Acinar cell carcinoma of the pancreas and related neoplasms: a review

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Abstract

Acinar cell carcinomas (ACCs) are rare tumours of the exocrine pancreas, accounting for up to 2% of all pancreatic neoplasms in adults and 15% of those in children. They are typically solid, cellular, stroma-poor tumours composed of sheets of relatively uniform cells. This sheet-like arrangement is usually punctuated by variable numbers of acinar structures. Variable amounts of neuroendocrine elements in the form of scattered individual cells are quite common, and some cases have more significant neuroendocrine or ductal elements (mixed acinar neuroendocrine carcinoma and mixed acinar ductal carcinoma).

Demonstration of acinar differentiation, usually by immunohistochemistry, is necessary for the diagnosis. Among the antibodies recognizing various pancreatic enzymes, trypsin and chymotrypsin are the most useful. Molecular alterations characteristic of ductal adenocarcinomas such as mutation in the *KRAS* oncogene are absent in ACCs. However, allelic loss on chromosomes 11p and mutations in the *APC/β-catenin* pathway have been identified in about 50% and 25% of cases, respectively.

ACCs are fairly aggressive tumours, although they are not as dismal prognostically as ductal adenocarcinomas. Those patients who present with localized disease have a much better prognosis than those who present with metastases (5-year survival rate of 25% vs. 50%). Unfortunately, metastases, usually involving the liver, are present in 50% of patients at the time of diagnosis.

Keywords acinar cell carcinoma; chymotrypsin; neuroendocrine tumour; pancreas; trypsin

General features

Despite the fact that the majority of the normal pancreas is composed of acinar cells, acinar cell carcinomas (ACCs) are extremely uncommon and represent only 2% of all pancreatic neoplasms. They can occur at any age but are much more common in adults (mean age = 58 years), and paediatric cases comprise only 6% of all ACCs. Males are affected more frequently (M:F = 3.6:1).[1,2]

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Clinical presentation

Most patients have non-specific symptoms including abdominal pain, bloating, nausea, vomiting, diarrhoea and weight loss. Since ACCs usually do not obstruct the common bile duct, jaundice is not common. Ten to 15% of the patients, almost invariably those with liver metastases, develop the lipase hypersecretion syndrome, a manifestation of excessive lipase secreted by the tumour into the serum.[3] The syndrome is characterized by diffuse subcutaneous fat necrosis and polyarthralgia with or without peripheral blood eosinophilia. Resection of the carcinoma may result in resolution of these symptoms.[1] The most common signs at presentation are a palpable abdominal mass, elevated liver enzymes, and anaemia. Serum α-fetoprotein levels are elevated in some patients, especially in younger adults.[4]

Radiographically, ACCs are usually large, relatively well-circumscribed enhancing pancreatic masses. Cystic change attributable to necrosis may occur.[5]

Gross features

ACCs may arise in any portion of the pancreas. Most are large, with a mean size of 11 cm, and they are generally more circumscribed than ductal adenocarcinomas. They are usually tan to red, soft and fleshy (Figure 1). Areas of haemorrhage, necrosis and cystic degeneration can be present. A few cases have a diffuse multicystic gross appearance; these acinar cell cystadenocarcinomas are discussed below. Rare ACCs involve the ductal system and, in addition to the solid areas, reveal intraductal polypoid projections as well as cystic dilatation of the ducts.[6] Invasion of the spleen, duodenum or other adjacent organs can occur.

Microscopic features

At low magnification, ACCs are markedly cellular and are devoid of the intervening desmoplastic stroma characteristic of ductal adenocarcinomas (Figure 2). The periphery of the carcinoma may appear circumscribed, often surrounded by a thin fibrous capsule, although capsular invasion and extension into adjacent parenchyma is common. In most cases, necrosis is not

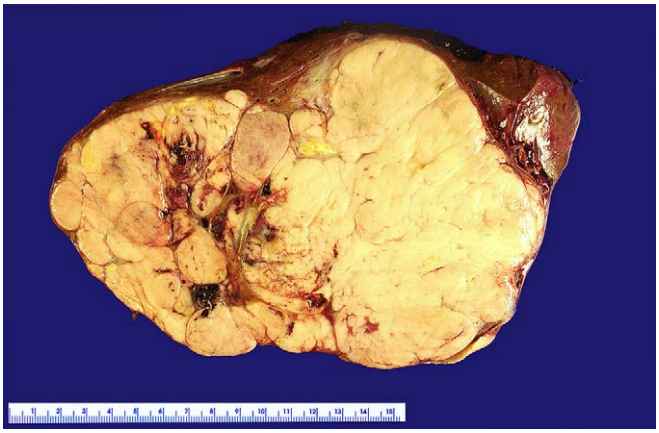

Figure 1 Grossly, ACCs are relatively well demarcated, solid tumours composed of tan, fleshy lobules. Foci of haemorrhage and necrosis are present.

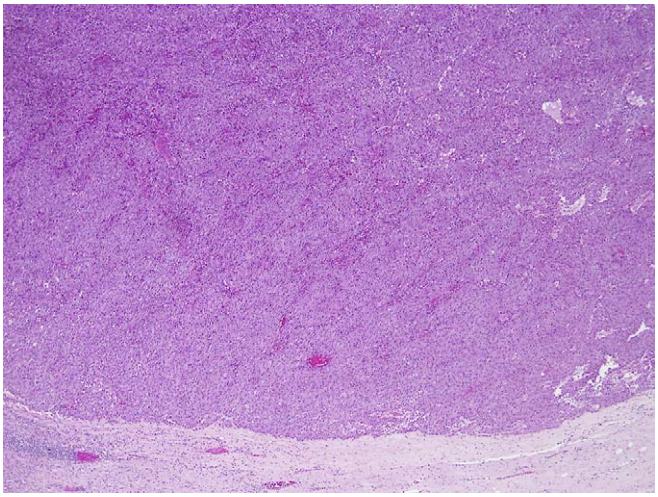

Figure 2 At low magnification, ACCs are highly cellular without significant stroma within the tumour nodules, and the periphery of the carcinoma is usually well-circumscribed.

prominent. Occasional tumours, however, have abundant coagulative necrosis.

Of the several different architectural patterns described, the most characteristic ones are the acinar and solid patterns. In the *acinar pattern*, the neoplastic cells are arranged in small back-to-back acinar units with minute lumina and basally located nuclei (Figure 3a). Although individual glandular units surrounded by stroma are not common, in some cases, a *glandular pattern* resulting from dilated acinar lumina may occur (Figure 3b). The *solid pattern* is characterized by sheets and nests of cells separated by a scant delicate fibrovascular stroma (Figure 3c). Nuclear polarization is limited to the cells that interface the stroma, and the amount of cytoplasm varies from minimal to moderate. Less commonly, abortive acini may form rosette-like structures, and interlacing ribbons composed of two rows of cells with peripherally arrayed nuclei can produce a *trabecular pattern* (Figure 3d). A mixture of patterns is often found within an individual tumour.[2]

As recently described, some ACCs show intraductal growth[6,7] and exhibit a *papillary pattern* usually characterized by intraductal tumour nodules punctuated by glandular lumina and microcystic areas. The cysts vary in size and configuration, and some may contain intraluminal pale, acidophilic amorphous material and crystals, characteristics of enzymatic condensations. True papilla formation, including well-defined projections with fibrovascular cores resembling intraductal papillary neoplasms may also be noted in these cases. Most such cases have more conventional patterns elsewhere in the neoplasm.[6]

At high magnification, the cytoplasm varies from amphophilic to eosinophilic and is finely granular, reflecting the presence of zymogen granules. ACCs with well-formed acinar structures often have abundant zymogen granules (Figure 4). In many cases, however, the cytoplasmic granularity is not so well developed, and special stains are needed to demonstrate enzyme production. The nuclei in ACCs are uniform, round to oval, and normochromatic.[8] Stippled chromatin and large, central, single nucleoli (Figure 5) are characteristic and can provide an important clue to the diagnosis in cases with the solid growth pattern. The mitotic

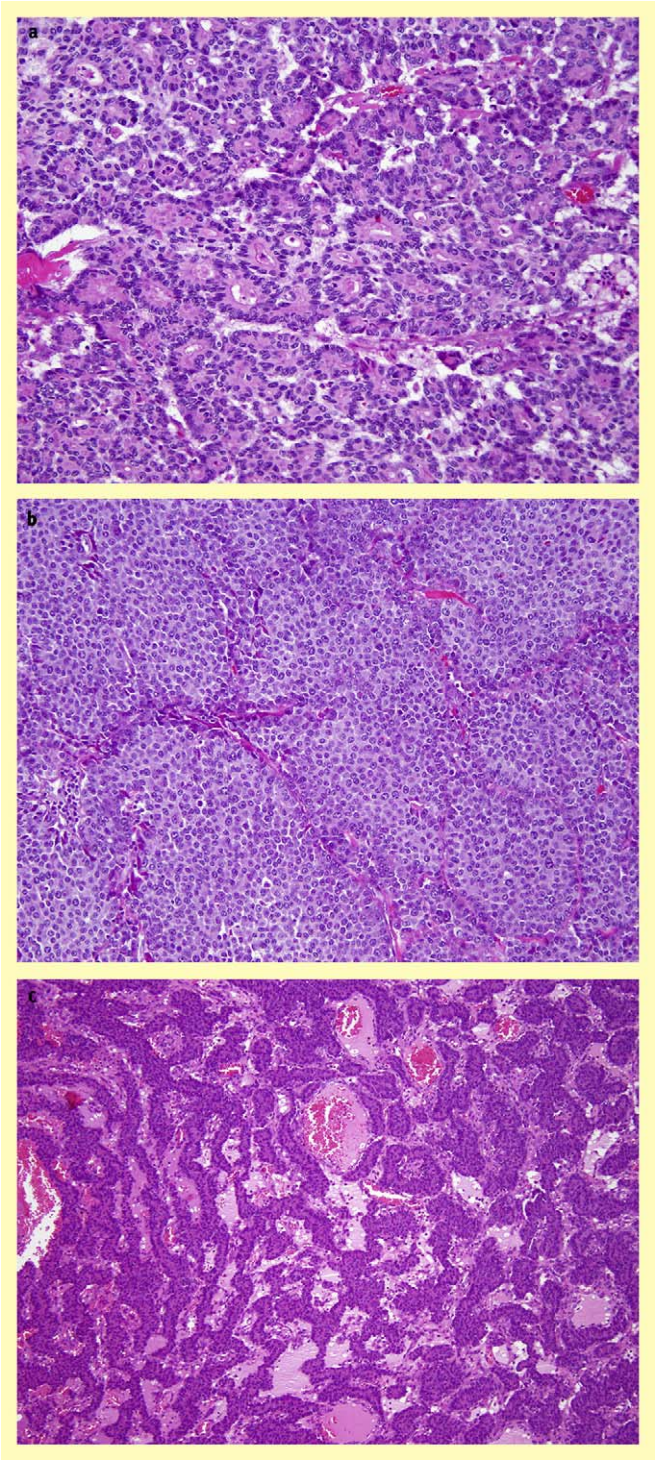

Figure 3 (**a**) *Acinar pattern*. The tumour cells arranged in acinar structures with minute lumina; the nuclei are basally located. (**b**) *Solid pattern*. Solid sheets of cells with delicate fibrovascular stroma. (**c**) The *trabecular pattern* is characterized by interlacing ribbons of cells containing two rows of cells with peripherally arrayed nuclei.

rate is variable, but most ACCs have easily detectable mitoses (mean, 14 per 10 high power microscopic fields) (Figure 6).

Variable amounts of neuroendocrine elements in the form of scattered individual cells, large zones, and hybrid foci, or even as separate well-established nodules are not uncommon. If the

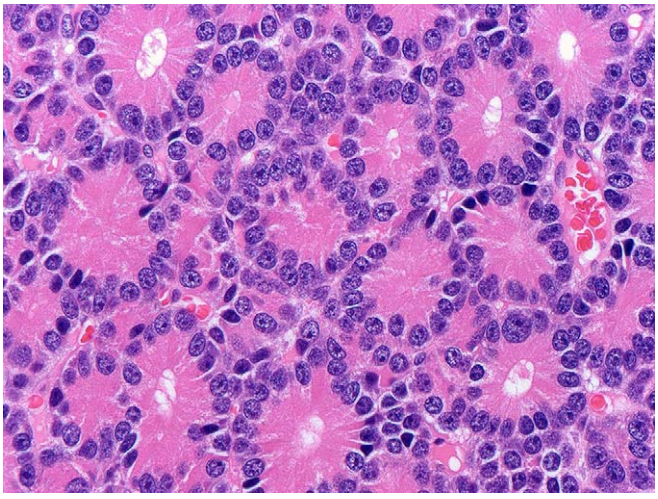

Figure 4 In ACCs with well-formed acinar structures, the nuclei are basally located, and there is a moderate amount of amphophilic to eosinophilic, finely granular apical cytoplasm, reflecting the presence of zymogen granules.

neuroendocrine component comprises more than 25% of the tumour, by arbitrary convention the case is classified as "mixed" (see below).

Vascular invasion and perineural invasion are identified in many cases, and extension into peripancreatic tissue may be seen.

Histochemistry

PAS staining after diastase digestion reveals small PAS-positive granules (Figure 7) corresponding to zymogen granules, particularly in the apical aspect of the cells.[9] However, the amount varies greatly from case to case and even within different areas of the same tumour. If present, intraluminal secretory concretions and crystals are also PAS-positive.[6] Unlike in ductal adenocarcinomas, no intracellular mucin is detected by mucicarmine or alcian blue stains, although occasional focal staining on the apical surfaces of cells lining acini may be seen.[9]

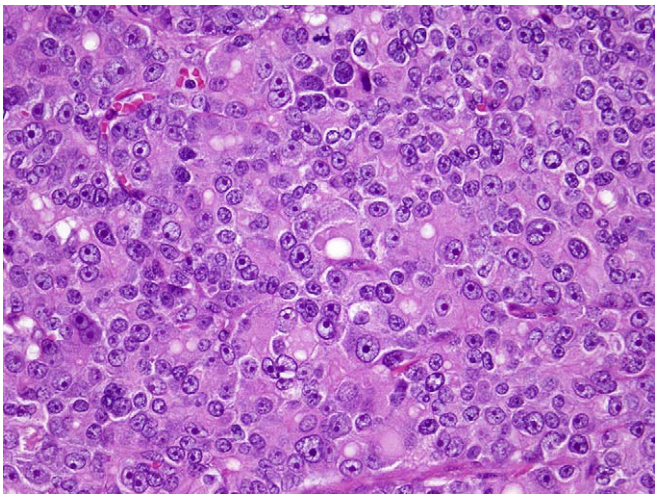

Figure 5 Relatively uniform nuclei with large, central, single nucleoli are a characteristic feature of ACC.

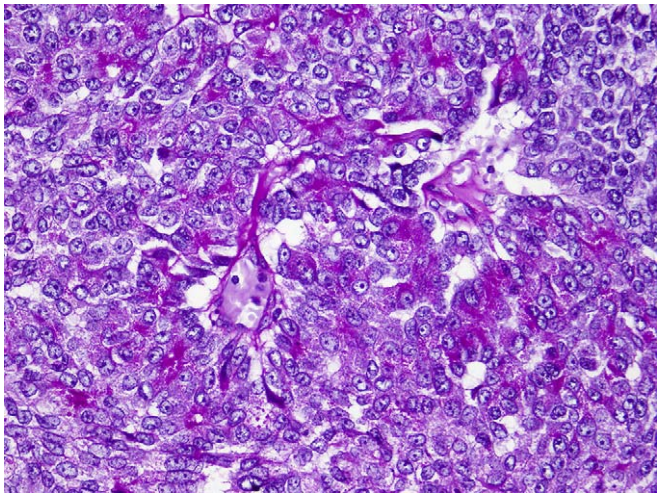

Figure 6 Periodic acid-Schiff stain after diastase pretreatment demonstrates positive zymogen granules.

Immunohistochemistry

The diagnosis depends on the demonstration of acinar differentiation, obtained using antibodies recognizing various pancreatic enzymes that, although specific, show different sensitivity for the diagnosis. Both trypsin (Figure 8) and chymotrypsin are detectable in over 95% of cases and are most diagnostically useful markers; however, some studies have shown less sensitivity for chymotrypsin. Lipase is less commonly identified, in approximately 70–85% of cases. Other markers that are reportedly positive in ACCs are alpha-1-antitrypsin, alpha-1-antichymotrypsin, phospholipase A2, and pancreatic secretory trypsin inhibitor. Amylase is rarely detectable. Recently, La Rosa et al[10] reported that the C-terminal portion of the BCL10 protein shows homology with carboxyl ester hydrolase, also known as phospholipase A1 or nonspecific lipase,[11] another enzyme produced by pancreatic acinar cells. In their study, monoclonal anti-BCL10 immunoreactivity (not to be confused with polyclonal anti-BCL10 recognizing the N-terminal portion of the BCL10 protein), parallelled that of carboxyl ester hydrolase and was restricted to acinar cells of

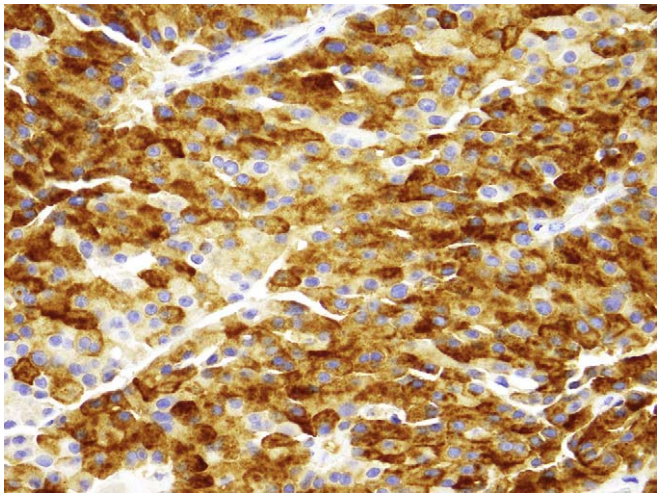

Figure 7 Immunohistochemical labelling for trypsin.

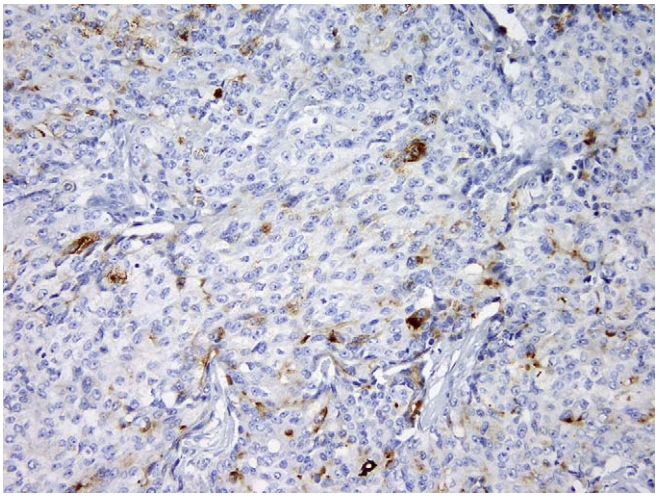

Figure 8 Scattered chromogranin positive cells are common in ACCs.

normal and ectopic pancreas, pancreatic metaplasia, and ACCs. Their results suggest that monoclonal anti-BCL10 antibody might be included in the panel used for diagnosing pancreatic neoplasms if antibodies directed against various pancreatic enzymes are not available.

Neuroendocrine components show immunoreactivity for synaptophysin and/or chromogranin (Figure 9) and, rarely, peptide hormones such as glucagon or somatostatin are expressed. In some cases, even the most typical acinar areas may show positivity with neuroendocrine markers.

Immunohistochemical positivity for α-fetoprotein has been reported in patients with and without elevated serum α-fetoprotein, but labelling is more diffuse and intense in patients with serum elevations.

ACCs are almost always positive for CAM 5.2, AE1/AE3, CK8 and CK18 while CK7, CK19, and CK20 are generally negative. EMA is expressed in about half of the tumours. Mucin-related glycoproteins and oncoproteins that are commonly expressed in the ductal adenocarcinomas (MUC1, MUC5AC, CEA, CA19-9, DUPAN-2, B72.3 and CA125) are either negative or only very focally positive. Markers typically present in solid–pseudopapillary neoplasms (vimentin, CD10, and progesterone receptors) are negative.

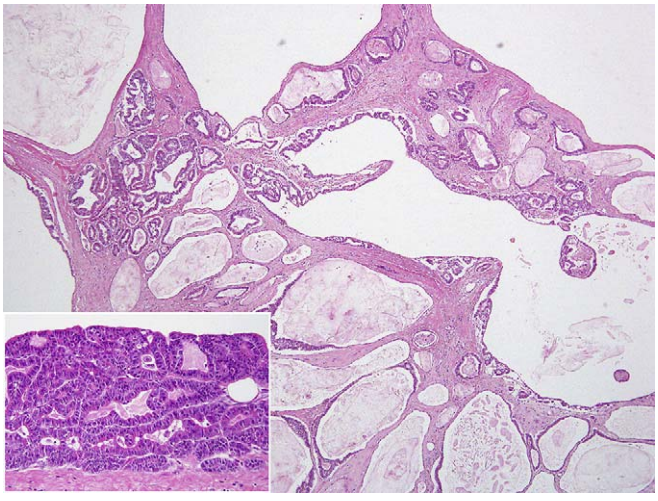

Figure 9 *Acinar cell cystadenocarcinoma* composed of numerous large and small cysts separated by thin fibrous walls. The cysts are lined by either single or several layers of neoplastic acinar cells sometimes forming complex, cribriform structures (inset).

Electron microscopy

Zymogen granules are the ultrastructural hallmark of acinar differentiation and occur as electron-dense granules that may vary in number, shape, size and distribution. Typical granules are round, range from 125 to 1000 nm in size and are usually concentrated in the apical cytoplasm, adjacent to the luminal border. A second population of granules has bizarre shapes with a fibrillary internal structure, ranging up to 3500 nm in size. Some of these appear to be membrane bound, but others are free within the cytoplasm. Transitional forms between these irregular fibrillary granules and classical types are also found.[1]

In addition, although non-specific, well-formed luminal spaces with short microvilli projecting from the surface of the cells are generally identifiable, and the cells contain basally oriented nuclei with dispersed chromatin and prominent nucleoli. There is abundant rough endoplasmic reticulum, arranged in parallel arrays. Golgi complexes and numerous mitochondria are also present.[12]

Molecular findings

By molecular genetic analysis, ACCs very rarely if ever show *KRAS*, *TP53*, *SMAD4 (DPC4)*, or *CDKN2A(p16)* gene mutations, in contrast to pancreatic ductal adenocarcinomas. As a result, immunohistochemically, only rare cases exhibit abnormal nuclear accumulation of the p53 protein, and DPC4 is retained. However, a high frequency of allelic loss on chromosomes 11p, 4q and 16q has been identified. In addition, 25% of ACCs have mutations in *APC*/β-*catenin* pathway, either activating mutations of the β-*catenin* gene or truncating *APC* mutations, a pattern similar to that of pancreatoblastoma. Therefore, abnormal nuclear immunolabelling for β-catenin can be seen, usually in a patchy or mosaic pattern (some cells showing abnormal nuclear and cytoplasmic labelling and others showing normal membranous labelling).[13,14]

Acinar cell cystadenocarcinoma

A cystic variant of ACC is well documented but is extremely uncommon; only a handful of cases have been reported.[15–19] Grossly, the lesions are large (mean, 24 cm), circumscribed and diffusely cystic with individual locules ranging from a few millimetres to several centimetres. Microscopically, the cysts are separated by delicate fibrous septa and lined by single or several layers of neoplastic acinar cells, sometimes forming minute lumina within the epithelial lining (Figure 10). Intraluminal proteinaceous acidophilic material and crystals, characteristics of enzymatic secretions, are evident within the larger cysts. The cells have characteristic cytologic features of acinar differentiation, including brightly eosinophilic, granular cytoplasm and round to oval, basally located nuclei with vesicular chromatin and prominent nucleoli. There is usually minimal to mild nuclear pleomorphism; however, solid nests of neoplastic cells, areas of

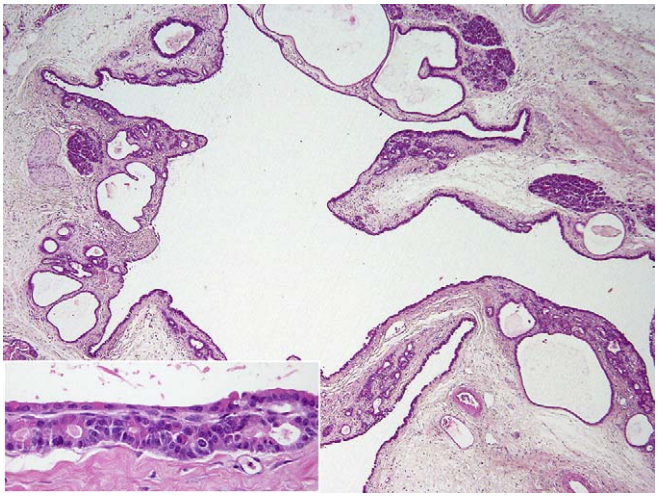

Figure 10 *Acinar cell cystadenoma*. At low magnification, these lesions show cystic structures interposed among residual parenchymal elements. Compared with acinar cell cystadenocarcinoma, their epithelium is much simpler; the cells are well polarized with basally located nuclei and eosinophilic granular, apical cytoplasm. There is no atypia or mitoses (inset).

necrosis, and easily identifiable mitotic figures support a malignant diagnosis. Special stains and immunohistochemical markers can be used to document the presence of acinar differentiation. The clinical behaviour of acinar cell cystadenocarcinomas does not appear to be different than that of ordinary ACCs.

The main differential diagnosis of acinar cell cystadenocarcinoma is serous cystadenoma due to the spongy macroscopic appearance. However, microscopically, acinar cell cystadenocarcinomas lack the glycogen-rich clear cells of serous cystadenoma and demonstrate evidence of acinar differentiation as described above. Acinar cell cystadenoma is also in the differential; however, the cysts in acinar cell cystadenoma are lined by one to several layers of undulating acinar cells. In some areas the luminal layer is flattened, resembling squamous epithelium or a transition to mucin containing ductal epithelium may be found. Areas of necrosis, solid nests of neoplastic cells, infiltration into the surrounding stroma or mitotic figures, features establishing a malignant diagnosis, are not detected (Figure 11).

Mixed acinar carcinomas

Mixed acinar carcinomas exhibit more than one line of differentiation (acinar and neuroendocrine; acinar and ductal; or acinar, neuroendocrine, and ductal), usually with the acinar component predominating. By arbitrary definition, each component must comprise at least 25% of neoplasm for a diagnosis of mixed acinar carcinoma. Although some mixed carcinomas have distinctive histologic features suggesting that more than one line of differentiation exists, in many cases, mixed differentiation is only detectable by immunohistochemistry, especially in mixed acinar neuroendocrine carcinomas.[9] For this reason, a thorough immunohistochemical evaluation is recommended for all acinar neoplasms.

Mixed acinar neuroendocrine carcinoma

The overall characteristics of mixed acinar neuroendocrine carcinomas are highly similar to those of ACCs, except for the sex

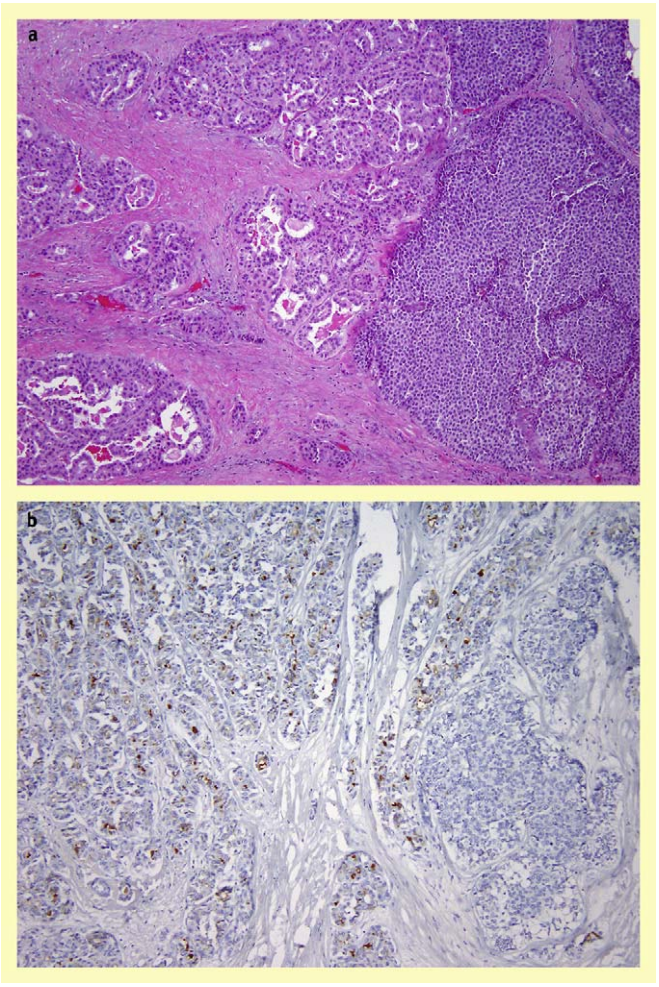

Figure 11 (**a**) *Mixed acinar neuroendocrine carcinoma* with histologically distinguishable two separate components. (**b**) By immunohistochemistry, the acinar elements are positive for trypsin, and the neuroendocrine elements are negative.

ratio. As opposed to the male preponderance of ACCs, mixed acinar neuroendocrine carcinomas occur more commonly in women than men (M:F = 3.6 vs.0.5, respectively).[9,20] Also, recently it has been speculated that the presence of a neuroendocrine component may be related to a more favourable outcome.[21] However, considering the small number of well-characterized mixed acinar neuroendocrine carcinomas on record, this difference could be coincidental.

The presence of synaptophysin and, to a minor degree, chromogranin expressing cells (Figure 12) in both ACCs and mixed acinar neuroendocrine carcinomas might indicate that the cells giving rise to these tumours are pluripotent and may differentiate towards acinar and neuroendocrine cells. The neuroendocrine cells, however, seem to remain at a low differentiation level, since most of these tumours lack clinical or immunohistochemical evidence of peptide hormone production, as is commonly seen in neuroendocrine tumours of the pancreas.[20]

A recently reported overlap in the majority of the differentially expressed microRNAs between ACCs and neuroendocrine tumours suggests a pattern of microRNA expression common to acinar and neuroendocrine derived tumours.[22]

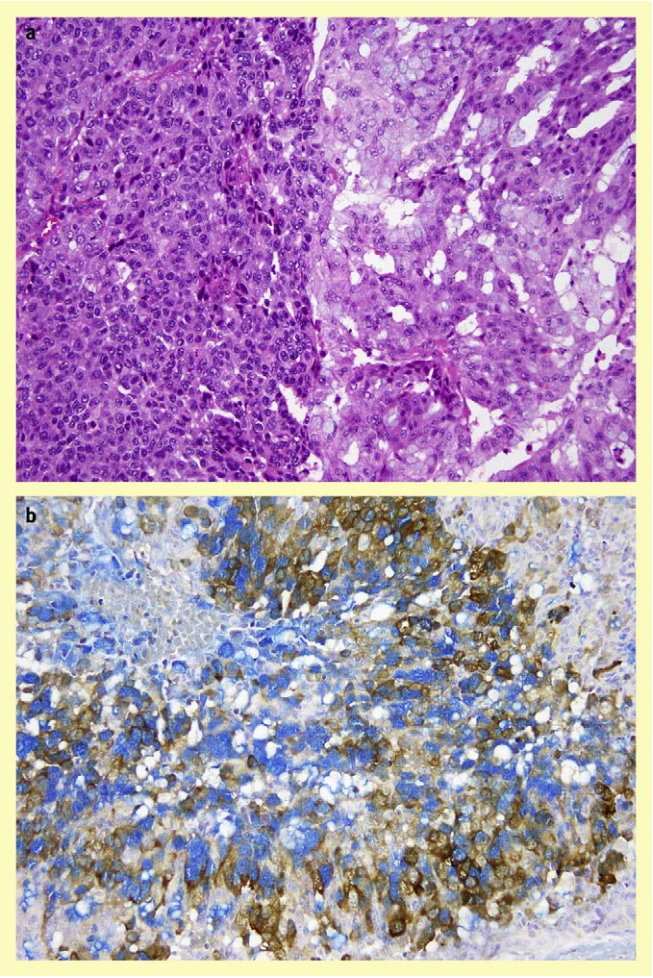

Figure 12 *Mixed acinar ductal carcinoma*. (**a**) Ductal elements (right) contain intracellular mucin and exhibit a cribriform glandular pattern. Acinar elements (left) are arranged in large nests. (**b**) The presence of both acinar and ductal elements is demonstrated by double staining for trypsin (immunohistochemistry) and intracellular mucin (alcian blue).

Mixed acinar ductal carcinoma

As mentioned above, focal ductal differentiation can be identified in ACCs by stains for mucins, mucin-related glycoproteins, or ductal-type cytokeratin types. Glandular structures can occur in conventional ACCs but they are usually superimposed on the solid, nesting architecture of these tumours. ACCs with individual glands surrounded by stroma and associated with obvious mucin production are rare. When morphologically evident ductal elements are significant (>25%), a diagnosis of mixed acinar ductal carcinoma is rendered. Only a handful of these tumours had been reported, largely in case reports.[5] Recently, Stelow et al published[23] a series of tumours with significant acinar and ductal differentiation (some with neuroendocrine differentiation as well) and described two different architectural patterns: 1) "mucinous acinar cell carcinoma" consists of intermingled conventional ACC and elements intracellular or extracellular mucin production, 2) "combined acinar and ductal carcinoma" is characterized by separate, morphologically distinct ductal adenocarcinoma components with individual glands surrounded by dense or desmoplastic stroma, alternating with typical ACC components. Regardless of the pattern, most cells expressing pancreatic enzymes (demonstrated by immunohistochemical labelling for trypsin and/or chymotrypsin) are negative for mucin stains (mucicarmine or alcian blue), and vice-versa, but in a small population of cells, both enzyme production and mucin staining can be shown. Also chromogranin and/or synaptophysin staining highlight the neuroendocrine component, if present in tumours designated mixed acinar ductal neuroendocrine carcinoma.

It has been shown that these mixed acinar ductal carcinoma carcinomas largely lack evidence of abnormalities in ductal carcinoma genes, although rare cases reveal *KRAS* mutations. Therefore, most of these tumours are probably biologically more closely related to ACCs than to ductal adenocarcinomas.[23]

Based on knowledge of embryologic development in the pancreas, the occurrence of pancreatic neoplasms with both acinar and ductal differentiation is somewhat counterintuitive and implies that pathways active in early pancreatic development may be reactivated during neoplastic transformation.

Differential diagnosis

The main differential diagnosis of ACC is with other pancreatic neoplasms that are characterized by a solid, cellular pattern, namely pancreatic neuroendocrine tumours, pancreatoblastoma, solid–pseudopapillary neoplasm and intraductal tubulopapillary neoplasm (Table 1).

Acinar cell carcinoma vs. pancreatic neuroendocrine tumour

Although ACCs usually show an acinar growth pattern, at least focally, cases with predominantly solid or trabecular patterns are not infrequent and, with minimal stroma and cytologic uniformity, these can represent a great diagnostic challenge. The characteristics that help distinguish ACCs from pancreatic neuroendocrine tumours (PanNETs) include basal basophilia of the neoplasm, and although not always prominent, basal nuclear localization in acinar formations or at the interface of solid nests with the stroma, forming a palisading pattern. The cytoplasm is, at least focally, eosinophilic and granular, reflecting aggregates of zymogen granules in the apical cytoplasm (which may be highlighted by d-PAS positivity), contrasting with the finely granular, non-polarized amphophilic cytoplasm of most PanNETs. Despite the nuclear uniformity, ACCs lack the typical "salt and pepper" chromatin of PanNETs and their large single nucleoli can provide an important clue to the diagnosis. Finally, the presence of readily identifiable mitoses (usually >10/10HPF) in an otherwise uniform appearing neoplasm suggests ACC.[24]

Immunohistochemical stains are invaluable in establishing the diagnosis (Table 2). Markers for acinar enzymes (trypsin, chymotrypsin, and lipase) are highly specific and sensitive. Among these, trypsin and chymotrypsin prove the most useful in our experience. Scattered neuroendocrine cells or a focal neuroendocrine component are common in ACCs, so labelling (especially focally) for neuroendocrine markers is not sufficient to exclude an ACC unless enzyme markers are known to be negative. Additionally, PanNETs may show focal immunoreactivity for acinar markers. Therefore it is important to use an immunohistochemical panel that includes markers for both acinar and neuroendocrine differentiation.

Differential diagnosis of acinar cell carcinoma

	Acinar cell carcinoma	Neuroendocrine tumour	Solid–pseudopapillary neoplasm	Pancreatoblastoma
Age	6th Decade	5th Decade	Young females	1st Decade, Rarely adulthood
Histology	Stroma-poor growth pattern Acinar units may be present Granular eosinophilic cytoplasm Prominent nucleoli	Various patterns "Salt & pepper" chromatin Nucleoli may be seen Amyloid deposition may occur	Pseudopapillae Hyaline globules Macrophages Nuclear grooves	Multiphenotypic differentiation Squamoid corpuscles
Histochemistry	PAS (+) granules in the cytoplasm	Grimelius (+)	PAS (+) globules in the cytoplasm	–

Table 1

Acinar cell carcinoma vs. solid–pseudopapillary neoplasm

Solid–pseudopapillary neoplasms typically arise in female patients in their twenties and have a distinctive microscopic appearance characterized with a combination of solid, pseudopapillary, and hemorrhagic pseudocystic areas. Foamy cells and eosinophilic globules composed of alpha-1-antitrypsin might also be seen. The cells are very uniform, nuclei are grooved, and nucleoli are not prominent. Solid–pseudopapillary neoplasms generally lack mitoses.[24] However, if a solid–pseudopapillary neoplasm displays a predominantly solid growth pattern without foamy cells and eosinophilic globules, it may be confused with ACC. Immunohistochemistry readily distinguishes these two neoplasms. Although, similar to ACC, solid–pseudopapillary neoplasms typically express non-specific acinar markers (alpha-1-antitrypsin and alpha-1-antichymotrypsin); labelling for more specific acinar markers (trypsin, chymotrypsin, and lipase) is not seen. Furthermore, in contrast with ACCs, solid–pseudopapillary neoplasms consistently express vimentin, CD10, CD56, and progesterone receptors but epithelial markers are usually either focal or weak.[25] Solid–pseudopapillary neoplasms have β-catenin mutations and consistently show diffuse nuclear β-catenin staining, which is unusual in ACCs. Also, loss of membranous E-cadherin staining is found. Recently, Comper et al.[26] has also shown that solid–pseudopapillary neoplasm has a peculiar claudin expression profile as compared with normal pancreas, as well as ACC, pancreatic neuroendocrine tumour and pancreatoblastoma, and that the pattern of claudins 5 and 7 expression (strong positivity of claudin 5 on the cell membrane with lack of expression of claudin 7) is highly specific in differentiating solid–pseudopapillary neoplasm from ACC as well as from PanNET and pancreatoblastoma.

Acinar cell carcinoma vs. pancreatoblastoma

Pancreatoblastoma is a rare pancreatic tumour showing differentiation towards all three lineages (acinar, ductal, and neuroendocrine) in variable amounts. Pancreatoblastoma is thus closely related to ACC and has been regarded as the paediatric counterpart

Immunohistochemistry in the differential diagnosis of acinar cell carcinoma

Antibody	Acinar cell carcinoma	Neuroendocrine tumour	Solid–pseudopapillary neoplasm	Pancreatoblastoma
Keratins	Positive	Positive	Negative or focal/weak positive	Positive
Trypsin/chymotrypsin	Positive	Rare, scattered cells	Negative	Positive
Alpha-1-antitrypsin	Positive	May be positive	Positive	(Focally) positive
Chromogranin	Focally positive	Positive	Negative	(Focally) positive
Synaptophysin	Focally positive	Positive	Positive	(Focally) positive
Vimentin	Negative	Negative	Positive	(Focally) positive
CD10	Focally positive	Focally positive	Positive	Negative
PR	Negative	May be positive	Positive	Negative
β-Catenin	Nuclear/cytoplasmic staining may be seen	Nuclear/cytoplasmic staining may be seen	Nuclear/cytoplasmic staining	Nuclear/cytoplasmic staining, usually in the squamoid corpuscles

Table 2

of ACC. It is the most common pancreatic neoplasm of childhood and occurs mostly <10 years of age, although one-third of reported cases have occurred in adults. Microscopically, the tumours have acinar, solid, and nested growth patterns. A hallmark of the diagnosis are highly characteristic squamoid corpuscles composed of whorled, plump spindle shaped cells that have optically clear nuclei rich in biotin and more abundant cytoplasm than the surrounding cell populations.[27] Acinar differentiation is the most common and the predominant pattern in the majority of the cases, which can cause diagnostic problems. In such cases, the patient's age is helpful suggesting the correct diagnosis if the histologic features are not well visualized (e.g., in cases of biopsies showing no squamoid corpuscles). Careful microscopic examination and additional sampling may also be useful in revealing ductal and or neuroendocrine components as well as squamoid nests and cellular stromal bands. Immunohistochemical labelling for markers of acinar, ductal, and neuroendocrine differentiation helps confirm the diagnosis.

Abnormal nuclear and cytoplasmic β-catenin expression can also be found in pancreatoblastomas and cannot be used to help with the distinction of pancreatoblastoma from ACC and solid–pseudopapillary neoplasm.

Acinar cell carcinoma vs. intraductal tubulopapillary neoplasm

There is a newly described entity referred to as intraductal tubulopapillary (or tubular) neoplasm, which has yet to be fully characterized.[28,29] It consists of intraductal nodules that have sheets of cells with variable degrees of gland formation, resulting in a cribriform pattern closely resembling the acinar pattern of ACC. Comedo-type necrosis and even desmoplastic stroma separating the glandular units are common, even in the absence of a component of extraductal invasive carcinoma. Further compounding the distinction, some cases of ACC have an intraductal growth pattern. The absence of expression of acinar markers (trypsin, chymotrypsin, and other enzymes) and positive labelling for ductal markers (CK19, CA19-9) help establish a diagnosis of intraductal tubulopapillary neoplasm.

Staging

Pure and mixed ACCs are staged using the TNM staging system for carcinomas of the exocrine pancreas, based on the size and extent of the primary neoplasm, and the presence of regional lymph node and distant metastases.[30]

Prognosis

The clinical course of ACC is aggressive, although it is usually not as dismal as that of stage-matched ductal adenocarcinomas. The five-year survival rate ranges from 6%[1] (based on cases recruited before 1999) to 50%[31–33] in different studies. Patients who present with localized disease have much better prognosis than those who present with metastases, which are most often found in regional lymph nodes and the liver[3] although occasionally in lung, cervical lymph nodes and ovary.[34] Longer survival of patients with ACC is also predicted by younger age (<65 years), and negative resection margins.[33] Although insufficient data have been accumulated on the paediatric ACCs, patients younger than 20 years of age may have better prognosis than adults.

Surgical resection appears to be the most effective treatment for those patients with localized disease.[32,35] In a review of 865 ACCs identified from the National Cancer Database,[33] 5-year survival in resected patients was significantly better than in patients who did not undergo resection: 36.2% (median, 27 months) vs. 10.4% (median, 7.1 months). For those patients with locally unresectable or metastatic tumours, chemotherapy and radiation may be considered in an attempt to downstage disease to afford surgical resection.[31]

Research directions

At the molecular level, ACC is very different from other types of pancreatic neoplasms, ductal adenocarcinoma in particular. These observations along with anecdotal demonstration of significant responses to treatment[1] suggest there may be promise to identify therapeutic targets for this variant of pancreatic cancer. Because ACCs harbour abnormalities in the *APC/β-catenin* pathway, chemotherapy directed more towards intestinal-type carcinomas has been tested with some success. Future research will explore the molecular features of ACC in a much more comprehensive way using whole exome sequencing, with the hope that novel pathways involved in the genesis of ACC will be discovered, potentially affording new treatment options. ◆

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Practice points

Clinical

- Uncommon; 1–2% of all pancreatic neoplasms in adults, 15% of those in children
- Mean age, 58 years
- Males affected more frequently (M:F = 3.6)
- Lipase hypersecretion syndrome in 10–15%
- 50% with metastasis (usually to liver) at presentation

Macroscopic

- Typically large (mean size, 11 cm)
- Well-delineated, nodular, yellow-tan, fleshy mass with fibrous bands
- Frequent necrosis resulting in degenerative cystic changes

Microscopic

- Sheet-like, stroma-poor growth pattern with or without acinar formations
- Overall basophilia
- Round nuclei with prominent nucleoli
- May contain cytoplasmic eosinophilic granules
- Easily detectable mitoses (mean, 14/10HPF)
- Variable amounts of neuroendocrine elements

Immunohistochemistry

- Immunohistochemical stains for exocrine enzymes, in particular, trypsin and chymotrypsin, but also lipase, serve as highly specific markers of acinar differentiation.
- Pancreatic ductal differentiation markers (mucins, mucin-related glycoproteins and ductal specific keratins) are either negative or only focally positive.
- A neuroendocrine component is very commonly present, and shows immunoreactivity for chromogranin or synaptophysin as well as other neuroendocrine markers.