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Case Report

Metastasis of pancreatic cancer within primary colon cancer by overtaking the stromal microenvironment

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Abstract: We report a unique case of a 74-old man, who presented with double cancers, showing metastasis of pancreatic cancer to colon cancer. Histopathological examination after surgery revealed that the patient had ascending colon cancer, which metastasized to the liver (pT4N0M1), as well as pancreatic cancer (pT2N1M1) that metastasized to the most invasive portion of the colon cancer, namely the serosal to subserosal layers. Although the mechanisms for this scenario have yet to be elucidated, we speculate that the metastatic pancreatic carcinoma overtook the stromal microenvironment of the colon cancer. Namely, the cancer microenvironment enriched by cancer-associated fibroblasts, which supported the colon cancer, might be suitable for the invasion and engraftment by pancreatic carcinoma. The similarity of histological appearance might make it difficult to distinguish metastatic pancreatic carcinoma within colon cancer. Furthermore, the metastasis of pancreatic carcinoma in colon carcinoma might be more common, despite it not having been previously reported.

Keywords: Cancer metastasis, metastatic pancreatic cancer, colon cancer, double cancer, tumor microenvironment

Introduction

Prevention and control of cancer metastasis is one of the most important problems in cancer care [1-4]. Therefore, it is critical to identify the mechanisms of cancer metastasis and invasion. Considering the typical clinical course of most malignancies, cancers progress and metastasize through the lymphatic vessels, vasculature, and the serosal cavities of anatomical regions near the primary cancer.

We experienced a case of dual, yet separate, pancreatic and colon cancer, in which the metastatic pancreatic cancer localized at the most invasive portion of the colon cancer, namely the serosal and subserosal layers. This is a unique metastasis, as pancreatic cancer metastasis to colon cancer has not been previously reported [5].

This case provides profound insights about cancer metastasis and microenvironment changes due to cancer invasion.

Case report

Clinical history

Herein we report a case of double cancer in a 74-year-old male patient. Anemia was found during a survey for pulmonary function. In order to detect the cause of the anemia, the doctors performed a colonoscopy and other physical examinations. The patient was found to have 3 cancerous lesions: colon cancer in the ascending colon, pancreatic cancer in the body of the pancreas, and a cancerous lesion in the liver. Therefore, the patient simultaneously underwent distal pancreatectomy, right hemicolectomy, partial liver resection, and lymph node dissection. Surgical specimens were subjected to histopathological examination.

The surgical margins of the pancreatic cancer were positive. Thus, surgeons had planned the complete surgical removal of the pancreatic cancer. However, approximately 3 months after the initial surgery, multiple peritoneal metasta-

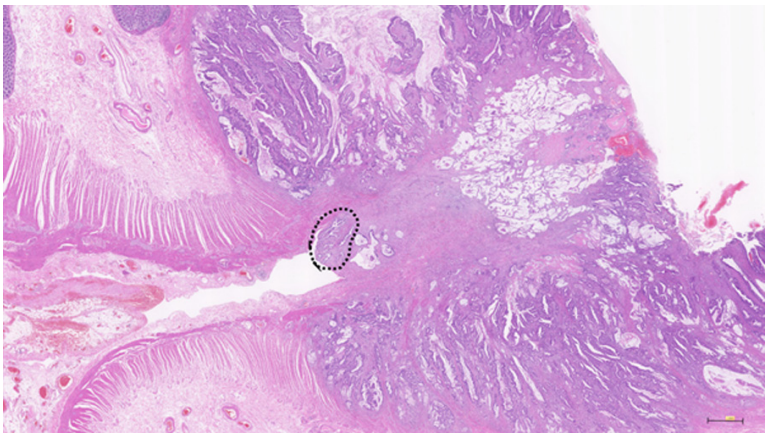

Figure 1. Hematoxylin and eosin staining of metastatic pancreatic cancer within colorectal cancer. The metastatic pancreatic cancer is denoted within the dotted line.

ses, and a 7-mm liver metastasis were detected by positron emission tomography and magnetic resonance imaging. Therefore, the second operation was not performed and chemotherapy (Tegafur) was administered to the patient.

Despite treatment with chemotherapy, the patient had cytologically-confirmed malignant ascites 9 months after surgery.

Results

Pathological findings

In total, there were surgical specimens from 3 regions: (1) right hemicolectomy specimens, including colorectal cancer and lymph nodes; (2) distal pancreatectomy specimens, including the primary pancreatic cancer, spleen and lymph nodes; and (3) partial hepatectomy specimens, including the metastatic liver cancer.

The colon carcinoma located at the ascending colon, was approximately 40 × 24 mm in size, had serosal invasion, and was classified as pT4N0M1 (**Figure 1**). The surgical specimen of ascending colon carcinoma did not have direct invasion of independent pancreatic carcinoma. The colon carcinoma consisted of moderately-differentiated tubular adenocarcinoma, papillary carcinoma, and mucinous carcinoma.

The small carcinoma component of the serosal invasion appeared slightly different from other parts of the colorectal carcinoma (**Figure 1**). This was the most commonly invaded region of the colon, namely the serosal and subserosal layers.

A magnified histopathological view of the serosal invasion is shown in **Figure 2**. The pancreatic carcinoma consisted of a shorter epithelium than the surrounding colon carcinoma. The surrounding colon carcinoma included mucinous material in the lumens, but the differentially looking carcinoma part did not (**Figure 2A**).

The primary pancreatic carcinoma also consisted of moderately-differentiated pancreatic ductal carcinoma. The primary pancreatic carcinoma had similar histopathological characteristics to the previously mentioned colon carcinoma (**Figure 3A**). The pancreatic carcinoma consisted of shorter epithelium, and included less mucinous material inside the lumens. The original pancreatic carcinoma invaded into anterior and posterior extra-pancreatic regions, lymphatic and blood vessels, and was classified as pT2N1M1.

These histopathological results suggested that the serosal portion of the colon cancer might be metastatic pancreatic carcinoma.

Immunohistochemistry clearly distinguished the metastasis of the pancreatic carcinoma from the primary colon carcinoma in the serosal layer of the colon (**Figure 2B-F**). The original colon carcinoma was CDX2 positive, CK7 negative, CK20 positive, MUC1 negative, and MUC2 partially-positive (**Table 1**). On the other hand, the region believed to be metastatic pancreatic carcinoma was CDX2 negative, CK7 positive, CK20 negative, MUC1 partially-positive, and MUC2 negative (**Table 1**). The primary pancreatic carcinoma was CDX2 negative, CK7 positive, CK20 negative, MUC1 positive, and MUC2 negative (**Figure 3B-F**) (**Table 1**). This expression pattern was the same for the metastatic carcinoma in the serosal region of the colon. These results showed that the metastatic carcinoma in the serosal layer of the colon metastasized from the pancreatic carcinoma. The patterns of immunohistochemical markers were sufficient to distinguish primary colon carcino-

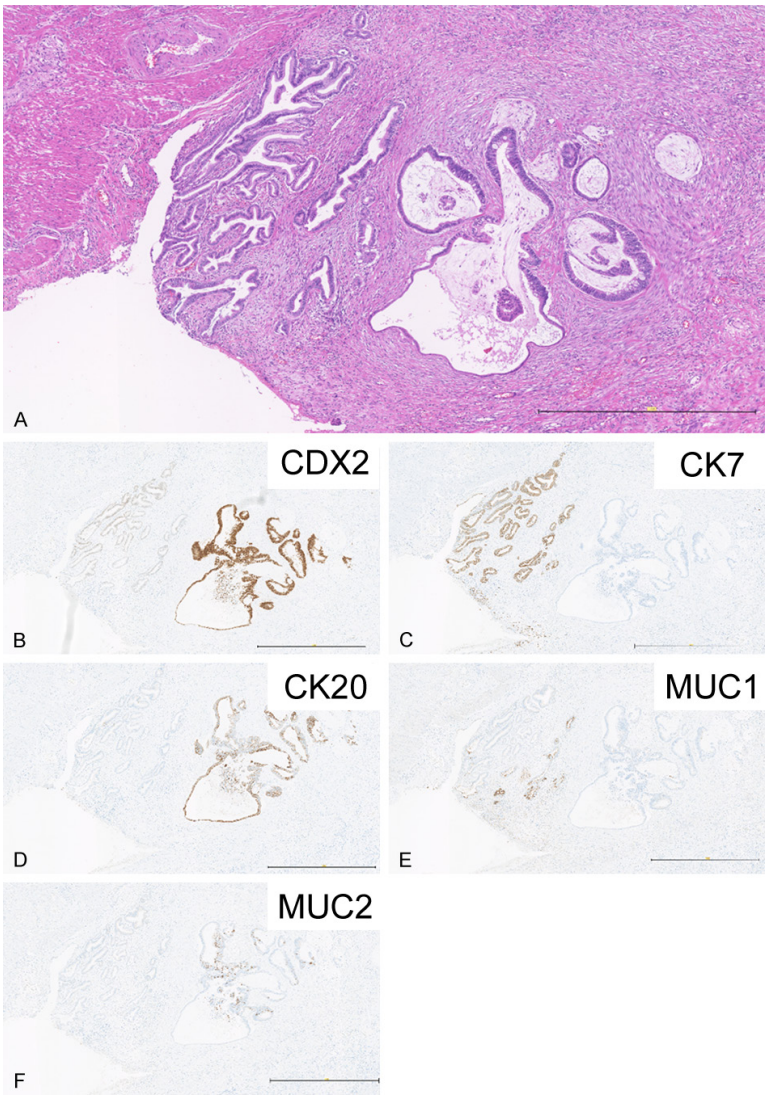

Figure 2. A. Magnified view of metastatic pancreatic cancer within colorectal cancer. The metastatic pancreatic carcinoma in the left side was shorter and had less mucinous compared with the right-sided colorectal cancer. B. Immunohistopathological staining of CDX2. The metastatic pancreatic carcinoma was negative for CDX2, while the colorectal carcinoma was positive for CDX2. C. Immunohistopathological staining of CK7. The metastatic pancreatic carcinoma was positive for CK7, while the colorectal carcinoma was negative for CK7. D. Immunohistopathological staining of CK20. The metastatic pancreatic carcinoma was negative for CK20, while the colorectal carcinoma was positive for CK20. E. Immunohistopathological staining of MUC1. The metastatic pancreatic carcinoma was positive for MUC1, while the colorectal carcinoma was negative for MUC1. F. Immunohistopathological staining of MUC2. The metastatic pancreatic carcinoma was negative for MUC2, while the colorectal carcinoma was positive for MUC2.

ma and metastatic pancreatic carcinoma in the colon [6, 7].

The liver lesion showed metastatic tubular adenocarcinoma. The carcinoma epithelium of the liver tumor had similar histopathological characteristics to the original colon adenocarcinoma. The liver carcinoma included mucinous material in the lumens and consisted of taller epithelium than the original pancreatic carcinoma. Histopathological staining patterns of the liver tumor were CDX2 positive, CK7 negative, CK20 positive, MUC1 weakly-positive, and MUC2 weakly-positive (**Table 1**). This immunohistopathological pattern was the same as that of the primary colon carcinoma, but different from that of the primary pancreatic carcinoma. These findings demostrated that the liver tumor was a metastatic tumor from the colon carcinoma.

Discussion

The metastasis of pancreatic cancer to a site where most invasive colorectal cancer exists, is a very interesting phenomena [8].

We formulated a hypothesis that the colorectal cancer stromal microenvironment, enriched by cancer-associated fibroblasts, might be suitable for the metastasis and engraftment of other metastatic carcinoma cells. More to this point, the metastatic pancreatic carcinoma in the colon cancer in this case was surrounded by fibrous tissue that was rich in cancer-associated fibroblasts (**Figures 1**, **2A**).

It has been reported that fibroblasts assist metastasis and the engraftment of pancreatic cancer [9, 10]. The cancer-associated fibroblasts might help the metastasis and engraftment of the other independent cancer. Moreover, pancreatic carcinoma cells might overtake the colon carcinoma-generated stromal microenvironment, which is suitable for cancer metastasis and development.

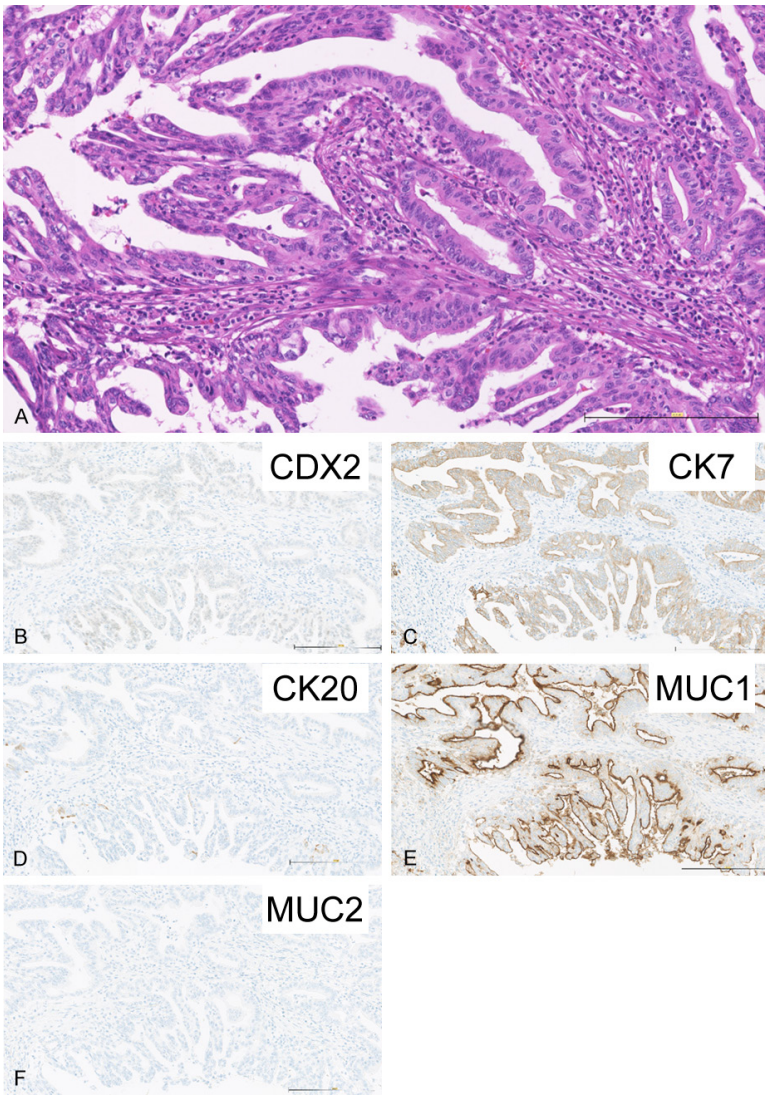

Figure 3. A. Histopathological view of the original pancreatic carcinoma with hematoxylin and eosin staining. B. The primary pancreatic cancer was CDX2 negative, which was consistent with metastatic pancreatic cancer in colorectal cancer. C. The primary pancreatic cancer was CK7 positive, which was consistent with metastatic pancreatic cancer in colorectal cancer. D. The primary pancreatic cancer was CK20 negative, which was consistent with metastatic pancreatic cancer in colorectal cancer. E. The primary pancreatic cancer was MUC1 positive, which was consistent with metastatic pancreatic cancer in colorectal cancer. F. The primary pancreatic cancer was MUC2 negative, which was consistent with metastatic pancreatic cancer in colorectal cancer.

Fibroblasts and myeloid cells can prepare the microenvironment for cancer metastasis, as well as accept the metastatic cancer cells into the microenvironment [11]. The colon cancer-produced fibroblasts may function like the fibroblasts associated with pancreatic cancer, which initiate the metastasis of pancreatic carcinoma cells. The metastatic pancreatic carcinoma might have an affinity for the fibrous tissue-resembling microenvironment produced by the independent colon cancer. As another possibility, exosome-mediated intercellular communication between stromal cells of colorectal cancer and metastatic pancreatic cancer cells, might support the metastasis and settlement of pancreatic cancer cells [12, 13].

Recent studies have demonstrated that stromal elements can restrain pancreatic ductal carcinoma, which was considered a controversial result [5, 14, 15]. It might be more informative to distinguish the phase of cancer metastasis and engraftment from that of the cancer growth after metastasis, considering the function of cancer-associated fibroblasts.

Pathologists are not typically able to detect metastasis of pancreatic cancer in colorectal cancer, since the histopathological appearance of metastatic pancreatic adenocarcinoma often resembles that of colorectal cancer in hematoxylin and eosin staining. In our case, the primary colon cancer showed mucinous features, but the metastatic pancreatic adenocarcinoma did not show a mucinous component, in addition to showing a slightly different histopathological appearance. Intensive examination in double cancer cases, such as pancreatic and colon cancer, might reveal metastases that may have otherwise been undetected.

There were a few possible routes of metastasis for the pancreatic cancer. The first possibility is that the pancreatic cancer metastasized via transcoelomic routes, which settle at the peritoneal site of the colorectal cancer invasion.

Table 1. Immunohistological patterns of the tumors

	CDX2	CK7	CK20	MUC1	MUC2
Original pancreatic carcinoma	-	+	-	+	-
Metastatic pancreatic carcinoma within independent colon cancer	-	+	-	+ (partial)	-
Original colon carcinoma	+	-	+	-	+ (partial)
Metastatic colon carcinoma in the liver	+	-	+	+ (weak)	+ (weak)

The most invasive part of colorectal cancer was enriched by cancer-associated fibroblasts and myofibroblasts, which were generated by the colorectal cancer (**Figure 1**). Cancer metastasis, especially via the transcoelomic route, is a more difficult and inefficient process than previously speculated [16]. In fact, a large number of cancer cells are required for achieving dissemination via transcoelomic routes, approximately 2×10^6 cells in an immunologically-normal hamster, and 1×10^5-10^6 cells in an immunologically-normal rabbit [17, 18]. Since the present case did not have malignant ascites at surgery, the transcoelomic pathway seems to make it difficult for cancer cells in the abdominal cavity to directly attach, invade, and settle in the surface of the abdominal cavity, covered by intact and smooth mesothelial cells. However, pancreatic cancer cells might prefer the fibrous microenvironment enriched by cancer-associated fibroblasts and myofibroblasts, established by colon cancer, to settle and invade, selectively compared to the vast area of the peritoneum. Exposure of the fibrous area produced by cancer-associated fibroblasts in the serosa layer might provide favorable conditions for cancer cells to settle among the intact mesothelial cells.

Two other possible routes of metastasis are the lymphogenous and hematogenous routes. We speculate that the lymphogenous metastatic route is more frequently utilized than the transcoelomic route, considering the difficulty of dissemination through transcoelomic routes [16, 19]. Pancreatic cancer cells that entered the vasculature or lymphatic vessels might find the colon cancer microenvironment suitable for metastasis within the circulation in either system. The pancreatic cancer in this case had not only lymphatic vessel invasion in the primary lesion but also lymph node metastasis outside the pancreas, which could support the lymphogenous metastasis to the colon via the retrograde lymph flow [20].

The primary colon cancer had metastasized into the liver. Liver metastasis from the primary colon cancer was accompanied in the tumor microenvironment by cancer-associated fibroblasts and fibrosis. In addition, most liver metastases from primary colon cancer utilize hematogenous routes. Therefore, colon cancer tumor microenvironment might provide a suitable point for metastasis of pancreatic cancer via a hematogenous route.

This case gave us profound insights in regards to cancer metastasis supported by the tumor microenvironment and peritoneal cancer metastasis.

Disclosure of conflict of interest

None.

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