Primary squamous cell carcinoma of the pancreas with effective comprehensive treatment
A case report and literature review
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Abstract
Rationale: Primary squamous cell carcinoma (SCC) of the pancreas is a rare entity since the pancreas lacks squamous cells. This condition is associated with a poor prognosis, and there is currently no optimal treatment strategy for it.

Patient concerns: A 64-year-old female patient with a complaint of epigastric pain for 3 months was referred to our hospital.

Diagnoses: She was finally diagnosed with primary SCC of the pancreas with lymph node metastasis on the basis of radiological and pathological findings.

Interventions: She received chemoradiation along with targeted therapy and was provided with treatment response evaluation through PET/CT.

Outcomes: She eventually died of tumor progression after 8 months.

Lessons: Primary SCC of the pancreas is associated with a poor prognosis. Comprehensive therapy and proper radiologic evaluation may facilitate prolonged survival of these patients.

Abbreviations: 
18FDG = 18F-fluorodeoxyglucose, CA = carbohydrate antigen, EUS-FNA = endoscopic ultrasound-guided fine-needle aspiration, GTV = gross tumor volume, IGRT = image-guided radiotherapy, IMRT = intensity-modulated radiation therapy, PECIST = PET response criteria in solid tumors, PET/CT = positron emission tomography/computed tomography, PMD = progressive metabolic disease, PMR = partial metabolic response, RECIST = response evaluation criteria in solid tumors, SCC = squamous cell carcinoma, SMD = stable metabolic disease, SUVmax = maximum standardized uptake value.

Keywords: carcinoma, pancreas, PET/CT, response, squamous cell

1. Introduction
Primary squamous cell carcinoma (SCC) of the pancreas is a rare entity since the pancreas lacks squamous cells. The histogenesis of pancreatic SCC is still unknown. In comparison with adenocarcinoma, the most common subtype of pancreatic carcinoma,[1] SCC shows similar epidemiological features and a worse survival rate.[2] Curative resection is the best treatment method with a median survival period of 7 months.[3,4] For patients with advanced pancreatic SCC, numerous treatment methods have been used with unsatisfactory results, and no optimal strategies have been reported to date. Here, we report a case of primary SCC of the pancreas that was managed by a comprehensive treatment protocol and is the first to include treatment response evaluations using positron emission tomography/computed tomography (PET/CT), and we review the related literature.
1.1. Case presentation

A 64-year-old female patient with acute hematochezia for 2 hours was referred to our hospital. She had been experiencing epigastric pain for 3 months and had shown unintentional weight loss of 7 kg. At her local hospital, she was diagnosed with superficial gastritis by endoscopic examination. During further examinations, a pancreatic mass was observed on ultrasound and CT, but the patient did not undergo treatment for it. Physical examination at our institution revealed a palpable mass with tenderness in her left upper abdomen. The results of digital rectal examination were unremarkable. She had no history of smoking or any family history of tumors. The serum levels of carbohydrate antigen (CA) 19–9 (112.7 U/mL, reference: 0–37 U/mL) and CA-125 (239.3 U/mL, reference: 0–40 U/mL) were elevated. Enhanced abdominal CT revealed a 7 cm lobulated low-density mass with rim enhancement at the body of the pancreas. The mass invaded the celiac trunk and firmly adhered to the posterior wall of the gastric body. Several retroperitoneal lymph nodes were enlarged. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) with a 22-gauge needle was performed. Histopathological assessments revealed a well-differentiated SCC characterized by clouds of squamous cells with keratin pearls (Fig. 1). 18F-fluorodeoxyglucose (18F-FDG) PET/CT examination showed high FDG accumulation in the parts equivalent to the pancreatic body mass (Fig. 2) with a maximum standardized uptake value (SUVmax) of 11.7, and SUVmax values of 7.7 and 10.9 for the lymph nodes and both lobes of the thyroid, respectively. Thyroid FNA biopsy was performed and results indicated Hashimoto’s thyroiditis (Fig. 3). Other evaluations
searching for the primary sites of SCC also showed unremarkable findings.

Considering her decreased performance status and the evidence of vascular invasion, the patient did not undergo surgery. The patient underwent 3 cycles of radical intensity-modulated radiation therapy (IMRT) at a dose of 3.8 Gy/f and 4 cycles of chemotherapy, including 1 cycle of paclitaxel (180 mg/m², d1) plus cisplatin (100 mg/m², d1) followed by 3 cycles of paclitaxel (200 mg/m², d1) plus gemcitabine (1000 mg/m², d1,8) every 21 days. During this period, nimotuzumab (200 mg/m², qw) and endostar (15 mg/m², d1–14) were administered for targeted treatment. After 3 cycles of chemotherapy, the pancreatic mass had shrunk to 2.6 cm on abdominal CT. Interim PET/CT showed partial metabolic response (PMR = −36, 8) of the pancreatic mass based on the PET response criteria in solid tumors (PECIST) [5] (Fig. 4A–B). After 4 cycles of chemotherapy, restaging PET/CT evaluation showed progressive metabolic disease (PMD +72, 4) (Fig. 4B–C). Local radiotherapy was performed with a dose of 51 Gy/17f to the gross tumor volume (GTV) of the primary tumor and metastatic lymph nodes. Nimotuzumab (200 mg/m², qw) was used for homochronous targeted treatment. After completion of these treatments, restaging PET/CT evaluations showed stable metabolic disease (SMD = −17, 4) (Fig. 4C–D). The patient then underwent follow-up examinations. Three months later, restaging CT revealed a 3 cm lesion metastasizing to the left lateral lobe of the liver with
enlargement of the pancreatic mass to 3.3 cm and invasion of the adjacent posterior gastric wall. Gemcitabine at 1000 mg/m² was administered through chemoembolization to the hepatic lesion. Image-guided radiotherapy (IGRT) with a dose of 8 Gy/f to the GTV was planned for the hepatic lesion. However, after 1 session of IGRT, the patient could not tolerate the treatment and underwent percutaneous endoscopic gastrostomy. She died of hemorrhagic shock caused by tumor invasion of the stomach in the eighth month after the initial comprehensive therapy.

2. Discussion

Primary SCC of the pancreas is a rare entity, accounting for 0.5% to 5% of all exocrine pancreatic cancers. Several hypotheses, including malignant transformation of squamous metaplasia as a result of chronic inflammation, differentiation from a bipotential primitive cell, or squamous transformation of preexisting adenocarcinoma, have been proposed to explain the origin of these tumors. The diagnosis of a primary pancreatic SCC must be made after excluding metastases from another squamous neoplasms. In this case, the patient underwent whole-body PET/CT and showed abnormal ¹⁸F-FDG avidity in the pancreas and thyroid. Although some case reports have described metastatic pancreatic carcinoma of the papillary and follicular subtypes from thyroid carcinoma, cases presenting with the primary squamous subtype of thyroid carcinoma itself are rare. To exclude this possibility, thyroid FNA biopsy was performed and the cytological findings indicated Hashimoto’s thyroiditis. The results of other endoscopic work-up examinations were also normal.

Since it was first reported by Lai et al., EUS-FNA has been increasingly used to identify pancreatic SCC. Adenosquamous carcinoma should be usually considered in the differential diagnosis of SCC. In this case, specimens were acquired at multiple levels and repeated analysis excluded the existence of a glandular component. Thus, the patient was diagnosed with primary pancreatic SCC.

No optimal treatment strategy has been established for inoperable pancreatic SCC. The most popularly used methods were based on data for other squamous carcinomas and pancreatic adenocarcinoma. Ntanasis-Stathopoulos et al. identified 54 cases of primary pancreatic SCC in the literature.

Since then, 6 more case reports have been identified by us in a Medline search for papers on primary pancreatic SCC in English published until August 12, 2018 (Table 1). Platinum-based drugs, gemcitabine, and 5-FU were the most frequently used therapeutic agents. For patients with unresectable pancreatic SCC, the overall survival was poor, except for one patient treated with radiotherapy and chemotherapy with 5-FU and capcitabine who lived for 18 months.

Several case reports have employed PET/CT scanning for excluding other conditions or for staging in the diagnosis of pancreatic SCC. To our knowledge, this is the first case that used PET/CT for treatment response evaluation. The interim PET/CT evaluation performed 2 months after the initial 3 cycles of chemotherapy and homochromous targeted therapy showed PMR (–36, 8) and a reduction in the long diameter of the pancreatic tumor from 7 to 2.6 cm. The second PET/CT evaluation after completion of the last cycle of chemotherapy showed PMD (+72, 4), which indicated resistance to treatment. CT images showed no significant increase in the diameter of the tumor, and local radiotherapy was used as a replacement. The last PET/CT evaluation after all therapeutic procedures showed SMD (–17, 4) of the pancreatic mass, with no enlargement of the tumor on CT images. Therefore, the patient began to undergo follow-up examinations. However, a metastatic site in the left lateral lobe of liver was observed subsequently, and the patient was treated with palliative chemoradiation. She died after 8 months of treatment.

In this case, we performed dynamic response evaluation to search for a better treatment strategy and to ensure better supervision of pancreatic SCC. PECIST allows more sensitive response evaluation than RECIST (response evaluation criteria in solid tumors), which evaluates the efficacy of treatment of solid tumors solely on the basis of systematic assessments of tumor size. In this patient, CT images showed no changes in the diameter of the pancreatic mass after completion of the last cycle of chemotherapy, while PET/CT evaluations indicated resistance to treatment. Unfortunately, the present case involved a relatively long follow-up period of 3 months without any radiologic evaluation, during which the tumor progressed but the patient did not receive timely changes in the treatment protocol. In summary, the patient in this case received an individualized treatment strategy through precise radiologic evaluation, which ensured a relatively long overall survival period. The findings of this case outline the possibility of improving the prognosis associated with this condition by implementing a dynamic response evaluation protocol and administering treatment on the basis of the findings in the response evaluations.

In conclusion, pancreatic SCC is a rare entity with a poor prognosis. For patients with unresectable disease, palliative treatment cannot result in decreased mortality. However, PET/
CT may allow timely and accurate evaluations of treatment response, thereby ensuring better survival and living status. Nevertheless, new treatment methods are required to improve the prognosis of patients with pancreatic SCC.

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References
[1] Capella C, Albarello L, Capelli P, et al. Carcinoma of the exocrine pancreas: the histology report. Dig Liver Dis 2011;43(suppl 1): S282–92.
[2] Makarova-Rusher OV, Ulahannan S, Greten TF, et al. Pancreatic squamous cell carcinoma: a population-based study of epidemiology, clinicopathologic characteristics and outcomes. Pancreas 2016;45:1432–7.
[3] Ntanasis-Stathopoulos I, Tsilimigras DI, Georgiadou D, et al. Squamous cell carcinoma of the pancreas: a systematic review and pooled survival analysis. Eur J Cancer 2017;79:193–204.
[4] Brown HA, Dotto J, Robert M, et al. Squamous cell carcinoma of the pancreas. J Clin Gastroenterol 2005;39:915–9.
[5] Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med 2009;50(suppl 1):1X122–30.
[6] Klaar JS, Kaur H, Vaid A, et al. Surviving primary pancreatic squamous cell carcinoma: a rare entity. J Gastrointest Cancer 2015;46:301–3.
[7] Becker HA, Castro MJ, Stewart J3rd. Cytologic differentiation of squamous elements in the pancreas. Diagn Cytopathol 2011;39:536–9, quiz 539–540.
[8] Borschitz T, Eichhorn W, Fottner C, et al. Diagnosis and treatment of pancreatic metastases of a papillary thyroid carcinoma. Thyroid 2010;20:93–8.
[9] Na HJ, Kim BH, Kim JR, et al. FDG PET/CT in the detection of pancreatic metastasis in a patient with follicular thyroid carcinoma and negative I-131 whole body scan findings. Intern Med 2014;53:2095–9.
[10] Basnet A, Pandita A, Fullmer J, et al. Squamous cell carcinoma of the thyroid as a result of anaplastic transformation from BRAF-positive papillary thyroid cancer. Case Rep Oncol Med 2017;2017:4276435.
[11] Lai LH, Romagnuolo J, Adams D, et al. Primary squamous cell carcinoma of pancreas diagnosed by EUS-FNA: a case report. World J Gastroenterol 2009;15:4343–4.
[12] Mehta M, Sinha J, Ogawa M, et al. Unusual case of squamous cell carcinoma of pancreas with review of literature. J Gastrointest Cancer 2013;46:426–9.
[13] Rowe K, Mehta N, Nehme F, et al. Primary squamous cell carcinoma of the pancreas as a cause of biliary obstruction. Cureus 2016;8:e856.
[14] Alajlan RA, Bernadt CT, Kushner VM. Primary squamous cell carcinoma of the pancreas: a case report and literature review. J Gastrointest Cancer 2017.
[15] Abedi SH, Ahmadzadeh A, Mohammad Alizadeh AH. Pancreatic squamous cell carcinoma. Case Rep Gastroenterol 2017;11:219–24.
[16] Modi RM, Kamboj AK, Shen R, et al. Endosonography and confocal endomicroscopy of primary keratinizing squamous cell carcinoma of the pancreas. ACG Case Rep J 2017;4:e17.
[17] Basil M, Pudusseri A, Lowe R. Weight loss and abdominal pain caused by pancreatic squamous cell carcinoma. Clin Gastroenterol Hepatol 2017;15:341–2.
[18] Lin E, Veeramachaneni H, Addisse B, et al. Squamous cell carcinoma of the pancreas. Am J Med Sci 2018;355:94–6.
[19] Kodavatiganti R, Campbell F, Hashmi A, et al. Primary squamous cell carcinoma of the pancreas: a case report and review of the literature. J Med Case Rep 2012;6:295.
[20] Ikeda A, Okuno T, Miki I, et al. A case report: pancreatic squamous cell carcinoma with effective response by S-1 therapy. Clin J Gastroenterol 2014;7:79–83.