Simultaneous presentation and resection of esophageal cancer and metastasis to the pancreas: A case report and literature review

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Abstract. The frequency of metastasis to the pancreas is limited, and the frequency of metastasis of a squamous cell carcinoma of the esophagus is limited even further. The curative resection of this type of metastatic lesion has been reported for some patients; however, the survival benefit that can be attributed to these procedures has not yet been clearly determined. The patient examined in the present study was a 54-year-old man who was diagnosed with a lower thoracic esophageal cancer. Computed tomography revealed a 2-cm tumor at the tail of the pancreas. Since no other obvious distal metastases were observed, the patient underwent simultaneous surgical procedures, excising the esophageal squamous cell carcinoma and the pancreatic metastasis. A histopathological examination confirmed squamous cell carcinoma in both specimens. The patient has been free of disease for 9 months since the resection. A literature review of all relevant cases to date also demonstrated that the primary tumor site in all cases of patients with esophageal cancer presenting with metastasis to the pancreas was the lower thoracic esophagus. Complete simultaneous resections of esophageal squamous cell carcinoma and a solitary metastasis to the pancreas is beneficial and may produce favorable outcomes. However, due to the reduced number of corresponding reports, further studies are required for the confirmation of the benefits of surgery.

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Introduction

The therapeutic outcomes of patients with esophageal cancer have improved in recent years due to the administration of multidisciplinary treatments, including surgery, chemotherapy and radiation therapy. However, the recurrence rate remains high and the prognosis poor. Even following radical esophagectomy, 30 to 50% of all patients develop hematogenous or lymphatic metastases (1-3).

However, metastasis from esophageal cancer to the pancreas is very rare, occurring in <1% of patients with esophageal cancer, and documented autopsies of patients with esophageal cancer having reported metastases to the pancreas in 0 to 11% of cases (4). Furthermore, <4.9% of metastatic tumors in the pancreas originate from primary esophageal cancers (5-8).

Overall, metastatic disease in the pancreas is rare, accounting for <2% of all pancreatic malignancies (9). The present study describes the case of a patient who underwent a simultaneous radical resection of an esophageal squamous cell carcinoma and a solitary metastasis to the pancreas, and a review of the literature is also presented. Solitary pancreatic metastases are rare and are usually resected when discovered. Moreover, to the best of our knowledge, there are only a few reports (10-13) available to date on patients who have undergone resection of a solitary metastasis.

Case report

A 54-year-old male patient was admitted to the Nagoya City University Hospital (Nagoya, Japan). The main issue that the patient reported was chest discomfort after eating, which had been occurring for several months. The patient was a smoker for >30 years and consumed alcohol daily.

An esophagogastroduodenoscopy revealed a tumor that involved almost the entire circumference of the esophagus at a site 36 to 39 cm from the incisors (Fig. 1). An examination of a biopsy using an esophagogastroduodenoscopy revealed squamous cell carcinoma. Two pathologists were involved in

this evaluation. Computed tomography revealed no obvious invasion of the surrounding esophageal cancer, and the 101R lymph node was enlarged (clinical T2N1M0, stage II; according to the eighth edition of the Union for International Cancer Control system) (14). A 22x20 mm-sized mass was also detected in the pancreatic tail. Contrast enhancement of the tumor was poor during the early phase and exhibited progressive enhancement (Fig. 2). The detected levels of tumor markers were as follows: i) carcinoembryonic antigen, 3.3 ng/ml (reference range, <4.1 ng/ml); ii) CA19-9, 2 U/ml (reference range, <37 U/ml); iii) squamous cell carcinoma antigen, 1.9 ng/ml (reference range, <2.5 ng/ml); iv) DUPAN-2, 25 U/ml (reference range, <150 U/ml), and v) Span-1, 6.8 U/ml (reference range, <30 U/ml). Due to esophageal stricture, an endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNA) could not be performed, and the neoadjuvant therapy was not administered, since primary pancreatic cancer could not be excluded. Subsequently, it was decided that the patient should undergo a resection of both the primary cancer in the esophagus and the metastatic tumor in the pancreatic tail.

Simultaneous robot-assisted resections were performed. The histological examination revealed the occurrence of a squamous cell carcinoma in both the specimens resected from the esophagus and pancreatic tail by H&E and p40 staining (Fig. 3). The esophageal tumor had invaded the intrinsic muscular layer, and no *in situ* carcinoma was detected (Fig. 4). The pancreatic mass was located near the superior margin of the pancreas; however, it was not in contact with either the main pancreatic duct or other organs. There was extensive infiltration around the splenic artery and vein (Fig. 5). These were performed using H&E staining, with a protocol of 4 min of GM hematoxylin (Muto Pure Chemicals Co., Ltd.) and 2 min of pure eosin (Muto Pure Chemicals Co., Ltd.) at room temperature. All resection margins were negative. Several of the lymph nodes near the pancreas demonstrated metastatic involvement. These analyses were performed by the Department of Experimental Pathology and Tumor Biology, Nagoya City University Graduate School of Medical Sciences. The surgical findings were diagnosed as esophageal cancer with pancreatic metastasis. The patient recovered without post-operative complications and was discharged on post-operative at day 34. The patients received two cycles of 5-fluorouracil (800 mg/m^2)/cisplatin (80 mg/m^2) chemotherapy following surgery. The patient remains recurrence-free at 9 months after surgery.

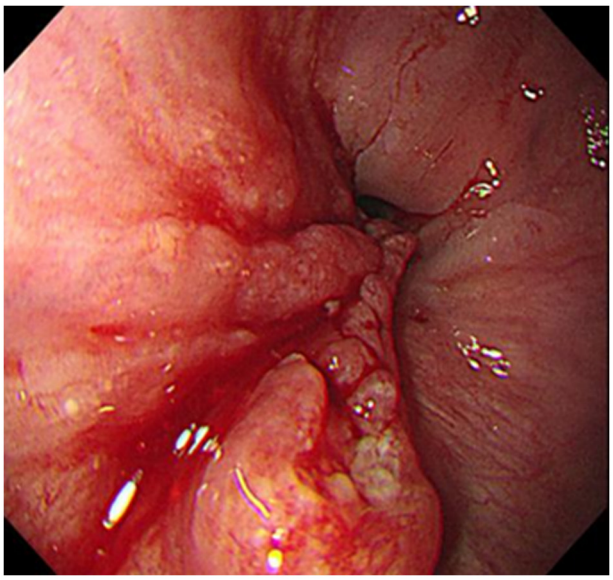

Figure 1. Esophagogastroduodenoscopy. A tumor encompassing 75% of the circumference of the lower thoracic esophagus. The tumor is located at a position 36 to 39 cm from the incisors.

Discussion

Primary pancreatic cancer or pancreatic metastasis are the most frequently diagnosed entities when squamous cell carcinoma is detected in pancreatic tumors. Adenocarcinoma accounts for 75 to 81% of primary pancreatic cancers, and pure squamous cell carcinoma is very rare (15-18). According to a 1992 report from Japan, squamous cell carcinoma accounted for only 0.7% of 1,300 cases of pancreatic cancer (19). Under normal circumstances, squamous epithelium is not located in the pancreas. However, inflammation from conditions including pancreatitis may lead to squamous epithelialization of ductal columnar cells.

Thus, squamous cell carcinoma of the pancreas is considered to arise from the squamous metaplasia of ductal columnar cells secondary to chronic inflammation (20). However, metastases to the pancreas accounts for <2% of all pancreatic malignancies (9). Metastases from kidney, lung, breast, colon and skin (melanoma) cancers, along with sarcomas, frequently involve the pancreas (7). However, even metastases from squamous cell carcinoma of the lung, which is the most frequently diagnosed primary cancer with the ability to metastasize to the pancreas, account for only 1.1% of cases (21). Consequently, simultaneous primary and metastatic squamous cell carcinoma of the pancreas is rare. Of note, a limited occurrence of metastases from a primary cancer of the esophagus to the pancreas have been reported, to the best of our knowledge; therefore, the advantages and disadvantages of resection remain unknown.

Resection for pancreatic metastases from renal cell or ovarian cancers and complete resection of metastases from any primary cancer have been reported to be beneficial through the prolongation of patient survival (8,9,22). Solitary pancreatic metastases are usually resected; however, a literature search by the authors revealed 4 patients who underwent resection of pancreatic metastases from esophageal squamous cell carcinoma (10-13). Furthermore, resection of simultaneous metastases was reported for only 1 of the 4 cases (13).

A review of the surgical data of 5 reported cases (4 from the literature search plus the case reported in the present study), demonstrated that every patient underwent distal pancreatectomy and was discharged without post-operative complications (Table I; 10-13). Post-operative adjuvant 5-fluorouracil/cisplatin chemotherapy was administered to 3 patients and there was a report of no recurrence for up to 24 months (10). The lower thoracic esophagus was the site of the primary tumor in 3 cases. One case report did not provide the location of the primary tumor. All pancreatic metastases occurred in the pancreatic tail.

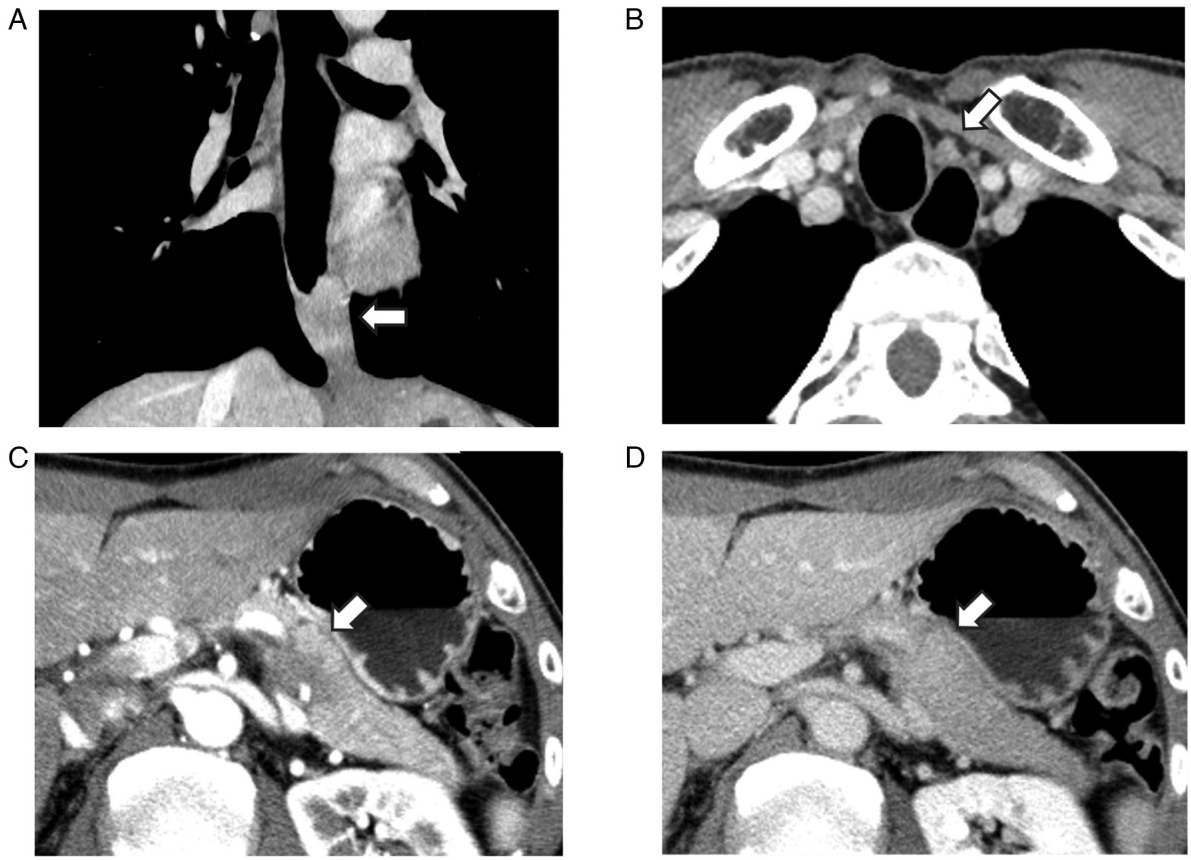

Figure 2. Contrast-enhanced computed tomography scan of the esophageal cancer. (A) Enlarged 106R lymph node, and (B) of the pancreatic tumor (indicated by the arrow), (C) in early phase and (D) in late phase. The pancreatic tumor exhibited gradual enhancement.

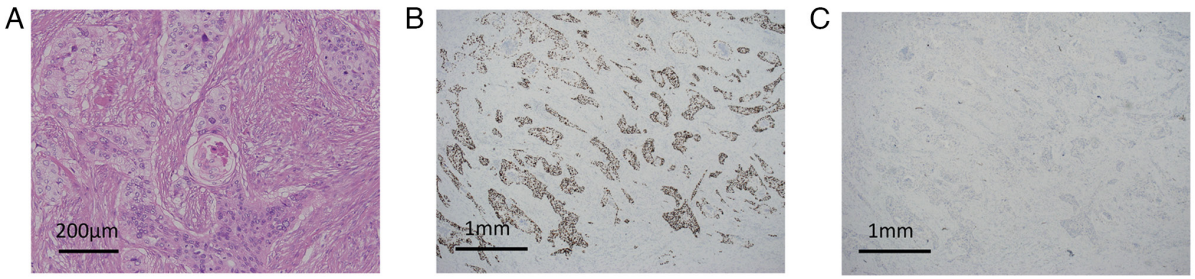

Figure 3. (A) Pathological findings of the pancreatic tumor showing squamous cell carcinoma. H&E staining; magnification, x40. (B) Immunohistochemical findings revealed staining positive for p40. (C) Control for the same tissue area.

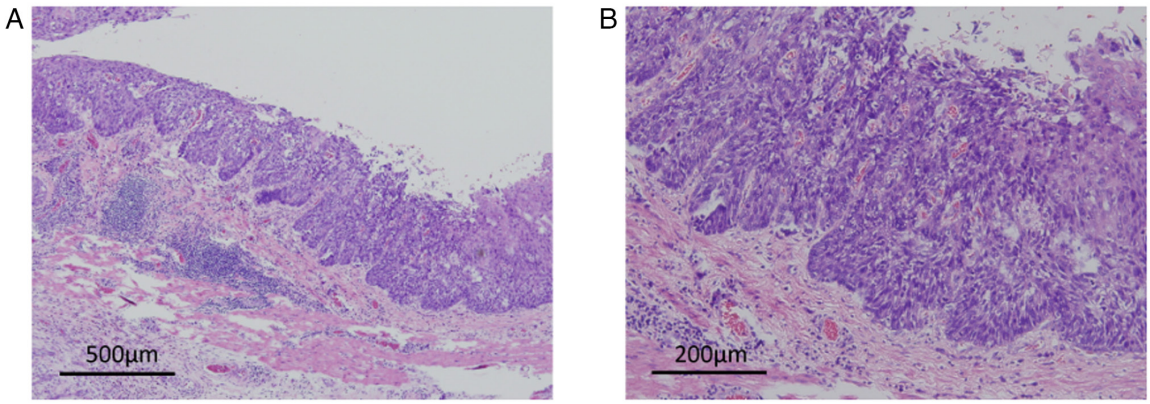

Figure 4. Pathological findings illustrating (A) that the esophageal cancer had invaded the intrinsic muscular layer, (B) also revealing carcinoma *in situ*. H&E staining; magnification, x40.

Table I. Reported cases of pancreatic metastasis from esophageal carcinoma.

Author(s)	Year of publication	Age, years	Sex	Location of esophageal cancer	Synchronous/ metachronous	TNM stage	Location of pancreatic metastasis	Surgery	Adjuvant therapy	Recurrence (follow-up time months)	(Refs.)
Esfehani *et al*	2011	59	F	Lt	Metachronous	T3N1M0	Pt	DP	5-FU	None (6)	(12)
Park *et al*	2013	59	F	Lt	Synchronous	T1bN1M1	Pt	DP	FP	None (4)	(13)
Okamoto *et al*	2014	68	M	Lt	Metachronous	T1bN0M0	Pt	DP	FP	None (9)	(11)
Koizumi *et al*	2019	81	F	-	Metachronous	T1bN0M0	Pt	DP	None	None (24)	(10)
Present study	2023	54	M	Lt	Synchronous	T3N3M1	Pt	DP	FP	None (9)	-

F, female; M, male; Lt, lower thoracic; Pt, pangreatic tail; DP, distal pancreatectomy; 5-FU, 5-fluorouracil; FP, 5-fluorouracil/cisplatin.

Figure 5. Pathological findings of the pancreatic specimen. H&E staining. The tumor was located at a distance from the main pancreatic duct (white arrow) and had extensively infiltrated the splenic vein (black arrow).

Blood drains from the cervical esophagus into the superior vena cava via the inferior thoracic vein, and blood drains from the upper or middle thoracic esophagus into the superior and inferior vena cava via the azygous and hemi azygous veins. By contrast, blood draining from the lower thoracic esophagus and the abdominal esophagus flows into the portal system via the paraesophageal vein and the left and short gastric veins (23). Thus, esophageal carcinoma in the lower thoracic esophagus may be more prone to metastasize to the pancreas in comparison with esophageal squamous cell carcinomas located elsewhere, since drainage via the paraesophageal vein to the splenic vein is the predominant route of blood flow. The frequency of pancreatic metastases to the pancreatic tail could be also attributed to the anatomy of the draining veins.

Squamous cell carcinomas discovered in the pancreas must be determined to be either a primary cancer or metastatic disease. The frequency of pancreatic metastases from squamous cell carcinoma is much higher than the frequency of primary squamous cell carcinoma of the pancreas; thus, it is generally reasonable to assume that a pancreatic tumor is a metastasis from squamous cell carcinoma of the esophagus (24). To the best of our knowledge, there is no immunostaining method that can further classify the primary squamous cell carcinoma. Instead, the histopathologic

findings in the patient analyzed in the present study revealed neoplastic changes in the esophageal mucosa, as well as carcinoma *in situ*. These findings indicated that the primary tumor was located in the esophagus. Additionally, the esophageal and pancreatic tumors exhibited extensive venous invasion and similar histopathologic profiles. Furthermore, squamous cell carcinoma of the pancreas is classified as adenosquamous carcinoma and contains a small amount of adenocarcinoma component. In the case reported in the present study, the carcinoma was composed of pure squamous cell carcinoma lacking an adenocarcinoma component, without being in contact with the main pancreatic duct and without exhibiting atypical findings in the main pancreatic duct. It is hypothesized that these findings serve as indicators excluding the possibility that the tumor is a primary pancreatic cancer. Considering these data, the tumor in the pancreas was finally diagnosed as a pancreatic metastasis from esophageal cancer. The pre-operative confirmation that the tumor in the pancreas is a solitary metastasis, which leads to the possibility of a complete resection, is crucial, as the resection of a solitary metastasis is associated with an improved survival rate (8,9). In general, the differentiation between a pancreatic metastasis of esophageal cancer and a primary pancreatic cancer can be made by a pre-operative EUS-FNA biopsy for tissue diagnosis (25,26). A pancreatic tumor should be considered as metastasis, when a tumor is detected in the pancreas concomitant with an esophageal squamous cell carcinoma being located in the lower esophagus. The confirmation of the diagnosis is important for deciding on the treatment, and should be obtained from a preoperative diagnosis of specimens from EUS-FNA or from positron emission tomography-computed tomography.

Thus far however, to the best of our knowledge, there have not been any published prospective or case-controlled clinical trials that compared the efficacy of resection with the non-operative treatment of pancreatic metastases. The surgical mortality of pancreatic surgery has been demonstrated to account for <5% of the total number of cases diagnosed (9). In addition, since the 5 patients in the published literature reviewed in the present study remained alive, surgery for patients with a solitary pancreatic metastasis from esophageal squamous cell carcinoma may improve outcomes and should be considered. However, the follow-up periods of the previous reports were brief, and further observation of these patients is necessary for the determination of the prognosis of this type of cases.

In conclusion, the case described in the present study was reported due to rarity of the solitary pancreatic metastasis from esophageal cancer and also requires careful therapeutic consideration. Finally, the treatment guidelines for esophageal cancer with a solitary pancreatic metastasis should be established.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YD participated in all aspects of the present case report, including management of the patient, conceptualization of the report, and writing of the draft. MY, IN and KH performed the pre-operative diagnosis of the patient with a biopsy using an esophagogastroduodenoscopy and provided advice on treatment administration. YH, HI, KS and MM managed the patient. HK performed the histological examination. KN and HM collected the patient's data. TK, RO and HT aided in interpreting the results and prepared the manuscript. YM and ST managed the patient and supervised the study. YM and ST confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from the patient depicted in the present study.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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