CASE REPORT

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Anaplastic Pancreatic Carcinoma Arising Within a Mucinous Cystic Neoplasm of the Pancreas: A Case Report and a Brief Review of the Literature

Alessandro Paniccia,¹ Robert Torphy,¹ Kalpana Devaraj,² and Richard D. Schulick^{1,*}

Abstract

Background: Anaplastic pancreatic carcinomas (APCs) are among the least frequently encountered pancreatic malignancies, ranging from 0.5% to 7% of all nonendocrine pancreatic malignancies. Furthermore, few cases of APCs have been described arising within a pancreatic mucinous cystic neoplasm (MCN).

Case Presentation: A 36-year-old female presented with left upper quadrant pain and a 10 × 8 cm complex cystic mass in the pancreatic tail. Fine needle aspiration of the cyst showed papillary clusters of cells with mild cytological atypia, cyst fluid carcinoembryonic antigen >4000 ng/mL, and amylase of 25 U/L. After an open distal pancreatectomy and splenectomy, the specimen revealed an MCN with multifocal microscopic foci of invasive well-differentiated adenocarcinoma. After additional sampling, foci of undifferentiated malignancy—morphologically resembling sarcomas but with immunohistochemical staining consistent with anaplastic carcinoma—were identified. The patient had an uneventful recovery and is currently undergoing a regimen of gemcitabine-based adjuvant chemotherapy; she remains disease-free at 5 months after initial diagnosis.

Conclusions: In this study, we describe a rare case of APC originating from a large pancreatic MCN lesion. This case underlines the importance of scrupulous pathological evaluation of the entire MCN epithelium and adds to the limited world literature of APC originating from pancreatic MCN lesions.

Keywords: anaplastic pancreatic carcinoma; APC; MCN; osteoclast-like giant cell; pancreatic cystic lesion; spindle cell

Case Report

A 36-year-old female presented with 5 days of abdominal pain, associated nausea, and a firm and tender left hypocondrium. She had no personal nor family history of pancreatitis or solid organ malignancy, and denied any history of alcohol, tobacco, or illicit drug use. After an unremarkable abdominal radiograph, the patient underwent a computed tomography (CT) scan of her abdomen and pelvis that showed a 10 cm complex cystic mass in the tail of the pancreas (TOP).

An upper endoscopy with endoscopic ultrasound confirmed a 10 × 8 cm lesion in the TOP. The lesion was thick walled with multiple internal septations and both cystic and solid components. The serum carcinoembryonic

antigen (CEA) level was 2.4 ng/mL (reference range 0.0–3.0 ng/mL) and CA-19 was elevated to 1175 U/mL (reference range 0.0–35.0 U/mL). The differential diagnosis for this lesion included a mucinous cystic neoplasm (MCN) or a solid pseudopapillary neoplasm. Fine needle aspiration of the cyst tissue and fluid was obtained that yielded papillary clusters of cells with mild cytological atypia, suspicious for neoplasm. The cystic fluid had a CEA level of >4000 ng/mL and an amylase level of 25 U/L.

She underwent a staging CT of chest, abdomen, and pelvis, which again showed the already mentioned mass and no evidence of metastatic disease (Fig. 1).

Based on the size of the lesion, an open distal pancreatectomy and splenectomy were performed. On frozen

Departments of ¹Surgery and ²Pathology, University of Colorado Anschutz Medical Campus, Aurora, Colorado.

*Address correspondence to: Richard D. Schulick, MD, MBA, Department of Surgery, University of Colorado Anschutz Medical Campus, 12631 East 17th Avenue, Aurora, CO 80045, E-mail: richard.schulick@ucdenver.edu

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FIG. 1. (A) 10×8 cm thick walled lesion with multiple thick internal septations and both cystic and solid components in the tail of the pancreas. (B) Splenic vein compression by the mass.

section, the pancreatic margin was found to be normal pancreas parenchyma with low-grade PanIN. The patient had an uneventful postoperative course and was discharged home on postoperative day 6.

Initial pathology sections of the cyst revealed an MCN with extensive high-grade dysplasia (HGD) and a few foci of microscopic invasive well-differentiated adenocarcinoma (Fig. 2A, B; Table 1). The remainder of the specimen was submitted for histological examination. Areas of undifferentiated malignancy with sarcomatous features were noted in some of the last histological sections (Fig. 2C). The lesion was negative for all mesenchymal markers but strongly positive for cytokeratin (CK), indicating an epithelial malignancy consistent with anaplastic pancreatic carcinoma (APC) (Fig. 2D). Three of 38 peripancreatic lymph nodes were positive for APC, highlighted on CK stain (Fig. 2E, F). The final pancreatic margin was negative for MCN, HGD, and malignancy.

The patient recovered well from the surgical resection and was seen in follow-up at 6 months from the date of surgery at which time a surveillance CT of abdomen did not reveal any evidence of recurrent disease. At her subsequent 8-month follow-up, she had completed six cycles of adjuvant chemotherapy (gemcitabine plus capecitabine) and had an Eastern Cooperative Oncology Group performance score of 1.

Discussion

In this study, we describe a rare case of APC originating from a large pancreatic MCN lesion with final histological analysis revealing areas of adenocarcinoma, as well as foci of APC amid mucinous cystadenoma epithelium.

APCs are among the least frequently encountered pancreatic malignancies, ranging from 0.5% to 7% of all nonendocrine pancreatic malignancies.^{1,2}

APCs are defined as epithelial malignancies, which are composed largely of neoplastic cells with no identifiable line of differentiation. According to the classification of the World Health Organization of tumors of the digestive system, APCs include the following entities: anaplastic carcinoma, undifferentiated carcinoma with osteoclast-like giant cells, pleomorphic giant cell carcinoma, undifferentiated carcinoma, pleomorphic carcinoma, and sarcomatoid carcinoma, among others.^{3,4}

To the best of our knowledge, only 12 cases of anaplastic carcinoma arising from MCNs are reported in the English language literature (Table 2).^{5–13}

The most commonly described clinical symptoms in the literature include loss of weight, fatigue, loss of appetite, abdominal pain, nausea, vomiting, and diarrhea.¹¹ Despite many morphology changes, the APC cells usually have reactivity to epithelial markers and vimentin, indicating an epithelial origin with dedifferentiation. Diagnosis of this type of tumor may be challenging because of lack of glandular structures or other features that indicate a direction of differentiation. Perineural/lymphovascular invasion is rarely mentioned in the identified case reports and case series of APC originating from MCNs; therefore, the true prevalence of perineural/lymphovascular invasion remains difficult to quantify. For example, Lane and Sanguenza were the only authors—among those selected for this review—to describe positive lymphovascular invasion.⁷ Similarly, the rate of metastatic lymph nodes with cellular deposits of APC originating from MCNs remains

FIG. 2. (A) Representative HE stained section of MCN demonstrating moderate grade (arrow) to high-grade (arrowhead) dysplasia and ovarian stroma (star) (10 $\times$). (B) Area of invasive pancreatic adenocarcinoma (arrow) within MCN (10 $\times$). (C) Representative HE region of highly cellular stroma within MCN specimen (20 $\times$). (D) Cellular stroma staining CK positive indicating epithelial cell type origin (20 $\times$). (E, F) Representative lymph node HE and CK stain showing CK-positive cells invading lymph node tissue (20 $\times$). CK, cytokeratin; HE, hematoxylin and eosin; MCN, mucinous cystic neoplasm.

unclear, as only 3 of the 10 selected authors reported on the status of the lymph nodes; of these Lane and Sanguenza⁷ described positive retroperitoneal lymph nodes involved with APC cellular deposits and, similarly, Nishihara et al. described peripancreatic and perigastric lymph nodes with APC cellular deposits.⁸ In the case herein described, we identified three metastatic lymph nodes with clear evidence of APC cellular deposits.

APCs are historically associated with dismal prognosis, with median overall survival for patients with unresected APC estimated at 3 months and for resected APC estimated at 59.1%, 30.7%, and 12.2%, respectively, at 1, 2, and 5 years.²

However, survival rates can be quite variable, because of the wide array of histopathology present under the umbrella of APCs. For example, a sarcomatoid lineage of APCs confers a dreadful prognosis, as shown by

Table 1. Summary of the Histomorphological and Immunohistochemical Features of the Mucinous Cystic Neoplasm Described in the Case Report

Histomorphology	MCN with abundant ovarian-type stroma (confirmed by positive ER/PR) with extensive high-grade dysplasia. Microscopic foci of invasive adenocarcinoma budding off the main epithelial lining. Multiple hypercellular areas, comprising markedly atypical cells without glandular differentiation. Atypical cells appear spindled or rhabdoid with eccentrically placed nuclei and dense purple cytoplasm.
Immunohistochemistry	SMA, desmin, myogenin, CD10, and INI1 are negative in the hypercellular areas, arguing against a diagnosis of sarcoma. Pancytokeratin and CK 7 are strongly and diffusely positive in the hypercellular areas, including the spindled and rhabdoid-appearing cells. EMA is weakly positive in the same population of cells. This staining pattern is most consistent with undifferentiated carcinoma (anaplastic carcinoma).

CK, cytokeratin; EMA, epithelial membrane antigen; ER, estrogen receptor; MCN, mucinous cystic neoplasm; PR, progesterone receptor; SMA, smooth muscle actin.

Wenig et al., with two of three patients deceased within 15 months from diagnosis.¹⁴ On the contrary, the osteoclast-like giant cell feature appears to confer a favorable prognosis with 5-year survival of 50%.⁴ Another open debate in the APCs literature is the pathogenesis of these lesions with recent evidence suggesting a monoclonal origin with subsequent differentiation toward an epithelial or a mesenchymal neoplastic component.^{15,16}

The choice of systemic therapy after surgical resection of APC remains an open question as no high-

quality studies have been completed comparing one adjuvant regimen versus another and, therefore, no consensus has been reached regarding the optimal adjuvant therapy. Several different adjuvant regimens have been described, including the use of adjuvant paclitaxel, S-1 (based on the result of the JASPAC-01 trial), and gemcitabine, among others.^{13,17–19} The choice seems to be driven by institutional preferences, and perhaps by the particular histological subtype of APC and associated molecular markers—although no

Table 2. Anaplastic Pancreatic Carcinoma Arising from Mucinous Cystic Neoplasm, Reported Cases in the Literature

Authors	Years	No. of cases	Age/gender	MCN greatest dimension	Morphology of anaplastic component	Adjuvant therapy	Follow-up
García Rego et al. ⁵	1991	1	45/Female	11 cm	Anaplastic carcinoma with transition from spindle cells to neoplastic glandular elements	ND	Alive at 16 months after diagnosis
Marinho et al. ⁶	1995	1	70/Female	4.5 cm	Dispersed anaplastic cells	ND	ND
Wenig et al. ¹⁴	1996	3	48/Female 66/Female 67/Male	19 cm ND 30 cm	Spindle cell	ND ND ND	Alive for 1 year Died after 9 months Died after 15 months
Lane and Sanguenza ⁷	1996	1	25/Female		Anaplastic morphology	ND	Alive 6 months after diagnosis with liver metastatic disease
Nishihara et al. ⁸	1997	1	52/Female	10 cm	Anaplastic with rhabdoid feature	ND	Died 19 months after diagnosis
Bloomston et al. ⁹	2006	1	67/Female	4 cm	Spindle cell morphology in addition to poorly differentiated and squamous areas	Did not receive	Died 4 months after diagnosis
Pan and Wang ¹¹	2007	1	70/Female	10.4 cm	Anaplastic with predominant spindle cell component	ND	Alive 4 months after diagnosis
Hakamada et al. ¹⁰	2008	1	38/Female	5 cm	Spindle cell, giant cells, and adenocarcinoma	ND	Alive at 4 years
Asberry et al. ¹²	2012	1	40/Female	8 cm	Spindle cell morphology	ND	Alive 48 months after diagnosis
Aldaoud et al. ¹³	2016	1	37/Female	10 cm	Highly dyscohesive anaplastic cells	Gemcitabine	Died 7 months after diagnosis
Paniccia et al. (present study)	2017	1	36/Female	16 cm	Anaplastic with predominant spindle cell morphology in addition to multifocal invasive adenocarcinoma	Gemcitabine and capecitabine	Alive at 5 months

ND, not described.

definitive agreement exists. We elected to administer a gemcitabine-based regimen—which has been proven to be efficacious in the adjuvant setting after resection of pancreatic adenocarcinoma—combined with capecitabine based on the data published in the ESPAC-4 trial showing increased response with acceptable toxicity profile.²⁰

Specifically, the patient herein discussed received adjuvant gemcitabine (1000 mg/m² intravenously on days 1, 8, and 15 every 28 days) with the addition of capecitabine (1600 mg/m²—in divided doses—on day 1 through day 21 every 28 days), and completed a total of six cycles with moderate systemic toxicity.

Finally, it is worth noting that malignant transformation—within the MCN lesion—is characterized by a focal skip pattern, wherein isolated areas of cancerous transformation can be found alongside normal-appearing cyst epithelial lining.¹² Therefore, partial or inaccurate cyst wall analysis can easily lead to misdiagnosis and the importance of a thorough pathological evaluation of the entire cyst wall cannot be overstated.

In fact, complete operative resection of MCNs lacking an invasive component (i.e., benign MCNs and, more importantly, noninvasive proliferative MCNs) ensures cure.²¹ These neoplasms are solitary and do not recur either locally or distally after complete operative resection.²¹ On the contrary, the presence of an invasive component—within the MCN—mandates that this lesion is treated similarly to pancreatic ductal adenocarcinoma (PDAC) for what concerns adjuvant therapy and follow-up, because of the high risk of local and systemic recurrence.^{21,22} Invasive adenocarcinoma arising within an MCN lesion appears to have a slightly different behavior from the more common PDAC arising *de novo* from the pancreatic duct. In fact, most series describe a lower rate of lymph node positivity ranging from 0% to 34% and a more favorable 3-year survival rate, ranging from 44% to 83%.^{23–28} Although it remains unclear whether this seemingly more indolent behavior of adenocarcinoma arising from pancreatic MCNs—compared with the *de novo* PDAC—is the result of actual biological differences or whether it is just a consequence of diagnosis and resection at an earlier cancer stage.

It is the authors' practice—in the setting of MCNs—to perform extensive, preferably complete, sampling of the cyst wall to (1) rule out malignancy and (2) rule out the presence of more than one kind of malignancy. In this case, the minute microscopic foci of adenocarcinoma are of less clinical consequence than the APC

that was found only because the entire lesion was scrupulously analyzed rather than stopping after the identification of the adenocarcinoma component. This case argues for scrupulous pathological evaluation of the entire MCN and adds to the limited world literature of APC originating from pancreatic MCNs.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

APC = anaplastic pancreatic carcinoma
CK = cytokeratin
CT = computed tomography
HE = hematoxylin and eosin
HGD = high-grade dysplasia
MCN = mucinous cystic neoplasm
PDAC = pancreatic ductal adenocarcinoma
TOP = tail of the pancreas

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