Current Practice

Cancer of the Pancreas

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Brit. med. J., 1968, 3, 169-171

The prevalence of pancreatic cancer is difficult to determine because of the considerable problems in making a clinical diagnosis and the frequency with which it is confused with cancer of the common bile duct. Cancer of the pancreas accounts for about 0.5% of all hospital admissions and between 1% and 2% of malignant tumours found at necropsy. The disease is twice as common in males, and the incidence reaches its maximum in patients over the age of 60 years. The cause of pancreatic cancer is unknown.

Pathology

The malignant growth may originate either in the duct cells or acini of the gland, or in the islets of Langerhans. Cancer of the islet cells is uncommon and is discussed in a later section. About 80% of tumours are adenocarcinomas which arise from ductular epithelium. The neoplasm is hard and scirrhous and the cells are columnar or cuboidal with clear-cut cellular outlines. Cancers arising from the acini account for 13% of growths. These tumours are softer and more bulky. The cells are polygonal or round with indistinct outlines and hyperchromatic nuclei. The site of origin is indeterminate in the remaining growths.

It is customary to distinguish between cancers arising from the head, the body, and the tail of the gland. Between 50% and 70% of cancers arise in the head. It is probable that the frequency of cancer in different anatomical subdivisions of the organ is proportional to the amount of tissue in the various parts. The growth may have a multicentric origin. Since the pancreas has no limiting capsule and has a rich venous and lymphatic drainage extrapancreatic extension of the growth is frequently early and widespread. Cancers of the head show early involvement of the bile duct, duodenum, and regional lymphatics. More distal metastases are less common and are usually seen in the liver. Extrapancreatic spread is more striking in cancer of the body and tail, possibly because the diagnosis is usually made at a later stage.

Clinical Features

Cancer of the pancreas is one of the most difficult diagnoses to establish with certainty. "No other malignancy offers a greater variety of non-specific symptoms or signs of more protean nature." The duration of symptoms prior to admission to hospital averages six to seven months. The central triad of complaints is loss of weight, pain, and jaundice. Loss of weight is one of the most characteristic symptoms, occurring in almost all patients.¹ The patient may lose 20 kg. in a few months, and there are few diseases in which weight-loss is as rapid.

Pain occurs in 60% of patients with cancer of the head and in more than 80% with tumours of the body and tail of the pancreas. The nature of the pain depends upon the site and extent of the tumour. Most characteristic is upper abdominal pain, which is felt continually and which radiates "through the

abdomen" directly to the lower thoracic and upper lumbar region. Typically the pain may be relieved by the patient leaning forward. This type of pain is more frequently found with cancers in the body and tail than in tumours of the head. The pain may be much more vague or it may resemble peptic ulcer disease closely by being periodic, related to meals, and relieved by food and antacid therapy.

Jaundice occurs in 85% of cancers of the head and in 20% to 40% of cancers in the body and tail of the pancreas. In the former group the jaundice is the result of partial or complete obstruction of the common bile duct, whereas in the latter the jaundice results from hepatic metastases. Pruritus accompanies the jaundice in 50% of the cases and precedes it in 4%. Painless jaundice, at one time regarded as the most characteristic symptom of pancreatic cancer, is uncommon and occurs in less than a third of the patients. However, the onset of jaundice brings the patient to surgery at an earlier stage, and most patients who are operable have had obstructive jaundice. Other symptoms include fatigue, anorexia, nausea, and vomiting. Almost 50% of patients experience a change in their bowel habits, constipation being more frequent than diarrhoea. Frank steatorrhoea may be present.

There are frequently no abnormal physical signs. The patient may adopt the characteristic posture of leaning forward to flex the spine, which affords some relief from the backache. Hepatomegaly develops in half of the patients and in more than three-quarters of those who become icteric. The enlarged liver is the consequence of either biliary stasis or hepatic metastases. The gall bladder is palpated in about half of the patients who are icteric and in rather more patients with cancer of the head of the pancreas. In 1890 Courvoisier described the association of thin-walled dilated gall bladders with cancers obstructing the biliary tree, as well as a high incidence of small shrunken gall bladders in the presence of gallstones. This information subsequently became known as "Courvoisier's Law." A palpable gall bladder in the presence of painless jaundice is found in 10% to 30% of patients. However, the gall bladder is frequently found to be enlarged at laparotomy when it was previously not detected clinically. A pancreatic tumour may be felt in some patients. Ascites sometimes occurs and may be the result of peritoneal seeding or splenic and portal vein thrombosis. Occasionally the supraclavicular nodes are palpable. Splenomegaly is rare.

Unusual Clinical Manifestations

Cancers of the pancreas have a variety of presentations which can be clinically misleading.

Acute Pancreatitis.—The growth may present with the acute onset of abdominal pain, nausea, vomiting, and fever. Occasionally the patient will become jaundiced. A clinical diagnosis of acute pancreatitis or cholangitis is often made, and indeed there is frequently acute inflammation of the pancreatic tissue superimposed upon an occult cancer.

Neuropsychiatric Syndrome.—Occasionally patients show emotional and personality changes, which accompany or even precede the somatic symptoms. The main features are anxiety and agitated depression.

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Thromboembolic Phenomena.—The cancer may manifest with thrombosis in peripheral veins, particularly the femoral and iliac. This is neither a characteristic of pancreatic cancers nor is it as frequent as was believed at one time, occurring in 10% to 20% of patients. Thromboembolic phenomena are a late indication of cancer and are found more frequently with growths of the body and tail. The nature of the coagulation defect has not been clearly defined.

Acute Gastrointestinal Haemorrhage.—Occasionally the first indication of a tumour is a massive gastrointestinal bleed. This may follow malignant erosion of the stomach or duodenum, but rarely it is from bleeding oesophageal varices which have resulted from splenic or portal vein obstruction.

Subcutaneous Fat Necrosis.—This is a rare presentation of an acinar cell cancer and has been reported exclusively in males above 50 years of age. Moderately tender nodules of fat necrosis first appear in the lower limbs and later become generalized. There is arthralgia and mild eosinophilia.

Cancer of the Pancreas in Childhood.—This is an uncommon tumour in children. The clinical features are similar to those in adults, the main differences being the equal sex distribution and the more frequent occurrence of gastrointestinal bleeding.

Investigations

The haemoglobin is normal in most of the patients and a leucocytosis is recorded in 25%. Glucose metabolism is abnormal in 20 to 30% and the patient may have frank diabetes mellitus.

Liver Function Tests.—The routine tests of liver function may show evidence of extrahepatic cholestasis: bilirubinuria, elevation of the serum conjugated bilirubin level, which may be as high as 20 mg./100 ml., and elevation of the serum alkaline phosphatase concentration, which is frequently greater than 35 King-Armstrong units/100 ml. The rise in serum alkaline phosphatase may be the only biochemical abnormality. The serum 5'-nucleotidase will also be increased if the serum alkaline phosphatase rise is the result of biliary obstruction. The serum transaminase levels are usually normal, but slight elevation of aspartate transaminase (less than 100 i.u./l.) is to be expected in prolonged extrahepatic biliary obstruction. The serum proteins show an increase in the α_2 and β globulins, and there may be an increase in the serum cholesterol values. Vitamin-K absorption will be reduced when there is steatorrhoea. There will be a raised prothrombin time. All these tests suggest the presence of extrahepatic biliary obstruction without indicating the pathogenesis of the block.

Pancreatic Enzyme Tests.—The serum concentrations of amylase, trypsin, and lipase are usually normal or only slightly elevated, depending on whether there is associated inflammation. A persistent and marked increase in serum amylase concentrations in the presence of a pancreatic mass is more suggestive of a pseudopancratic cyst than a cancer. Leucine aminopeptidase is a widely distributed enzyme, and serum concentrations may be elevated in biliary obstruction from any cause. This enzyme is of no help in the diagnosis of pancreatic tumours.

Stool Examination.—The stool colour may be normal or pale. Stool occult blood tests are usually negative, becoming positive when a cancer of the head involves the duodenal or gastric mucosa. Steatorrhoea occurs in less than a fifth of patients and is usually associated with cancers in the head of the pancreas.

Tests of Pancreatic Exocrine Functions.—There is a variety of function tests which use secretin, pancreozymin, or both. The gland is stimulated to produce fluid, bicarbonate, and enzymes, and these are collected by duodenal aspiration. The most widely used test is the secretin test. The results differ from one laboratory to another depending on the dose of the

stimulus given, the duration of collection, and the method of expressing the results. In cancers of the head and body of the gland there is a reduction in the volume of pancreatic secretion with normal bicarbonate and enzyme output. When there is diffuse malignant infiltration of the gland the enzyme and bicarbonate output are also reduced. Exocrine function is usually normal in cancer of the tail. Hartley *et al.*² have described an augmented secretin test in which 2 mg. secretin/kg. body weight is infused intravenously. The authors claim that the test not only is reliable in distinguishing normal from abnormal but also in the differentiation of chronic pancreatitis from cancer.

The secretion of pancreatic enzymes in response to various test meals can be measured and duodenal tryptic activity is usually estimated. Reduced tryptic activity is found in pancreatic cancer, but the results are frequently within the range for patients with chronic inflammatory pancreatic insufficiency.

Cytology.—Duodenal samples obtained during the secretin test may be examined for malignant cells. Positive results have been recorded in 86% of proved cancers in both the head and body and tail of the gland.

Radiology.—Plain roentgenography of the abdomen has little to offer in the diagnosis of pancreatic cancer. Cancer of the pancreas has been reported in 25% of patients with calcific pancreatitis. Rarely calcification may occur in a primary pancreatic tumour.

The barium examination of the stomach and duodenum can be helpful. It is essential to carefully screen the retrogastric space, the posterior wall and antrum of the stomach, and the duodenum. The retrogastric space may be enlarged and the stomach displaced anteriorly. There may be rigidity and irregularity of the posterior stomach wall or the antrum.

Cancer of the head of the pancreas can alter the medial aspect of the duodenum: there is displacement and alteration of mucosal relief and pressure defects may be observed. The inverted 3 sign of Frostberg may be present, but this is an indication of a pancreatic mass and not necessarily a cancer. Extension of the growth around the duodenum causes compression and rigidity of the lateral aspect of the descending duodenum. Hypotonic duodenography will detect many of these features at an early stage. There may be disturbed peristalsis and some degree of duodenal obstruction. Abnormal features are found in most barium examinations of patients with cancer of the pancreas, but skilful interpretation is necessary to detect the presence of pancreatic disease and to decide upon its aetiology.

Cholecystography and cholangiography are seldom of value and become unnecessary in the presence of jaundice. A pneumoperitoneum may provide information about the size of the pancreas. Splenic venography has been used to diagnose tumours of the pancreas. The lateral portion of the splenic vein may be displaced by a growth in the body and tail of the pancreas, whereas a tumour in the head usually affects the portal vein and the medial segment of the splenic vein. Selective arteriography of the coeliac and superior mesenteric arteries has provided useful information. Abnormal features may include invasion of vessels, which is the most helpful sign, the presence of tumour vessels—which is seen in only a few cases because the malignant pancreatic tumours are relatively avascular—and vascular displacement, which is non-specific and indicates only that there is pancreatic enlargement. Arteriography is also of help in determining whether a tumour is operable. However, Nebesar and Pollard³ caution against over-optimism for the accuracy of arteriography, and find that 10% of patients without cancer of the pancreas will show false positive arteriographic changes. Percutaneous transhepatic cholangiography is of value, since the technique differentiates the various causes of extrahepatic obstruction with a high degree of accuracy. In cancer of the head there is usually marked extra- and intrahepatic duct and gall-bladder dilatation. The

site of obstruction is seen as a convex filling defect, and the duct may be completely obstructed.

⁷⁶Se-selenomethionine has been introduced as an agent for scanning the pancreas, and experience is accumulating with this technique. The investigation is relatively simple for the patient, but careful attention to the scanning technique is required and the interpretation of the scans is not without difficulty. Tumours of the pancreas show either as a single filling defect or as a diffuse failure of uptake by the pancreas, which is indistinguishable from the changes associated with chronic pancreatitis. False negative results occur in 4 to 8% and false positive in 15 to 34% of patients.

The diagnosis of pancreatic cancer can also present difficulties at laparotomy. It is sometimes impossible to tell visually or by palpation whether chronic inflammation or cancer is present, and the two conditions may coexist. Operative pancreatic biopsy remains a controversial procedure, and many surgeons hold strongly that it is unsafe. On the other hand, some authorities believe that a wedge biopsy is mandatory prior to radical resection. Complications of the biopsy include fistula, haemorrhage, and wound-seeding, and the morbidity is not reduced by using a Vim-Silverman needle. The biopsy is also claimed to be inadequate because of the high rate of false-negative and a significant number of false-positive findings. A variety of techniques have been described in an attempt to reduce the hazards of the biopsy. It has been suggested that the removal of a lymph node from the root of the small intestinal mesentery is a safe method of obtaining a tissue diagnosis. Material aspirated from the pancreatic duct has been examined for malignant cells by conventional cytological methods, but again this procedure is associated with a high percentage of false negative results.

Differential Diagnosis

Because of the insidious onset and varied presentation of cancer of the pancreas the differential diagnosis includes a great number of diseases. The essential steps in making a diagnosis are: (1) to consider pancreatic disease as the cause for the patient's symptoms; (2) to demonstrate that there is pancreatic dysfunction; and (3) to prove that there is malignant disease. The distinction between cancer of the head of the pancreas and periampullary cancer must be stressed, because the latter cancers have a five-year survival of 30% to 50% in contrast to the dismal prognosis for pancreatic cancers. Periampullary cancers present at an early stage with jaundice, they are frequently associated with occult gastrointestinal bleeding, and they have often not metastasized when they are seen. Hypotonic duodenography may be used to differentiate between these two cancers.

Treatment

Occasionally cancers in the tail of the pancreas are resectable, but published studies have been concerned mainly with the surgery of cancer in the head of the gland. The results are disappointing. The majority of patients have metastases at the time of operation, and in fewer than 10% can an attempt be made to remove the growth. The standard procedure is a "Whipple operation" in which the head and part of the body of the pancreas are removed together with the duodenum. This operation does not remove all the primary tumour in a significant number of patients, and the five-year survival rate is 5%. Total pancreatectomy has been suggested as an alternative form of radical surgery, but at present there is insufficient experience with this form of surgery for cancer of the head. Pancreaticoduodenal resection is not customarily undertaken as a palliative procedure, and for this a choledochojejunostomy or a cholecystjejunostomy with an enteroanastomosis is performed. Some authors advise gastroenterostomy in addition

so as to avoid the difficulties which arise from duodenal obstruction. The survival after palliative operations is about six months.

Therapy with the fluorinated pyrimidines such as 5-fluorouracil (5-FU) has been used in inoperable growths, but there is no evidence that the survival is prolonged. Radiation therapy is equally unrewarding, although it is occasionally of value in the management of severe back pain. Supportive measures include the relief of pain and the alleviation of pruritus. Diabetes mellitus is seldom a problem and usually can be managed by oral hypoglycaemic agents. Occasionally steatorrhoea is sufficiently troublesome to require a low-fat diet and large doses of pancreatic supplements. The average duration of survival in patients who are not operated on is six months.

Cancer of the Islets of Langerhans

Cancer of the islets of Langerhans are rare but are of clinical interest because of the hormones which they secrete.

Cancers of the β Cells.—Only 10% of functioning β cell tumours are malignant. They are distributed equally throughout the gland. The clinical features are the consequence of insulin hypersecretion, and include the symptoms and signs of hypoglycaemia. "Whipple's triad" (spontaneous hypoglycaemia, repeated blood sugar levels below 50 mg./100 ml., and relief of symptoms by glucose) is not specific for patients with insulin-secreting tumours of the pancreas. Diagnostic procedures include prolonged fasting, the intravenous tolbutamide test, the glucagon test, assays of blood insulin, and, in adults, sensitivity to leucine. The tumour should be removed surgically whenever possible. About 20% of tumours diagnosed histologically as cancer have not shown evidence of recurrence over a number of years. In inoperable patients frequent intravenous glucose administration is necessary. Glucocorticoids and benzothiazide compounds have been used in an attempt to raise the blood sugar.

Zollinger-Ellison Syndrome.—In this syndrome non- β cell tumours are associated with gastric hypersecretion and multiple recurrent peptic ulcers. There may be steatorrhoea. The tumours arise either in the δ or α cells of the islets of Langerhans and 60% are malignant. Some 3% of patients with the Zollinger-Ellison syndrome have multiple endocrine adenomas. At the time the diagnosis is made two-thirds of patients will have metastases in the liver or regional lymph nodes. The tumours have been shown to secrete gastrin. Radiological features include gastric rugal hypertrophy, duodenal dilatation, and multiple atypically located ulcers. The diagnosis is suggested by tests of gastric acid secretion and in particular by a greatly increased basal acid output.

The surgical management of patients with the Zollinger-Ellison syndrome is controversial. Total or subtotal pancreatectomy and/or total or subtotal gastrectomy and vagotomy have been recommended. Total gastrectomy is regarded as the treatment of choice by many authors because of the difficulty in removing the primary tumour and the frequency of metastases.

A clinical entity which must be separated from the Zollinger-Ellison syndrome is the syndrome of severe diarrhoea and hypocalcaemia in the absence of gastric hypersecretion. This is associated with islet cell tumours which are histologically indistinguishable from those causing gastric hypersecretion. Other hormone-secreting islet cell tumours which have been recorded include an α cell cancer which secreted glucagon and another tumour which secreted substances resembling gastrin, A.C.T.H., and melanophore-stimulating hormone (M.S.H.).

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