Adenocarcinoma of the pancreas

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Ralph H. Hruban, MD, David S. Klimstra, MD

Paola Parente
Anatomia Patologica Casa Sollievo della Sofferenza
San Giovanni Rotondo (FG)
Introduction

“In this review, we do not throw out the clinically tested and well-established standard gross, microscopic and immuno-labeling approaches to diagnosing ductal adenocarcinoma, instead we look for ward to an integration of genetics as a fourth arm in our diagnostic tool box.”
Gross features

The gross and microscopic changes of chronic pancreatitis are commonly associated with ductal adenocarcinomas, and sometimes the fibrosis of pancreatitis can mimic the sclerotic appearance of the carcinoma, obscuring the gross distinction between regions of carcinoma and pancreatitis. Some localized forms of pancreatitis also can simulate a carcinoma due to the appearance of a fibrotic mass involving only a portion of the organ.
Light microscopy

Two features stand out about this cancer type. **First**, ductal adenocarcinomas elicit an intense desmoplastic reaction. **Second**, despite the highly lethal nature of this cancer, the neoplastic glands are often extremely well-differentiated. In fact, at the light microscopic level, *it can be very difficult to distinguish between the neoplastic glands of infiltrating carcinoma and the reactive glands of chronic pancreatitis*. Because of this, **well-defined histologic criteria need to be carefully and systematically applied when interpreting biopsies and evaluating resections.**
<table>
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<th><strong>Ductal adenocarcinoma</strong></th>
<th><strong>Reactive glands</strong></th>
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<tr>
<td>Haphazard arrangement of the glands</td>
<td>Lobular arrangement of glands</td>
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<tr>
<td>Perineural invasion</td>
<td>Neuroendocrine cells can abut nerves</td>
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<tr>
<td>Vascular invasion</td>
<td>Not seen</td>
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<td>Gland immediately adjacent to a muscular artery</td>
<td>Glands separated from muscular vessels by acinar cells or by orderly rounded connective tissue</td>
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<td>Luminal necrosis</td>
<td>Can have PMN leukocytes, but not epithelial necrosis</td>
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<td>Incomplete lumina</td>
<td>Epithelial cells form a complete ring around lumina</td>
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<td>Four-to-one rule</td>
<td>Nuclei in a single gland vary by less than four to one</td>
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<td>“Naked” glands in fat</td>
<td>Glands in fat have associated connective tissue</td>
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</table>
Eight features supportive of the diagnosis of ductal adenocarcinoma

(A) Glands arranged haphazardly, (B) perineural invasion, (C) venous invasion, (D) a gland immediately adjacent to a muscular artery

(A) Luminal necrosis and incomplete lumina, (B) nuclear variation in a single gland of greater than four to one
Most ductal adenocarcinomas have abnormal nuclear labeling with antibodies to TP53, and 55% show a loss of Smad4 (*PDC4*) expression.

Loss of expression of Smad4 (A) and over-expression of tp53 (B) by immunolabeling can be used as surrogate markers for genetic alterations in these genes.
Genetic sequencing

The exomes (all known coding genes) of all of the major tumor types of the pancreas have been sequenced and tumors of the pancreas are among the best characterized neoplasms at the genetic level.

There are four genetic “mountains” in ductal adenocarcinomas (genes that are targeted in >50% of the cancers). These include an oncogene, KRAS, and three tumor-suppressor genes, TP53, p16/CDKN2A, and SMAD4 (PDC4).

There are a number of “hills” genes that are targeted in a minority of pancreatic cancers. These include ARID1A, ATM, AKT2, MAP2K4, MLL3, TGFβR2, and FBXW7.
SMAD4 is genetically inactivated in 55% of invasive ductal adenocarcinomas, and SMAD4 is only rarely targeted in other tumor types. Immunolabeling for Smad4 (PDC4), the protein product of the SMAD4 gene, accurately reflects gene status. Therefore loss of Smad4 immunoexpression by cells in the pancreas would support a diagnosis of carcinoma rather than reactive atypia.

Smad4 loss can also point to a pancreatic primary in a metastasis of unknown origin, although adenocarcinomas of other organs can also exhibit Smad4 loss less commonly.

In addition, SMAD4 gene status has prognostic significance, with loss of Smad4 being associated with a worse prognosis and more widespread metastases in patients with ductal adenocarcinomas.
Genetics can also be used to define subtypes of ductal adenocarcinoma. **Undifferentiated “medullary” carcinomas are often microsatellite unstable** and microsatellite unstable medullary carcinomas carry a better prognosis than do classic ductal adenocarcinomas (but medullary carcinomas may not respond well to 5-flourouracil-based chemotherapeutic regimens). Patients with a medullary carcinoma are more likely to have a positive family history of cancer than are patients with a standard ductal adenocarcinoma of the pancreas. This latter observation may be explained by the increased risk of pancreatic cancer observed in individuals with hereditary non-polyposis colorectal cancer syndrome.
1. Applying advances to tumor treatment

**SPARC** (secreted protein acidic and rich in cysteine), also known as osteonectin, is overexpressed in desmoplastic stroma of pancreatic cancer, and it has been suggested that the albuminized form of taxol, called **nab-paclitaxel**, preferentially binds to SPARC. This suggests a **mechanism to selectively deliver a chemotherapeutic agent to the tumor**.

Gene expression by the neoplastic cells themselves can also guide therapy. The expression of the human equilibrative nucleoside transporter (**hENT1**) is a predictive marker for **gemcitabine sensitivity**.
2. Applying advances to tumor treatment

Has been suggested that invasive ductal adenocarcinoma with inactivating mutations in RNF43 may be selectively sensitive to agents that block the β-catenin pathway.

A number of inherited (germline) genetic alterations are also potentially therapeutically targetable and provide a unique opportunity for personalized medicine

(mutations in one of the Fanconi anemia pathway genes, including BRCA1, BRCA2, and PALB2, germline mutations in the ATM)
Take home messages

“...soon pathologists will be asked not only about cancer morphology, but also about the genetic background in which the cancer has arisen. As William Osler said, “the good physician treats the disease; the great physician treats the patient who has the disease”.”