Acinar neoplasms of the pancreas—A summary of 25 years of research

David S. Klimstra, MDa,*, Volkan Adsay, MDb

aDepartment of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065
bDepartment of Anatomic Pathology, Emory University, Atlanta, GA

Keywords:
Acinar
Pancreas
Carcinoma
Pancreatoblastoma

Abstract
Our understanding about the family of acinar neoplasms of the pancreas has grown substantially over the past 25 years. The prototype is acinar cell carcinoma, an uncommon variant of pancreatic carcinoma that demonstrates production of pancreatic exocrine enzymes, verifiable using immunohistochemistry, and exhibits characteristic histologic features. Related neoplasms include mixed acinar carcinomas such as mixed acinar neuroendocrine carcinoma and mixed acinar ductal carcinoma. In the pediatric age group, pancreatoblastoma is also closely related. Cystic and extrapancreatic forms have been described. These neoplasms share molecular alterations that are distinct from the more common ductal and neuroendocrine neoplasms of the pancreas. Although there is a broad range of genetic findings, a number of potential therapeutic targets have emerged. This review explores the clinical and pathologic features of pancreatic acinar neoplasms along with their more common molecular phenotypes. The differential diagnosis with other pancreatic neoplasms is explored as well.

© 2016 Elsevier Inc. All rights reserved.

Pancreatic neoplasms usually exhibit predominantly ductal differentiation, which are associated with mucin production or expression of glycoproteins and display a characteristic spectrum of molecular alterations.1 Neoplasms of neuroendocrine and acinar lineage are much less common. Acinar differentiation is defined as the production of pancreatic exocrine enzymes by the neoplastic cells, but acinar cell neoplasms also have highly characteristic histologic features, and their emerging molecular characteristics are also largely distinct from those of other pancreatic neoplasms.2 This article traces the evolution of our understanding of pancreatic acinar neoplasms—including acinar cell carcinoma, mixed acinar carcinomas (ACCs), acinar cystic lesions, and pancreatoblastoma—from pathological and clinical characterization to molecular genetic analysis over the past 25 years. This journey was initially inspired and heavily influenced by the mentorship of Dr. Juan Rosai, who not only recognized a gap in our understanding of pancreatic neoplasia but also provided the tools to stimulate pathological investigation and thematic research on this related family of entities.

Historical perspective

Early recognition of ACC as a distinct variant of pancreatic carcinoma was based on clinical findings rather than on pathological insight. Rare patients with pancreatic cancer were reported to develop disseminated fat necrosis, particularly in the subcutaneous tissues, along with
polyarthralgia. These cases of the classic lipase hypersecretion syndrome, shown to result from secretion by the tumor of massive amounts of lipase into the blood, were ultimately associated with carcinomas with a distinctive histologic appearance. The pattern often resembled that of the normal acinar elements of the pancreas; thus, the term “acinar cell carcinoma” was proposed. Until the early 1980s, ACCs were reported mostly as individual cases, many of which displayed the lipase hypersecretion syndrome. Only in 1977, a report of 11 cases of ACC appeared that emphasized the distinctive histologic features that could allow the diagnosis of ACC in the absence of a paraneoplastic syndrome. At this time, ancillary studies to prove the presence of acinar differentiation had not been developed, and only limited examples had been evaluated with electron microscopy. In fact, the high frequency of acinar cell carcinomas in this study (nearly 10%) among pancreatic tumors raised some concerns whether all of these cases would be classified as ACC based on contemporary criteria.

One this backdrop, one of the authors (D.S.K.) entered pathology residency at Yale-New Haven Hospital in 1988, under the directorship of Dr. Rosai. In late 1989, a case appeared in the department that sparked a series of studies that have redefined this entity, leading to its in-depth characterization and ultimately to the identification of molecular targets for therapy. This case is worth a brief description, as it raised a number of issues that continue to make the diagnosis of ACC a challenge for pathologists. The patient was a 62-year-old male with a prior history of organ-confined prostatic adenocarcinoma, Gleason score $3 + 4 = 7$, treated with radiation therapy 5 years prior to presentation. When seen in 1989, he had presented acutely with upper gastrointestinal hemorrhage, and an abdominal CT scan revealed a mass in the head of the pancreas or duodenum and multiple liver metastases. A core needle biopsy of a liver lesion was interpreted as metastatic prostatic adenocarcinoma, although no immunohistochemical stains were performed and the prior prostate primary was not available for comparison. Upper endoscopy revealed a large polypoid tumor projecting into the duodenum, and given the ongoing bleeding, a pancreatoduodenectomy was performed emergently. The histology of this tumor revealed a densely cellular neoplasm that was sharply circumscribed from the underlying pancreas (Fig. 1). The architecture was solid and trabecular, with areas showing a gyriform pattern. Although these features raised the possibility of a neuroendocrine neoplasm, the cells were well-polarized at the periphery of the nests, focal rudimentary acinar structures were present, and the nuclei had distinct nucleoli. Immunohistochemical stains for chromogranin and synaptophysin were completely negative, and the tumor had easily identifiable mitotic figures, considering that the initial diagnostic impression was that of a well-differentiated neuroendocrine neoplasm. Dr. Rosai reviewed the case and suggested the correct diagnosis of acinar cell carcinoma, which was later supported by the ultrastructural finding of large (250–500 nm) homogeneous dense core granules, apically located in the cells, along with a second unfamiliar granule type that was large (3500 nm), angulated, irregular in shape, and had a fibrillary internal matrix (Fig. 2). Interestingly, despite presenting with significant hepatic disease, the patient had no other distant metastases and survived for 42 months following a number of variably effective chemotherapeutic regimens.

In the aftermath of this case, Dr. Rosai mentioned to D.S.K. that ACC, although recognized for many years as a distinct entity, had never been the subject of a definitive pathological evaluation. Furthermore, there were no confirmatory immunohistochemical stains, despite the high likelihood that the neoplastic cells were producing pancreatic exocrine enzymes. A commercial source for antibodies against trypsin, chymotrypsin, and lipase was found, and Dr. Rosai proposed that these antibodies be characterized for diagnostic use.

![Fig. 1 – Histology of pancreatic neoplasm projecting into duodenum. At low power (A) the tumor is highly cellular, with minimal fibrovascular stroma between nests and cords of cells. At high power (B), there is a trabecular architecture composed of uniform cells with basally oriented oval nuclei. The chromatin pattern is coarsely granular. Mitotic figures are readily evident.](image-url)
Collaboration with Drs. Clara Heffess and James Oertel at the Armed Forces Institute of Pathology was further suggested by Dr. Rosai, and their numerous cases were added to those from the archives at Yale. After eliminating mixed acinar carcinomas, pancreatoblastomas, and other entities, the remaining 28 cases of ACC formed the basis of the first contemporary study of this entity, which also established immunohistochemical staining for enzymes as an extremely helpful tool to support the diagnosis.10 This article has been followed by many others providing additional insights into ACC11 and describing mixed acinar neuroendocrine carcinoma,12 mixed acinar ductal carcinoma,13 pancreatoblastoma,14 and so-called acinar cell cystadenoma.15 Numerous other clinical and molecular characterizations of these entities have since been undertaken.

Clinical and pathological features of acinar cell carcinoma

Approximately 1–2% of pancreatic neoplasms are ACCs or mixed acinar carcinomas.16 Most patients are adults, with a mean age of 60 years, but approximately 6% ACCs occur in childhood, and 15% of pediatric pancreatic neoplasms are ACCs.17,10,18–20 Males are affected more commonly than females. Because ACCs have a relatively circumscribed, expansile growth pattern, invasion of the common bile duct is much less frequent than in ductal adenocarcinomas. Therefore, the presenting symptoms uncommonly include jaundice and are usually non-specific (abdominal pain, weight loss, nausea, etc.). The classic lipase hypersecretion syndrome is actually uncommon (<10% of patients) and was probably over-reported in the earlier literature because of its dramatic presentation.10,20 Patients affected by the lipase hypersecretion syndrome generally have hepatic metastases or extremely bulky primary disease. Serum lipase levels may be in excess of 10,000. In addition to subcutaneous fat necrosis and arthralgia, eosinophilia may be found. Uncommon clinical associations of ACC include thrombotic endocarditis7 and myeloma-like cast nephropathy.71 Alpha-fetoprotein production can occur.22 Hereditary cases are very unusual, although a number of cases have occurred in patients with familial adenomatous polyposis,23,24 Lynch syndrome,25,26 or Carney syndrome,27 providing some hints about the molecular underpinnings of acinar neoplasms (see below).

ACCs are somewhat more common in the head of the pancreas. They are usually large (mean size: 8 cm) and solid, although cystic degeneration can occur in larger examples.10,20,11 Grossly, ACCs have a well-circumscribed or multinodular appearance and may seem to be encapsulated (Fig. 3). The tumors are red to brown, homogeneous, and have a very soft consistency. Hemorrhage or necrosis may occur. Occasionally there is polypoid extension into the pancreatic ducts.28,29

ACCs are also circumscribed microscopically (Fig. 4), but invasion through the peripheral fibrous pseudocapsule or into vessels or nerves is common. Within the tumor lobules, ACCs are characteristically highly cellular, lacking significant fibrous stroma and devoid entirely of desmoplasia. The neoplastic cells are uniform and arranged in various architectural patterns, most typically acinar or solid (Fig. 5), but also trabecular or even gyriform can occur (Fig. 1). Rare cases exhibit a papillary architecture, which can occur in the component of intraductal extension of the tumor.28 The cells have minimal to moderate cytoplasm that varies from amphophilic to lightly eosinophilic (Fig. 6A). A helpful finding is eosinophilic cytoplasmic granularity, which is often more pronounced in regions with an acinar or glandular architecture. The granules, which are PAS-positive resistant to diastase, represent zymogen granules and are often oriented toward the apical pole of the cells. The nuclei range from round to oval, and although they are enlarged compared to those of non-neoplastic acinar cells, they are typically uniform and lack marked pleomorphism. Central prominent nucleoli are a helpful diagnostic feature (Fig. 6B). The mitotic

Clinical and pathological features of acinar cell carcinoma

Approximately 1–2% of pancreatic neoplasms are ACCs or mixed acinar carcinomas.16 Most patients are adults, with a mean age of 60 years, but approximately 6% ACCs occur in childhood, and 15% of pediatric pancreatic neoplasms are ACCs.17,10,18–20 Males are affected more commonly than females. Because ACCs have a relatively circumscribed, expansile growth pattern, invasion of the common bile duct is much less frequent than in ductal adenocarcinomas. Therefore, the presenting symptoms uncommonly include jaundice and are usually non-specific (abdominal pain, weight loss, nausea, etc.). The classic lipase hypersecretion syndrome is actually uncommon (<10% of patients) and was probably over-reported in the earlier literature because of its dramatic presentation.10,20 Patients affected by the lipase hypersecretion syndrome generally have hepatic metastases or extremely bulky primary disease. Serum lipase levels may be in excess of 10,000. In addition to subcutaneous fat necrosis and arthralgia, eosinophilia may be found. Uncommon clinical associations of ACC include thrombotic endocarditis7 and myeloma-like cast nephropathy.71 Alpha-fetoprotein production can occur.22 Hereditary cases are very unusual, although a number of cases have occurred in patients with familial adenomatous polyposis,23,24 Lynch syndrome,25,26 or Carney syndrome,27 providing some hints about the molecular underpinnings of acinar neoplasms (see below).

ACCs are somewhat more common in the head of the pancreas. They are usually large (mean size: 8 cm) and solid, although cystic degeneration can occur in larger examples.10,20,11 Grossly, ACCs have a well-circumscribed or multinodular appearance and may seem to be encapsulated (Fig. 3). The tumors are red to brown, homogeneous, and have a very soft consistency. Hemorrhage or necrosis may occur. Occasionally there is polypoid extension into the pancreatic ducts.28,29

ACCs are also circumscribed microscopically (Fig. 4), but invasion through the peripheral fibrous pseudocapsule or into vessels or nerves is common. Within the tumor lobules, ACCs are characteristically highly cellular, lacking significant fibrous stroma and devoid entirely of desmoplasia. The neoplastic cells are uniform and arranged in various architectural patterns, most typically acinar or solid (Fig. 5), but also trabecular or even gyriform can occur (Fig. 1). Rare cases exhibit a papillary architecture, which can occur in the component of intraductal extension of the tumor.28 The cells have minimal to moderate cytoplasm that varies from amphophilic to lightly eosinophilic (Fig. 6A). A helpful finding is eosinophilic cytoplasmic granularity, which is often more pronounced in regions with an acinar or glandular architecture. The granules, which are PAS-positive resistant to diastase, represent zymogen granules and are often oriented toward the apical pole of the cells. The nuclei range from round to oval, and although they are enlarged compared to those of non-neoplastic acinar cells, they are typically uniform and lack marked pleomorphism. Central prominent nucleoli are a helpful diagnostic feature (Fig. 6B). The mitotic
rate varies from nearly undetectable to moderate but is often in excess of 20 mitoses per 10 high power microscopic fields.

In the presence of classic cytoarchitectural features, the diagnosis of ACC can be strongly suspected based on routine histology. However, there are a number of significant mimics (see “Differential Diagnosis,” below), so ancillary diagnostic studies are generally employed to support the diagnosis. Demonstration of dPAS-positive granules can be helpful, but this is neither sensitive nor specific. Currently, immunolabeling for pancreatic exocrine enzymes is the primary means to demonstrate acinar differentiation. Antibodies against trypsin and chymotrypsin are the most widely used and sensitive (Fig. 7); lipase can also be demonstrated in about 65% of cases. Interestingly, amylase is not usually detectable and antibodies against this enzyme are not used diagnostically. Another more recent acinar marker is bc110, although in routine practice the use of trypsin and chymotrypsin is generally adequate. The ultrastructural features of ACC describing the case vignette above are also highly characteristic, and the so-called irregular fibrillary granules appear to be specific for neoplasms with acinar differentiation, as they recapitulate the morphology of the earliest granules observed in the acinar cells of the developing embryonic pancreas. However, the general decline in the use of electron microscopy for tumor diagnosis has rendered this diagnostic tool nearly obsolete.

ACCs are aggressive carcinomas. Approximately half of patients have metastases at presentation, and another 25% develop them subsequently. Metastatic disease usually affects the lymph nodes and liver; even late in the course of disease extrahepatic metastases are uncommon. However, rare cases present with ovarian metastases, where the differential diagnosis can include a wide array of primary and metastatic neoplasms. The outcome of ACC is better than that of conventional ductal adenocarcinoma. Data reported more than 15 years ago suggested a median survival for all stages of disease of 18 months, with patients presenting without metastases surviving more than 3 years on average. Anecdotes also existed of patients with stage IV disease at presentation surviving several years. Recent data have shown an even more favorable prognosis, presumably due to earlier detection and some responses to chemotherapy. An overall 5-year survival rate of 43% (72% for patients undergoing resection; 22% for those with unresectable disease) and a median survival of 57 months for resectable disease and 20 months for those with metastases are now reported; however, most patients ultimately succumb to their disease. Prognostic factors include only staging features (primary tumor size, lymph node status, and presence of metastases). There is no predictive grading scheme for ACC.

Mixed acinar carcinomas

ACCs resemble pancreatic neuroendocrine neoplasms, and many cases (40%) also exhibit a minor population of cells that...
express neuroendocrine lineage markers (chromogranin and synaptophysin) by immunohistochemistry. Less commonly, acinar neoplasms have a component of neuroendocrine differentiation that constitutes >25% of the neoplasm, based on the proportion of cells labeling immunohistochemically. These tumors are designated mixed acinar neuroendocrine carcinomas (Fig. 8). In almost all cases, the acinar component predominates. A few exceptional examples have shown morphologically obvious and separate components reflecting the two different cell lineages, but most mixed acinar neuroendocrine carcinomas have a more homogeneous morphology, with only subtle regional variations raising the potential of both acinar and neuroendocrine elements being present. In these cases, immunohistochemistry is required to recognize the mixed nature of the neoplasm. In contrast to other mixed neuroendocrine carcinomas that may have separate, definable components of small cell carcinoma or large cell neuroendocrine carcinoma, mixed acinar neuroendocrine carcinomas appear to be fundamentally acinar neoplasms with divergent differentiation toward the neuroendocrine lineage that varies in extent throughout the tumor. Individual cells appear to have so-called “amphicrine” differentiation, expressing both trypsin (or chymotrypsin) and chromogranin (or synaptophysin).

There are neither prognostic nor molecular differences between mixed acinar neuroendocrine carcinomas and pure ACCs, so the main importance of this entity is to avoid its confusion with pure neuroendocrine neoplasms, which may be suggested based on the finding of immunolabeling for chromogranin or synaptophysin in a significant proportion of cells.

Another more recently described mixed acinar carcinoma is mixed acinar ductal carcinoma. In these cases, the ductal elements can resemble conventional ductal adenocarcinomas, with individual infiltrating glands associated with stromal desmoplasia, or there can be frank mucin production by a subset of neoplastic cells (Fig. 9). The mucin may be intracellular or there may be pools of extracellular mucin with suspended tumor cells, similar to colloid carcinomas. As in the mixed acinar neuroendocrine carcinomas, there is usually a predominance of acinar differentiation, which can be present throughout all patterns of the tumors. In fact, some cells appear to produce both mucin and exocrine enzymes based on double staining preparations. Rarely, a mixed acinar ductal carcinoma will also exhibit neuroendocrine marker expression in >25% of the cells, qualifying for a diagnosis of mixed acinar ductal neuroendocrine carcinoma.

A few of these mixed acinar carcinomas with ductal differentiation have had mutations more characteristic of ductal than acinar neoplasms (e.g., KRAS mutations) but in general these tumors resemble pure acinar cell carcinoma in their biology.

Pancreatoblastoma

Pancreatoblastoma is a pediatric neoplasm of the pancreas that has predominantly acinar differentiation. In fact, pancreatoblastoma can be considered the pediatric
counterpart of ACC, in the same manner than hepatoblastoma is the pediatric counterpart of hepatocellular carcinoma. Pancreatoblastomas usually arise in the first decade, with a mean age of 4 years, and cases in children older than 10 years are rare. Cases in adults have also been described. They are usually sporadic, but some arise in patients with the Beckwith–Weidemann syndrome, and pancreatoblastomas in these patients can be congenital and are often cystic. A case of FAP-associated pancreatoblastoma has been reported as well. Rarely, acinar neoplasms with the histologic features of pancreatoblastomas arise in adults. Alpha-fetoprotein production can occur, with serum elevations that can be used as a biomarker, both in pancreatoblastomas and in ACCs occurring in childhood.

The morphology shares much with ACC (Fig. 10), including solid and acinar architecture and dense cellularity. There is usually pronounced lobulation, and the stroma between the lobules is hypercellular, sometimes with heterologous mesenchymal differentiation. The epithelial components are formed of small, uniform cells arranged in acini, usually with less evident eosinophilic granularity than in ACC. The nuclei in these regions are small, round, and hyperchromatic. A characteristic feature, considered the sine qua non of the diagnosis, is the squamoid nest (or corpuscle). Squamoid

Fig. 8 – Mixed acinar neuroendocrine carcinoma. The tumor shows variable cytologic features (A), with some cells having the eosinophilic granular cytoplasm of an acinar neoplasm whereas others have less cytoplasm lacking granularity. A double immunohistochemical stain (B) reveals labeling for both trypsin (blue reaction product) and chromogranin (brown reaction product), largely in separate cell populations that are intimately intermixed throughout the tumor.

Fig. 9 – Mixed acinar ductal carcinoma. The tumor grows in nests with marked nuclear pleomorphism and obvious cytoplasmic mucin (A). By immunohistochemistry (B), there is labeling for trypsin (brown reaction product) as well as alcian blue positivity in the mucin-containing cells (blue stain). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
nests vary in number and distribution throughout the tumor and are composed of larger cells with more cytoplasm than the surrounding acinar components. The cells are vaguely spindled and arranged in whorls, sometime with focal keratinization. The nuclei are also larger, more oval, and have an open chromatin pattern with clearing due to nuclear biotin accumulation. Rare pancreatoblastomas include ductal structures with intracellular mucin.

Pancreatoblastomas exhibit acinar differentiation consistently, with expression of trypsin, chymotrypsin, and other acinar markers. There is also commonly labeling for neuroendocrine and occasionally for ductal lineage markers. AFP is expressed in cases with serum elevation. The squamoid nests do not seem to reflect a particular cell lineage, although they preferentially express EMA and CEA. Interestingly, they also show nuclear labeling for β-catenin, which is implicated in the molecular histogenesis of acinar neoplasms, but the acinar components of the tumors retain normal membranous labeling for β-catenin.

Pancreatoblastomas can behave aggressively, but like pediatric ACCs, they are less aggressive in children than in adults. Patients without metastases at presentation may be cured, and favorable responses to chemotherapy have been documented.

Cystic acinar lesions

Although some large ACCs have degenerative cystic change, due to necrosis, truly cystic ACCs in which the neoplastic

Fig. 10 – Pancreatoblastoma. At lower power (A) the tumor is lobulated and the stroma between the epithelial regions is hypercellular. The neoplastic cells are arranged in nests and acini. A higher power view (B) shows a squamoid nest adjacent to an acinar region. The squamoid cells are larger, somewhat spindled and have oval nuclei and eosinophilic cytoplasm.

Fig. 11 – Acinar cell cyst adenocarcinoma. The multicystic tumor is lined by flattened to complex epithelium (A). The nodules are cytologically acinar (B), with lumina showing apical eosinophilic granularity and basal atypical nuclei with prominent nucleoli.
cells line cystic locules are very rare (Fig. 11). Other than a few old case reports, acinar cell cystadenocarcinomas have been occasionally included among large studies of conventional ACCs. Acinar cell cystadenocarcinomas are fully malignant and share all other features of ACCs, other than their multicystic nature, which presumably results from the massive dilatation of the acinar lumina that constitute the majority of the tumor architecture.

Another pancreatic cystic lesion with acinar differentiation has been more recently described as acinar cell cystadeno-noma. These lesions can represent incidental microscopic cystic structures lined by benign-appearing acinar cells, some of which are likely pancreatic ducts with acinar metaplasia. Macroscopically identified cases have a microcystic gross appearance and may diffusely involve large regions of the pancreas. Microscopically, there is cystic dilatation of the entire acinar and ductal units, resulting in complex, branching cysts intermingled with normal-appearing parenchyma (Fig. 12). The cysts are lined variably by flat, non-mucinous ductal cells and by acinar cells, which sometimes form grape-like clusters budding from the cyst walls. These lesions are cytologically bland and uniformly benign. In fact, the initial name of acinar cell cystadennoma, which connotes a benign neoplasm, has been questioned recently when molecular studies failed to prove the lesions to be neoplastic. An alternate designation of acinar cystic transformation of the pancreas has been proposed.

Extrapancreatic acinar neoplasms

A few neoplasms with the morphologic and immunohistochemical features of pancreatic acinar neoplasms have been reported outside of the pancreatic itself. Some appear to arise on the basis of neoplastic transformation of heterotopic pancreatic tissue; at least, they arise in locations where pancreatic heterotopia is well recognized to occur. But evidence of residual non-neoplastic heterotopic tissue is rarely documented. Most examples have involved the liver and stomach (Fig. 13). In the stomach, mixed acinar neoplasms with neuroendocrine differentiation are described. Given the propensity for the gastric mucosa to undergo pancreatic acinar metaplasia, acinar neoplasms in this location may arise on the basis of aberrant differentiation of a gastric mucosal neoplasm, rather than from heterotopia. The gastric examples have also been smaller, less aggressive neoplasms than the few cases reported in the liver, which are more faithful phenocopies of the primary pancreatic neoplasm. An additional unusual scenario for the origin of extrapancreatic acinar neoplasms is somatic transformation of a germ cell tumor. Non-neoplastic pancreatic tissue occurs in teratomas of the mediastinum and gonads, and presumably primary acinar neoplasms arising in these locations represent secondary malignancy of these teratomatous elements.

Molecular features of acinar neoplasms

Molecular data related to pancreatic acinar neoplasms have been accumulating steadily over the past 20 years as the technology to study them has improved. But the rarity of these neoplasms has hindered their comprehensive molecular analysis until only recently. Initially, the genes found to be involved in ductal adenocarcinoma of the pancreas were studied in acinar neoplasms, and it was shown that the most frequent genetic abnormalities (mutations in KRAS, TP53, and SMAD4) are uncommon. A more recent, comprehensive study of TP53 mutations, deletions, and promoter methylation has shown much more frequent TP53 abnormalities, however. The hereditary associations of ACC and pancreatoblastoma provided hints as to the genetic alterations in sporadic cases. The rare association of both neoplasms with FAP led to the study of the APC/β-catenin pathway, and in about 20–50% of cases, abnormalities in either APC or β-catenin were found, including activating mutations, losses, and promoter methylation of APC, and inactivating mutations in CTNNB1. Copy number alterations and methylation of the promoter of APC have also been described. Curiously, immunohistochemical staining of pancreatoblastoma for β-catenin shows aberrant nuclear labeling largely restricted to the squamous nests. Beckwith-Wiedemann syndrome with which pancreatoblastomas may be associated is caused by various abnormalities involving chromosome 11p15, including methylation defects, uniparental disomy, or mutations in the CDKN1C, HB1, IGF2, or KCNQ1OT1 genes. Losses at 11p were also found in both pancreatoblastoma (80%) and ACC (50%). Due to the rare cases of ACC in Lynch syndrome, mismatch repair abnormalities were studied in ACC and were found both in Lynch-associated and in 14% of sporadic cases. Finally, Carney syndrome has rarely been associated with ACC, and the PKR1A gene responsible for Carney syndrome is also mutated in some sporadic ACCs.

More recent genomic studies have taken advantage of next-generation sequencing to perform more comprehensive genomic analysis. Whole exome sequencing as well as more targeted broad-spectrum sequencing studies have revealed a high degree of genomic instability on both the chromosome and base pair levels in acinar neoplasms. Many different genes were mutated across the tumors studied, with no single gene being mutated in more than 30% of cases. The lack of common alterations in ductal adenocarcinoma (KRAS, SMAD4, TP53, and CDKN2A), cystic neoplasm (GNAS and RNF43), and neuroendocrine tumor (MEN1, DAXX, and ATRX)...
genes was confirmed, although 24% of acinar neoplasms had point mutations or truncations in TP53, 18% had SMAD4 mutations, and CDKN2A/CDKN2B was also deleted in a minority of cases. Also confirmed were the alterations in APC and CTNNB1 described previously. Rare mutations were found in DNA repair genes associated with familial pancreatic cancer, such as MLH1 and MSH2 as well as ATM, PALB2, BRCA2, the last three of which were mutually exclusive. Additional recurrently altered genes included JAK1, BRAF, RB1, PTEN, ARID1A, NF1, SKT11, MLL3, PRKAR1A, and BAP1. Thus, the spectrum of mutations is broad but does include a variety of potential therapeutic targets, such as JAK1, BRAF, and genes of the mTOR and DNA repair pathways. An additional molecular alteration of potential therapeutic significance is the finding of BRAF fusions in 23% of acinar neoplasms. Most such fusions (which are rare in other solid tumor types) involved SND1, although several other fusions partners were identified. The fusions are functional, leading to activation of the MAPK pathway, sensitive in vitro to MEK inhibitors. A rapid FISH assay to identify BRAF fusions in pancreatic acinar neoplasms has also been developed.

Differential diagnosis

The differential diagnosis for pancreatic acinar neoplasms largely includes other tumors with a solid, hypercellular low power appearance—which typically excludes ductal adenocarcinoma and cystic neoplasms, unless a mixed acinar ductal carcinoma or an acinar cystic lesion is under consideration. Conventional ductal adenocarcinomas are uncommonly confused for ACC, although many cases originally classified as “microadenocarcinoma,” a microglandular variant of ductal adenocarcinoma, proved to be ACC or mixed acinar neuroendocrine carcinoma after additional study using IHC for pancreatic enzymes. The most common solid, cellular pancreatic neoplasms that are confused for acinar neoplasms are pancreatic neuroendocrine neoplasms [both well differentiation pancreatic neuroendocrine tumor (PanNET) and poorly differentiation neuroendocrine carcinoma (PanNEC)] and solid pseudopapillary neoplasm. PanNETs share many architectural features with ACC, especially when the latter has solid or trabecular patterns. The nuclei in both are uniform, the cytoplasm can be amorphophilic, and ACCs can show focal labeling for neuroendocrine markers. And mixed acinar neuroendocrine carcinomas show extensive labeling for chromogranin or synaptophysin. Markedly prominent nucleoli favor an acinar neoplasm, although PanNETs can also have prominent nucleoli. Apical granular eosinophilic cytoplasm and exocrine cell polarization also favor ACC. When an organoid architecture suggests a well-differentiated PanNET, recognition of frequent mitoses (more than 20 per 10 high power fields) can help raise the possibility of ACC. But the resemblance of ACC to poorly differentiated PanNEC can prove even more vexing: 15.9% of cases referred from specialty institutions for a study on poorly differentiated PanNEC proved to be ACC or mixed acinar neuroendocrine carcinoma on further review. For these reasons, immunolabeling for trypsin, chymotrypsin, or bcl10 is suggested to exclude an acinar neoplasm whenever a putative neuroendocrine neoplasm of the pancreas does not have perfectly classic histologic features. On cytologic preparations, this difficulty is also apparent, and immunohistochemistry can also be helpful in this situation.

Solid pseudopapillary neoplasms have a number of highly characteristic histologic features that strongly suggest the diagnosis, including loosely cohesive epithelial cells that form degenerative pseudopapillae around the microvasculature, large cytoplasmic hyaline globules (much larger than zymogen granules), and nuclear grooves. Peripheral blood lakes, stromal hyalinization, and cytoplasmic clear vacuoles are also typical of solid pseudopapillary neoplasm. In
contrast, the formation of true luminal spaces is not found in solid pseudopapillary neoplasm and strongly suggests an alternative diagnosis. If the distinction from ACC is challenging, immunohistochemistry will resolve the issue. Solid pseudopapillary neoplasms never express exocrine enzymes, instead labeling for vimentin, CD10, CD56, alpha-1-antitrypsin, synaptophysin, and other assorted markers.45,46 Nuclear labeling for p-catenin is also consistent found,46 although the presence of APC-p-catenin pathway abnormalities in acinar neoplasms suggests a degree of caution in the use of this marker as the sole diagnostic support for solid pseudopapillary neoplasm.

Finally, the distinction of ACC from pancreatoblastoma may be challenging. In the pediatric age group, pancreatoblastomas usually have well-developed squamoid nests and cellular stroma, and the former features are regarded as necessary to confirm the diagnosis. In adults, these two features may be more subtle. In the end, the distinction may be less critical than it seems, since the treatment and prognosis of these two tumors is essentially the same in children and in adults. For cases with unclear histologic findings (e.g., for biopsies with limited tumor for review), it is suggested to favor pancreatoblastoma in children and ACC in adults.

Conclusions

Much new information about the family of pancreatic acinar neoplasms has appeared in the past 25 years. The distinguishing histologic features are better defined, and immunohistochemical markers to support the presence of acinar differentiation are more widely available. An awareness of mixed acinar carcinomas has helped properly classify these unusual neoplasms among the other members of the acinar family. A wealth of molecular information has provided histogenetic insights and suggested therapeutic targets. In many ways, this evolution has paralleled the increase in pathologic knowledge about many tumor entities over this time period. Yet it is tempting to believe that a single seminal case of ACC, in the hands of a talented morphologist and potent mentor, contributed to this advance in knowledge, as part of the broad academic legacy of Dr. Juan Rosai.

References

25. Liu W, Shia J, Gonen M, Lowery MA, O’Reilly EM, Klimstra DS. DNA mismatch repair abnormalities in acinar cell carcinoma


