Laboratory Aids in the Diagnosis of Tumors of the Pancreas

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ABSTRACT

Newer laboratory aids complement evaluation of a patient with suspect pancreatic tumor, pancreatic adenocarcinoma, pseudocyst of the pancreas and islet cell adenoma. Hypertonic duodenography, arteriographic study of the celiac trunk and superior mesenteric tree when combined may yield invaluable diagnostic information in patients with ampullary carcinoma. The new techniques of transduodenal visualization of pancreatic ducts have allowed dye injection and cytologic brushings, techniques which further the diagnostic armamentarium in these patients. Pancreatic isotopic scanning, although still in its developmental phase, holds enormous diagnostic promise. Cytologic examination of secretin-stimulated duodenal drainage and direct biopsy of tumor mass at laparotomy offer further diagnostic and operative disposition. The advent of the remarkably sensitive immunoassay for gastrin, insulin, glucagon and secretin has introduced new diagnostic certainties for patients with functioning islet cell carcinoma not heretofore possible. The application of these combined techniques may yield the opportunity to detect and to treat pancreatic neoplasms earlier and more effectively and, thereby, reduce the morbidity and mortality.

Introduction

The development of laboratory aids for the diagnosis of pancreatic tumors has sought to determine type, site and extent of involvement and, ideally, to detect early, asymptomatic and premetastatic disease. Various refinements on radiologic approaches have accomplished significant improvement in delineating both the origin and extent of tumors within the pancreas. The symptomatic presentation of pancreatic cancer bodes such poor prognosis that exact and non-invasive maneuvers which can accurately diagnose the early case are still sought. Functioning endocrine tumors, benign or malignant, may so disturb the metabolic milieu that earlier diagnosis and effective management can be anticipated. The radioimmunoassay of peptide hormones in this group of patients has helped
immeasurably in the diagnostically elusive case.

**Tumor Types: Clinical Aspects**

The types of pancreatic tumors most commonly encountered during laparotomy are pancreatic adenocarcinoma, pseudocyst of the pancreas and islet cell adenomas.

Pancreatic carcinoma accounts for less than 10 percent of malignancies in patients autopsied. Most patients are in their 60's; the disease is twice as common in men as in women. Although alcoholism, bile toxins, pancreatitis, ductal strictures and diabetes mellitus have been causally implicated, supporting evidence is wanting. About 70 percent of pancreatic adenocarcinomas involve the head of the pancreas, about 5 percent are diffusely within the entire organ and 20 percent or so arise within the body and tail. More than 90 percent arise from ductular systems, the remaining from acinar groupings.

Weight loss, depression and pain are the most conspicuous clinical symptoms. Pain, although traditionally described as epigastric with radiation through to the back, can be of almost any type. Exacerbation during sleep is common, however, perhaps because of stretching of the solar plexus over the tumor mass. Cancer involving the ampullary region or head of the pancreas will eventually cause jaundice, often painless at the outset, whereas patients with disease confined to the body and tail may succumb without ever developing biliary obstruction. With bile duct obstruction, enlargement of the gall bladder and liver will occur. Ascites and constipation are more frequent symptomatic manifestations in patients with cancer within the body and tail. Although thrombophlebitis is an often quoted companion to other clinical signs and symptoms in patients with pancreatic cancer, several reported series have failed to bear out the general suspicion that this condition is unusually common in patients with pancreatic cancer.

Pancreatic pseudocysts may present clinically with many of the features of pancreatic malignancy, but striking weight loss is unusual. The development of these lesions may be related to post-inflammatory phenomenon arising from pancreatitis, frequently alcoholic, from trauma, from neoplastic necrosis or even from parasitic involvement. Congenital cysts are seen rarely. Epigastric pain with radiation through to the back, postprandial nausea and a palpable mass are frequently present. Jaundice is very occasionally seen if bile duct compression results and leftsided hydrothorax is rarely present.

Non-functioning pancreatic neoplasms of endocrine or islet of Langerhans origin may be relatively non-aggressive tumors with symptoms and signs originating after massive hepatic or pulmonary metastases. By contrast, functioning beta cell tumors, benign or malignant, frequently present because of fasting hypoglycemia and less commonly because of postprandial hypoglycemia. Gastrin secreting islet cell neoplasms may be associated with intractable peptic ulcer disease or appear causally related to intractable diarrhea, so-called pancreatic cholera. The few reported cases of glucagon secreting islet cell tumors have presented a variegated clinical picture with signs and symptoms related more to metastatic involvement of the liver. Mild diabetes mellitus and a peculiar bullous phemphigoid dermopathy have been noted in several (table I).

Islet cell tumors are somewhat more common in the tail of the pancreas (32 percent) and 15 cases of ectopic islet cell tumors have been reported with the most frequent sites for this phenomenon being in or near the duodenum. Multiple islet tumors are present in about 4 percent of cases and approximately 13 percent of islet cell tu-
TABLE I
CLINICAL FEATURES OF FUNCTIONING ISLET CELL TUMORS

<table>
<thead>
<tr>
<th>Type</th>
<th>Syndrome</th>
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<tr>
<td>Insulinoma</td>
<td>Fasting and/or postprandial hypoglycemia</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Diabetes, rash, disordered bowel motility</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Intractable ulcer disease</td>
</tr>
<tr>
<td>Other (?secretin)</td>
<td>Watery diarrhea and hypokalemia</td>
</tr>
<tr>
<td>Other (ectopic</td>
<td>Signs of excess ACTH, parathyroid hormone, Serotonin or other</td>
</tr>
<tr>
<td>peptide secretion)</td>
<td></td>
</tr>
</tbody>
</table>

Tumors are malignant with metastases spread at the time of operation.

Laboratory Aids: Radiographic Techniques
Radiographic techniques are shown in table II.

ROUTINE CONTRAST X-RAYS
A large mass in the head of the pancreas or neoplasm originating from the ampullary area with spread into the head may widen and distort the second and third portion of the duodenal sweep Routine contrast x-rays of the stomach and duodenum may demonstrate a tell-tale reverse three sign in some cases. Clear-cut instances of this sign in a patient with jaundice are almost inevitably associated with advanced disease, but these radiographic signs may be seen with benign disease as well. Nevertheless, pyloric or duodenal obstruction, pressure indentation of greater curvature of the stomach (figure 1), shortening and rigidity of mucosal folds and the presence of a duodenal diverticulum strongly suggest neoplasm, particularly when accompanied by other suspicious signs and history.

HYPOTONIC DUODENOGRAPHY
The adaptation of hypotonic duodenography (figure 2) in evaluation of suspect cancer of the pancreas has added a useful dimension to routine radiographic study of this region and is a more sensitive technique for detecting earlier disease involving the duodenum. This is reflected in subtle alteration of the duodenal mucosa and in appearance of the ampulla of Vater. The successful application of this technique depends upon pharmacologic aids, anticholinergics and local anesthetic agents, which reduced tonus and peristalsis and cause more complete evacuation of the stomach.

ARTERIOGRAPHIC STUDIES
Arteriographic studies of the celiac trunk and superior mesenteric tree, while of im-

![Figure 1. Marked indentation of the greater curvature of the stomach caused by the presence of a pancreatic pseudocyst. (Reproduced, with permission, from *Surgical Diseases of the Pancreas.*)](image-url)
COMBINED SELECTIVE ARTERIOGRAPHY AND HYPOTONIC DUODENOGRAPHY

The combination of selective arteriography and hypotonic duodenography has recently been advocated. Advocates of this diagnostic approach have emphasized the fallacy of trying to superimpose separate studies because of the wide variability in the anatomic relationship of the duodenal sweep and the arterial tree supplying the pancreatic head. Furthermore, this procedure has the potential added advantage of preoperative assessment of the extent of involvement and can provide the surgeon with information on anatomic variations and carcinomatous involvement within the celiac trunk and superior mesenteric tree. Thus, there is potential in this combined procedure for preoperative planning of the kind and extent of resection and for predicting the clinical course in a given patient.

TRANS DUODENAL VISUALIZATION OF PANCREATIC DUCTS

The availability of the flexible fiberoptic, side viewing duodenoscope has yielded an

![Figure 2. Imprint of tumorous involvement of second and third portions of duodenal mucosa brought out by hypotonic duodenography. (Reproduced, with permission, from The Early Radiological Diagnosis of Diseases of the Pancreas and Ampulla of Vater.)](image)

mense use in demonstrating the extent of large tumors of the body and tail, frequently fail to reveal lesions involving the duodenum or ampullary area. Furthermore, attempts to interpret accurately abnormalities of the fine vessel plexus serving this area have led to a fairly high incidence of false-positive interpretations.

![Figure 3. X-ray of normal pancreatic duct obtained by transduodenal injection of contrast medium. (Reproduced, with permission, from Hospital Practice, June, 1973.)](image)
additional dimension to radiographic studies of this region. Recently, using this endoscopic tool it has been possible to visualize directly the ampulla of Vater, to cannulate the ductal orifice and to inject contrast medium.\textsuperscript{3,12} Thus, transduodenal visualization of the biliary and pancreatic ducts can be accomplished (figure 3). In patients with pancreatic carcinoma, this procedure may demonstrate stricture and ductal obstruction, occasionally with dye entering the necrotic or cystic center of the neoplasm. Stricture of the pancreatic duct and rapid dye filling of the cavity is also seen in patients with pseudocyst of the pancreas so that added diagnostic measures may be needed to differentiate the lesion. In patients with pancreatitis, experience has indicated ductal changes characterized by tortuous dilatation of the main duct and blunted, shortened secondary branches. Experience continues to accumulate with this relatively new procedure. Complications have included instances of pain, febrile reactions, hyperamylasuria and unequivocal acute pancreatitis. A case of fatal necrotizing pancreatitis was reported in the early days of this application.

Isotopic Pancreatic Scanning

Isotopic pancreatic scanning is also being developed in hopes of obtaining a sensitive, selective and non-invasive technique for detecting pancreatic neoplasms with greater certainty and earlier. \textsuperscript{75} Se-Selenomethionine is adequately absorbed by pancreatic parenchyma. Because of simultaneous hepatic uptake, sufficient definition and differentiation of the pancreatic bed was not possible with usual single channel display. Using a dual-channel scanning method with \textsuperscript{198} gold in order to color differentiate or to subtract the liver image, Kaplan and associates have produced remarkable scans of both normal and diseased pancreas.\textsuperscript{9} The hope is, as these scanning techniques improve and experience is gained, that small lesions of the pancreas can be discovered and treated earlier.

Cytologic Examinations

Two approaches for obtaining samples to look for exfoliated neoplastic cells are in use; one obtains pancreatic secretions by duodenal drainage and the other by direct biopsy or aspiration of the tumor mass. Duodenal drainage is performed by the method described by Raskin.\textsuperscript{9} In this technique, a double lumen catheter is passed in such a way that gastric secretions are suctioned away to prevent contamination of duodenal juices. Control samples are obtained and again obtained after the intravenous injection of secretin in a dose of \textsuperscript{1} unit per kg. The aspirates are centrifuged for 10 minutes at 5,000 rpm, the supernatant decanted and the sediment smeared on slides and fixed in 95 percent ethyl alcohol and stained by the Papaniocalou method (figures 4 and 5).

Based upon the extensive experience from the University of Chicago, this procedure is accurate about 60 percent of the time.\textsuperscript{8} There is the expectation that by direct cannulation of the pancreatic ducts, utilizing the Japanese fiberoptic duodenoscope, this yield may improve as experience accumulates.

Although direct biopsy of the pancreatic mass at laparotomy may allow differentiation of a benign from a malignant process, arguments against such an approach have pointed to the high risk of bleeding, pancreatic fistula formation or pancreatitis resulting from such a procedure. Concern has also been voiced that malignant cells would be spread by this approach. Recently, however, aspiration of the tumor mass has been advocated\textsuperscript{4} by use of the Franzén one-hand-grip syringe, mounted with a \textsuperscript{26} guage needle. This procedure has been successfully applied to breast and thyroid cancer without evidence that it adds to the threat of metastatic spread. Forsgren and Orell
have successfully applied this technique to 40 patients with pancreatic lesions. The aspirations were performed, in most, at the time of laparotomy, but percutaneous aspiration was accomplished in three patients without mishap.

**Chemical Laboratory Aids in Diagnosis of Pancreatic Tumors**

Occult blood in the stool, abnormalities of glucose tolerance, elevated serum and urinary amylase and lipase and disorders of hepatic function are variably encountered and, although far from diagnostic, can be used to support a suspicion firm enough to advise laparotomy. When jaundice is present because of pancreatic neoplasms, laboratory features of obstruction to bile flow are present with an elevated bilirubin and high alkaline phosphatase. Elevated serum hepatic enzyme levels are not seen unless obstruction to bile flow is sufficiently severe and prolonged as to cause secondary hepatic damage.

The diagnosis of functioning islet cell tumors may be furthered by the finding of inappropriately raised levels of insulin, glucagon, secretin or gastrin by radioimmunoassay of serum as shown in table III.

The presence of hypoglycemia and an insulin level of greater than 20 μU per ml, a rise to more than 100 μU during the first 10 minutes after intravenous administration of one gram of Tolbutamide, or the presence of large amounts of proinsulin supports the diagnosis of insulinoma. These patients frequently display a diabetic glu-
cose tolerance test, often with marked reactive hypoglycemia. Urinary insulin determinations have been resorted to in an occasional insulin treated diabetic since the presence of antibodies to commercial insulin prevents the successful radioimmunoassay of serum levels. This problem is encountered because insulin producing islet cell adenomas are somewhat more frequent in patients with diabetes mellitus.

Gastrin producing tumors frequently cause the patient to come to operation for surgical management of intractable ulcer disease at which time a search for an islet cell tumor in the pancreatic bed or in recognized ectopic sites can be carried out. Patients without peptic ulcer disease, but suffering from the watery diarrhea syndrome, occasionally seen in such patients, are more challenging diagnostically. Preoperatively, it may be possible to demonstrate excessive gastric volume and acid production. However, both basal secretion in excess of 10 mEq of HCl per hour or a lower than normal ratio of basal to histamine-stimulated acid secretion (presumably representing maximum secretion in the basal state) may fall into the range noted for normal subjects. Experience with the application of the immunoassay for gastrin to preoperative diagnosis of gastrin producing tumors is meager, but McGuigan and associates have reported that serum gastrin levels in four patients with Zollinger-Elli-
son’s syndrome exceeded normal levels by more than ten-fold. Further, Vance and associates have noted elevated radioassayed gastrin levels in the kindred of patients with polyadenomatosis, including Zollinger-Ellison-like picture, in some. The opportunity to screen such a population may ultimately serve as a basis for more extensive work-up and earlier diagnosis and treatment if the kind of experience with medullary carcinoma of the thyroid and raised calcitonin measurements can be developed.

Glucagonomas and glucagon producing islet cell carcinomas have been described in recent years. Mild diabetes mellitus and extraordinarily high levels of circulating immunoreactive glucagon have been present.

References


