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Case Report

Appraisal of Aggressive Excisional Biopsy for a Possible Isolated Lung Metastasis of Pancreatic Cancer: Repeated Extirpation Contributes to Long Survival

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Although rare, there is a group of patients in whom lung metastases of pancreatic cancer develop isolatedly. We here report two cases of isolated lung metastasis of pancreatic cancer who gained long survival by repeated surgical resections of the nodules. Case 1: A 63-year-old man developed a 5-mm isolated lung metastasis 25 months after distal pancreatectomy for the primary cancer. He underwent an excisional biopsy for diagnosis and treatment. Although new lesions developed after this excision, additional extirpation of the chemotherapy-resistant tumor nodule realized a tumor-free survival for 15 months and total 74 months survival since pancreatectomy. Case 2: A 75-year-old man developed a 10-mm isolated lung metastasis of pancreatic cancer 13 months after distal pancreatectomy and underwent an excisional biopsy. In spite of adjuvant chemotherapy, 18 months later, a new lesion developed in the lung field neighboring the site of the first metastasis. He received a redo resection and has had a tumor-free period for 20 months until now. He has survived for 55 months since distal pancreatectomy. Aggressive excisional biopsy and repeated surgical resection could be recommended as a treatment option for isolated lung metastasis of pancreatic cancer.

Key words: Isolated lung metastasis – Pancreatic cancer – Excisional biopsy – Survival

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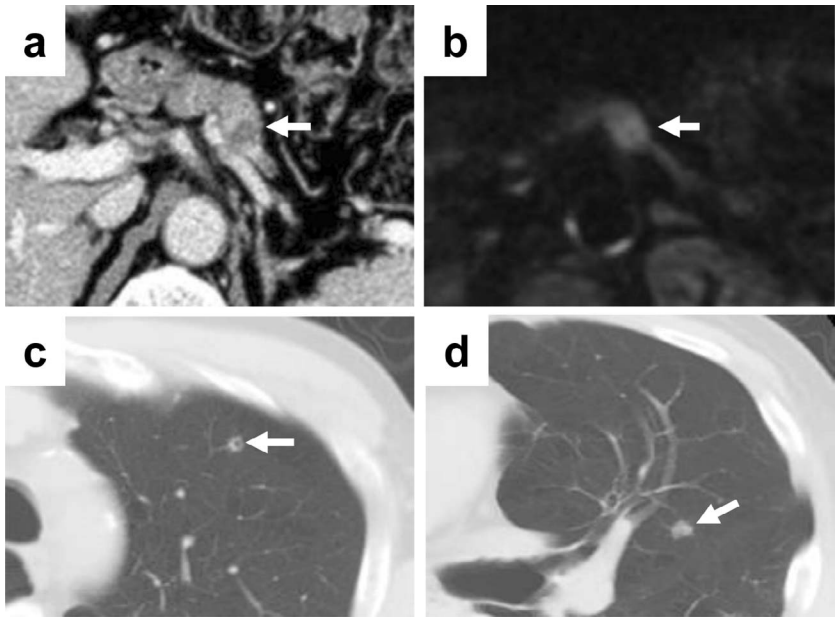

Fig. 1 Images of Case 1. (a) Computed tomography (CT) shows a tumor in the body of the pancreas with an invasion to the splenic vein (white arrow). (b) Diffusion-weighted MRI demonstrates high intensity at the body of the pancreas (white arrow). (c) Twenty-five months after distal pancreatectomy. Follow-up chest CT shows a nodular shadow of 5 mm with a small cavity in segment 3 of left lung (white arrow). (d) Fifty-six months after distal pancreatectomy. A tumor in segment 4 of the left lung enlarged to 8 mm in diameter in spite of chemotherapy (white arrow).

Pancreatic cancer remains as a lethal disease. Pancreatic cancer with distant metastasis is a stage IV disease according to the TMN classification of the UICC. It is usually difficult to achieve long-time survival in patients at this stage. Patients with liver metastasis from pancreatic cancer are hardly a candidate for surgical resection not only for liver lesions, but also the primary lesion. Since the drainage vein of the pancreas is the portal vein, the liver is the foremost destination of metastasis from pancreatic cancer. Therefore, liver metastasis usually occurs shortly after surgery, often in a multiple manner, and rapidly deteriorates the patient's prognosis. When distant metastasis exists in other organs than the liver, liver metastases also frequently exist simultaneously. However, there is a group of patients in whom isolated lung metastases—metastasis only in the lung—develop after a considerable period has passed since curative resection of the pancreatic cancer primary. Since isolated lung metastasis is rarely diagnosed, clinical characteristics and the treatment for it have not yet been fully investigated. Here we report 2 patients with isolated lung metastasis from pancreatic cancer who could have long survival by virtue of repeated resections.

Case Report

Case 1

A 63-year-old man underwent distal pancreatectomy due to a pancreatic cancer 12 mm in diameter at the body of the pancreas; with a suspicion of splenic vein invasion but without distant metastasis (Fig. 1a, 1b). Histological examination confirmed that the tumor was a well-differentiated adenocarcinoma with an invasion to the splenic vein and lymph node metastasis (T3M0N1; according to the TMN classification of the UICC; Fig. 2a). The postoperative course was uneventful, and gemcitabine was administered for 6 months as adjuvant chemotherapy. Twenty-five months after distal pancreatectomy, chest computed tomography (CT) detected a 5-mm nodular shadow in segment 3 of the left lung (Fig. 1c). Although primary lung cancer could not to be excluded for this lung lesion, metastasis from the pancreatic cancer was most likely from his clinical course. Pulmonary tuberculosis was also dubious from CT findings, but it was ruled out by sputum culture. For differential diagnosis of the tumor and expedient treatment, he underwent thoracoscopy-assisted partial resection of the lung with an implication of excisional biopsy. In histological examination, the tumor was composed of large columnar epithelial cells with a dense arrangement (Fig. 2b), and this morphological feature was similar to that of the previously resected pancreatic cancer. Immunohistochemical staining uncovered that the tumor was negative for thyroid transcription factor (TTF)-1 and cytokeratin 20 (CK20), and positive for cytokeratin 7 (CK7; Fig. 2c–2e). From these results, this lung lesion was diagnosed as a metastasis from the pancreatic cancer. After this treatment, gemcitabine was given again for 6 months. Nine months

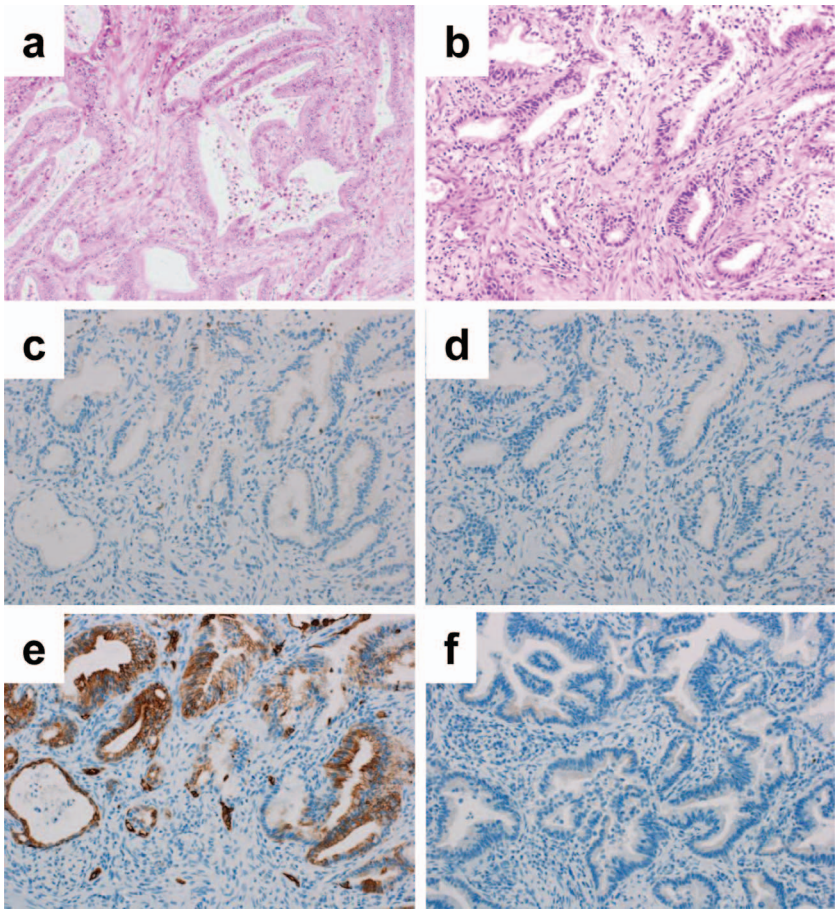

Fig. 2 Histopathological findings of Case 1. (a) Hematoxylin and eosin (HE) staining of original pancreatic cancer (objective, ×20). (b) HE staining of the first lung metastasis (objective, ×20). (c–e) Immunohistochemical staining. The first lung metastasis is negative for antithyroid transcription factor-1 (TTF-1) (c) and anti-cytokeratin 20 (d), and positive for anti-cytokeratin 7 (e) (objective, ×20). (f) Immunohistochemical staining of the second lung metastasis (objective, ×20). It is negative for anti-TTF-1.

later, 2 new lesions of about 4 mm appeared in the bilateral lung (right lung segment 3 and left lung segment 4). At this time point, the patient did not seem a good candidate for surgery, because more metastases were very probable. Therefore, he received second-line chemotherapy with S-1, an oral fluoropyrimidine. Fourteen months after starting chemotherapy, the tumor of the right lung segment 3 disappeared. On the other hand, the tumor in the left lung segment 4 was enlarged slowly to 8 mm (Fig. 1d). Fortunately, no other lung metastasis appeared. Therefore, the lesion in the left lung segment 4 was removed again surgically. The tumor was a well-differentiated adenocarcinoma similar to the original pancreatic cancer. The expressions of TTF-1 (Fig. 2f), CK20, and CK7 were also in parallel with those of the first lung metastasis. Since the last resection, 15 months have passed without either developing new lesions or reappearance of the lesion in the right lobe segment 3. He has been alive for 74 months since distal pancreatectomy against the primary lesion in the pancreas.

Case 2

A 75-year-old man with a past history of hepatocellular carcinoma (HCC) was diagnosed as having a pancreatic cancer of 21 mm in diameter at the body of pancreas (Fig. 3a, 3b). Tumor makers for HCC (alpha-fetoprotein and protein induced by vitamin K absence or antagonist-II) were negative. Pancreatic tumor marker CEA was elevated to 8.2 ng/mL (reference range: <5.0 ng/mL), and CA 19-9 was 0.8 U/mL (reference range: <37.0 U/mL). He underwent distal pancreatectomy and the histology was a moderately differentiated adenocarcinoma with an invasion to the splenic vein, but without metastasis to other organs including lymph node (T3M0N0; according to TMN classification of the UICC; Fig. 4a). Postoperatively, adjuvant chemotherapy with gemcitabine was given for 6 months. Thirteen months after pancreatectomy, chest CT detected a 10-mm tumor at the left lung segment 9 (Fig. 3c). Lung metastasis either from the pancreatic cancer or from HCC was mostly suspected from his clinical course. For diagnosis and treatment, he underwent

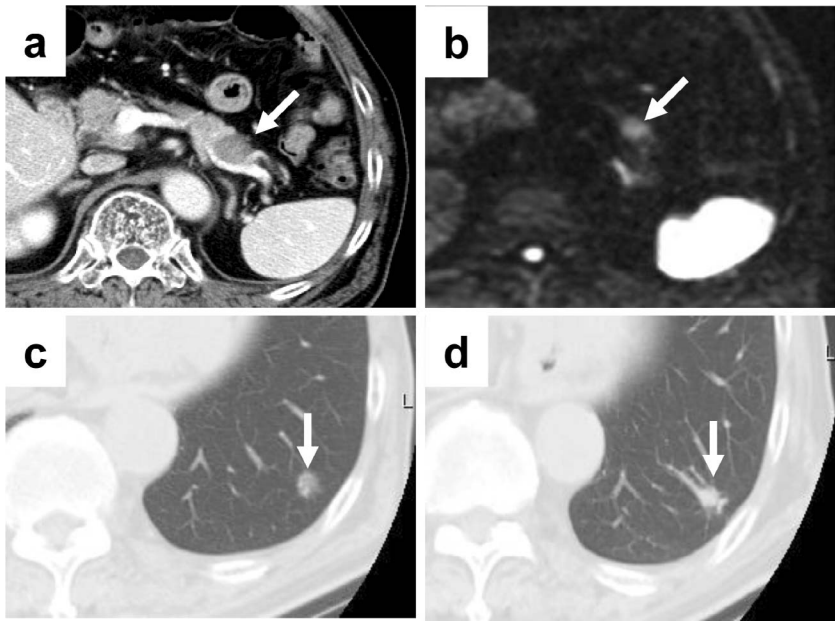

Fig. 3 Images of Case 2. **(**a) Computed tomography (CT) shows a tumor in the body of the pancreas with an invasion to the splenic vein (white arrow). (b) Diffusion-weighted MRI demonstrates high intensity at the body of the pancreas (white arrow). (c) Thirteen months after distal pancreatectomy. Follow-up chest CT shows a nodular shadow of 10 mm in diameter of the left lung segment 9 (white arrow). (d) Thirty-one months after distal pancreatectomy. The second lung metastasis was detected at the left lung segment 9, which occurred near the first metastatic tumor (white arrow).

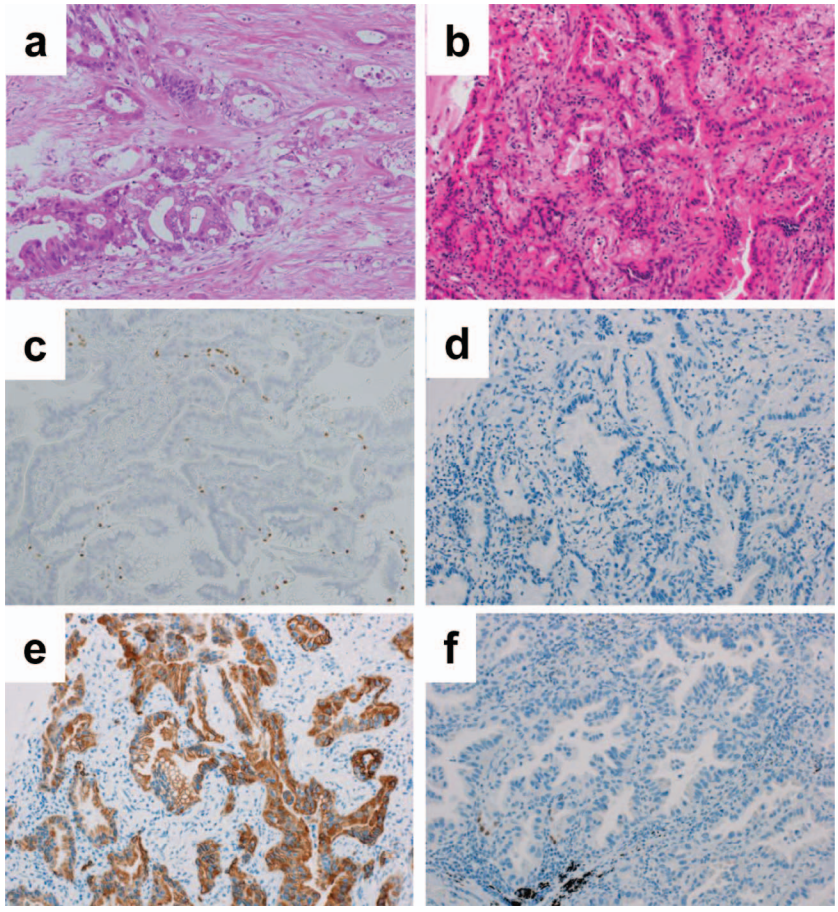

Fig. 4 Histopathological findings of Case 2. (a) Hematoxylin and eosine (HE) staining of original pancreatic cancer (objective, ×20). (b) HE staining of the first lung metastasis (objective, ×20). (c–e) Immunohistochemical staining. The first lung metastasis is negative for anti-thyroid transcription factor-1 (TTF-1) (c) and anti-cytokeratin 20 (d), and positive for anti-cytokeratin 7 (e) (objective, ×20). (f) Immunohistochemical staining of the second lung metastasis (objective, ×20). It is negative for anti-TTF-1.

an excisional biopsy of the lung tumor. Histological examination revealed that the tumor was an adenocarcinoma of which morphological features were similar to that of the original pancreatic cancer (Fig. 4b). Immunohistochemically, the tumor was negative for TTF-1 and CK20, and positive for CK7 (Fig. 4c–4e). Taking these results, gemcitabine was readministered for 6 months. Eighteen months after extirpating the lung lesion, there appeared a recurrent nodule in the lung field neighboring the site where the previously resected lung metastasis was located (Fig. 3d), and therefore redo surgical resection was done. The tumor was also lung metastasis from the pancreatic cancer, showing the same immunohistochemical feature for TTF-1 (Fig. 4f), CK20, and CK7. This time, he received S-1 for 6 months. Since the second resection of the lung metastasis, 20 months have passed without developing new lesions; and he has been alive for 55 months since distal pancreatectomy against the original pancreatic cancer.

Discussion

According to Shrikhande *et al*,[1] the median survival time after surgical treatment for pancreatic cancer with synchronous hepatic metastasis was 11.4 months, which is almost equal to that of FOLFIRINOX chemotherapy for unresectable pancreatic cancer.[2] This actuality is enough to discourage us from resecting liver metastasis of pancreatic cancer. However, in the case of isolated lung metastases—that appear after a considerable period has passed since curative resection of the pancreatic cancer primary—removal of the lung metastasis has been tried in some patients as a treatment option. So far, concerning the significance of this treatment, only one study has been reported by Arnaoutakis *et al*.[3] They evaluated the pulmonary resection for isolated lung metastasis from pancreatic cancer. In that study, 9 patients received pulmonary resection and 22 patients did not receive surgical treatment (control). Median survival was significantly better in the pulmonary resection group: 51 (39–53) versus 23 (18–52) months. Unlike the case of liver metastasis, this result may offer surgical resection as a treatment option for isolated lung metastasis. Of course, before eliciting its clinical implication, it should be emphasized that the patients who enrolled in their study were a unique and highly selected group of patients who developed isolated metastasis in the lung, and metachronously after considerable intervals with a median of 34 months postpancreatectomy. Such a situation is seldom experienced in the case of liver metastasis, but it is true beyond doubt that such a unique group of patients exists in the case of lung metastasis. Katz *et al*[4] analyzed 329 resected cases of pancreatic cancer and evaluated the pattern of recurrence associated with long-time survival. Recurrence rate was 70% and long-term survival for more than 5 years was 26.7%. Of these long survivors, 6.4% patients experienced recurrence and the most frequent recurrent site was the lung (62%). In the patients of the present report, they developed isolated lung metastasis either 25 months (Case 1) or 13 months (Case 2) after pancreatectomy. They never developed metastases in other organs than the lung during 74 or 55 months, and are now enjoying cancer-free lives 15 and 20 months following the surgical resections of lung metastases. These facts will sound an alarm on a myopic thinking that the surgery does not contribute to the patient prognosis without exception when he/she has distant metastasis of pancreatic cancer.

From the practical point of view for diagnosing a small lesion in the lung, exclusion of other diseases than metastatic lesion is very difficult, especially when time elapse between the surgery for the primary tumor and an appearance of lung lesions is considerably long; this difficulty affects the treatment strategy. If the tumor is a benign one such as granuloma, surgical intervention should be abstained. If the tumor is a primary lung cancer, lobectomy with lymph node dissection would be recommended. In our first patient, primary differential diagnosis was a metastasis of the pancreatic cancer from his clinical course, but a primary lung cancer could not to be excluded. In the second patient, HCC was also a candidate of the primary lesion. Recent noninvasive diagnosing modalities, such as positron emission tomography or diffusion-weighted imaging MRI, have a good sensitivity, but their space resolution is limited in tumors of small size.[5,6] Therefore, these modalities are still diagnostic assistance, and the "gold standard" of differential diagnosis of pulmonary mass is still a histopathological examination. Formerly, obtaining tissues by open thoracotomy was very invasive, and therefore an exploratory resection or biopsy of the pulmonary lesions that are strongly suspicious for the metastasis of pancreatic cancer has not been agreeably accepted in a balance of its diagnostic merit and surgical risk. However, recent advancement of endoscopic surgery has enabled partial

resection of the lung to be safe and incomparably less invasive than former open surgery.

Taking the favorable result of pulmonary resection for lung metastasis in Arnaoutakis's study into consideration, aggressive excisional biopsy will be encouraged in the patient in whom isolated lung metastasis of the pancreatic cancer is very suspicious. It would contribute not only to having a correct diagnosis of the lung lesion for a further treatment, but also to a plausible improvement of patient survival by a tumor extirpation even when the result is a metastasis of pancreatic cancer. In our cases, repeated excisional biopsy brought us a tumor extirpation, correct diagnosis, and convinced chemotherapy, and resulted in a longer survival of patients without tumor burden. Of course, further investigation is necessary to know whether this proposal comes under the lately developed isolated lung metastasis only; under metastatic lung lesions of pancreatic cancer in general; or not limited to the lung, under lately developed isolated distant metastatic lesions including liver metastasis.

In conclusion, we reported 2 patients with isolated lung metastasis from pancreatic cancer, who won a long survival by virtue of surgical resection under the name of excisional biopsy. Aggressive excisional biopsy and repeated surgical resection could be recommended as a treatment option for isolated lung metastasis of pancreatic cancer.

Acknowledgments

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