The role of heme in hemolysis-induced acute pancreatitis.


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The aim of this study was to reveal the mechanism of hemolysis-induced acute pancreatitis and to evaluate the role of heme and heme oxygenase activity in inducing pancreatic inflammation in an experimental hemolysis model. Hemolytic anemia was induced in rats by intraperitoneal injection of 60 mg/kg acetylphenylhydrazine (APH). To evaluate the toxic effect of free heme after hemolysis, heme oxygenase inhibitor (HOI) was used to inhibit the enzyme which decreases the free heme concentration after hemolysis. One hundred and fifty rats were divided into two treatment and three control groups. Rats in the hemolysis group were given APH intraperitoneally. Rats in the HOI+hemolysis group were given Cr(III)mesoporphyrin IX chloride as HOI and then APH intraperitoneally. Serum amylase and lipase levels as well as pancreatic tissue cytokine content were determined and histological examination performed. Results: No hemolysis or pancreatitis was seen in the control groups. Massive hemolysis was seen in 22 of the 30 rats of the hemolysis group and 20 of the 30 rats of the HOI+hemolysis group. The total pancreatitis rates were 60% and 76.6% in the hemolysis and HOI+hemolysis groups, respectively (P<0.05). Pancreatic cytokine levels were significantly higher in the HOI+hemolysis and hemolysis groups than in all control groups. The highest ICAM-1 and MCP-1 levels were in the HOI+hemolysis group. Histological signs of acute pancreatitis were also more severe in this group. Conclusions: Acute massive hemolysis can induce acute pancreatitis. Excess of free vascular heme seems to be an inducer of inflammation by modulating ICAM-1 and MCP-1.

Scintigraphic evaluation of acute pancreatitis patients with 99mTc-HMPAO-labelled leukocytes.

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The authors aimed to demonstrate the localization of leukocytes in the pancreas during acute pancreatitis and to evaluate the potential use of Tc-HMPAO-labelled leukocytes in the diagnostic assessment of patients with acute pancreatitis. The study was performed with 20 patients (11 females, nine males; ranging in age from 26 to 86 years, mean 55 years). Labelled leukocyte scintigraphy using planar imaging was performed on all patients, seven of whom were also examined by single photon emission computed tomography (SPECT). According to Ranson criteria, 10 patients had mild pancreatitis (group A), six had severe pancreatitis (group B) and four had necrotic pancreatitis (group C). Twelve patients had biliary pancreatitis and the other eight patients had no obvious cause. All patients of group C, four of group B, two of group A had a positive leukocyte scan. The positive leukocyte scintigraphy value for the detection of a lethal course of acute pancreatitis was 100%; of a severe course, 66.7%; and of a mild course, 20%. These findings are statistically significant (P=0.005 in chi-
squared test result). The results of leukocyte scintigraphy compared with those of CT were also statistically significant (P=0.001 in chi-squared test). All the patients diagnosed with pancreatic necrosis by CT had a positive leukocyte scan, but only three of 13 patients without pancreatic necrosis that could be detected by computed tomography had a positive leukocyte scan. There was a significant correlation between the severity of the disease and leukocyte infiltration. Considering these results, the authors believe that leukocyte infiltration in acute pancreatitis can be demonstrated rapidly and accurately and by noninvasive Tc-HMPAO labelled leukocyte scintigraphy.


**UGT1A7 polymorphisms in chronic pancreatitis: an example of genotyping pitfalls.**


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UDP-glucuronosyltransferases (UGT) catalyze the glucuronidation of various compounds and thus inactivate toxic substrates. Genetic variations reducing the activity of UGT1A7 have been associated with various gastrointestinal cancers. Most recently, the UGT1A7*3 allele has been reported as a significant risk factor for pancreatic disorders, but the authors could not confirm these data. This study focused on the possible causes for the noted discrepancy. UGT1A7 genotypes were assessed in 37 samples, which were previously analyzed for UGT1A7 polymorphisms by others. The authors determined genotypes by melting curve analysis and by DNA sequencing. Additionally, the authors produced UGT1A7*1 and *3 constructs with or without a mutation at position -57 of UGT1A7 and analyzed various combinations of these constructs. In 14/37 samples UGT1A7 genotyping results differed. The discrepancy could be explained by polymerase chain reaction bias owing to an unbalanced allelic amplification which was caused by a -57T>G variant located within the sequence of the chosen primer template in previous studies. These findings indicate that most of the previously reported genetic associations between UGT1A7 and gastrointestinal cancers are based on primer-dependent genotyping errors.


**Clinical and morphological features of duodenal cystic dystrophy in heterotopic pancreas.**


Cystic dystrophy in heterotopic pancreas (CDHP) is an uncommon complication of pancreatic heterotopia, only described in surgical series, whose natural history is not known. The aim of this study was to determine clinical and morphological features of CDHP in a medical-surgical series of patients and to ascertain the relationship of CDHP with chronic pancreatitis (CP) in the pancreas proper. All patients who had duodenal CDHP diagnosed radiologically both with CT scan and endoscopic ultrasonography between 1995 and 2004 were included. The diagnosis was confirmed by surgical specimens when available. One hundred five patients were included (91% men, 86% chronic alcoholic) with a median follow-up of 15 months. The median age at first symptoms was 46 years. CDHP was associated with CP in the pancreas proper in 71% of patients. Presenting symptoms were pancreatic pain (91%), severe weight loss...
(73%), acute pancreatitis (45%), vomiting (30%), steatorrhea (23%), diabetes mellitus (20%), jaundice (13%), and upper gastrointestinal hemorrhage (5%). Cysts were multiple in 75% (median 3). The median diameter of the largest cyst was 10 mm. Endoscopy was normal in 36% of patients and showed duodenal stenosis in 52% (complete 6%, incomplete 46%). Surgical treatment was necessary in only 27% of patients (Whipple procedure 16%). CDHP may arise in patients with or without CP and with or without chronic alcoholism. Symptoms may be severe but warrant surgery in less than one-third of patients.


Outcomes after clearance of pancreatic stones with or without pancreatic stenting.


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Extracorporeal shockwave lithotripsy (ESWL) and endoscopic lithotripsy are useful for the fragmentation and extraction of pancreatic stones. However, pancreatic stones often recur, for which an adequate strategy is needed. Treatment for stricture of the main pancreatic duct (MPD) with a pancreatic stent after clearance of pancreatic stones may reduce the recurrence of pancreatic symptoms and stones. Forty patients with chronic pancreatitis with MPD stones were treated with ESWL in combination with endoscopic stone extraction. After clearance of the stones, a pancreatic stent was inserted when a stricture of MPD was observed on pancreateography. The stent was exchanged every 3 months and removed after a total of 1 year. The authors examined episodes of recurrent pain and pancreatitis in patients with and without stenting, as well as the MPD diameter, during follow-up. MPD stricture was seen in 27 patients, and a stent was successfully inserted in 24 of them. Pancreatic symptoms recurred in five patients (21%) in the stenting group and in three patients (23%) in the control group during a mean follow-up period of 1.5 and 1.2 years, respectively. The diameter of the MPD, before, just after, and 1 year after treatment, was 7.6, 5.4, and 5.8 mm, respectively. It was significantly decreased after 1 year of follow-up, as well as just after stent removal, compared with before treatment (P<0.05). Additional stenting for MPD after extraction of pancreatic stones may reduce the risk of recurrence of pancreatic symptoms.


Evaluation of pancreatic endocrine and exocrine function in patients with autoimmune pancreatitis.


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Up to now, the characteristics of pancreatic endocrine and exocrine functions in autoimmune pancreatitis (AIP) are still unclear. The aim of this study is to evaluate pancreatic functions in AIP compared with those of chronic pancreatitis (CP). Twelve patients with AIP and 25 patients with CP were examined for exocrine and endocrine pancreas. Exocrine function was evaluated by a secretin test. Concerning endocrine function, insulin secretion (C-peptide response) was examined with the glucagon tolerance test and glucagon secretion was examined with the arginine tolerance test. Pathological examination of pancreatic tissues was done on the operative specimens of AIP and CP that could not be clinically excluded from pancreatic cancer. For the secretin test, 8.3% of patients with AIP showed 1-factor abnormality, which was a reduction in volume, and 41.7% showed 2-factor
abnormalities, which were a reduction in volume and amylase output. On the other hand, 44.0% of patients with CP showed only 1-factor abnormality, which was the reduction in the maximum bicarbonate concentration. Autoimmune pancreatitis accompanied with diabetes mellitus showed a reduction both in DeltaC-peptide response (beta-cell response) and Deltaglucagon (alpha-cell response). Histologically, AIP showed lymphoplasmatic cells infiltration surrounding the pancreatic ducts, but basement membranes were intact. Moreover, basement membranes of the duct were injured in CP. Furthermore, islet cells in AIP were revealed as almost intact even though they were surrounded by fibrosis. These findings indicate that exocrine dysfunction with AIP is different from CP because AIP induces stenosis of the pancreatic ducts, but ductal cells that possess the function of bicarbonate secretion are intact, and that endocrine dysfunction with AIP was secondary pancreatic diabetes.


Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis.


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For patients with chronic pancreatitis and a dilated pancreatic duct, ductal decompression is recommended. The authors conducted a randomized trial to compare endoscopic and surgical drainage of the pancreatic duct. All symptomatic patients with chronic pancreatitis and a distal obstruction of the pancreatic duct but without an inflammatory mass were eligible for the study. The patients were randomly assigned to undergo endoscopic transampullary drainage of the pancreatic duct or operative pancreaticojejunostomy. The primary end point was the average Izbicki pain score during 2 years of follow-up. The secondary end points were pain relief at the end of follow-up, physical and mental health, morbidity, mortality, length of hospital stay, number of procedures undergone, and changes in pancreatic function. Thirty-nine patients underwent randomization: 19 to endoscopic treatment (16 of whom underwent lithotripsy) and 20 to operative pancreaticojejunostomy. During the 24 months of follow-up, patients who underwent surgery, as compared with those who were treated endoscopically, had lower Izbicki pain scores (25 vs. 51, P<0.001) and better physical health summary scores on the Medical Outcomes Study 36-Item Short-Form General Health Survey questionnaire (P=0.003). At the end of follow-up, complete or partial pain relief was achieved in 32% of patients assigned to endoscopic drainage as compared with 75% of patients assigned to surgical drainage (P=0.007). Rates of complications, length of hospital stay, and changes in pancreatic function were similar in the two treatment groups, but patients receiving endoscopic treatment required more procedures than did patients in the surgery group (a median of eight vs. three, P<0.001). Surgical drainage of the pancreatic duct was more effective than endoscopic treatment in patients with obstruction of the pancreatic duct due to chronic pancreatitis.


Tumor-suppressor function of SPARC-like protein 1/Hevin in pancreatic cancer.


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SPARC-like protein 1 (SPARCL1), a member of the SPARC family, is downregulated in various tumors. In the present study, the
expression and localization of SPARCL1 were analyzed in a wide range of nontumorous and neoplastic pancreatic tissues by quantitative reverse transcription-polymerase chain reaction, laser capture microdissection, microarray analysis, and immunohistochemistry. For functional analysis, proliferation and invasion assays were used in cultured pancreatic cancer cells. Pancreatic ductal adenocarcinoma (PDAC) and other pancreatic neoplasms exhibited increased SPARCL1 mRNA levels compared to those of the normal pancreas. SPARCL1 mRNA levels were low to absent in microdissected and cultured pancreatic cancer cells, and promoter demethylation increased SPARCL1 levels only slightly in three of eight cell lines. SPARCL1 was observed in small capillaries in areas of inflammation/tumor growth and in some islet cells. In PDAC, 15.4% of vessels were SPARCL1-positive. In contrast, the percentage of SPARCL1-positive vessels was higher in chronic pancreatitis and benign and borderline pancreatic tumors. Recombinant SPARCL1 inhibited pancreatic cancer cell invasion and exerted moderate growth-inhibitory effects. In conclusion, SPARCL1 expression in pancreatic tissues is highly correlated with level of vascularity. Its anti-invasive effects and reduced expression in metastasis indicate tumor-suppressor function.

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An aggressive surgical approach is warranted in the management of cystic pancreatic neoplasms.

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Cystic pancreatic neoplasms encompass a range of benign to malignant disease. Recommendations for surgical management vary. Records of patients with cystic pancreatic neoplasms from January 1996 through December 2005 were retrospectively reviewed. Sixty resections were performed for 16 serous cystic neoplasms, 7 mucinous cystic neoplasms (MCNs), and 37 intraductal papillary mucinous neoplasms (IPMNs). Twenty-five percent (15/60) of neoplasms contained invasive cancer. Patients with MCN or IPMN invasive neoplasms experienced significantly diminished overall 5-year survival compared to patients with IPMN carcinoma in situ neoplasms and to patients with MCN or IPMN adenoma/borderline neoplasms (22% vs. 73% vs. 94%, P=0.004). Given the poor long-term survival of patients with cystic pancreatic neoplasms containing invasive cancer and the current difficulty to preoperatively distinguish among the various types of lesions in a reliable manner, these data support an aggressive surgical approach to the management of cystic pancreatic neoplasms.