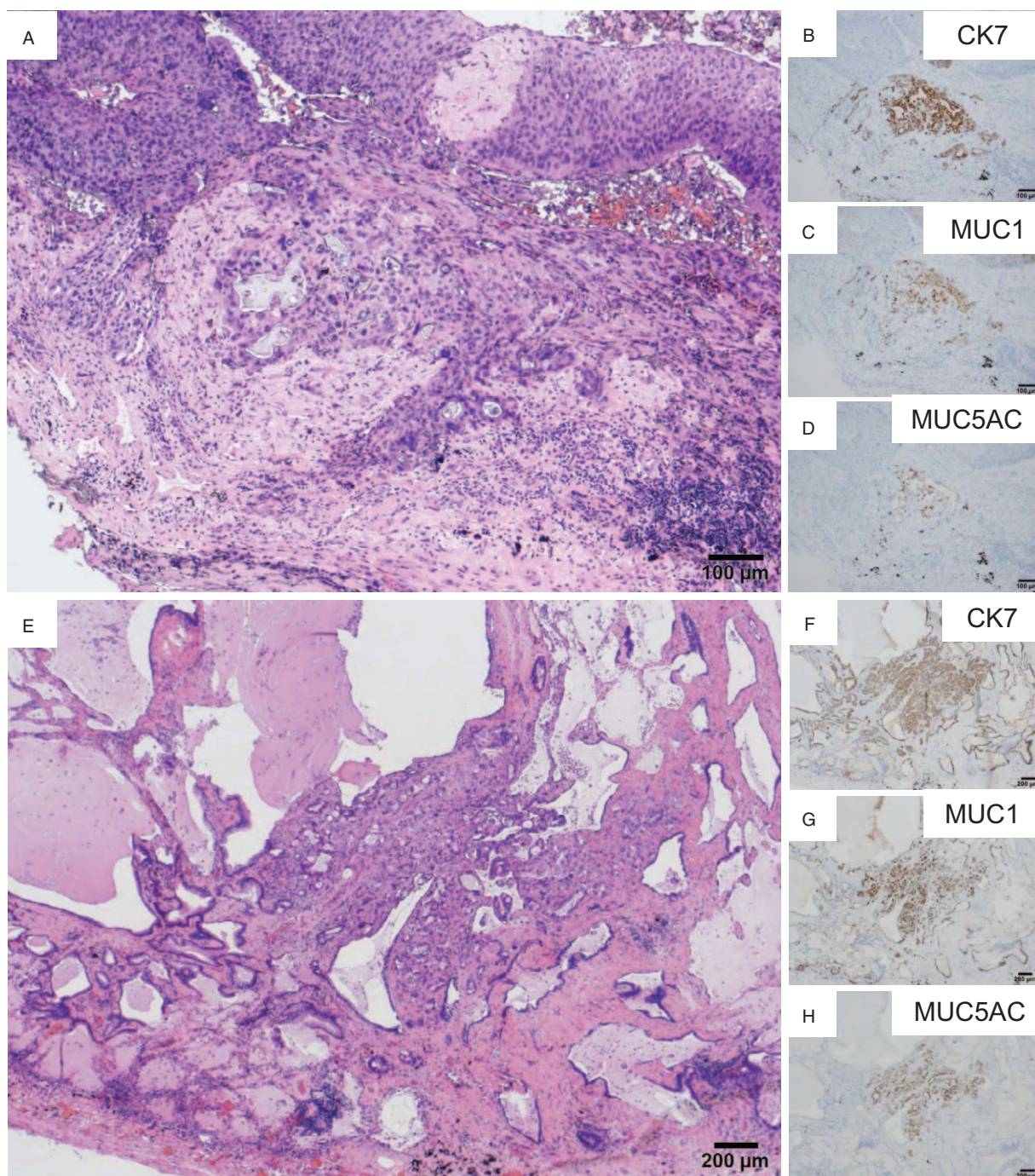


Figure 1. The pancreatic adenocarcinoma metastasized to the independent lung squamous cell carcinoma and pulmonary fibrotic regions associated with bronchiolization. (A) The pancreatic adenocarcinoma metastasized to the independent primary lung squamous cell carcinoma and the resulting surrounding fibrotic lesions. (B, C, D) The metastatic adenocarcinoma was positive for CK7 (B), MUC1 (C) and MUC5AC (D), and its immunohistopathological staining pattern was the same as that of the primary pancreatic adenocarcinoma (cf. Fig. 2 and Table 1). (E) The pancreatic adenocarcinoma metastasized to the pulmonary fibrotic regions associated with bronchiolization. (F, G, H) The metastatic adenocarcinoma was positive for CK7 (F), MUC1 (G) and MUC5AC (H), and its immunohistopathological staining pattern was the same as that of the primary pancreatic adenocarcinoma (cf. Fig. 2 and Table 1).

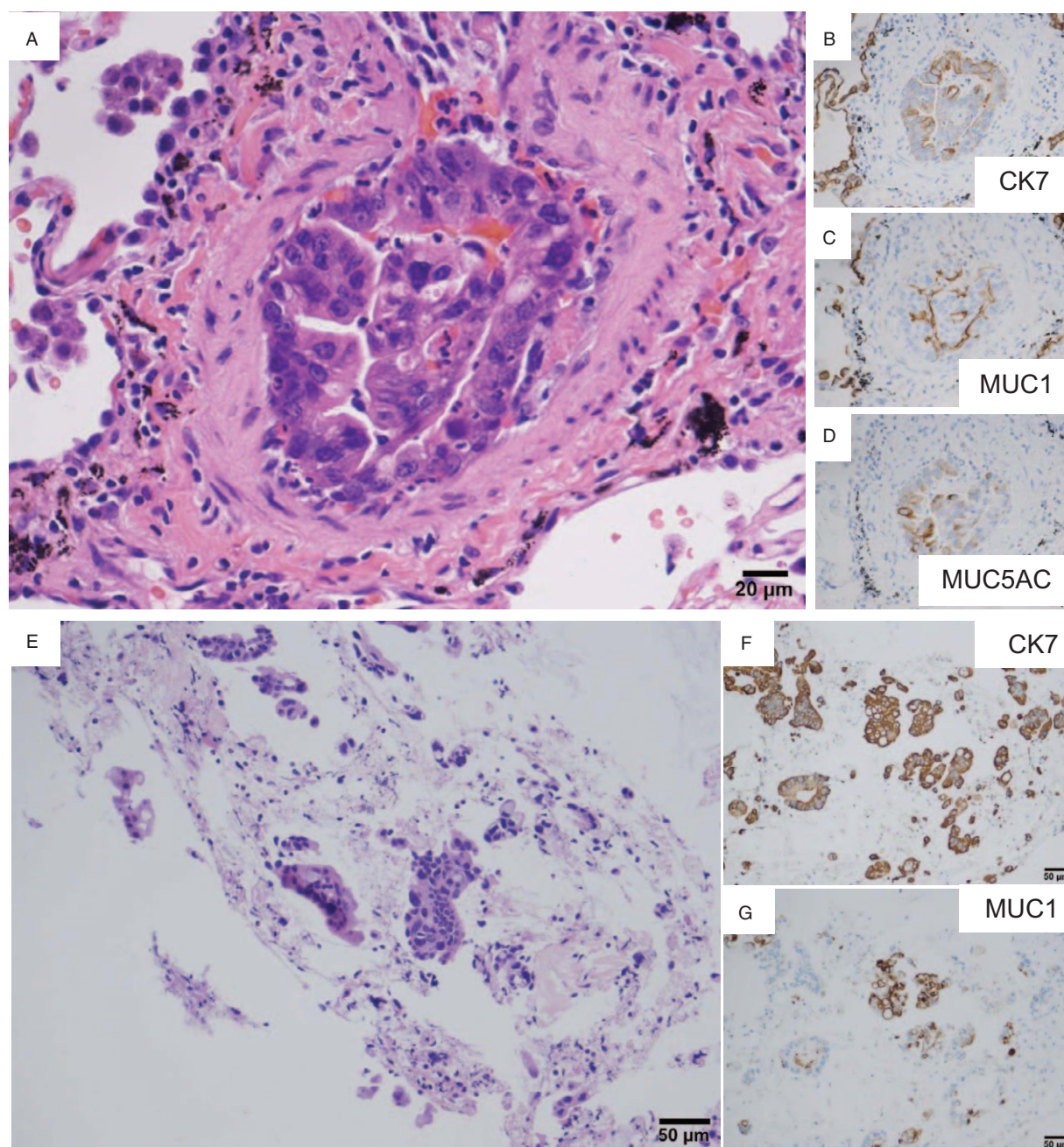


Figure 2. The pancreatic adenocarcinoma was detected in a small artery of the lung. Biopsy of primary pancreatic carcinoma. (A) The pancreatic adenocarcinoma was detected in a small artery of the lung. (B, C, D) The metastatic adenocarcinoma in the artery was positive for CK7 (B), MUC1 (C) and MUC5AC (D), and its immunohistopathological staining pattern was the same as that of the primary pancreatic adenocarcinoma (cf. Fig. 2F, G). (E) Hematoxylin-eosin staining of the primary pancreatic adenocarcinoma biopsy specimen. (F, G) The primary pancreatic adenocarcinoma was positive for CK7 (F) and MUC1 (G), and its immunohistopathological staining pattern was the same as that of the metastatic adenocarcinoma in the lung (cf. Figs. 1–2).

These results support our hypothesis that activated myofibroblasts in both the cancer microenvironment and other fibrotic lesions might be therapeutic targets. α SMA has been regarded and used as a representative molecular marker of myofibroblasts. However, α SMA is not a good marker of myofibroblasts because of its poor specificity. Therefore, discovering good biomarkers of myofibroblasts is necessary

to elucidate the molecular mechanism underlying cancer metastasis and to suppress cancer metastasis by depleting myofibroblasts, which selectively support cancer metastasis and cancer progression.

In conclusion, this case provides profound insights into cancer metastasis and microenvironmental changes and the relationship between cancer metastasis and noncancerous fibrosis.

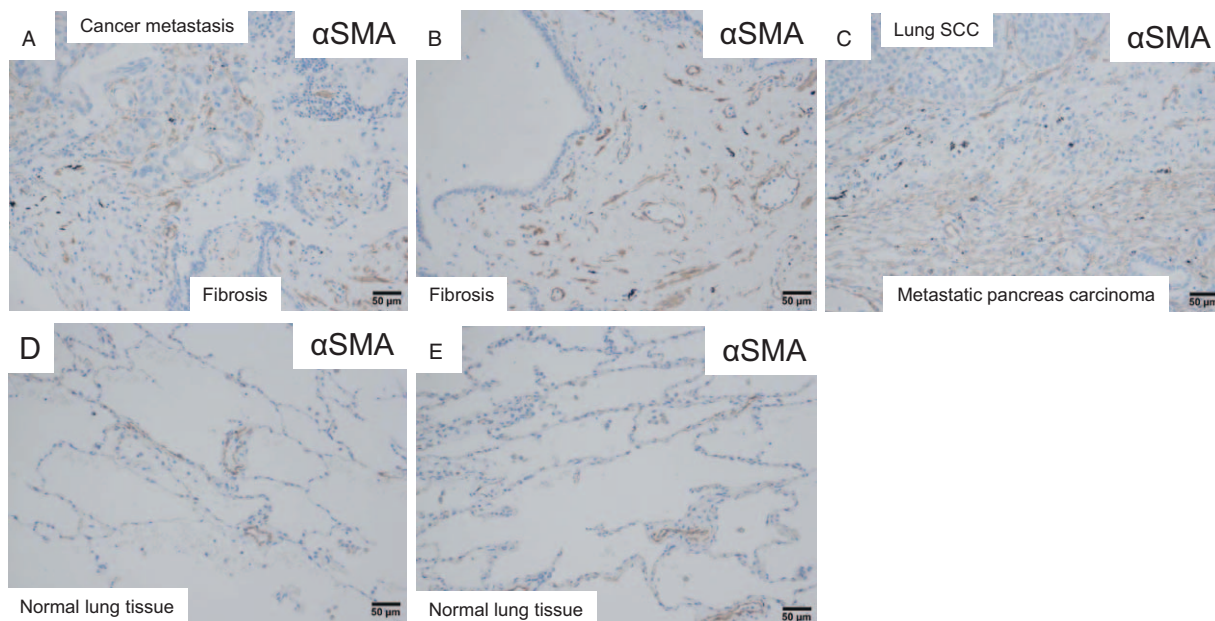


Figure 3. The stromal tissues of the metastatic pancreatic adenocarcinoma included α SMA-positive myofibroblasts. (A, B, C) The stromal tissues of the lung cancer and fibrotic regions, in which the pancreatic cancer had metastasized, included abundant α SMA-positive myofibroblasts. (D, E) Normal lung tissues did not include abundant α SMA-positive myofibroblasts.

Table 1

Immunohistopathological features of the cancer lesions.

	Lung squamous cell carcinoma	Lung adenocarcinoma	Adenocarcinoma in small arteries of the lung	Pancreatic adenocarcinoma (biopsy)	Liver adenocarcinoma (biopsy)
CK7	—	+	+	+	+
CK20	—~±	—	—	—	—
D2-40	—	—	—	—	—
MUC1	—	+	+	+	+
MUC2	—	—	—	—	—
MUC5AC	—	+	+	+	+
MUC6	—	—	—	—	—
Napsin A	—	—	—	—	—
TTF1	—	—	—	ND	—
p40	+	ND	ND	ND	ND
p63	+	ND	ND	ND	ND

CK = cytokeratin, MUC = mucin, ND = not done, TTF1 = thyroid transcription factor 1, α SMA = α -smooth muscle actin.

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References

- [1] Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. *Nat Rev Cancer* 2003;3:453–8.
- [2] Orimo A, Gupta PB, Sgroi DC, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell* 2005;121:335–48.
- [3] Hermann PC, Huber SL, Herrler T, et al. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. *Cell stem cell* 2007;1:313–23.
- [4] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *New Engl J Med* 2011;364:1817–25.
- [5] Langley RR, Fidler IJ. Tumor cell-organ microenvironment interactions in the pathogenesis of cancer metastasis. *Endocr Rev* 2007;28:297–321.
- [6] Nakaya T, Oshiro H, Saito T, et al. Metastasis of pancreatic cancer within primary colon cancer by overtaking the stromal microenvironment. *Int J Clin Exp Pathol* 2018;11:3141–6.
- [7] Ozdemir BC, Pentcheva-Hoang T, Carstens JL, et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. *Cancer Cell* 2014;25:719–34.
- [8] Rhim AD, Oberstein PE, Thomas DH, et al. Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. *Cancer Cell* 2014;25:735–47.
- [9] Hwang RF, Moore T, Arumugam T, et al. Cancer-associated stromal fibroblasts promote pancreatic tumor progression. *Cancer Res* 2008;68:918–26.
- [10] Vonlaufen A, Joshi S, Qu C, et al. Pancreatic stellate cells: partners in crime with pancreatic cancer cells. *Cancer Res* 2008;68:2085–93.
- [11] Orimo A, Weinberg RA. Stromal fibroblasts in cancer: a novel tumor-promoting cell type. *Cell Cycle* 2006;5:1597–601.
- [12] Otranto M, Sarrazy V, Bonte F, et al. The role of the myofibroblast in tumor stroma remodeling. *Cell Adh Migr* 2012;6:203–19.
- [13] Phan SH. The myofibroblast in pulmonary fibrosis. *Chest* 2002;122(6 Suppl):286S–9S.
- [14] Scotton CJ, Chambers RC. Molecular targets in pulmonary fibrosis: the myofibroblast in focus. *Chest* 2007;132:1311–21.