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CIRCULATING PANCREATIC POLYPEPTIDE IN PATIENTS WITH ADENOCARCINOMA OF THE BILE DUCT

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Using radioimmunoassay methods, the blood of patients with pancreatic tumors was screened for circulating polypeptide hormones. This screening discovered pancreatic polypeptide in abnormally high concentration in the serum of six of seven patients with adenocarcinomas of the bile duct. The assay appears to be very sensitive finding excessive residual pancreatic polypeptide production after palliative resections. Serum pancreatic polypeptide assays warrant evaluation as an aid in the diagnosis and management of patients with bile duct tumors.

Endocrine screening was added to a pancreatic cancer treatment program due to the success of new treatments (1–3). The patients' unexpectedly good survival created a need to provide supplementary proof that patients did not have endocrine tumors.

A patient was referred with a diagnosis of pancreatic cancer. Blood work and radiological re-evaluation was done as part of the entry evaluation. The patient was found to have a distal bile duct tumor associated with a very high level of circulating pancreatic polypeptide. This led to assays of serum pancreatic polypeptide in other patients with proven bile duct cancers.

Material and Methods

Venous blood was collected in EDTA tubes. The patients were in a rested 4-h fasting state. They were physiologically intact following either surgical bypass or percutaneous stenting in order to relieve their bile duct obstruction. None had abnormal liver function or poor general nutrition. Initially, none were undergoing treatment with either chemotherapy or radiotherapy. Pancreatic polypeptide was measured by the Ohio State Laboratory (4). Concurrent radioimmunoassays measured carcinoembryonic antigen (CEA), CA 125, and CA 19-9 in the serum of these patients.

Results

Six of seven patients with bile duct tumors were found to have abnormally high concentrations of pancreatic polypeptide (1 200–11 000 pg/ml (Table)) in their peripheral blood. These values are greater than two standard deviations above the upper limit for the age groups (465 pg/ml is the upper limit of the 95th percentile and 160 pg/ml is the standard deviation). The concentration of pancreatic polypeptide was markedly increased in the serum of patients with asymptomatic, even the one patient with a localized surgically staged and resected, bile duct tumor (Table). Serum assays for CEA, CA 125, and CA 19-9 found these concentrations to be within the normal range in all 6 of these patients with abnormally high pancreatic polypeptide concentrations in the blood.

Discussion

Elevated pancreatic polypeptide values are generally viewed as being associated with endocrine tumors (4–7).

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Table

Location–Bile duct		Age	Sex	Surgery	Residual volume and stage	Highest assay pancreatic polypeptide pg/ml
Patient	Proximal vs. Distal					
FA	Proximal	76	F	B	Large, M + Peritoneum	1 325
FB	Distal	82	F	S	Thin 5 cm segment M0	11 000
LG	Proximal	72	M	B	Large, M + Liver	1 200
JR	Proximal[a]	72	M	R	Small N + M0	1 210
MS	Proximal	68	F	B	Large, M + Liver	2 400
NS	Proximal	63	M	S	Large, M + Liver	4 240
AT	Proximal	52	M	B	Large, M + Liver	64

[a] no recognized residual disease.
R = Resection; B = Bypass; S = Stent

This clinical program has now found greater than normal amounts of circulating pancreatic polypeptide in association with both pancreatic and bile duct tumors. These tumors have no easily recognizable pathologic resemblance to endocrine tumors (8). Several lines of evidence indicating a common origin of pancreatic and endocrine tumors were recently reviewed (9, 10). There are now several findings of endocrine features in gastrointestinal tumors which do not have the light microscopic morphology of endocrine tumors (9, 10).

The findings provide support for prospective studies, in particular a search for other endocrine features which can be exploited for therapy, such as somatostatin receptors. In addition, one can test both chemotherapy and biologics which are useful against endocrine tumors against pancreatic polypeptide producing tumors.

Serial assays, now being collected, will test the utility of pancreatic polypeptide as a sensitive measure of both occult residual disease and the success or failure of treatments. Initial assays support such testing. The assay also warrants testing as an aid to differential diagnosis, for example where there are difficulties differentiating between sclerosing cholangitis and a low-grade bile duct cancer.

These results are preliminary. Other types of carcinomas may warrant similar evaluation. Also patients with bile duct tumors may warrant a wider search for other possible types of associated polypeptide production.

One could postulate a possible nonspecific disturbance of pancreatic polypeptide secretions, but most of these patients were in exceptionally good condition. They were clinically free of pancreatitis and both the distal bile and pancreatic ducts were either patent or successfully bypassed. None of the surgery involved the distal bile duct or pancreas. Biliary obstruction is not recognized to produce this frequency or degree of rise in circulating polypeptides.

The primary tumors have not yet been assayed for pancreatic polypeptide. Of interest, in preliminary attempt here, some immunohistochemical reagents 'found' pancreatic polypeptides in breast cancer tissues which had been intended to serve as control tissues in order to set up an assay. It is unknown if this is a reagent artifact, but the reagent was not the one used for the serum assays reported herein.

A general hyperplasia of cells producing polypeptides, or resetting of physiologic reaction thresholds due to earlier perturbation of the enterohepatic circulation cannot be ruled out as an alternative explanation for the reported findings. Pancreatic and other tumors can be associated with hyperplasia of endocrine cells, but this only infrequently involves cells which produce pancreatic polypeptides (10). The mechanism of hyperplasia and its applicability to the bile duct tumors, if any, remains unknown (10).

The conventional microscopic appearance of the bile duct tumors in this series provided no indication of an endocrine origin. The current findings support further investigation for a possible common origin of both proximal bile duct tumors arising at the bifurcation and some 'ductal' pancreatic tumors and endocrine tumors.

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