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Salvage Pancreaticoduodenectomy After Complete Response to Chemoradiotherapy for a Previously Unresectable Pancreatic Adenosquamous Carcinoma

A Case Report

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Abstract: Pancreatic cancer is known for its typically late presentation and poor survival rates, with overall 5-year survival of less than 5%. The role of chemotherapy alone or with radiotherapy in the management of locally advanced tumors continues to be an area of debate.

We report a case of locally advanced, pancreatic adenosquamous carcinoma that was initially deemed unresectable intraoperatively. Nonetheless, the tumor was resected after radiological response to gemcitabine-capecitabine chemoradiotherapy regimen similar to the Selective Chemoradiation in Advanced LOcalised Pancreatic cancer trial. Histological examination revealed complete pathological response with extensive fibrosis (ypT0 N0). On 12-month follow-up CT, a single liver lesion in the left lateral segment was identified and confirmed to be a metastasis with cytological diagnosis via EUS and FNA. The disease remained stable and confined to the solitary hepatic metastasis after further gemcitabine chemotherapy. Therefore, a further successful resection was performed.

The 2 main strategies for the management of locally advanced unresectable pancreatic cancer are chemotherapy induction followed by consolidation chemoradiotherapy or chemotherapy alone, with conflicting published evidence. Evidence for the optimal management of the rare histological type of adenosquamous carcinoma is scant. We present a case of such tumor with a complete pathological response to chemoradiotherapy. The results of future studies in the area are eagerly awaited.

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Abbreviations: 5-FU = 5-fluorouracil, CBD = common bile duct, CT = computerized tomography, EUS = endoscopic ultrasound, FNA = fine needle aspiration, MDT = multidisciplinary team, MRI = magnetic resonance imaging, PET = positron emission tomography.

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INTRODUCTION

Pancreatic cancer is known for its typically late presentation, early metastasis, and poor survival rates, with overall 5-year survival of less than 5%.[1] In the United Kingdom, pancreatic cancer is the fifth most common cause of cancer-related mortality.[2] The majority of pancreatic cancers are ductal adenocarcinomas, while less common types include acinar cell, adenosquamous, colloid, hepatoid, signet-ring cell and undifferentiated carcinomas.[1–3] Surgical resection when possible is the mainstay of treatment.[2–4] However, the optimal management of locally advanced tumors continues to be an area of debate. Chemotherapy alone is the standard treatment in Europe and induction chemotherapy followed by consolidation chemoradiation in selected patients is preferred in the United States.[5]

We report a case of locally advanced, initially unresectable pancreatic adenosquamous carcinoma that was resected after complete response to chemoradiotherapy (Figure 1).

CASE PRESENTATION

A 57-year-old woman presented with a 10-day history of jaundice. Further symptomatology included 5 months history of colicky abdominal pain and weight loss. On examination, she was jaundiced without any palpable abdominal masses or lymphadenopathy. The rest of the clinical examination was unremarkable. Initial investigations were suggestive of biliary obstruction with raised bilirubin of 221 μmol/L, ALP of 966 U/L, and ALT of 689 U/L. An ultrasound of the biliary tract showed a dilated common bile duct (CBD) secondary to a 37-mm head of pancreas mass. Further investigation with endoscopic ultrasound (EUS) confirmed a mass causing obstruction to the pancreatic duct and the CBD, abutting but not invading the portal venous system. During the procedure the CBD was decompressed with a plastic stent. Diagnosis from EUS fine needle aspiration (FNA) was of a poorly differentiated pancreatic carcinoma, with features of adenosquamous differentiation (Figure 2). Further staging with a computerized tomography (CT) scan of chest, abdomen, and pelvis with contrast showed no evidence of nodal or metastatic disease and no portal vein involvement (Figure 3A).

After discussion with the multidisciplinary team (MDT), the patient was scheduled for a pancreaticoduodenectomy. Intraoperatively, a 360° encasement of the portal vein by the tumor was identified and was deemed unresectable; a palliative biliary and gastric bypass was therefore performed. After an

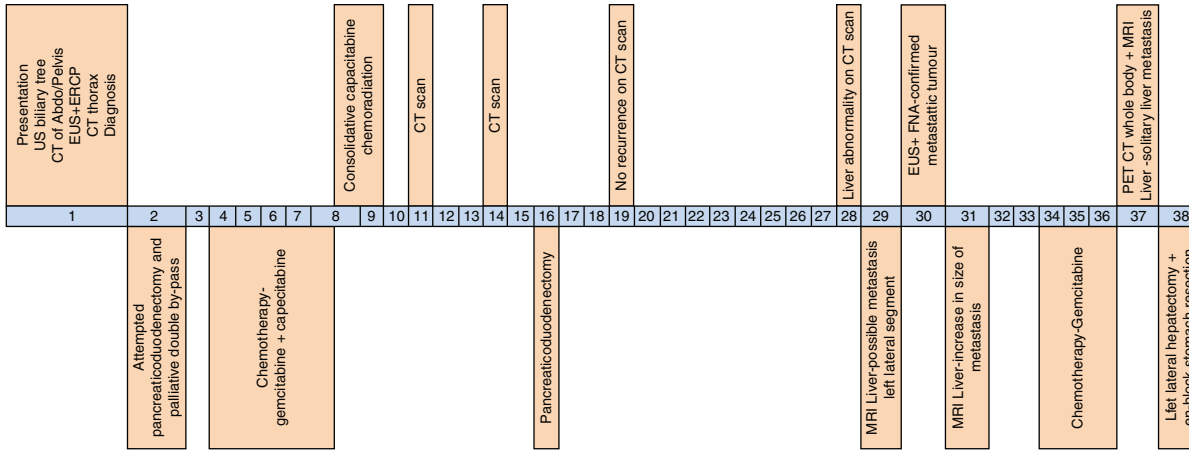

FIGURE 1. Timeline of patient's management (months).

uneventful recovery, the patient was referred to the oncology team for palliative chemoradiotherapy. The patient received 4 cycles of gemcitabine-capecitabine and subsequent consolidative chemoradiation receiving 50.4 grays in 28 fractions with concomitant capecitabine over the next 2 months. Response was assessed with a CT scan 2 months after completing chemoradiotherapy when she was found to have stable disease. A CT scan 5 months after the end of chemoradiotherapy revealed a substantial regression in tumor size (2.0×2.4 cm from 4.7×3.7 cm) (Figure 3B). In view of the marked radiological response, the MDT decided to proceed with a laparotomy for possible salvage pancreaticoduodenectomy. During the second operation (14 months after the first operation), the tumor was deemed resectable and a pancreaticoduodenectomy was performed. The patient made an uneventful recovery and was discharged after 7 days. Examination of the resected specimen revealed an ill-defined firm 22-mm tumor in the head of the pancreas. Histological examination revealed complete pathological response with extensive fibrosis, endarteritis, and evidence of previous haemorrhage, within the pancreas, peripancreatic fatty tissue and wall of the duodenum. Several atrophic and nondysplastic ducts were evident. No lymph node metastases were identified (ypT0 N0) (Figure 4). No evidence of disease was noted on a 3-month follow-up CT scan. However, a CT scan at 12 months postoperatively suggested a single liver lesion in the left lateral segment consistent with a metastatic deposit with a concomitant increase in the CA19–9 levels. This was confirmed on magnetic resonance imaging (MRI) (Figure 5). Cytological diagnosis via EUS and FNA confirmed this as metastatic carcinoma, with morphology similar to the initial pancreatic lesion. A positron emission tomography (PET) CT scan confirmed the solitary liver lesion and excluded any other areas of metastatic disease (Figure 5). The MDT opinion was in favor of further chemotherapy, due to the previous excellent response, with a view to proceeding to liver resection if the disease remained stable. The patient received three cycles of gemcitabine (due to intolerance to gemcitabine-capecitabine regimen) and subsequent imaging with MRI and PET-CT confirmed once again the liver lesion as the only metastatic deposit. Therefore, the patient was offered surgery. Intraoperatively the tumor in the left lateral segment of the liver was directly invading the lesser curvature of the stomach and a successful en block resection was performed. The patient made an uneventful recovery and was discharged after 6 days. Histological examination showed metastatic adenosquamous carcinoma with evidence of necrosis and extensive lymphovascular invasion. Breach of the liver capsule and infiltration of outer gastric wall were identified with clear resection margins.

DISCUSSION

Approximately one-third of patients with pancreatic adenocarcinoma are found to have an inoperable, locally advanced tumor at the time of diagnosis, with typical survival less than 1 year.[1,2,5] Furthermore, between 4% and 13% of patients with radiologically operable pancreatic cancer are

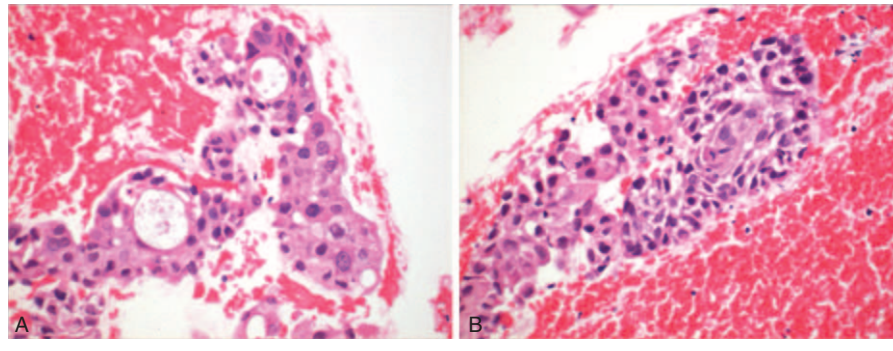

FIGURE 2. FNA cytology demonstrating poorly differentiated pancreatic carcinoma, with features of adenosquamous differentiation (hematoxylin-eosin staining). (A) glandular-like epithelium. (B) squamous-like epithelium.

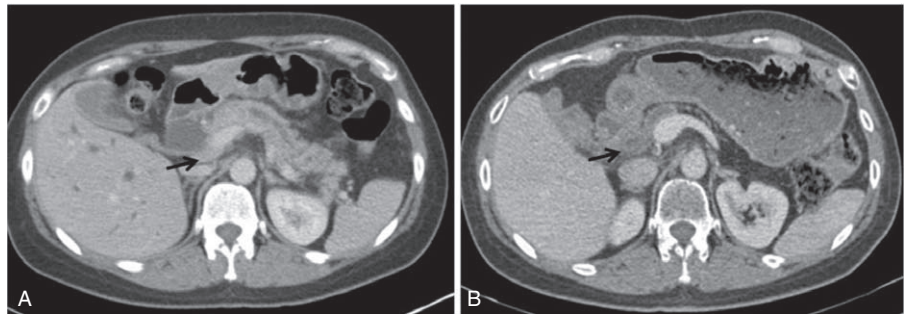

FIGURE 3. CT images demonstrating the tumor (arrows). (A) Initial staging scan. (B) Scan after chemoradiotherapy demonstrating tumor regression.

deemed unresectable at the time of surgery.[6] Optimal management of these patients continues to be an area of debate.

The 2 main strategies are chemotherapy induction followed by consolidation chemoradiotherapy or chemotherapy alone, with conflicting published evidence. One of the first randomized studies, the Gastrointestinal Tumor Study Group (GITSG) 9273 study, compared high-dose radiotherapy alone versus moderate-dose radiotherapy and 5-fluorouracil (5-FU) versus high-dose radiotherapy and 5-FU.[7] The study concluded that both 5-FU-based chemoradiation regimens produced significant improved survival compared to radiation alone. No difference in survival was noted between the high- and low-dose 5-FU chemoradiation regimens. The randomized Federation Francophone de Cancerologie Digestive-Societe Francaise de Radiotherapie Oncologique (FFCD/SFRO) trial compared an intensive induction regimen with 5-FU, cisplatin, and radiotherapy with gemcitabine alone induction, both followed by gemcitabine maintenance.[8] The results suggested a significantly reduced median overall survival with the intensive induction, as well as a substantially reduced 1-year survival and higher rate of toxicity. The most recent LAP 07 study, a phase III randomized trial in patients with pancreatic adenocarcinoma, showed no significant difference in overall survival between treatment with gemcitabine-based chemotherapy versus capecitabine-based chemoradiation after gemcitabine induction with or without erlotinib.[9]

In contrast to the GITSG and LAP 07 studies, evidence supporting the use of induction chemotherapy followed by consolidative chemoradiotherapy in selected patients has also been published. Results from nonrandomized studies suggested an overall survival of 15 to 19 months with chemoradiotherapy regimens.[10–18] The randomized, phase III Eastern Cooperative Oncology Group (ECOG) 4201 study, comparing gemcitabine alone versus gemcitabine-based chemoradiotherapy, showed a significant improved median overall survival with chemoradiotherapy.[19]

The Selective Chemoradiation in Advanced LOcalised Pancreatic cancer (SCALOP) trial, a UK-based, multicenter, randomized, two-arm phase II study, looked at gemcitabine- or capecitabine-based chemoradiotherapy for patients with locally advanced pancreatic adenocarcinoma.[20] All patients initially received 12 weeks of induction with gemcitabine and capecitabine. Patients with stable or responding disease after induction chemotherapy were randomized to receive gemcitabine- or capecitabine-based consolidative chemoradiotherapy. The results suggested that following a course of induction chemotherapy, a capecitabine-based consolidative chemoradiotherapy regimen might be preferable to a gemcitabine-based one, with significantly better survival and toxicity outcomes. The study also reported a median overall survival of 14.6 months with chemoradiotherapy versus 8.1 months with chemotherapy alone (patients with no response to the induction regimen). Twelve-month survival with chemoradiotherapy was 77.5% compared to 16.9% with chemotherapy alone. While supportive of chemoradiotherapy, interpretation of these data must be undertaken with caution as this study was not designed to compare chemotherapy alone versus chemoradiotherapy.

We present a case of a locally advanced pancreatic adenosquamous carcinoma, which was deemed unresectable intraoperatively due to complete encasement of the portal vein. Nonetheless, the tumor showed radiological response to systemic chemoradiotherapy and was resected about 1 year

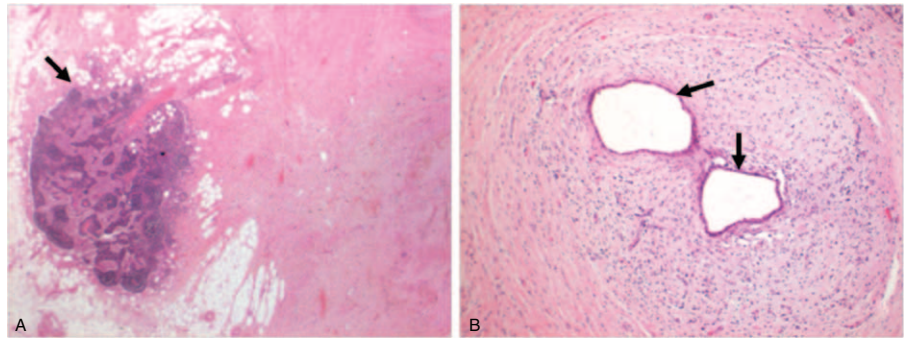

FIGURE 4. Histology of pancreas specimen following resection (hematoxylin-eosin staining). (A) Featureless fibrosis involving lymph node (arrow) (low power magnification). (B) Residual ducts (arrows) surrounded by fibroblastic tissue (high power magnification).

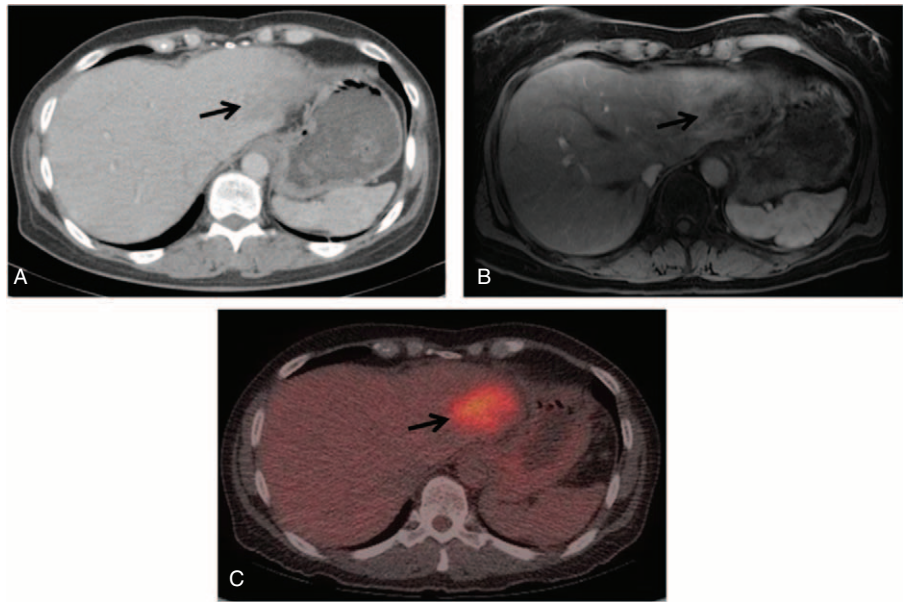

FIGURE 5. (A) CT, (B) MRI, and (C) PET-CT scans demonstrating lesion in left lateral segment (arrows).

later. Histopathological examination of the specimen revealed a complete pathological response to chemoradiotherapy. One year after the resection the patient was diagnosed with a solitary liver metastasis, managed with chemotherapy and surgical resection as the disease remained limited. We acknowledge the use of a chemoradiotherapy protocol similar to, but outside, the SCALOP trial in a case of adenosquamous carcinoma of the pancreas, while in the trial only patients with adenocarcinomas were included. Evidence for the optimal management of this rare histological type of pancreatic cancer, estimated to represent 3% to 4% of primary pancreatic cancer cases[21,22], is scant, although it has been reported that squamous differentiation is associated with more biologically aggressive behavior and that chemoradiotherapy can be associated with improved overall survival.[21]

Management of locally advanced pancreatic tumors still poses a medical challenge. Recently, more cytotoxic regimens, such as FOLFIRINOX, have also been used. The presented case demonstrates the potential advantage of chemoradiotherapy for the control and downstaging of the primary tumor in selected patients, which may make subsequent surgical management feasible. The results of important studies in the area are eagerly awaited, such as the recently opened PRICKLE trial, a single-center phase IIa trial assessing the effectiveness of gemcitabine and nab-paclitaxel in downstaging borderline unresectable locally advanced pancreatic cancer.

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