CASE REPORT

Mixed acinar-neuroendocrine-ductal carcinoma of the pancreas: a tale of three lineages

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Accepted 12 May 2016

SUMMARY

Most pancreatic cancers arise from a single cell type, although mixed pancreatic carcinomas represent a rare exception. The rarity of these aggressive malignancies and the limitations of fine-needle aspiration (FNA) pose significant barriers to diagnosis and appropriate management. We report a case of a 54-year-old man presenting with abdominal pain, jaundice and a hypodense lesion within the uncinate process on CT. FNA suggested poorly differentiated adenocarcinoma, which was subsequently resected via pancreaticoduodenectomy. Pathological analysis yielded diagnosis of invasive mixed acinar-neuroendocrine-ductal pancreatic carcinoma. Given the rare and deadly nature of these tumours, clinicians must be aware of their pathophysiology and do practice with a high degree of clinical suspicion, when appropriate. Surgical resection and thorough pathological analysis with immunohistochemical staining and electron microscopy remain the standards of care for mixed pancreatic tumours without gross evidence of metastasis. Diligent characterisation of the presentation and histological findings associated with these neoplasms should continue in order to promote optimal diagnostic and therapeutic strategies.

BACKGROUND

Most pancreatic malignancies are known to arise from a single cell type of either endocrine or exocrine origin. Ductal adenocarcinomas represent about 85% of all pancreatic neoplasms with several subtypes sharing a similarly poor prognosis.¹ Pancreatic neuroendocrine tumours make up only 5–8% of all pancreatic tumours and have been shown to exhibit a more indolent course amenable to surgical resection. Acinar cell carcinoma is much less common, constituting only 1–2% of all pancreatic exocrine tumours.² An even rarer entity, however, are instances in which pancreatic neoplasms are composed of mixed exocrine and endocrine cell lines. With 27 confirmed cases reported in English literature, mixed acinar-neuroendocrine carcinomas (MANEC) of the pancreas represent one of the rarest known pancreatic malignancies. According to the WHO 2010 classification, a diagnosis of MANEC requires that each component represent at least 30% of the lesion.³ These neoplasms differ from pancreatoblastoma in that they do not contain undifferentiated cells. In 2013, Yu *et al*⁴ reviewed published to date cases of pancreatic MANEC in order to characterise the clinical and pathological features of this malignancy. They concluded that 23 verifiable cases had been

reported with appropriate quantification of their respective acinar and endocrine components. Since this publication, four additional cases were reported in 2013.^{5–7}

Tumours with tri-lineage differentiation (acinar, ductal, neuroendocrine) are an even rarer entity. Notably, Newman *et al* reported a case in 2009 of a 56-year-old man presenting with abdominal pain and a 3.2 cm mass in the pancreatic body with distal ductal dilation on CT. Following distal pancreatectomy, there was no evidence of lymphadenopathy and the patient was discharged on postoperative day 6 without complication. Pathologically, this tumour displayed unique tri-lineage (acinar, neuroendocrine and ductal) differentiation.⁸ While quantification of respective cytological components was not included in their analysis to verify their diagnosis, we include their work in this review due to its relevance to our patient's rare histological findings. As stated in their review, only five similar cases had been reported prior to publication, most without the immunohistochemical staining and quantitative analysis required for diagnostic confirmation.^{9–13}

Schron *et al* reported a 62-year-old woman who presented with vomiting, jaundice and weight loss. CT revealed a mass in the head of the pancreas (size not specified) and dilated intrahepatic ducts. She underwent pancreaticoduodenectomy, which revealed positive peripancreatic lymph nodes. The patient's condition deteriorated over the subsequent 3 months with complications including bilateral malignant pleural effusions, lower extremity oedema secondary to inferior vena cava compression, and Gram-negative septicaemia. The patient died 5 months post incision with widespread tumour dissemination.⁹

Tanakaya *et al* reported a 72-year-old woman with altered mental status, hypoglycaemia, hyperinsulinemia and a 1.4 cm mass in the body of the pancreas that was first visualised on abdominal ultrasound. The tumour was excised in May 1994 with subsequent resolution of fasting blood glucose and insulin levels. The patient was alive without evidence of disease recurrence at 6 years post incision.¹⁰

Nonomura *et al* reported a case describing a 76-year-old man who had died of intrahepatic cholangiocarcinoma. A tumour in the pancreatic tail was discovered incidentally during autopsy and displayed tri-lineage differentiation.¹¹

Okada *et al* reported a 21-year-old man with mumps and an incidentally discovered 2.5 cm tumour in the pancreatic body. The patient was asymptomatic and was found to have a slightly

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To cite: Anderson MJ, Kwong CA, Atieh M, *et al*. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213661

elevated serum glucagon. Surgical resection of the tumour was performed in February 1994, and the patient was discharged with normalised glucagon level and no complications. No follow-up was provided.¹²

Tadashi *et al* reported a case of a 34-year-old Japanese man presenting with abdominal pain and elevated pancreatic enzymes. With no tumour identified on CT or MRI, endoscopic retrograde cholangiopancreatography (ERCP) was conducted and showed an 18 mm filling defect within the main pancreatic duct. Biopsy of the intraductal lesion revealed atypia and positive synaptophysin, CA 19-9 and CEA. The body and tail of the pancreas were resected, and the patient's postoperative course was without metastasis or recurrence. However, the time frame of his follow-up was not provided.¹³

Finally, Stelow *et al* reviewed cases of pancreatic acinar cell carcinomas with ductal differentiation in surgical pathology databases of two academic centres. They identified three cases of pancreatic neoplasms with mixed acinar-neuroendocrine-ductal differentiation.¹⁴ All of these tumours had formed in the pancreatic head with a diameter ranging from 2 to 5.5 cm. Most patients underwent primary resection with variable participation in adjuvant chemotherapy or radiation. Mean length of follow-up was 29 months, with the majority of patients dying of their disease.

Therefore, at the time of submission, this case represents the 10th reported instance of mixed tri-lineage carcinoma of the pancreas and the fourth case that is supported by immunohistochemical staining and a Ki-67 index >30% required for diagnostic confirmation according to WHO standards.

While pancreatic tri-lineage tumours are scarce, this phenomenon has been known to arise elsewhere along the gastrointestinal tract, particularly in the caecum (8 cases) and stomach (36 cases).¹⁵ Similar to the clinical course of most pancreatic MANECs, these tumours appeared highly malignant and prone to distant metastasis. The aggressiveness of these cases were similarly determined by their neuroendocrine components. We report a case of a 54-year-old man who underwent a Whipple procedure for a pancreatic neoplasm with invasion of the ampulla, common bile duct, main pancreatic duct and duodenal wall. Histology and immunostaining confirmed a diagnosis of high-grade mixed acinar-neuroendocrine-ductal carcinoma of the pancreas.

CASE PRESENTATION

A 54-year-old Hispanic male presented to an outside hospital with postprandial midline abdominal pain along with jaundice, pruritus, clay-coloured stools, and anorexia with a 1 month,

20-pound unintentional weight loss. Medical history was significant for hypercholesterolaemia, recently diagnosed diabetes mellitus—type II, a 15-pack year smoking history and heavy alcohol use. The patient's serum direct bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase were elevated at the time of admission.

INVESTIGATIONS

Abdominal ultrasound showed dilation of the common bile duct (CBD) and MR cholangiopancreatography confirmed intrahepatic and extrahepatic bile duct dilation with abrupt tapering of the CBD just proximal to the ampulla. CT of the abdomen showed a hypodense lesion within the uncinate process of the pancreatic head immediately adjacent to the third portion of the duodenum (figure 1A, C). MRI confirmed an estimated 1.2×1.5 cm lesion in the head of the pancreas (figure 1B). ERCP was then performed with partial sphincterotomy and CBD stent placement. The patient was then referred to our institution for further evaluation of this highly suspicious mass.

DIFFERENTIAL DIAGNOSIS

Endoscopic ultrasound-guided FNA, in conjunction with a hypoattenuating mass within the uncinate process, provided a working diagnosis of poorly differentiated adenocarcinoma of the pancreas. However, due the diagnostic limitations of this modality and the risk of sampling error, a wide differential diagnosis was maintained until postoperative pathological analysis could be conducted. This differential diagnosis also included neuroendocrine tumour, acinar cell carcinoma, MANEC, intraductal papillary mucinous neoplasm and pancreatoblastoma. In the absence of metastatic disease, resection can, therefore, be diagnostic and therapeutic.

TREATMENT

After discussing the role of surgical intervention for pancreatic cancer, including risks and benefits of the procedure, the patient wished to proceed with surgery. We then performed diagnostic laparoscopy, laparoscopic liver biopsy and pancreaticoduodenectomy with C-loop reconstruction. The proximal common bile duct margin, pancreatic margin and liver biopsy were all negative for carcinoma on frozen section; the specimen was successfully resected and sent to pathology.

OUTCOME AND FOLLOW-UP

Three of 37 lymph nodes recovered were positive for carcinoma, staging the mass as pT3N1Mx. The patient's postoperative

Figure 1 Imaging studies demonstrating pancreatic neoplasm. (A) Axial CT with contrast demonstrating hypodense lesion (arrow) in the head of the pancreas, uncinate process. (B) Corresponding axial MRI demonstrates well-encapsulated 1.2×1.5 cm lesion (arrow) within the uncinate process. (C) Coronal CT with contrast demonstrating hypodense pancreatic lesion (arrow) and markedly dilated biliary tree (asterisk) which abruptly tapers in the periampullary region.

Figure 2 Infiltrating tri-lineage mixed carcinoma of the pancreas. Low power H&E stain showing an infiltrating, high-grade carcinoma in relation to uninvolved bowel mucosa. As labelled, this tumour was characterised throughout by neuroendocrine, acinar and ductal components.

course was uncomplicated and on discharge, on postoperative day six, he was tolerating a diabetic diet, voiding spontaneously, ambulating at baseline and tolerating pain with oral analgesia.

On dissection of the pancreaticoduodenectomy specimen, the tumour was described as an ill-defined, firm, pale, tan-yellow

2.7 cm mass within the head of the pancreas invading the ampulla, CBD, pancreatic duct, duodenal wall (muscularis propria) and focally extending into the peripancreatic adipose tissue. Histology revealed that the tumour grew predominantly in a nested, trabecular pattern and staining was positive for

Figure 3 Neuroendocrine component of mixed pancreatic carcinoma. (A) Low-medium power view of an area demonstrating neuroendocrine differentiation with tumour cells forming irregular nests and trabecular cords. (B) Synaptophysin positive in areas of neuroendocrine differentiation. (C) CD56 positive in areas of neuroendocrine differentiation. (D) Ki-67 positive with proliferation fraction of 60–70%.

Figure 4 Acinar component of mixed pancreatic carcinoma. (A) Medium power and (B) Medium–high power magnification of H&E stain demonstrating rosette-like pattern. (C) Trypsin stain positive in areas of acinar differentiation.

pancytokeratin (figure 2). The neoplasm also exhibited characteristics and nuclear features characteristic of neuroendocrine differentiation, such as irregular nests and trabecular cords (figure 3A). These findings were supported by synaptophysin and CD56 (figure 3B, C, respectively). Ki-67 labelling index of >60% initially qualified this mass as a high-grade (poorly differentiated) neuroendocrine carcinoma (figure 3D).

However, the tumour also exhibited characteristics indicative of other cell lineages. Areas with foci of rosette-like acinar formations and convincing trypsin positivity supported an acinar cell carcinoma component (figure 4). Lastly, the carcinoma exhibited a ductal component with abortive attempts of glandular differentiation with areas of cord-like infiltration and tubule formation (figure 5A). These findings were supported by immunostaining showing positivity for MUC1, CK19 and CEA in abortive glandular areas of the tumour (figure 5B–D).

According to 2010 WHO classification, these morphological findings in conjunction with the above immunostaining test results and Ki-67 index of >30% are consistent with a diagnosis of mixed acinar-neuroendocrine-ductal carcinoma of the

pancreas. At the time of submission of this report, the patient has completed eight cycles of adjuvant gemcitabine and cisplatin therapy in addition to 5-fluorouracil chemoradiation therapy in hopes of eradicating micrometastatic disease. Follow-up imaging has shown no evidence of disease.

DISCUSSION

Mixed carcinoma of the pancreas is a rare, highly aggressive malignancy that is being reported with increasing prevalence. This phenomenon is likely due to improved diagnostic modalities, heightened interdisciplinary awareness of the entity, and increasing detection and resection rates of pancreatic neoplasms. Owing to its scarcity, however, sufficient characterisation of the typical presentation and clinical course of this disease is a persistent challenge. Therefore, it remains imperative that physicians continue to report cases of this malignancy with detailed accounts of the presenting symptoms, clinical and surgical findings, histological characteristics and patient outcomes.

Although the CT scan remains the imaging modality of choice for pancreatic tumours, the increasing prevalence of mixed

Figure 5 Ductal component of mixed pancreatic carcinoma. (A) High power magnification H&E stain demonstrating abortive glandular and ductal structures (arrows). These areas were (B) MUC1 positive, (C) CK19 positive and (D) CEA positive confirming the ductal component of the mixed acinar-neuroendocrine-ductal carcinoma of the pancreas.

neoplasms supports a multimodal approach to diagnosis. Cytological analysis via FNA is a valuable supplement to CT, and can greatly impact management decisions due to the morphology-dependent prognoses of differing pancreatic malignancies. However, due to limitations of cytology, false preoperative diagnoses remain prevalent in cases of mixed pancreatic tumours, and this places these patients at risk for inopportune care. Sullivan *et al* illustrate that common pitfalls to accurate cytological diagnosis include sampling error and overlapping cytomorphological features among various tumour types. A common false diagnosis of Pan-NET, for example, may permit inappropriately conservative treatment. Alternatively, our patient was initially diagnosed with poorly differentiated adenocarcinoma based on concordant findings on CT and FNA (hypoattenuating mass in the head of pancreas and glandular formation on cytology, respectively). This initial diagnosis fortunately prompted expedient resection.

Discrepancies during the workup of pancreatic neoplasms, such as discordant CT and FNA findings, should therefore raise clinical suspicion for more aggressive mixed tumours and prompt timely surgical resection and immunohistochemical staining of cytological specimens. Although surgical resection remains the only standard of care for mixed pancreatic tumours without gross evidence of metastasis, thorough postoperative analysis along with continued reporting of these cases should be advocated in order to improve our collective understanding of the disease process and standardise optimal therapy.

Learning points

- ▶ Most pancreatic cancers arise from a single cell type, although 27 cases of mixed acinar-neuroendocrine carcinoma (MANEC) of the pancreas have been reported.
- ▶ This case represents the 10th reported case of mixed pancreatic carcinoma with tri-lineage origin, and the first of which that is supported by immunohistochemical staining and Ki-67 index >30% required for diagnosis according to WHO standards.
- ▶ Challenges to accurate diagnosis and appropriate management include the rarity of this neoplasm and the limitations of fine-needle aspiration.
- ▶ Although surgical resection and postoperative pathological analysis remain the standards of care when metastatic disease is not apparent, clinicians should continue to report cases of mixed pancreatic carcinomas in order to better characterise the disease process and standardise optimal therapy.

Acknowledgements The authors would like to acknowledge the contributions of Dr Stefan Pambuccian and Dr N. Volkan Adsay who were consulted for pathological analysis, staining and immunohistochemistry. Additionally, the authors would like to acknowledge Dr Gerard Abood for his support and review of this publication.

Contributors MJA researched the topic and relevant literature, conducted chart review, drafted, edited, finalised and submitted the manuscript. CAK prepared pathology slides, created images and legends. MA conducted pathological analysis & immunostaining, edited images and legends. SGP performed the surgery, consented the patient, conceived the publication and edited the manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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