Pathology of incipient pancreatic cancer

R. H. Hruban, R.E. Wilentz, M. Goggins, G.J.A. Offerhaus, C.J. Yeo, & S.E. Kern

Departments of Pathology, Oncology, and Surgery, The Johns Hopkins Medical Institutions, Baltimore, MD, USA; and the Department of Pathology, the Academic Medical Center, Amsterdam, The Netherlands.

Summary

Background: An understanding of incipient pancreatic neoplasia is an essential foundation for the future development of effective screening tests for pancreatic cancer. Only when we understand early pancreatic neoplasms will we be able to detect tumors that are curable with surgical resection.

Method: Two approaches have helped define incipient pancreatic neoplasia. First, the histologic examination of pancreata has helped identify the most common histologic lesions in pancreatic tissues adjacent to infiltrating carcinomas. The assumption is that some of these lesions represent the precursors to the infiltrating cancers. Second, advances in molecular genetics now make it possible to define the genetic alterations present in small lesions. The demonstration that a suspected precursor lesion and an infiltrating pancreatic carcinoma share the same genetic alterations would help establish that the lesion is indeed a precursor to infiltrating pancreatic carcinoma.

Introduction

By the time most patients with pancreatic cancer develop symptoms, they already have advanced stage disease and are no longer candidates for surgery (1). These patients have a >95% 3-year mortality rate (2). By contrast, patients with small lymph-node negative pancreatic carcinomas have 5-year survival rates approaching 40% following surgical resection of their neoplasms (3). Clearly, we need to improve our understanding of early pancreatic neoplasms, so that new techniques can be developed to detect these neoplasms early while they are still surgically treatable.

Morphologic studies

The histologic examination of pancreatic parenchyma adjacent to infiltrating pancreatic carcinomas was the first step in the identification of the precursors to infiltrating carcinomas of the pancreas. In 1976, Cubilla and Fitzgerald published a landmark paper in which they reported that papillary epithelial proliferations in pancreatic ducts are more common in pancreata with infiltrating carcinoma than they are in pancreata without cancer (4). Furthermore, papillary duct lesions with atypia were seen only in pancreata with infiltrating carcinomas (4). In 1979, Kozuka et al extended these observations by Fitzgerald and Cubilla and reported that, like infiltrating adenocarcinoma of the pancreas, pancreatic duct lesions are extremely rare in children, increase with advancing age, and are more common in the head of the pancreas than they are in the body or tail of the gland (5). These similarities in anatomic distribution and age of onset suggest a relationship between pancreatic duct lesions and invasive carcinomas; however, they do not establish a precursor role for duct lesions (6). In order to demonstrate that duct lesions are the precursors to infiltrating carcinoma, one needs to examine serial samples taken over time. This has recently been accomplished by Brat et al (7). Brat et al reported 3 patients from Johns Hopkins who had a portion of their pancreas resected. Histologic examination of the resected portion of the pancreas from these patients revealed duct lesions and these 3 patients were remarkable because they later developed an infiltrating adenocarcinoma of the pancreas (7). Therefore, not only is there an anatomic association between pancreatic duct lesions and infiltrating cancers, but duct lesions have also been documented in pancreata which later developed an infiltrating carcinoma. These observations strongly support a precursor role for duct lesions in the development of infiltrating adenocarcinoma of the pancreas.

Histologic classification of duct lesions

The next step in the evaluation of duct lesions is to define the molecular genetic alterations present in these lesions. Before this can be accomplished, however, we need a standard terminology and uniform classification scheme for...
these duct lesions. We have therefore suggested the
classification scheme illustrated in Figure 1. "Flat duct
lesions" are epithelial proliferation composed of a single
layer of columnar cells without significant nuclear atypia
(Figure 1A). "Papillary duct lesions without atypia" are
papillary proliferations in which the epithelial cells lack
significant cytologic and architectural atypia (Figure 1B).
"Atypical papillary duct lesions" are characterized by a
papillary architecture and epithelial cells with nuclear atypia,
including prominent nucleoli and occasional mitoses (Figure
1C). "Carcinoma in situ" are markedly atypical papillary
proliferations which lack fibrovascular stalks and which
contain significant nuclear and cytologic atypia, including
epithelial bridge formation, multiple nucleoli, and atypical
mitoses (Figure 1D). While it is recognized that duct lesions
in fact form a continuum, this classification scheme does
provide a set of standards which can be referred to when
defining the molecular alterations present in a given lesion.

Genetic changes in early pancreatic neoplasia

Duct lesions have been shown to harbor a number of genetic
changes, and many of these genetic changes are similar to
those seen in infiltrating adenocarcinomas of the pancreas.
These include activation of K-ras and inactivation of the
p16, p53, and BRCA2 tumor-suppressor genes.

K-ras

Activating point mutations in codon 12 in the K-ras
oncogene are one of the most common genetic alterations in
infiltrating adenocarcinomas of the pancreas (8-14). It is
therefore not surprising that K-ras mutations were among
one of the first genetic alterations identified in early duct
lesions in the pancreas (15-23). In general, histologically
normal ductal epithelial cells lack K-ras mutations, and the
prevalence of these mutations increases as one moves from
flat duct lesions, to papillary duct lesions without atypia, to
papillary duct lesions with atypia, to carcinoma in situ (21).

p16

The p16 tumor-suppressor gene is inactivated in >95% of
infiltrating adenocarcinomas of the pancreas (24-31), and
Moskaluk et al have recently demonstrated that p16 is also
inactivated in some duct lesions (21). Moskaluk et al
analyzed duct lesions adjacent to four infiltrating
adenocarcinomas which harbored p16 mutations. They
found that 3 of the 9 duct lesions adjacent to these
carcinomas harbored p16 alterations (21). In two patients the
p16 mutations identified in the infiltrating carcinoma and in
the duct lesions were the same, but in one patient two
separate duct lesions were identified, each of which harbored
a different p16 mutation (21). These findings suggest a field
effect in which multiple duct lesions develop in the pancreas.
Some progress to infiltrating carcinomas while others do not
(32).

p53

The p53 tumor-suppressor gene is inactivated in 50-70% of
infiltrating adenocarcinomas of the pancreas (33-40).
Although an imperfect surrogate for sequencing,
immunohistochemical staining for the p53 gene product has
been used to analyze duct lesions for p53 alterations (34,41).
The expression of the p53 gene product to
immunohistochemically detectable levels suggest a p53
mutation, while failure of a cell to label with antibodies to
p53 suggests wild-type p53. This is because mutated p53 is
more stable than its wild-type counterpart. DiGiuseppe et al
labeled a large series of pancreatic carcinomas using anti-
p53 antibodies and demonstrated immunohistochemically
detectable levels of p53 in in situ carcinomas (34). These
observations, and similar ones made by Hameed et al,
suggests that p53 is inactivated in duct lesions with
significant cytological and architectural atypia (34,41).

BRCA2

Although BRCA2 is only rarely inactivated in infiltrating
adenocarcinoma of the pancreas, approximately 7% of
patients with pancreatic carcinomas harbor germline BRCA2
mutations (42,43). These patients provide a unique
opportunity to study duct lesions for inactivation of BRCA2.
Goggins et al microdissected pancreata resected from 3
patients with germline BRCA2 mutations (44). The second
allele of BRCA2 was intact in all 12 papillary duct lesions
without atypia and in the two flat duct lesions examined,
while the single papillary duct lesion with atypia included in
the series demonstrated loss of the wild-type BRCA2 allele
(44). BRCA2 function would therefore have been lost in this
atypical papillary duct lesion. These findings suggest that
inactivation of BRCA2 is a rare and relatively late event in
the development of pancreatic neoplasia.

Figure 1. Illustration of the spectrum of duct lesions. (A) Flat duct lesion;
(B) Papillary duct lesion without atypia; (C) Papillary duct lesion with
atypia; and (D) Carcinoma in situ. Artwork by Bob Morreale.
Discussion

Morphologic and molecular analyses have demonstrated that duct lesions are the precursors to infiltrating carcinoma of the pancreas. We believe that there is a progression from normal duct epithelium, to flat duct lesions, to papillary duct lesions without atypia, to papillary duct lesions with atypia, to carcinoma in situ, to infiltrating carcinoma. This progression is associated with the accumulation of mutations in a variety of cancer-causing genes, including K-ras, p53, p16, and BRCA2. Duct lesions are therefore best considered true neoplasms and not reactive processes. Furthermore, because these genetic alterations occur while the neoplasm is still in situ, before it has spread beyond the pancreas, genetic alterations may form the foundation for new screening tests to detect early pancreatic neoplasms.

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References


Correspondence to:
Ralph H. Hruban, M.D.
Department of Pathology
The Johns Hopkins Hospital
600 N. Wolfe St.
Baltimore, MD 21287 USA