Adenosquamous Carcinoma of the Pancreas

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ABSTRACT: A 60-year-old woman presented to hospital with abdominal pain and massive weight loss. Imaging studies confirmed the presence of a tumor of the pancreas. Histologic analysis of the sampling performed by echoendoscopic ultrasound fine-needle aspiration found aspects evocative of adenosquamous carcinoma. This case report highlights the difficulties of clinical pathologic diagnosis for these occasionally composite tumors. The patient underwent palliative chemotherapy based on platinum and 5-fluorouracil, followed by second-line chemotherapy with FOLFIRI after progression. Adenosquamous carcinoma of the pancreas remains a rare tumor with very poor prognosis and limited therapeutic options.

KEYWORDS: pancreatic cancer, endoscopic ultrasound, core needle biopsy, PET scan, adenosquamous cell carcinoma

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Introduction

Adenosquamous carcinoma (ASC) of the pancreas is a rare malignancy. ASC is defined as at least 30% malignant squamous cell carcinoma mixed with ductal adenocarcinoma.[1] Using the California Cancer Registry, Katz et al[2] identified 95 cases of ASC between 2000 and 2007, representing 0.4% of 24 604 newly diagnosed pancreatic malignancies, including 14 746 ductal adenocarcinoma. A SEER (The Surveillance, Epidemiology, and End Results) database review published in 2012 by Boyd et al[1] identified only 415 cases of ASC between 1988 and 2007 compared with 45 693 patients with adenocarcinoma of the pancreas. ASC incidence is estimated between 0.38% and 10% of all exocrine pancreatic tumors.[1,3,4] This large range is probably explained by the fact that most of ASC are misdiagnosed by a biopsy and some unresected tumors are classified as adenocarcinoma rather than ASC.[1,3] Major risk factors identified are tobacco and alcohol consumption, chronic pancreatitis, ABO blood group, and some genetic predispositions such as BRCA2, PALB2, ATM, and p53.[1,3] Given their rarity, diagnosing these tumors can be difficult. We report a case of ASC of the pancreas, which was diagnosed in our center by endoscopic ultrasound biopsy using a ProCore biopsy needle.

Case Presentation

A 60-year-old woman was seen in consultation for epigastric and left hypochondrium girdle pain radiating toward the left lumbar region. This was combined with loss of appetite and weight loss of 8 kg in 4 months. The patient had no significant medical history. Tobacco consumption, estimated at 30 pack-years, was noted. Her 84-year-old father had recently begun treatment for primary pancreatic adenocarcinoma, which initially presented as jaundice. There was no other family history of cancer. Clinical examination identified that the patient was fatigued, had lost weight, and was depressed. Abdominal examination revealed no abnormal masses. Complete physical examination was normal, notably with the absence of hepatomegaly, ascites, or peripheral lymphadenopathy. A chest, abdomen, and pelvis computed tomography (CT) scan revealed extensive organ involvement of the pancreatic tail, with locoregional progression up to the back of the stomach (Figure 1). This was combined with a metastatic-type lesion of less than 1 cm in liver segment VI. Laboratory tests revealed anicteric cholestasis twice the upper limit of normal (2× ULN) and C-reactive protein at 34 mg/L (N < 5 mg/L). Carcinoembryonic antigen and CA 19-9 levels were normal at 2.7 ng/mL and 32 IU/L, respectively. An endoscopic ultrasound biopsy was performed, revealing a

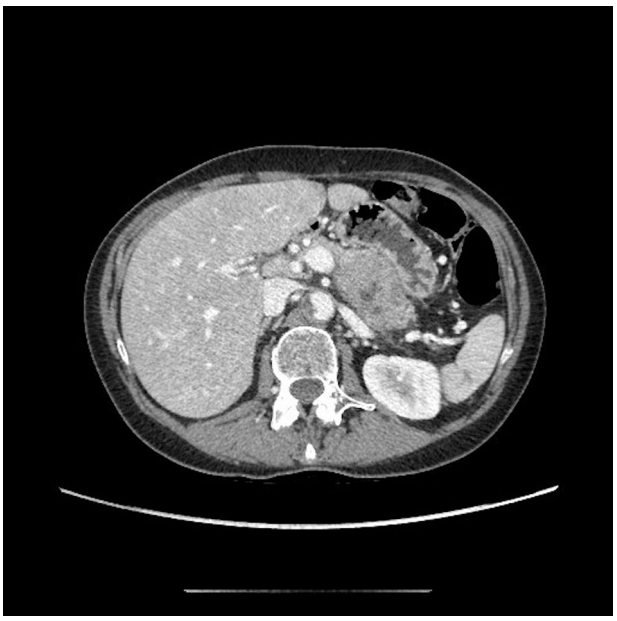

Figure 1. Locally advanced organ involvement of the pancreatic tail.

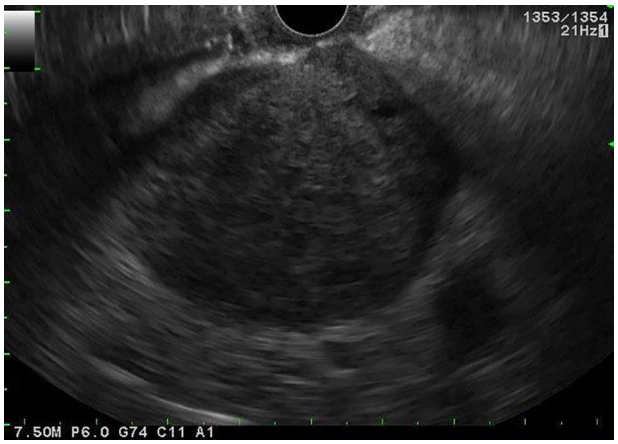

Figure 2. Endoscopic ultrasound showing a 5.3 × 4 cm anechoic cystic lesion with an irregularly thick wall and multiple mural nodules in the pancreatic tail.

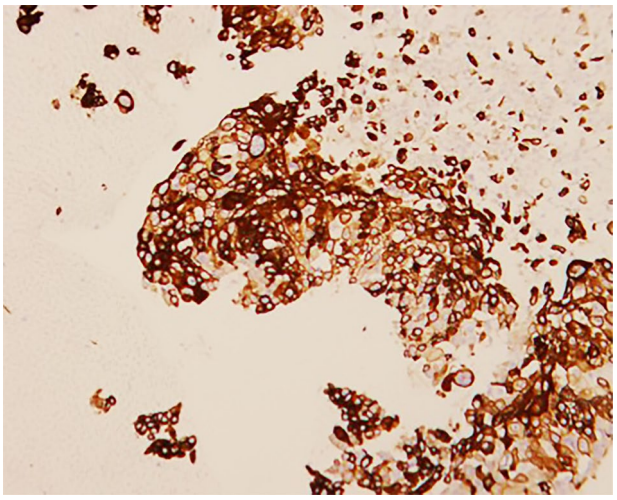

Figure 3. Immunohistochemistry showing a positive expression of CK7.

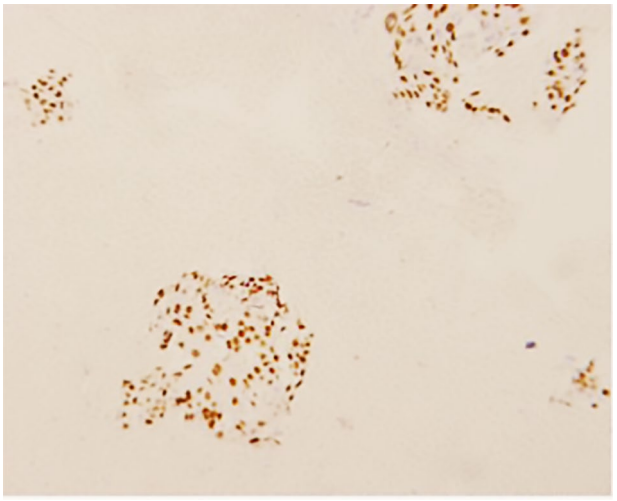

Figure 4. Immunohistochemistry showing a positive expression of P40.

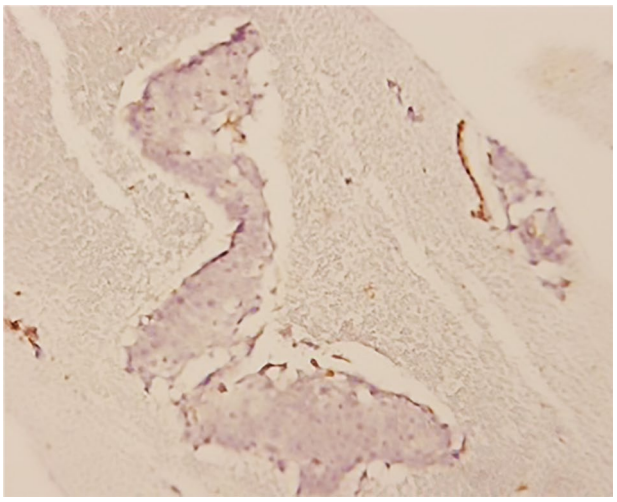

Figure 5. Immunohistochemistry showing that the tumor cells were negative for CDX2.

relatively well-defined tumor-like lesion located at the junction of the body and tail of the pancreas. It appeared hypoechoic and homogeneous on the ultrasound, very different from the typical ultrasound features of primary pancreatic adenocarcinoma. Small intralesional hyperechoic structures could be seen along with mural nodules and a fine vascular network clearly visualized using Doppler ultrasound (Figure 2). This was combined with hyperechoic posterior enhancement. A fine-needle aspiration biopsy was performed with 3 needle passages using the Cook® ProCore 20 gauge needle. During the biopsy procedure, the lesion did not display typical hardness of a primary adenocarcinoma. The samples were not bloody. Histopathology revealed numerous polyhedral carcinomatous cells with a dense eosinophilic cytoplasm and highly atypical vesicular nuclei with prominent nucleoli. Immunohistochemistry showed that the tumor cells expressed CK7 (Figure 3) and P40 (Figure 4) but were negative for CDX2 (Figure 5) and CK20. The great majority of the tumor cells were squamous cells with P40 expression. Only 2% of the tumor cells were positive with alcian blue staining indicating rare positive mucin-producing glandular elements. The diagnosis of ASC was established given that CK7 is expressed in adenocarcinomas and not in pure squamous cell carcinomas. The sample taken using the ProCore needle provided sufficient material to eliminate other differential diagnoses, including primary adenocarcinoma, pancreatic acinar cell carcinoma, and in particular, squamous cell carcinoma. A positron emission tomography (PET) scan was performed revealing rapid tumor growth compared with the baseline CT scan performed 15 days earlier, with the appearance of new liver metastases at the junction of segments VII and VIII and in segment VI (Figure 6). No biopsy was performed for the liver metastasis. The patient was not tested for *BRCA1/2* mutations prior to chemotherapy. Chemotherapy using the FOLFU-CDDP regimen (5-fluorouracil: 400 mg/m^2 as a bolus over 2 hours on D1, then 2400 mg/m^2 over 46 hours plus cisplatin: 50 mg/m^2 on D1) every 14 days was introduced. A follow-up CT scan after 6 cycles revealed disease progression quantified at over 43.4% using RECIST (Response Evaluation Criteria In Solid Tumors), with primarily hepatic metastases. Second-line

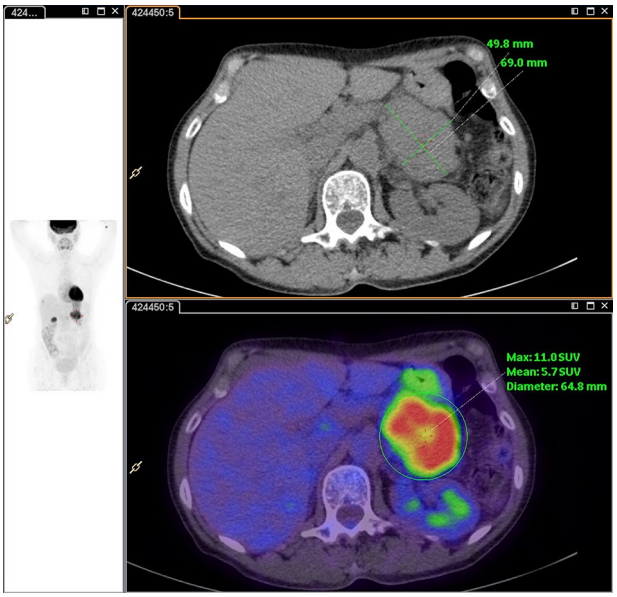

Figure 6. Tumor hyperfixation with PET scanner. PET indicates positron emission tomography.

chemotherapy using the FOLFIRI regimen was introduced (5-fluorouracil: 400 mg/m^2 as a bolus over 2 hours on D1, then 2400 mg/m^2 over 46 hours plus irinotecan: 180 mg/m^2 on D1) every 14 days. After 3 cycles of FOLFIRI, the clinical course was characterized by rapid deterioration in the patient's general condition, with increased abdominal pain. Pure palliative care was provided until the patient's death.

Discussion

Although there is no squamous differentiation in the normal pancreas, autopsy studies have shown squamous metaplasia in 17% to 48% of cases.[3,5] Squamous metaplasia may also be found in chronic pancreatitis lesions and following stent placement in the main pancreatic duct.[6,7] It has also been described in the wall of benign pancreatic cysts.[8]

The pathophysiology of ASC of the pancreas remains poorly understood, and several hypotheses have been proposed. The first is that under the influence of chronic inflammation caused by chronic pancreatitis or obstruction by a tumor, ductal cells undergo squamous metaplasia, which then converts to ASC.[9,10] A second collision theory proposes that 2 histologically distinct neoplastic cell populations arise independently in the pancreas and subsequently combine to form ASC.[10-12] The third theory posits that there are multipotent primitive cells able to differentiate either to adenocarcinoma or to squamous cell carcinoma which become a combination of both.[4,10] ASC of the pancreas typically presents with poorly differentiated tumors, with survival of 12 months in patients who undergo surgery and 4 months in those who do not.[2] Boyd et al[1] reported 1- and 2-year overall survival of 50.7% and 29%, respectively. This median survival period is shorter than that for primary pancreatic adenocarcinoma (60.1% and 35.8%, respectively).[1] For over 50% of patients, the disease is metastasized before diagnosis is made.[2]

Table 1. Main differences between pancreatic ductal adenocarcinoma (n = 97,923) and adenosquamous carcinoma of the pancreas (n = 801).[16]

	DUCTAL ADENOCARCINOMA (%)	ASC (%)
Primary tumor location		
Head of pancreas	62.4	49.1
Body/tail of pancreas	26.3	37
Differentiation		
Well	10.3	2.3
Moderately	35.2	21.6
Poorly	27.2	49.4
Management		
Surgery	15.6	36
No surgery	84.4	64
Stage		
Localized	7.6	8.7
Regional	31	36.3
Distant	61.4	54.9
Lymph node status		
N0	60.8	54.7
N1	39.2	45.3

Abbreviation: ASC, adenosquamous carcinoma.

The rarity of ASC of the pancreas and the rapidity of progression explain the difficulty of diagnosing this malignancy. Clinically, anorexia and weight loss on a background of abdominal pain, with or without jaundice, are the typical initial symptoms, similar to those used to diagnose primary pancreatic adenocarcinoma.[4] Diagnosis is based on CT imaging and endoscopic ultrasound biopsy in the absence of metastatic sites, as in our case report. CT imaging of ASC lesions commonly shows the presence of central necrosis within the tumor mass and the propensity for vascular and nerve encasement.[13] To our knowledge, the endoscopic ultrasound features have been rarely described in the literature and ASC usually appears as a solid and hypoechoic lesion, not well defined.[14] ProCore biopsy needles have shown superior diagnostic performance compared with conventional needles in the diagnosis of pancreatic tumors.[15] In the case of ASC, they make it possible to obtain more tumor material and to eliminate pure squamous forms, or other more common diagnoses, primarily primary adenocarcinoma. In the SEER database review published by Boyd et al,[1] patients with ASC were more likely to have tumors in the body or tail of the pancreas (29.2% vs 19% for adenocarcinoma). Table 1 highlights the main differences between pancreatic ductal adenocarcinoma and pancreatic ASC, according to the

large series published by Luo et al[16] who analyzed the features of all pancreatic uncommon histological subtypes.

Interestingly, ASC pathology shows that the squamous carcinoma component frequently appears to be more focal and located in the periphery of the tumor, whereas the adenocarcinoma component is in the center.[3] There is a transitional zone where the glandular structures blend into the squamous component. Immunohistochemistry shows the tumor to be positive for CK5/6, CK7, p40, and p63 and negative for CK20, p16, CDX2, and p53.[9] Characterizing this disease on a molecular level may further elucidate the requirements for classifying pancreatic carcinomas as adenosquamous or adenocarcinoma. Furthermore, molecular characterization could indicate sensitivity to specific chemotherapy agents and could point to the use of novel therapeutic combinations.[3]

When it is possible, obtaining a genetic history is informative, as in some cases of primary pancreatic adenocarcinoma. Only *BRCA1/2* mutations have been found in ASC of the pancreas, with probable greater sensitivity to gemcitabine in combination with a platinum agent.[17]

Most case reports in the literature describe disease that is generally advanced at the time of diagnosis. Surgical resection is possible in rare cases. The role of neoadjuvant chemotherapy and adjuvant chemotherapy and/or radiotherapy is unclear.[18,19] In a retrospective series of 62 patients, the 14 patients who received platinum therapy in the adjuvant setting had an overall median survival of 19.1 months as opposed to 10.7 months for those who did not.[18] For metastatic disease, the primary treatment method is chemotherapy, including regimens that combine 5-fluorouracil with cisplatin or irinotecan, or combinations of gemcitabine with carboplatin or 5-fluorouracil.[3] The rarity of these tumors makes studies assessing such treatments difficult.

Conclusions

ASC of the pancreas is a rare malignancy with a poorly understood pathophysiology. ASC is often poorly differentiated and characterized by a more aggressive behavior than pancreatic adenocarcinoma. Differential diagnosis from other pancreatic malignancies with similar clinical pathology features is important, and this case report highlights the benefit of fine-needle aspiration biopsy with ProCore endoscopic ultrasound needles. BRCA mutation testing may be sought for subsequent family screening. The prognosis for these tumors remains very poor, even in cases of surgical resection.

Author Contributions

DB contributed to study concepts. HDA, CCB, LS, and DB contributed to manuscript preparation, editing, and review.

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