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CASE REPORT

# Adenosquamous and squamous cell carcinoma of the pancreas: two histopathological variants of ductal adenocarcinoma

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**Introduction**: Primary squamous cell carcinoma (SCC) and adenosquamous carcinoma of the pancreas are rare malignancies for which diagnostic and treatment strategy are challenging. In this paper we present a literature review of these tumors based on two case reports. **Case presentation**: In the first case, a 55-year-old male presented with an inoperable pancreatic head/body junction tumor. Endoscopic ultrasound-guided fine needle aspiration was practiced, and histopathological examination revealed a squamous cell carcinoma of the pancreas. After exclusion of any another tumor, the diagnosis of cT4N0M0-staged primary pancreatic SCC was made. The patient is under treatment with gemcitabine and oxaliplatin. The second case is represented by a 73-year-old patient in which imagistic examinations highlighted a cystic mass of the pancreatic body. Following coporeo-caudal splenic-pancreatectomy and histopathological-proved diagnosis of adenosquamous carcinoma, the patient started chemotherapy but died at 11 months after surgery. Both tumor components displayed positivity for markers which prove ductal (cytokeratin19, maspin) and squamous differentiation (p63, cytokeratin5/6) same as vimentin, as indicator of epithelial mesenchymal transition (EMT). **Conclusions**: SCC and adenosquamous carcinoma of the pancreas are aggressive malignancies which prognosis remains highly reserved. These tumors might be variants of ductal adenocarcinomas which are dedifferentiated through EMT phenomenon.

**Keywords**: squamous cell carcinoma, adenosquamous, pancreas, vimentin, maspin

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## Introduction

Most of the malignant tumors of the exocrine pancreas are ductal adenocarcinomas [1-3]. Rare variants such papillary of adenosquamous pancreatic carcinomas are also encountered in daily diagnosis but pure primary squamous cell carcinoma (SCC) of the pancreas is an unusual tumor which differential diagnosis is difficult to be done [4,5]. For such diagnosis, metastatic lesions need to be excluded [1,6,7].

Under microscope, diagnosis of adenosquamous carcinoma is based on the presence of the squamous component in a minimum of 30% of tumor mass [2,4,8]. Extensive clinical examination in association with imagistic investigations and specialist consults (ear-nose throat, gastroenterology, pneumology, dermatology) corroborated with specific investigations must be done to exclude a possible squamous secondary lesion of pancreas [1,6].

Most of the papers from Medline-indexed literature, focused on adenosquamous carcinomas, were published as case reports. As regards primary SCC of the pancreas, to our best knowledge, the number of reported cases is below 215. Considering the rarity of both histopathologic types, we present two cases, one of primary SCC and one adenosquamous carcinoma along with a pertinent review of literature. Signed informed consent was obtained from both patients, before surgery, for using and publishing scientific data related to their cases, with keeping their anonimity.

## Presentation of cases

### Case 1

A 55-year-old male presented to Gastroenterology Clinic with upper abdominal pain, loss of appetite, and loss in weight (about 5 kilos in two months). Abdominal ultrasound examination revealed an heterogeneous mass at the head/body junction of the pancreas, measuring 67/60 mm, without cleavage plan between the described structure and liver segment II, with possible invasion of segment II. Computed tomography scan of the abdomen confirmed the well-defined 55/50/67 mm iodophilic mass located at junction of the head and body of the pancreas. It also emphasized invasion of the lesser curvature of stomach (without mucosa involvement), portal vein, and coeliac trunk. No suspected lymph nodes, no free fluid in abdominal cavity and no distant metastases were found.

The endoscopic ultrasound-guided fine needle aspiration was performed to obtain a tissue specimen. Histo-

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pathological examination revealed proliferation of clusters of atypical polygonal-shaped medium to large cells, with high pleomorphism and poorly defined cell limits. Areas of dyskeratosis, along with keratin pearls and desmoplastic stroma, were also seen. The tumor cells were marked by cytokeratin (CK) 5/6, carcinoembryonic antigen (CEA), CK19, p63, maspin and vimentin and were negative for CK7 and CK20 (Fig. 1). Focal positivity for CDX2, and GATTA-3 was also described. The adhesion molecules E-cadherin and β-catenin showed significant downregulation in tumor cells, compared with the pancreatic ducts. Based on histopathological aspect and immunoprofile of tumor cells, the diagnosis of poorly differentiated SCC was made.

To confirm the primary nature of the lesion and to differentiate it from a metastasis, imagistic investigations (CT-scan and MRI) along with interdisciplinary consults were done. Therefore, patient was examined by the otorhinolaryngologist (ENT surgeon) and pulmonologist and a primary head and neck or pulmonary origins were denied. Serum level of CA 19-9, post-operatively, was of 6.09 U/mL (normal ranges 0-37 U/mL).

Based on the clinical data and histopathological information, the case was considered as a primary pancreatic SCC and was staged as cT4N0M0 (stage III). At the moment of therapeutic decision, patient performance status (PS) was 1, he was accusing periumbilical pain and physical examination revealed an epigastric induration with weak delimitation, with no other pathologic findings. According to international recommendations, published case reports and national guidelines we initiated chemotherapy with Gemcitabin 1000mg/m2 in combination with Oxaliplatin 100mg/m2 q21 days. The patient is under therapy with favourable outcome after three cures.

**Case 2**

A 73-years-old male patient was admitted with epigastric pain and weight loss of about 6 kg in one month. The abdominal CT highlighted a cystic mass of the pancreatic body associated with the atrophy of the caudal pancreatic portion. As the status of the patient was deteriorated, an emergent laparotomy was done. The cystic tumor of the pancreatic body proved to penetrate in the transverse mesocolon and stomach. Peripancreatic lymphadenopathies were also seen to be accompanied by portal hypertension. The procedure consisted of a corporeo-caudal splenic-pancreatectomy with partial resection of the transverse mesocolon, gastric suture, lymph node dissection, drainage of the splenic lodge and the omental bursa, respectively.

Macroscopically, the 130x70x40 mm pancreatic fragment shows a cystic tumor which replaced the body and tail of the pancreas and was surrounded by thin solid areas with necroses and hemorrhages.

Under microscope, proliferation of both atypical tubular structures and solid areas with polygonal-shaped cells, each of them representing over 30% of tumor cells, were seen. The resection margins were positive (R1). The splenic

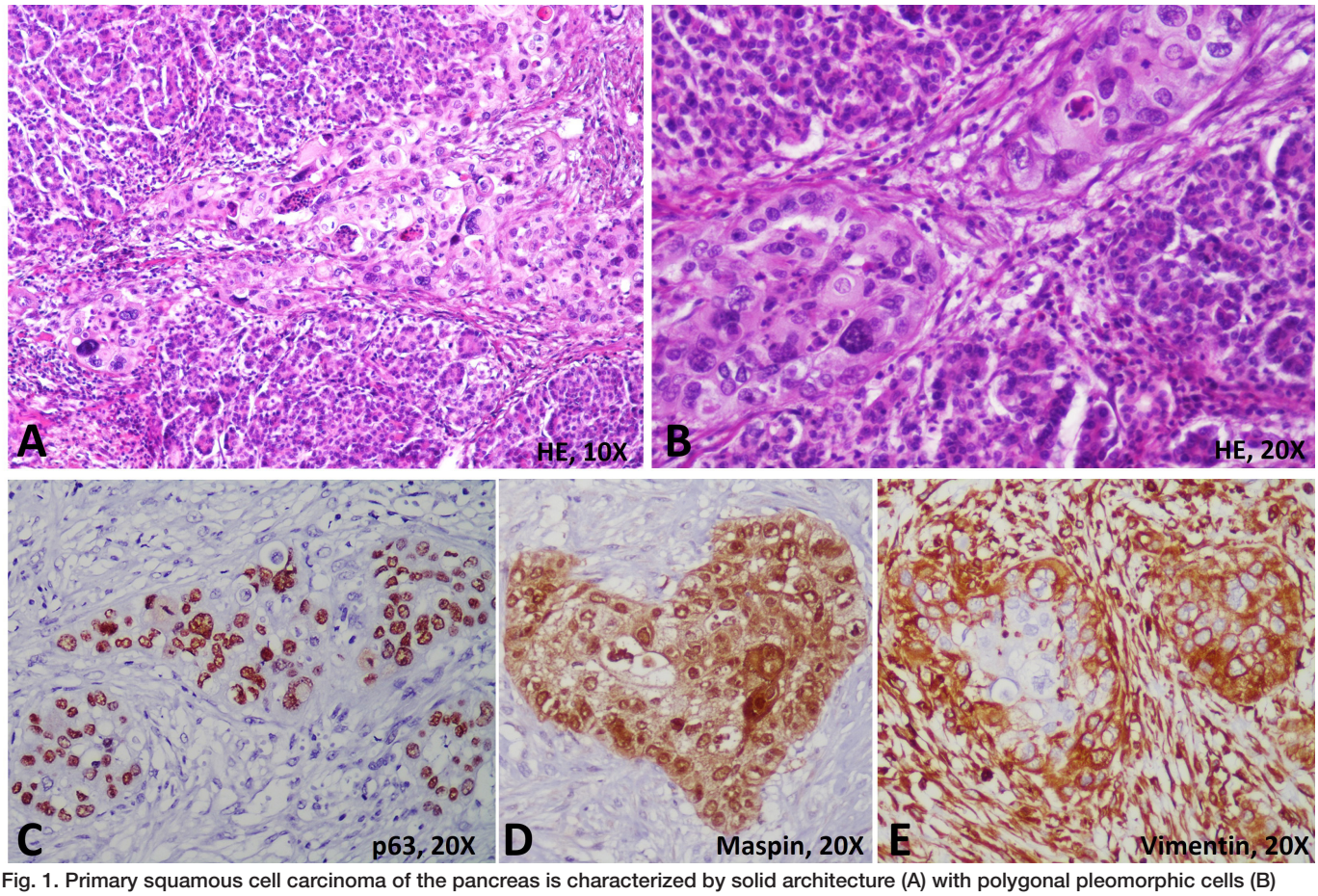


Fig. 1. Primary squamous cell carcinoma of the pancreas is characterized by solid architecture (A) with polygonal pleomorphic cells (B) which display immunohistochemically positivity for markers which indicate squamous (C) as well as adenocarcinoma phenotype (D) and epithelial-mesenchymal transition (E)

artery was infiltrated, and metastases were identified in 2 of the 20 peripancreatic lymph nodes which were surgically removed. Tumor cells were marked by CK5/6, p63, CEA, CK19, maspin, and vimentin, in both tumor components (glandular and squamous) (Fig. 2). In both components, E-cadherin and β-catenin were focally expressed in the cell membrane (<50% of the tumor cells) without nuclear positivity.

The case was diagnosed as a primary pancreatic adenosquamous carcinoma and was staged as cT4N1M0 (stage III). The patient underwent chemotherapy with gemcitabine but died 11 months after diagnosis.

## Discussions

Primary SCC and adenosquamous carcinoma are rare histopathological subtypes of pancreatic cancers [4,5]. Amongst non-endocrine pancreatic malignancy, the incidence of primary pancreatic squamous cell carcinoma is estimated at 0.5-5% of all pancreatic carcinomas [9,10], respectively 0.5-2% of all primary pancreatic neoplasms [5,11]. For adenosquamous carcinoma, the estimated incidence is 3-4% of all pancreatic malignancies [4]. In the most recent study published in 2019, based on a representative cohort, which included 57804 patients who underwent surgery for pancreatic cancer diagnosis during 2004-2014, Pokrzywa CJ et al. identified only 39 primary pure SCCs (0.07%) and 655 adenosquamous carcinomas (1.13%) [3].

The stereotype of patient diagnosed with primary pancreatic carcinomas with squamous component is, like our cases, a male in his 6th decade of life showing an infiltrative tumor of the head of the pancreas [9,10].

As the normal pancreatic tissues does not include squamous epithelium, it is still unclear the histogenesis of primary tumors with squamous component [4,5,6,12]. It was even postulated the origin in a pluripotent primitive- or remnant aberrant squamous cell from embryonal period [1,4-7,11,13-15], or, based on other authors, it is rather about a collision tumor than a really pure SCC, in which the tumor stem cells from glandular part might be dedifferentiated in cells with squamous arhitecture [1,6,7,11]. On the other hand, as most of the pancreatic cancers occur on the background of chronic pancreatitis, metaplastic transformation can be the precursor lesion [1,4-7]. As in our second case the immunoprofile was similar in both glandular and squamous component we tend to believe that like adeno-neuroendocrine tumors (MANEC), adeno-squamous and SCC of the pancreas have the same origin in a

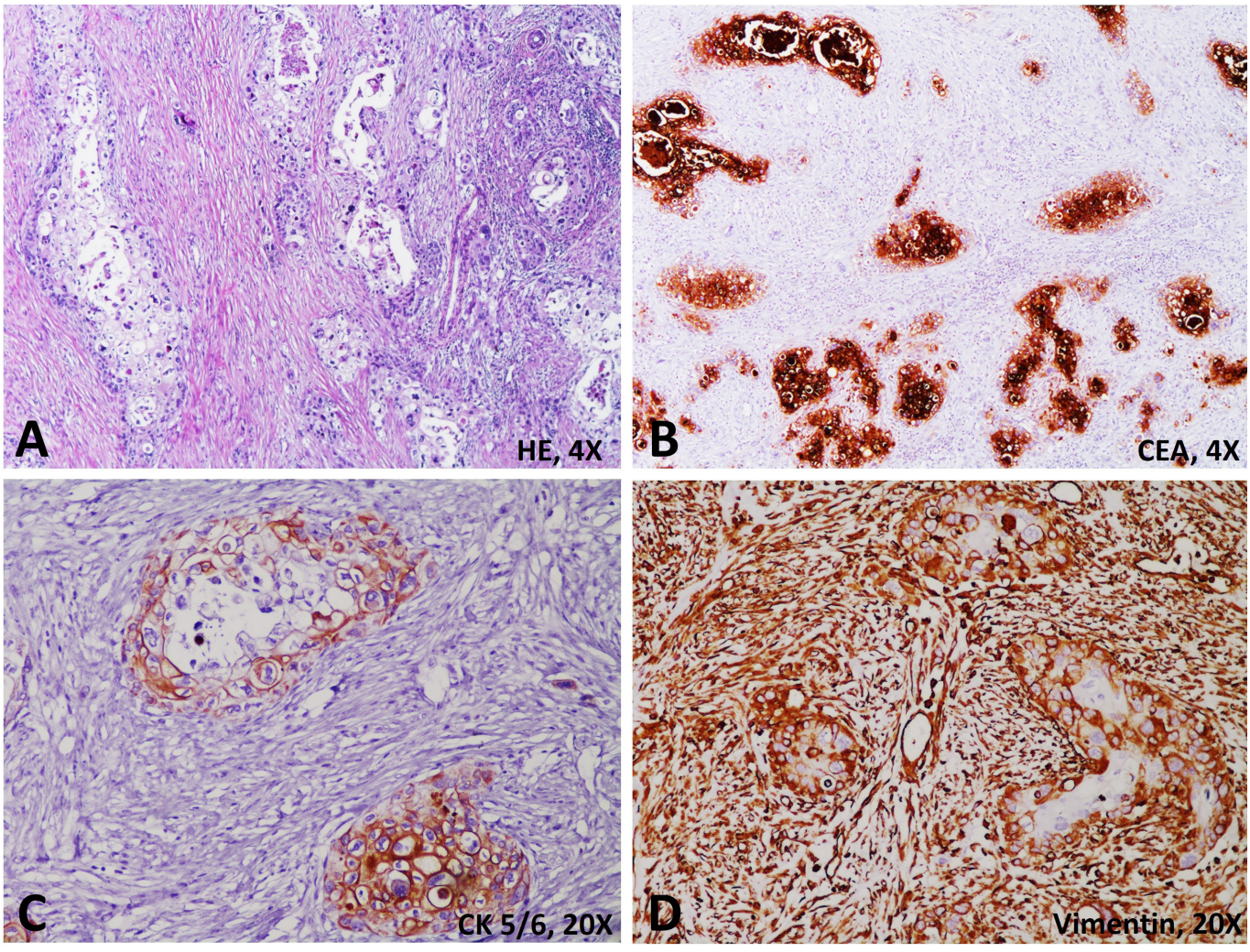


Fig. 2. Adeno-squamous cell carcinoma of the pancreas is characterized by proliferation of ductal structures and solid areas (A). Both components showed an immunophenotype suggesting ductal (B) and squamous differentiation (C) through an epithelial-mesenchymal transition (E)

pluripotent stem tumor cell which might show dual differentiation [1,6,7,11,16-19]. Vimentin positivity was suggestive for the epithelial-mesenchymal transition (EMT) phenomenon, which, like other histopathological subtypes of pancreatic cancer, seems to explain the tumor aggressivity [20]. The hypothesis of adenocarcinoma dedifferentiation via EMT was also sustained by loss of polarity and simultaneous downregulation of E-cadherin and β-catenin in tumor cells, compared with normal epithelial of pancreatic ducts. Moreover, EMT plays role in genesis and maintenance of cancer stem cells [21], which might show pluripotent differentiation. This process is mediated in pancreas by transforming growth factor-β (TGF-β), siRNA or NF-κB, the latest gene being involved in pancreatitis-induced pancreatic ductal adenocarcinoma (PDAC) [21]. Putting together the above information, it can be concluded that pancreatic carcinomas with squamous cells might be variants of PDAC developed via EMT of PDAC-cells.

These malignancies are mostly diagnosed in advanced or metastatic stage [6,9,12]. Ntanasis-Stathopoulos *et al.* in a study that included 54 patients reported a median overall survival of 7 months [9,22]. It was slightly higher (about 10 months) in patients who underwent surgery [9]. These data prove that it is still difficult to find a proper therapy which might inhibit both tumor parts of these challenging malignancies. The preferred chemotherapy regimens are based on various association of gemcitabine, platinum salts, fluoropyrimidines and irinotecan (e.g gemcitabine+oxaliplatin, gemcitabine+carboplatin, gemcitabine+ cisplatin, etc.) [1,3,6-8,17,22]. Although nab-paclitaxel seems to be superior to platinum salts ones [10], it is not reimbursed in medium-income countries and gemcitabile is the therapy of choice in such cases. Immunotherapy might be the election choice in cases with high PD-L1 expression [17].

*Limitations of the study:* Lack of molecular examinations and limited availability of dataset which was based on two cases only. Large cohorts need to be examined to confirm or infirm our hypothesis.

## Conclusions

Primary SCC and adenosquamous carcinoma of the pancreas are rare tumors which therapeutic management need a transdisciplinary approach. Despite development of the imagistic techniques, independently from the histopathological subtypes, pancreatic cancers are still diagnosed in advanced stages. These rare tumors might be a variant of ductal adenocarcinoma which occur as result of EMT phenomenon.

## Authors' contribution

STB (writing – original draft, visualization, clinical follow-up, resources and formal analysis); TC (investigation, validation and oncologic therapy); KZ (conceptualization, methodology and literature review); SAD (data curation, analysis, and literature review); BTJ (data curation, surgical intervention and postoperative follow-up); RD (investigation, data curation, and oncologic therapy); GS (histopathological diagnosis, writing – review and editing, funding acquisition, supervision).

## Conflict of interest

None to declare.

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