Rare Variants of Ductal Adenocarcinoma of the Pancreas

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Histologic variants of ductal adenocarcinoma are neoplasms characterized by a specific histological pattern different from that of conventional pancreatic cancer, which is typically an adenocarcinoma. It has been estimated that these variants account for 2–10% of all pancreatic ductal cancers.

13.1 Adenosquamous Carcinoma

Among rare pancreatic neoplasms, adenosquamous carcinoma (ASC) comprise 0.9–4.4% of all pancreatic malignancies [1-3]. These patients have a worse prognosis than those with the more common ductal pancreatic cancer. Little is known about this rare subtype, as its biological behavior has been derived only from case reports and small retrospective series, often with in homogeneous results that are, accordingly, difficult to compare. More recent reports have shown that the median survival rate of patients with ASC undergoing surgical resection with radical intent (R0-R1) along with adjuvant treatment (chemotherapy alone or in conjunction with external beam radiation) is similar to that of patients with resectable pancreatic cancer (PC) [4, 5].

13.1.1 Pathology and Genetics

The first histological description of ASC reported in the literature was that of Herxheimer, in 1907, who defined this unusual entity as "cancroide" [6]. The characteristic cellular mixture of squamous and adenomatous cellular lines led

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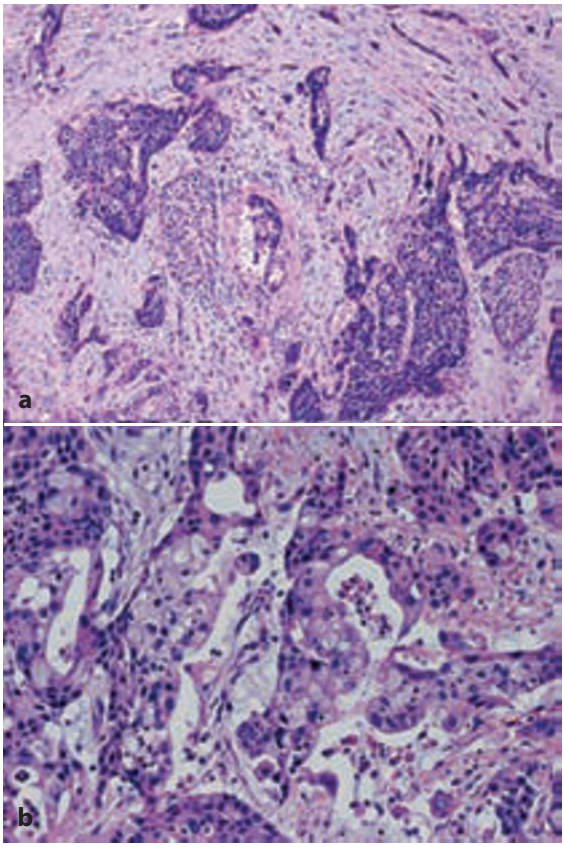

Fig. 13.1 a Squamous adenocarcinoma without keratinization. **b** Carcinoma with evident mucin secretion at seen at higher magnification

other authors to various definitions of ASC, such as adenoacanthoma, mixed squamous and adenocarcinoma, or mucoepidermoid carcinoma [2, 3].

It was not until 2000 that the World Health Organization clearly indicated the presence of at least 30% squamous cell carcinoma differentiation as a mandatory criterion for the diagnosis of ASC (Fig. 13.1). Since then, tumors showing a lower squamous proportion are designated as PC with "squamous differentiation" [7].

Many theories have been proposed to explain the origin of ASC. In the "squamous metaplasia theory," squamous metaplasia was postulated to occur as a result of ductal inflammation due to chronic pancreatitis or obstruction by an adenocarcinomatous tumor that ultimately became a malignant adenosquamous pancreatic tumor. A second theory, termed "the collision theory," suggested that two histologically distinct tumors, adenocarcinoma and squamous cell carcinoma, arise independently from different sites and then fuse. According to the third theory, the "differentiation theory," ASC reflects the

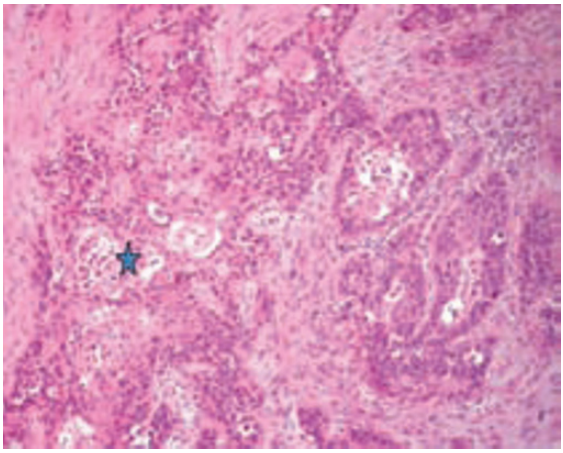

Fig. 13.2 Squamous cell carcinoma with aspects of squamous differentiation (*star*)

malignant differentiation of a pluripotent ductal cell into two distinct histological types.

Currently, the most widely accepted theory postulates a metaplasia from a focal adenocarcinomatous cancer towards a squamous histotype [2, 8, 9] (Fig. 13.2). This consideration originates from a common observation during specimen examination, i.e., that only adenocarcinomatous foci show a characteristic cytological spectrum from ductal hyperplasia to carcinoma in situ, and are typically surrounded by squamous cell lines without a transitional margin [8, 9]. Furthermore, even ASC with a particular squamous predominance consistently contains *KRAS2* gene mutations, similarly to the more common PC [8, 10-13].

13.1.2 Clinical Presentation and Diagnostic Work-up

The preoperative differential diagnosis between ASC and PC is often difficult. Similar to PC, ASC shows a slightly greater prevalence in males (M/F ratio: 1.5:1), with a mean age of 62 years. The most frequent symptoms at the time of presentation are weight loss, jaundice, and non-specific abdominal pain. Even the radiological and macroscopic appearance of ASC may completely mimic a typical PC [3, 8]. However, expression of the tumor markers CEA and CA 19-9 directly correlate with a more aggressive biological behavior and an advanced stage of disease [3, 8, 11, 14, 15].

Preoperatively, fine-needle aspiration (FNA) is a useful tool to obtain the correct diagnosis, although it requires careful pathological examination of the specimen in order to accurately distinguish the squamous cell cancer component from “atypical cells” (also referred to as “epidermoid”). The latter are

also found in patients with chronic pancreatitis or in those undergoing endoscopic biliary stent placement [16, 17].

13.1.3 Clinical Management

By the time symptoms occur, the vast majority of patients with ASC will present with advanced disease and thus succumb early, due to local or systemic dissemination. A potentially curative surgical resection (R0-R1) of the tumor, followed by adjuvant treatment (chemoradiation) is the only therapeutic option that can potentially lead to a significantly better survival [5, 8, 11].

Indeed, in a recent retrospective study by Voong et al. [5], based on a long-term follow-up of 38 patients who had undergone radical surgery for histologically confirmed ASC, the 1-, 2- and 5-year overall survival rates were 34, 11, and 5%, respectively. Furthermore, the authors found that adjuvant chemoradiation (5-FU or gemcitabine or capecitabine plus 5.040 Gy), but not other well-established prognostic determinants (T stage, nodal involvement, residual microscopic tumor), significantly correlated with a better median survival when compared to surgery alone (13.6 vs. 8.6 months respectively; $p = 0.05$). This favorable course was also confirmed in a series from our institution, in which four patients who had undergone pancreatic resection with negative resection margins (R0) plus adjuvant chemotherapy (5-FU, or gemcitabine plus or minus oxaliplatin) had a median survival of 14.5 months (R0; n = 2; 27 months; R1; n = 2; 13.5 months) [4].

Furthermore, alternative treatments such as intraoperative radiation therapy (IORT) for locally advanced ASC and surgery plus adjuvant locoregional chemotherapy also have been reported, although the results are controversial due to the small sample sizes [14, 18, 19]. Therefore, in the absence of further evidence, radical resection of the primary tumor plus adjuvant chemoradiation should be considered the gold standard approach in the multidisciplinary management of ASC.

13.1.4 Prognosis

ASC still represents a particularly aggressive disease associated with poor prognosis. For those patients suffering from locally advanced or metastatic ASC, the median overall survival rate is exceptionally dismal (4.5 months) [8, 11, 14, 20, 21].

Early studies published in the literature failed to document any significant improvement in survival comparing adjuvant chemotherapy with standard resection alone [3, 14, 21, 22]. However, these conclusions might have been biased by the small and heterogeneous samples and the lack of details regarding well-established prognostic factors, such as margin status and TNM stage [3, 8, 21]. Notably, more recent studies, in which detailed surgical and patho-

logical data were included, reported a significantly more favorable outcome within the subset of patients undergoing radical surgery plus adjuvant chemoradiation, with a median overall survival comparable to that of patients with PCs of similar characteristics [5, 11].

13.2 Colloid Carcinoma

Colloid carcinoma is a distinct variant of pancreatic ductal adenocarcinoma, with unique clinical, radiological (Fig. 13.3), and biological characteristics.

Also referred to as mucinous non-cystic carcinoma, colloid carcinoma is almost always observed in association with intestinal-type intraductal papillary mucinous neoplasm (IPMN) and presents macroscopically as a large, well-demarcated gelatinous lesion [23, 24] (Fig. 13.4a). Microscopically, colloid carcinoma is characterized by a paucity of stromal and vascular components and by large pools of mucins, surrounded at least partially by well-dif-

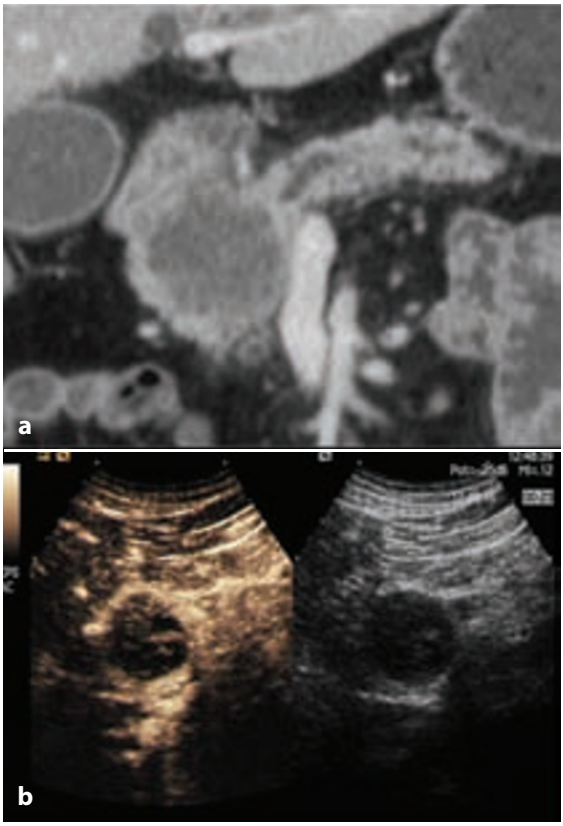

Fig. 13.3 Colloid carcinoma. A hypodense mass in the pancreatic head as seen on CT (**a**) with innervated viable tissue better seen at CEUS (**b**), resulting inhomogeneous vascularization

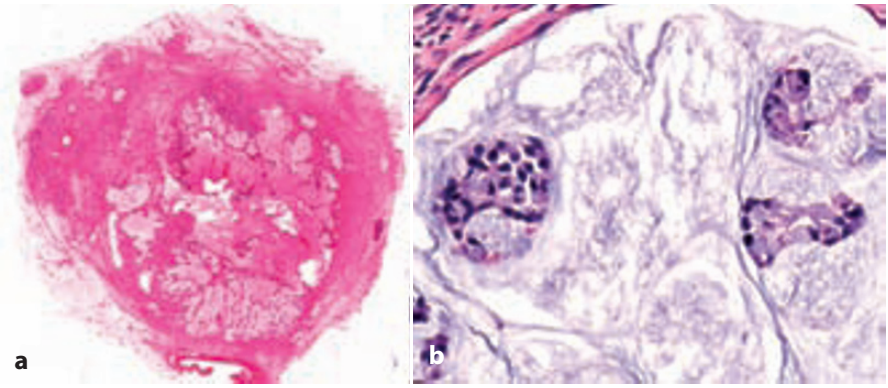

Fig. 13.4 Colloid carcinoma (mucinous non-cystic carcinoma). **a** Gelatinous mass better demarcated than ductal adenocarcinoma. **b** Cluster of cells floating in abundant extracellular mucin

ferentiated cuboidal to columnar neoplastic cells. In addition, clusters of suspended neoplastic cells are observed [23, 24] (Fig. 13.4b).

Colloid carcinomas display intestinal differentiation markers at immunohistochemistry, such as the expression of CK20, MUC2, and CDX2. From a molecular standpoint, these tumors frequently exhibit *KRAS2* and *TP53* mutations, although less frequently than in conventional pancreatic ductal adenocarcinoma [25]. Interestingly, a loss of DCP4/SMAD4 is uncommonly observed in colloid carcinomas. Such biological differences may be responsible for the significantly different behaviors of these tumor types. In fact, recent studies reported the more favorable clinical course and improved long-term survival of patients with colloid carcinoma compared with those with ductal adenocarcinoma [26]. Therefore, a precise recognition at pathologic examination is of paramount importance.

13.3 Medullary Carcinoma of the Pancreas

Medullary carcinomas of the pancreas are a recently described, histologically distinct subset of poorly differentiated adenocarcinomas with a unique pathogenesis and clinical course. This entity, first described in 1998, displays histological characteristics similar to medullary carcinomas observed in other organs, such as the breast and large intestine, i.e., a typical syncytial growth pattern, with poorly differentiated cells, expanding tumor borders without a significant desmoplastic reaction, and T-cell infiltration [27].

From a genetic standpoint, medullary carcinomas are distinct from conventional PC. The majority of these tumors (69%) harbor wild-type K-*RAS* genes,

as opposed to pancreatic ductal adenocarcinomas [28]. Also, it has been estimated that one-fourth of all medullary carcinomas display microsatellite instability (MSI) [27], a typical genetic feature but one that is only rarely observed in conventional PC. Thus, standard ductal adenocarcinomas of the pancreas are characterized by genomic instability and chromosomal aberrations [28]. Of note, in the few cases in which MSI was reported, concomitant tumors affecting other organs (more frequently colorectal cancer) but with the same genetic landscape were present, suggesting an inherited basis for the development of these carcinomas.

Remarkably, because of the special genetic, immunohistochemical, and clinical features of medullary carcinoma, recognition of the medullary variant of pancreatic adenocarcinoma is important. Furthermore, an awareness of the distinct histological characteristics of the various forms of PC may be useful to identify an inherited susceptibility to cancer. In such case, any cancer in a first-degree relative of the patient should be carefully investigated.

13.4 Anaplastic Carcinoma

Anaplastic carcinoma is a rare variant, accounting for 5–7% of all pancreatic tumors. It is preferentially located in the tail of the pancreas and it macroscopically appears as a voluminous mass with a variegated aspect on cut section, due to degenerative changes such as necrosis and hemorrhage [29, 30] (Fig. 13.5).

At imaging, anaplastic carcinoma appears as a markedly enhanced mass, with the exception of necrotic areas. Microscopically, it is composed of pleomorphic large cells, giant cells, or spindle cells (Fig. 13.6). The prognosis of

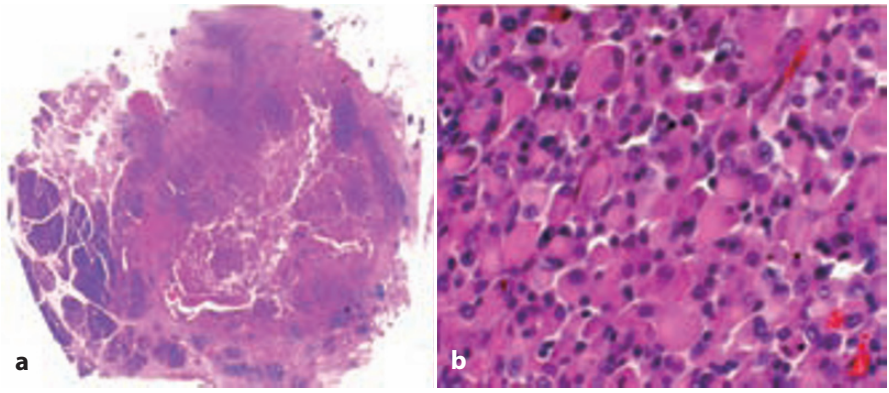

Fig. 13.5 Anaplastic carcinoma. Neoplastic cells show extreme anaplasia and grow in poorly cohesive sheets supported by a scant desmoplastic stroma in this well-demarcated tumor mass with hemorrhagic necrosis

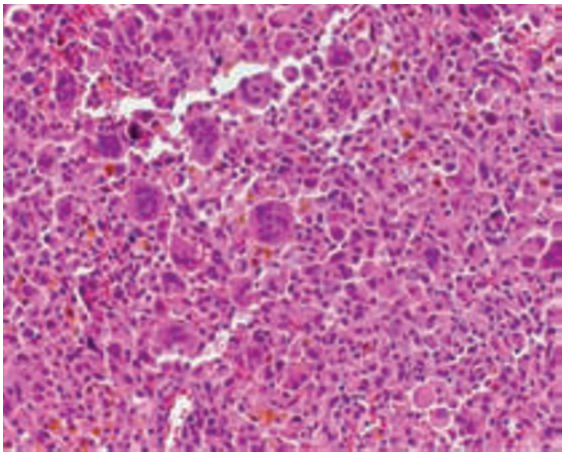

Fig. 13.6 Anaplastic carcinoma, characterized by the presence of non-neoplastic osteoclast-like giant cells

patients with anaplastic carcinoma is worse than that of patients with conventional ductal adenocarcinoma, with distant metastasis frequently present at the time of diagnosis [30].

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