Case Report

Primary squamous cell carcinoma of the pancreas: case report and literature review

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Abstract: Squamous cell carcinoma of the pancreas (SCCP) is a rare histological variety of exocrine pancreatic carcinoma of unknown aetiology and nonspecific symptomatology. Diagnosis is usually made by tissue sampling followed by a comprehensive search for a primary SCC elsewhere. The disease is more aggressive and has a poorer survival rate than the more common pancreatic adenocarcinoma. We report a case of primary SCCP with regional lymph node metastasis in a 73-year-old female patient.

Keywords: Carcinoma; squamous; pancreas; adenocarcinoma; malignancy

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Introduction

The pancreas is entirely devoid of squamous cells, thus squamous cell carcinoma of the pancreas (SCCP) has historically been a debated entity (1,2). However, squamous metaplasia of the ductal columnar cell has been noted in the setting of chronic pancreatitis, after pancreatic duct stenting (2,3) and lining certain non-malignant pancreatic cysts. SCCP are seldom addressed in the literature and only as case reports. Comprehensive clinical trials are not reported (2,4). Ntanasis-Stathopoulos *et al.* described 54 cases throughout the years of 2000–2012 (constituting 0.5–0.2% of all pancreatic tumours) (5-7). Since then 6 more case studies have been reported by Zhang *et al.* (8). Majumdar SKD *et al.* stated that pancreatic tumours had a very low cure rate at 7% (7). Pure squamous histology has poor prognosis (7,9,10) and has an inferior survival rate compared with adenosquamous (A-SCC) and adenocarcinoma (AD), which have similar survival rates to each other (4,11-13). Locally metastatic or locally advanced disease at presentation is associated with higher mortality rates in SCCP than that of adenocarcinoma (6). However, PSCC has a diverse survival rate that varied significantly according to increasing age, and stage of the disease at presentation (6). The disease is aggressive and characteristically does not respond to chemotherapy or radiotherapy (7,14). A previous study reported that chemotherapy or radiotherapy resistance of the disease is recognised as a consequence of intratumoral hypoxia that induce hypoxic microenvironment, and subsequently stimulates tumour invasion and progression (15). However, the role of the hypoxic microenvironment in pancreatic neoplasm is complicated and necessitates further investigation (15).

Case presentation

A 73-year-old female with a background history of atrial fibrillation and hypertension presented with persistent nausea and epigastric discomfort. Laboratory investigation revealed a slightly elevated AST and Gamma GT. CEA was elevated at 11.16 ng/mL (0–3.0). Gastroscopy was unremarkable apart from distal gastritis. Abdominal ultrasound (*Figure 1A*) revealed a mixed solid and cystic mass (5.8 cm) possibly arising from the pancreas. Subsequent contrast enhanced abdominal computed tomography CT (*Figure 1B*) demonstrated a large pancreatic

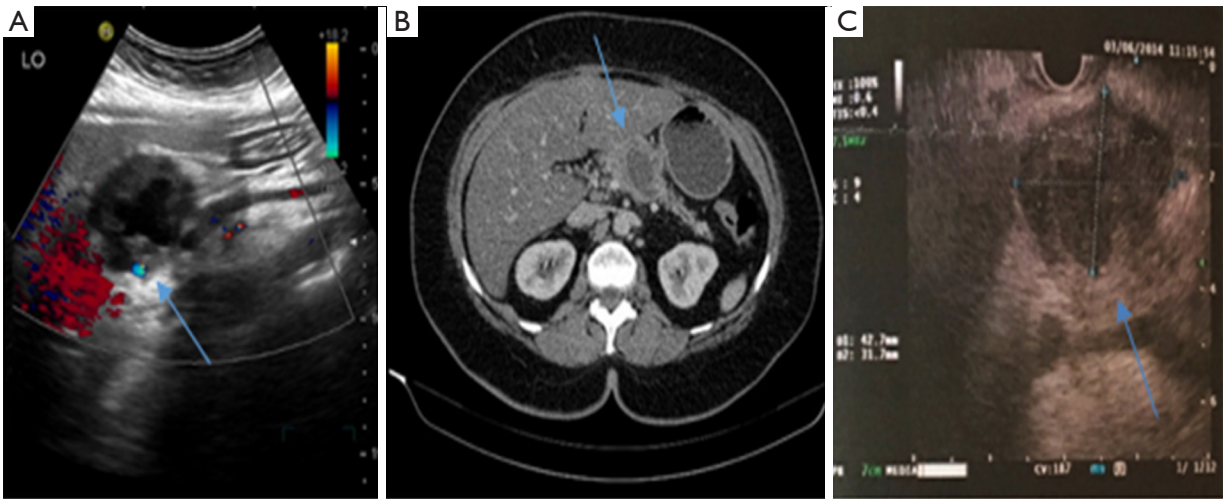

Figure 1 Carcinoma of the pancreas. (A) Abdominal ultrasound revealed a mixed solid and cystic, mass (5.8 cm) possibly arising from the pancreas. (B) Contrast enhanced CT demonstrated a large mass in the neck and body of the pancreas with a dilated distal pancreatic duct and two peritoneal nodes. (C) Endoscopic ultrasound demonstrated a 50 mm × 35 mm hypoechoic solid and cystic lesion in the body of pancreas. Two discrete rounded hypoechoic nodules immediately adjacent to the lesion were demonstrated.

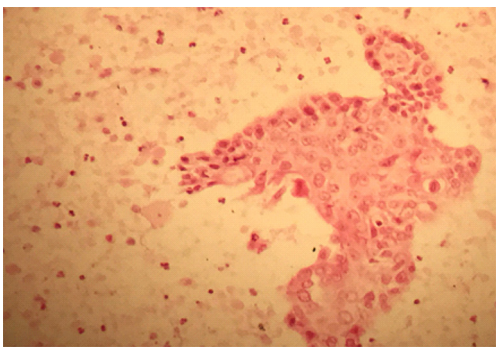

Figure 2 Photomicrograph of a cell block section, stained with HE (magnification of microscope, ×10). A micro biopsy of squamous cell carcinoma is seen.

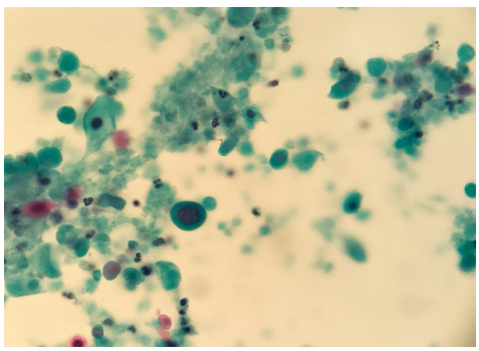

Figure 3 Photomicrograph of a Papanicolaou stained cytospin preparation from the EUS-FNA of the pancreatic lesion (magnification of microscope, ×40). A malignant squamous cell is seen, on a background of necrotic cell debris.

mass in the neck and body with a dilated distal pancreatic duct and two peritoneal nodes.

Endoscopic ultrasound (EUS) (*Figure 1C*) revealed a 50 mm × 35 mm hypoechoic solid and cyst mass in the neck and body of the pancreas and two adjacent nodules corresponding to the nodules detected at CT. An endoscopic ultrasound guided fine needle aspiration (EUS-FNA) of the mass was performed, using a 25-gauge ProCore and samples were sent for cytopathology, which confirmed the diagnosis of SCCP (*Figures 2,3*).

Subsequently, a workup for detecting an alternative squamous cell primary tumour was negative. Staging scan shown no evidence of distant metastatic disease. Ultimately, the diagnosis of locally advanced SCCP with lymph nodes metastasis (peritoneal nodes in the greater and lesser omentum) was confirmed. The tumour was inoperable at specialist multi-disciplinary conference. The management plan was adjuvant chemotherapy. Following completion chemotherapy, the patient developed quite significant epigastric discomfort. CT abdomen and pelvis revealed progressive pancreatic tumour measuring 7.4 cm × 6.5 cm with central necrosis and local extension to the liver and a large intrahepatic fluid collection. Then patient was

commenced on broad spectrum antibiotics (ciprofloxacin and metronidazole) and no chemotherapy was commenced. The discussion was thoroughly explained to the patient and her family. Palliative supportive care was sought with regards to pain control (opiate medication) and patient was transferred to hospice care with symptom management. However, the patient died approximately four months after being diagnosed.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's next of kin (deceased patient) for publication of this case report and any accompanying images.

Discussion

The first case of SCCP was described by Lowry in 1949 (11). Baylor and Berg described the incidence of pure SCCP as 0.5% of pancreatic carcinomas (4). In 1992, in a survey in Japan, 1,300 cases of pancreatic cancers observed at autopsy, only 0.7% were squamous cell carcinoma. Halpert, in a series of 120 patients, described an incidence rate of 5% pure SCCP (4). However, no cases of SCC were found in the 1,211 pancreatic carcinomas collected from pancreatic cancer archives in Japan (as quoted by Anagnostopoulos *et al.*) (2,4).The discrepancy in the reported incidence rates may be explained by the fact that a greater proportion of the cases represent adenosquamous carcinoma rather than pure SCCP (2,11). Additional origins might include the ability of stem cells to differentiate into either squamous or glandular carcinoma, an adenocarcinoma undergoing squamous transformation, squamous metaplasia of the ductal epithelium (chronic inflammation) or an aberrant squamous cell experiencing malignant change (2,16). Characteristically patients are asymptomatic, thus the diagnosis of SCCP for the majority of patients occurs during the advanced stage of the disease (2,14).

In our case, diagnosis was confirmed by EUS-FNA (*Figure 1C*). Since it was first reported by Lai *et al.* EUS-FNA has been considered to be gold standard investigation (11,17). In 2017, Modi *et al.* documented utilization of *in vivo* needle-based confocal laser endomicroscopy (nCLE) in order to achieve an early detection of the PSCC and subsequent therapeutic approach (10). The treatment options for SCCP are limited (8,14). Majuμdar SKD *et al.* suggested that PSCC tumours are very aggressive, do not respond to chemotherapy or radiotherapy and an exceptionally short overall survival rate (7,14). Rowe *et al.* revealed that in cases of unresectable disease, the optimal treatment strategy is poorly understood (5,7,8). Surgical resection is deemed the only conceivably curative treatment (14,17) and adjuvant chemotherapy with gemcitabine or S-1 (an oral fluoropyrimidine derivative) is frequently given after surgery (17). Furthermore, surgical resection of the primary tumour was associated with longer OS in stages I–II (9), whereas chemotherapy was associated with longer overall survival in stage IV disease (18).

Regrettably, the patient described in this case report developed intrahepatic fluid collections and no chemotherapy was offered following repeat presentation. Without effective treatment, a median survival of only 3 to 4 months is generally expected in metastatic disease.

Taibi *et al.* stated that Gemcitabine is considered the gold standard adjuvant drug (9). Neoadjuvant chemotherapy followed by surgical exploration has been studied in patients with locally advanced pancreatic cancer with gemcitabine or a fluoropyrimidine (fluorouracil plus leucovorin or S-1 in Japan) has been shown to significantly improve outcomes and is recognized as standard care in patients with resectable pancreatic tumour (8,19). Platinum-based drugs, Gemcitabine, Platinum-based drugs, and 5-FU are the most frequently used therapeutic agents. Zhang *et al.* addressed that survival rates were poor for unresectable pancreatic SCC, excluding one patient who lived for 18 months following radiotherapy and chemotherapy with 5-FU and capecitabine (8). Adjuvant therapy for resected pancreatic tumour with a modified FOLFIRINOX regimen led to considerably longer survival than gemcitabine, at the expense of a higher incidence of toxicity (14,19). With respect to, metastatic and unresectable disease, FOLFIRINOX [fluorouracil, folinic acid (leucovorin), irinotecan, and oxaliplatin] and gemcitabine plus nanoparticle albumin-bound paclitaxel (nab-paclitaxel) are considered the treatments of choice (17,19,20). Regarding metastatic adenocarcinoma of the pancreas, the same therapeutic approach is generally applied (9,19).

KRAS, CDKN2A, TP53, and SMAD4 are the major driver genes for pancreatic cancer. KRAS mutation and alterations in CDKN2A are early events in pancreatic tumorigenesis (17,21). Furthermore, checkpoint blockade cancer immunotherapy, including anti-PD-1 (programmed death-1) and anti-PD-L1 (programmed death-1 ligand-1) antibody immunotherapy has revealed durable efficacy in different types of human tumours. However, pancreatic

cancer is one of the few malignancies that does not respond to anti-PD-1/PD-L1 immunotherapy (21,22). It has been shown that targeted therapy can increase the efficacy of checkpoint immunotherapy against pancreatic cancer, but the mechanisms underlying the non-response of pancreatic cancer is still unidentified.

PD-L1 expression and microsatellite instability (MSI) status is considered as a predictive and prognostic of immune responsiveness in several malignancies. In pancreatic cancer, single agent immunotherapies are ineffective. Preliminary outcomes are more promising for a combined integrated approach utilizing vaccines, chemotherapy, radiation therapy, immunotherapy, and other targeted agents to augment the immune response in pancreatic tumor (21). Although phase I-II data support the concurrent administration of standard-dose checkpoint blockade with full-dose systemic therapies including chemotherapy, Gong *et al.* revealed that several questions are remaining regarding dose, timing, toxicity, and patient selection for checkpoint inhibitor-based combination therapies in pancreatic tumours that merit further prospective endorsement (23).

This strategy may present some hope, which has been obscure in the disease (21).

Conclusions

In summary, pure SCCP is a rare tumour. Metastasis from other primary squamous cell cancers (lung, oesophagus, cervix, kidney, and skin) should always be excluded in the first instance at initial diagnosis (16,24). The disease is highly aggressive, most often locally advanced, or metastatic at diagnosis. Based on the rare incidence of the histologic subtype of tumour, diagnosis and treatment will remain an enormous challenge (3,14). With respect to lack of evidence based data, randomized controlled trials should be addressed (8,14). Collective epidemiological reports are considered essential to confirm outcomes stemming from the limited amount of published case studies of this rare entity in order to ultimately improve patient outcomes and survival rates.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apc-19-51). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's next of kin (deceased patient) for publication of this case report and any accompanying images.

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