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Pathology and genetics of pancreatic neoplasms with acinar differentiation

Laura D. Wood, MD, PhD^{a,b,*} and David S. Klimstra, MD^c

^aDepartment of Pathology, the Sol Goldman Pancreatic Cancer Research Center, the Johns Hopkins University School of Medicine, Baltimore, MD 21231 ^bDepartment of Oncology, the Sol Goldman Pancreatic Cancer Research Center, the Johns Hopkins University School of Medicine, Baltimore, Maryland ^cDepartment of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York

Abstract

Pancreatic neoplasms with acinar differentiation, including acinar cell carcinoma, pancreatoblastoma, and carcinomas with mixed differentiation, are distinctive pancreatic neoplasms with a poor prognosis. These neoplasms are clinically, pathologically, and genetically unique when compared to other more common pancreatic neoplasms. Most occur in adults, although pancreatoblastomas usually affect children under 10 years old. All of these neoplasms exhibit characteristic histologic features including a solid or acinar growth pattern, dense neoplastic cellularity, uniform nuclei with prominent nucleoli, and granular eosinophilic cytoplasm. Exocrine enzymes are detectable by immunohistochemistry and, for carcinomas with mixed differentiation, neuroendocrine or ductal lineage markers are also expressed. The genetic alterations of this family of neoplasms largely differ from conventional ductal adenocarcinomas, with only rare mutations in *TP53*, *KRAS*, and *p16*, but no single gene or neoplastic pathway is consistently altered in acinar neoplasms. Instead, there is striking genomic instability, and a subset of cases has mutations in the APC/ β -catenin pathway, mutations in *SMAD4*, *RAF* gene family fusions, or microsatellite instability. Therapeutically targetable mutations are often present. This review summarizes the clinical and pathological features of acinar neoplasms and reviews the current molecular data on these uncommon tumors.

Keywords

acinar cell carcinoma; pancreatoblastoma; pancreatic cancer; pancreatic pathology

Clinical and pathological features

Acinar cell carcinoma is an uncommon pancreatic neoplasm, accounting for <2% of all pancreatic cancers. They are more common in men (male-to-female ratio of 3.6:1) and most

occur in adults with a mean age at diagnosis of 58 years, although a small proportion occurs in children.¹ Patients with acinar cell carcinoma present most frequently with non-specific abdominal symptoms such as pain, vomiting, and weight loss. Jaundice due to biliary obstruction occurs only rarely. Approximately 15% of patients with acinar cell carcinoma present with a unique clinical syndrome of subcutaneous fat necrosis, eosinophilia, and polyarthralgia.¹ This syndrome, which occurs due to secretion of lipase by tumor cells, is more common in patients with metastatic disease. Although acinar cell carcinoma is not firmly associated with any known genetic syndromes, cases have been reported in patients with Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC), as well as in patients with germline *BRCA1* and *BRCA2* mutations.^{2,3} The prognosis of acinar cell carcinoma is poor, with a 5-year survival of only 25%, and stage is the best predictor of outcome.¹ In 1 study, the median survival of patients with localized disease was 57 months, while the median survival of patients with metastatic disease was 19 months.²

Grossly, acinar cell carcinomas most often form solitary, well-demarcated, solid masses (Fig. 1A). The cut surface is often soft and fleshy, but necrosis and even cystic degeneration may be present. They are often large (with an average size of 10 cm) and have a slightly increased prevalence in the head of the pancreas. Predominantly intraductal growth of acinar cell carcinoma is uncommon but has been reported.^{4,5} Microscopically, acinar cell carcinomas are composed of cells with architectural, cytological, and/or immunohistochemical evidence of acinar differentiation. Acinar architecture occurs when pyramidal-shaped cells surround small lumina (Fig. 1B), but acinar cell carcinomas can also have solid or less commonly trabecular growth patterns. Although the masses are grossly well-demarcated, microscopically invasive growth with vascular and/or perineural invasion is common. Cytologically, acinar cell carcinomas typically contain amphophilic or eosinophilic zymogen granules in the cytoplasm, but in some cases, these granules may not be well developed and thus can be difficult to identify on routinely stained sections. The malignant cells have round nuclei with single prominent nucleoli (Fig. 1C). Immunohistochemically, acinar cell carcinomas stain with markers of acinar differentiation—trypsin, chymotrypsin, and BCL10 are the most reliable.⁶

In addition to pure acinar cell carcinomas, mixed neoplasms also occur. If more than 25% of cells in a carcinoma have neuroendocrine differentiation (as demonstrated by morphology and/or immunohistochemistry from chromogranin or synaptophysin), the carcinoma should be classified as a mixed acinar–neuroendocrine carcinoma. Similarly, mixed acinar–ductal carcinomas occur as well, with the ductal component accounting for at least 25% of the malignant cells. Some mixed acinar–ductal carcinomas exhibit intracellular or stromal mucin as evidence of ductal differentiation, whereas others have separate components composed of infiltrating individual glands surrounded by desmoplastic stroma.⁷ Rare cases of mixed acinar–neuroendocrine–ductal carcinoma have also been reported.⁷

Pancreatoblastomas also display acinar differentiation but are unique in several ways. First, although they occur rarely in adults, the majority of pancreatoblastomas occur in children, accounting for 25% of pancreatic neoplasms in the first decade of life.⁸ The majority of pancreatoblastomas occur in children less than 10 years old, with a median age in children of 2.4 years.¹ There is a slight male predominance, with a male-to-female ratio of 1.3–2:1.¹

Several cases of pancreatoblastoma have been reported in patients with Beckwith–Wiedemann syndrome, a disorder associated with imprinting dysregulation on chromosome 11p, leading to overgrowth of various organs and predisposition to embryonal tumors.^{9,10} In addition, pancreatoblastoma has been reported as an extracolonic manifestation of familial adenomatous polyposis (FAP), which is caused by germline mutations in the *APC* gene.^{2,11} In young patients, pancreatoblastoma is often diagnosed due to a palpable abdominal mass. Although vague abdominal symptoms such as pain, vomiting, and weight loss can also occur, jaundice is uncommon. A significant minority of patients with pancreatoblastoma have elevation in serum alpha-fetoprotein due to production by the tumor. Overall survival is only 50%, and like acinar cell carcinoma, stage is the best predictor of outcome.

Grossly, pancreatoblastomas are similar to acinar cell carcinomas—solitary, well-demarcated, solid masses that are usually large, though they are not associated with a specific location in the pancreas (Fig. 2A). However, there are important microscopic differences between pancreatoblastoma and acinar cell carcinoma. The acinar component of pancreatoblastoma is similar to acinar cell carcinoma and is often the predominant component—it consists of cells with architectural and cytological features of acinar differentiation, including granular cytoplasm, prominent nucleoli, and polarization around small lumina (Fig. 2B and C). In contrast to acinar cell carcinomas, pancreatoblastomas have other histological components. Squamoid nests are a characteristic feature and are required to establish the diagnosis. These squamoid nests are composed of whorled groups of plump cells with eosinophilic cytoplasm and clear nuclei and can even display focal keratinization (Fig. 2D). In addition to the acinar component and squamoid nests, some pancreatoblastomas also contain neuroendocrine components (with neuroendocrine cells with finely stippled chromatin scattered as solitary cells or forming solid nests and trabeculae). Ductal components (with columnar cells forming glands and even producing mucin) and/or primitive components (with monotonous small round blue cells) can also occur. A cellular stromal component is also commonly present, especially in pediatric cases, and rarely there may be heterologous bone or cartilage formation. Immunohistochemically, each component labels with markers of its differentiation: the acinar component with trypsin and chymotrypsin, the neuroendocrine component with chromogranin and synaptophysin, and the ductal component with CK7 and CK19. The squamoid nests are negative for most immunohistochemical markers, but the clear nuclei in these nests contain biotin; thus, they may nonspecifically label with a variety of antibodies.

Genetic features

Because acinar cell carcinomas and pancreatoblastomas are rare tumors, until recently only a handful of studies have examined the genetic alterations that underlie these malignancies. In acinar cell carcinomas, molecular alterations in the *APC*- β -catenin pathway occur in approximately 20% of tumors, including inactivating mutations in *APC* and activating mutations in *CTNNB1*.¹² Copy number alterations and promoter hypermethylation of *APC* have also been reported.¹³ Several studies have examined the potential genetic overlap between acinar cell carcinoma and more commonly occurring pancreatic ductal adenocarcinoma. Some studies have reported rare mutations in *KRAS* and *TP53* as well as rare loss of *SMAD4* expression, though several studies have also reported no alterations in

these genes in acinar neoplasms.^{12,14–18} Microsatellite instability has also been reported, although uncommonly, in acinar cell carcinoma, occurring in less than 10% of cases.¹² Large chromosomal gains and losses in acinar cell carcinomas have been reported in several previous studies, including several regions that are altered in multiple tumors; however, the target genes (if any) in most of these alterations remain to be identified.^{12,15,19,20} However, some of these alterations have compelling potential to be drivers, for example, trisomy 3 with gain of *CTNNB1* occurred in 5 of 5 acinar cell carcinomas in a study.²⁰

Pancreatoblastomas share some genetic alterations with acinar cell carcinomas but are in some ways genetically distinct. Loss of chromosome 11p (at the locus affected in Beckwith–Wiedemann syndrome) occurs in more than 80% of pancreatoblastomas—this loss of 11p has also been reported in other embryonal neoplasms (such as hepatoblastoma and Wilms tumor), suggesting the possibility of a common genetic pathway in embryonal tumors.^{11,21–23} Although loss of 11p also occurs in almost 50% of acinar cell carcinomas, it is not clear whether this region is unique among the numerous regions recurrently lost in this tumor type.¹² Pancreatoblastomas also have frequent alterations of the APC- β -catenin pathway; unlike acinar cell carcinomas (which more frequently have inactivating *APC* mutations), pancreatoblastomas more frequently have activating *CTNNB1* mutations, though mutations in both genes have been identified.¹¹ Interestingly, immunohistochemical staining for β -catenin often shows abnormal nuclear labeling restricted to the squamoid nests. Mutations in genes frequently altered in pancreatic ductal adenocarcinoma are uncommon in pancreatoblastoma; in a study, loss of *SMAD4* was infrequent, and no alterations in *KRAS* or *TP53* were identified.¹¹ At least a subset of pancreatoblastomas also contain large chromosomal alterations; there have been several case reports of complex karyotypes with several large regions of loss and gain, and trisomy 8 has been reported. However, these data are difficult to interpret, as no target genes for these large chromosomal alterations have been identified.

Recent whole exome sequencing studies have systematically cataloged the genetic alterations in pancreatic neoplasms with acinar differentiation, including acinar cell carcinoma, pancreatoblastoma, and mixed neoplasms.²⁴ Intriguingly, these studies revealed striking genomic instability on the chromosomal and base pair levels in acinar cell carcinomas. Approximately 10% of the analyzed neoplasms had microsatellite instability, and although one carcinoma had a somatic mutation in *MSH2*, the mechanistic basis for the microsatellite instability in the remaining tumors was unclear, as none of the other tumors with microsatellite instability had methylation of *MLH1* or mutations in other genes in the mismatch repair pathway. In keeping with previous reports, many of the acinar cell carcinomas also showed instability at the chromosomal level, as evidenced by high fractional allelic losses in many tumors. Sites of frequent loss included chromosome 11p, which has been previously reported to be lost in a large proportion of acinar cell carcinomas, as well as tumor suppressor gene loci on chromosomes 17p (*TP53*) and 18q (*SMAD4*).¹²

In the whole exome sequencing analyses, there was a striking diversity in the altered genes. No gene was mutated in >30% of the tumors analyzed.²⁴ Intriguingly, in a small subset of cases, mutations were identified in genes commonly altered in other pancreatic neoplasms, including those frequently altered in ductal adenocarcinoma (*SMAD4* and *TP53*), cystic

neoplasms (*GNAS* and *RNF43*), and neuroendocrine neoplasms (*MEN1*). *SMAD4* was the most frequently altered gene in this series, with mutations in approximately 25% of tumors. In addition, homozygous deletion of *P16/CDKN2A* (which is also common in ductal adenocarcinomas) occurred in a minority of cases. Rare somatic mutations were also identified in genes whose constitutional alterations are associated with familial ductal adenocarcinoma, including *ATM*, *BRCA2*, and *PALB2*, and somatic mutations were identified in genes known to be altered on other extrapancreatic tumor types. These included mutations in *APC* and *CTNNB1*, confirming previously reported findings.¹² Other known driver genes with mutations in acinar neoplasms included *JAK1*, *BRAF*, *RBI*, *PTEN*, *ARID1A*, *MLL3*, and *BAP1*. Although the types of mutations identified (such as oncogenic hotspot mutations in *BRAF* and inactivating mutations in *RBI*) strongly support that these alterations are drivers, each occurred in no more than 20% of tumors. In addition, many other genes had somatic mutations at a frequency of 10–20%. However, mutation data alone cannot determine the role of these genes (if any) in tumorigenesis in the pancreas, and further functional studies will be needed to classify these genes as drivers or passengers. Overall, the mutational data from this whole exome sequencing study highlight the mutational heterogeneity of acinar cell carcinoma. Importantly, almost half of the carcinomas sequenced had somatic mutations that are potentially targetable by existing therapeutics, including mutations in *JAK1*, *BRAF*, and the Fanconi anemia pathway.

Although the recent whole exome sequencing study included only a few pancreatoblastomas and mixed carcinomas, some observations can be made.²⁴ First, the pancreatoblastomas contained fewer somatic mutations than almost all acinar cell carcinomas (17 and 18 somatic mutations per tumor, compared to an average of 131 somatic mutations per tumor for the remaining acinar cell carcinomas). This observation is concordant with the results of other sequencing studies that show decreased somatic mutation frequency in pediatric-type cancers.²⁵ Second, both pancreatoblastomas contained mutations in *CTNNB1*, which agrees with previous studies showing frequent alteration of the APC- β -catenin pathway (and specifically activating *CTNNB1* mutations) in pancreatoblastoma.¹¹ In addition, the mixed acinar–ductal carcinomas were also unique—they contained a higher frequency of *P16/CDKN2A* and oncogenic *BRAF* mutations compared to other acinar cell carcinomas. However, the mixed acinar–ductal carcinomas did not contain more frequent mutations in other genes that are mutated in ductal adenocarcinomas or cystic neoplasms. The single mixed acinar–neuroendocrine carcinoma studied did not contain mutations in genes previously reported to be frequently altered in pancreatic neuroendocrine tumors (such as *MEN1*, *ATRX*, and *DAXX*).

In addition to the recent whole exome sequencing study, a targeted DNA and RNA sequencing study revealed recurrent chromosomal rearrangements in acinar cell carcinomas. In this study of 44 acinar cell carcinomas, *RAF* gene family fusions were identified in 23% (10 of 44 tumors).²⁶ The most common fusion involved the *SND1* and *BRAF* genes on chromosome 7q, occurring in 6 cases. Three additional cases had *BRAF* fusions involving other partners, and one more case had a fusion involving *RAF1*. Functional analyses of the *SND1–BRAF* fusion revealed that it leads to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, which can be reversed, at least *in vitro*, by targeted MEK

inhibitors. This fusion has been previously reported in a gastric cancer cell line with resistance to Met inhibition^{27,28} but has not been previously reported in any primary pancreatic neoplasm. In addition, this study confirmed many of the findings of the previous whole exome sequencing, including infrequent mutations in genes in the APC/ β -catenin pathway (*APC* and *CTNNB1*), genes frequently altered in ductal adenocarcinoma (*SMAD4*, *TP53*, and *CDKN2A*), and driver genes from other tumor types (*BRAF* and *RBI*). Inactivating alteration in DNA repair genes (including *BRCA1*, *ATM*, and *PALB2*) occurred in almost half of the cases in this study. The occurrence of these *BRAF* fusions in addition to oncogenic hotspot point mutations in *BRAF* strongly suggests that *BRAF* and MEK inhibitors are a promising potential therapeutic target in acinar cell carcinomas. In addition, the alterations in DNA repair genes suggest these cancers may be specifically susceptible to specific chemotherapeutic agents, including PARP inhibitors.

Applications in pathology

The results of genetic characterization of acinar cell carcinoma, pancreatoblastoma, and mixed acinar neoplasms complement the data from other whole exome sequencing studies of pancreatic neoplasms to demonstrate that each type of pancreatic neoplasm has its own mutational profile. Acinar cell carcinomas demonstrate striking genomic instability (at both the base pair and chromosomal level); ductal adenocarcinomas have *SMAD4*, *TP53*, *KRAS*, and *P16/CDKN2A* mutations; pancreatic neuroendocrine tumors have *MEN1*, *DAXX*, *ATRX*, and mTOR pathway mutations; solid-pseudopapillary neoplasms have *CTNNB1* mutations; serous cystadenomas have *VHL* mutations; intraductal papillary mucinous neoplasms have *GNAS* and *RNF43* mutations (in addition to mutations in some genes altered in ductal adenocarcinomas); and mucinous cystic neoplasms have *RNF43* mutations (in addition to mutations in some genes altered in ductal adenocarcinomas).^{29–32} This suggests the power of genetic analyses to classify challenging tumors. Although acinar cell carcinomas lack frequent mutations in genes altered in other pancreatic tumor types, the infrequent overlap with mutations in other tumor types must be addressed in any diagnostic algorithms. For example, APC- β -catenin pathway alterations in acinar cell carcinomas and pancreatoblastomas may result in aberrant nuclear accumulation of β -catenin in immunohistochemical assays. This phenotype, which is most commonly seen in solid-pseudopapillary neoplasm, could cause diagnostic confusion if this overlap is not recognized. In addition, loss of *SMAD4* protein expression by immunohistochemistry can be used as evidence for pancreatic ductal adenocarcinoma; *SMAD4* mutations in acinar cell carcinomas occur less frequently than in ductal adenocarcinoma but should still be considered when interpreting results of *SMAD4* immunohistochemical staining in a pancreatic tumor.

The identification of targetable genetic alterations in a significant proportion of acinar cell carcinomas points to another potential clinical use for genetic data. As the list of targetable genetic alterations continues to expand, genetic characterization of clinical samples to identify such alterations will become more routine. Current data supports further exploration of JAK inhibitors, *BRAF* inhibitors, MEK inhibitors, and PARP inhibitors (which are particularly effective in tumors with mutations in the Fanconi anemia pathway) in acinar neoplasms. However, considering the large number of alterations in each acinar cell

carcinoma and the overlap between acinar cell carcinomas and other tumor types, these tumors may be amenable to additional therapies as they are developed.

The systematic characterization of cancer genomes has revolutionized the practice of oncology. This characterization of pancreatic neoplasms has demonstrated a unique mutational profile in each tumor type—genetics mirroring morphology. In acinar neoplasms, whole exome sequencing has revealed striking genetic instability, mutational heterogeneity, significant overlap in mutated genes with pancreatic and extrapancreatic neoplasms, and targetable alterations in over half of the cases. These studies pave the way for refined diagnostic and therapeutic algorithms taking advantage of genetic insights.

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Fig. 1. Pathologic features of acinar cell carcinoma: (A) acinar cell carcinoma (gross photograph) and (B) acinar cell carcinoma ($\times 20$). Note the acinar architecture. (C) Acinar cell carcinoma ($\times 40$). Note the cytoplasmic granules and single prominent nucleoli.

Fig. 2. Pathologic features of pancreatoblastoma: (A) pancreatoblastoma (gross photograph), (B) pancreatoblastoma ($\times 10$), (C) Pancreatoblastoma, acinar component ($\times 40$), and (D) pancreatoblastoma, squamoid nest ($\times 40$).