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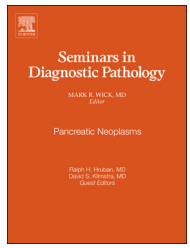

Adenocarcinoma of the pancreas

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ABSTRACT

Infiltrating ductal adenocarcinoma of the pancreas is a real enigma. On one hand, it is one of the most deadly of all of the solid malignancies. On the other hand, the neoplastic glands can be remarkably well-differentiated, and it can be difficult to distinguish between a reactive non-neoplastic gland and a gland of invasive adenocarcinoma. In this review, we will present diagnostic criteria that one can "hang your hat on" when establishing the diagnosis of infiltrating ductal adenocarcinoma of the pancreas. We will also review clinically important features of the disease, and, with the impending incorporation of molecular genetics into everyday practice, we will emphasize clinical applications of cancer genetics.

Introduction

Pancreatic cancer was described in the 1760s by Giovanni Battista Morgagni in his classic book *De Sedibus et Causis Morborum per Anatomen Indigatis*.[1] Pathologists greatly refined our understanding of the gross and microscopic features of this disease in the ensuing 200 years, and gross and microscopic examination has remained the mainstay of diagnosis for centuries. The introduction of immunohistochemical labeling in clinical practice in the late 1970s and early 1980s fundamentally changed our approach to diagnoses. Soon an integration of gross and microscopic findings and immunolabeling characteristics was the norm in diagnosis. This status quo is about to be disrupted by the revolution in genetic sequencing.[2–5]

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

Gross features

Ductal adenocarcinomas are usually not subtle lesions grossly. They tend to be large (the mean size of surgically resected adenocarcinomas is 3 cm), firm, white infiltrative masses (Fig. 1).[6] The margins of the tumor are usually ill defined, and projections of tumor can be seen extending well beyond the main mass. Larger neoplasms can have central necrosis and secondary cystic change. These cancers typically invade and obstruct associated duct systems. As a result, cancers in the head of the gland often narrow both the pancreatic duct and the distal common bile duct, producing upstream dilatation of both ducts, a finding referred to

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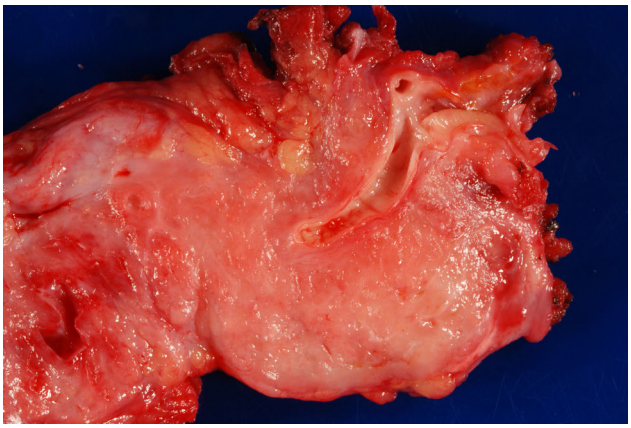

Fig. 1 – Gross feature of a fibrotic pancreatic cancer. The carcinoma surrounds a large artery.

radiographically as the "double duct sign." Cancers in the tail of the pancreas are far from the bile duct and will only obstruct the pancreatic duct. As expected, cancers in the tail of the gland are therefore often associated with a normal caliber bile duct and upstream dilatation of the pancreatic duct (Fig. 2). When these obstructive changes in the pancreatic duct system are significant, they can mimic an associated cystic or intraductal neoplasm.

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

Infiltrating ductal adenocarcinomas are defined, as the name suggests, by the presence of invasive neoplastic glands. Two features stand out about this cancer type at the light microscopic level. First, ductal adenocarcinomas elicit an intense desmoplastic reaction, especially within the pancreas itself (desmoplasia may be less pronounced or absent in metastatic foci). This desmoplastic response can outstrip the neoplastic glands such that neoplastic cells are actually outnumbered by non-neoplastic cells in many of these tumors. The desmoplastic reaction is composed of a mixture of dense collagen, fibroblasts, delicate vessels, and inflammatory cells. The second feature that stands out about infiltrating ductal adenocarcinomas of the pancreas is that, 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.

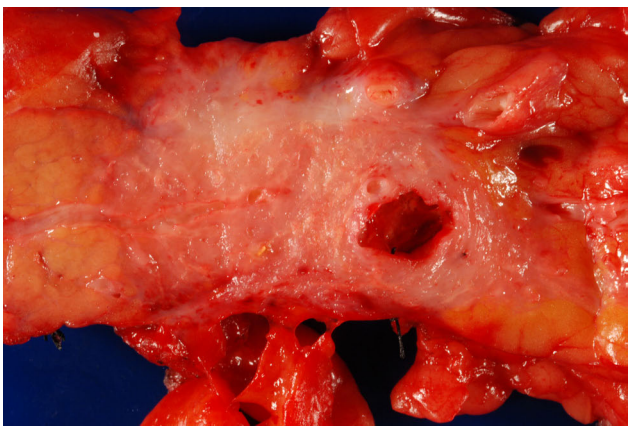

Fig. 2 – Gross feature with upstream ductal dilatation. The normal duct is seen on the left, the tumor is present in the center, and a dilated duct upstream from the cancer is on the right.

As listed in Table 1, eight histologic features are particularly useful in the differential diagnosis of infiltrating ductal adenocarcinoma and reactive glands: (1) haphazard arrangement of the glands, (2) perineural invasion, (3) vascular invasion, (4) a gland immediately adjacent to a muscular artery, (5) luminal necrosis, (6) incomplete lumina, (7) variation in the size of nuclei in a gland by more than four to one, and (8) "naked" glands in fat.[6] Let us go over each of these in greater detail, since they are so very important.

The normal pancreas is composed of orderly back-to-back lobules. Small ducts are normally present at the center of these lobules and the lobules themselves are composed predominantly of acinar cells. This structure is analogous to grapes (the lobules of acinar cells) on a vine (the duct system). Chronic pancreatitis is associated with fibrosis and acinar drop-out. Even though there is loss of acinar tissue in chronic pancreatitis, the orderly rounded architecture is maintained. Extending the analogy, chronic pancreatitis can be thought of as dried grapes on a vine or, in its extreme form, a vine stripped of grapes. By contrast, infiltrating

Table 1 – Eight features supportive of the diagnosis of ductal adenocarcinoma.[6]

Ductal adenocarcinoma	Reactive glands
Haphazard arrangement of the glands	Lobular arrangement of glands
Perineural invasion	Neuroendocrine cells can abut nerves
Vascular invasion	Not seen
Gland immediately adjacent to a muscular artery	Glands separated from muscular vessels by acinar cells or by orderly rounded connective tissue
Luminal necrosis	Can have polymorphonuclear leukocytes, but not epithelial necrosis
Incomplete lumina	Epithelial cells form a complete ring around lumina
Four-to-one rule	Nuclei in a single gland vary by less than four to one
"Naked" glands in fat	Glands in fat have associated connective tissue