Pitt Digest

Summer 2006

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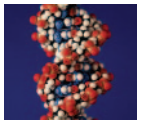

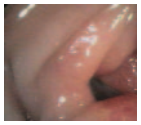

Centers of Excellence:

- Pancreas & Biliary Diseases
- Inflammatory Bowel Disease
- Liver Diseases
- Neurogastroenterology and Motility Diseases
- Intestinal Health & Nutrition Support
- Gastrointestinal Cancer Prevention & Treatment
- Women's Digestive Health

Pitt Digest
is a publication of the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition

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Early Detection of Colorectal Cancer: New Developments

by Robert E. Schoen, MD, MPH

The University of Pittsburgh's Division of Gastroenterology, Hepatology, and Nutrition is at the vanguard of new approaches to early colorectal cancer detection. The Division is pursuing research on the putative precursors of adenomatous polyps, known as aberrant crypt foci, or ACFs (*Figure 1*).

ACFs are detected in the rectum through a limited flexible sigmoidoscopy using chromoendoscopy with methylene blue. Without chromoendoscopy, these lesions would otherwise go undetected. Aberrant crypt foci express molecular abnormalities in K-ras and the APC gene, genes associated with progression of adenoma to cancer. ACFs offer promise for use as an intermediate endpoint in chemoprevention trials. In the past, chemoprevention trials have used the adenomatous polyp as the endpoint and have had to enroll 1,000 or more subjects. If ACFs could be used as an intermediate endpoint, enrollment in trials could be reduced to 100 or 200 subjects, and trial duration could be months instead of years.

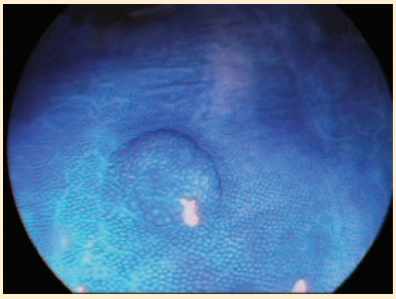


Figure 1 - *Aberrant Crypt Foci:* ACF's have larger individual crypts with a thicker epithelial lining

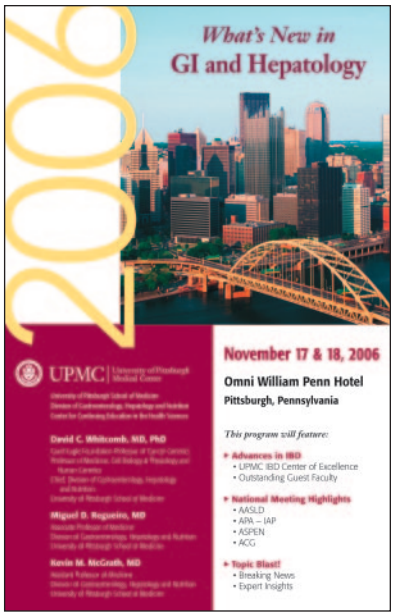
My team and I are completing a multicenter natural history study of ACF lesions with over 125 patients enrolled in Pittsburgh. A new multicenter chemoprevention trial sponsored by the National Cancer Institute (NCI) is just beginning. This trial is using ACFs to examine the chemoprevention effect of Sulindac, Atorvastatin and Raftilose (a carbohydrate which spurs bacterial growth). Recently, we enrolled the first patient in the country in this trial.

I was honored to present groundbreaking research sponsored by the Early Detection Research Network (EDRN) and NCI at this year's Digestive Disease Week meetings. In collaboration with Dr. Robert Getzenberg, formerly of the University of Pittsburgh and now at Johns Hopkins Hospital, our research team has spent seven years developing a serum-based assay for early detection of colorectal cancer and advanced adenoma. Imagine how different things would be if a blood test for colorectal cancer were available! Preliminary data examining patients with the full spectrum of normal to cancerous pathological findings demonstrates that a serum test can detect cancer and advanced adenoma with excellent sensitivity and specificity. The assay is based on nuclear matrix proteins specific to colorectal cancer. A manuscript from this work is in preparation. However, don't throw away your colonoscopes, because even if a serum test identifies individuals with lesions, colonoscopy will still be required to remove them. If validated and verified in coming years, a serum test could mean less colonoscopy for subjects unlikely to have important findings but may lead to more subjects undergoing testing, as subjects unwilling to undergo screening with invasive gastrointestinal procedures may be willing to undergo a blood test.

Dr. Schoen is a Professor of Medicine and Epidemiology with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition and directs the Division's Gastrointestinal Cancer Prevention & Treatment Center.

Division Highlights

By all accounts, the Division of Gastroenterology, Hepatology and Nutrition at the University of Pittsburgh has undergone unprecedented growth and success. These achievements resulted from the coordinated efforts of outstanding faculty – evidenced by the DDW highlights in this *Pitt Digest* issue – combined with the vision of the Department of Medicine and multiple levels of support from the UPMC Health Care System.



We recently completed a thorough five-year review and have been rewarded with solid support for the next five years. We are pleased to announce the strengthening and expansion of our Division's seven clinical *Centers of Excellence* and the launch of several new initiatives.

The first major initiative is a strategic partnership among our Division and Pitt's Departments of Anesthesiology and Neurobiology. With strong support from the Dean and UPMC, we have launched the *UPMC Comprehensive Pain Center*, including the Visceral Inflammation and Pain (VIP) Program. Professor **Gerald Gebhart, PhD**, one of the world's preeminent visceral pain scientists and current chair of the University of Iowa's Department of Pharmacology, will be the Center's founding director. More detail and what this new Center will mean for our division will be highlighted in a future *Pitt Digest.*

Additional key expansions include a GI cancer biology program and a joint translational and basic immunology initiative with our University's Division of Pulmonary, Allergy and Critical Care Medicine. Our division's research focus on mucosal immunology and neuron immunology will complement the strengths of the Division of Pulmonary, Allergy and Critical Care Medicine. Currently, we are recruiting a new director for GI Immunology.

I am happy to announce the addition of six new faculty. **Dhiraj Yadav, MD, MPH, Georgios Papachristou, MD, Michael Sanders, MD,** and **Neraj Jani, MD,** will join our pancreaticobiliary group; **Refaat Hegazi, MD, PhD,** will join our nutrition support group; and **Jaideep Behari, MD, PhD,** will be joining our hepatology group. Several additional faculty recruits are in late stages of negotiation.

Join us on **November 17 & 18** for our annual **What's New & What To Do GI & Hepatology Update**. In addition to ACG and AASLD highlights, this year's symposium will emphasize cutting-edge advances in inflammatory bowel disease and upper GI diseases.

In good health,

David C. Whitcomb, MD, PhD
Giant Eagle Foundation Professor of Cancer Genetics
Professor of Medicine, Cell Biology & Physiology and Human Genetics
Chief, Division of Gastroenterology, Hepatology and Nutrition

Ruptured Cervical Diverticulum

by Allen Banegura, MD
Gastroenterology Fellow

Case Presentation

A 41-year-old white female with a history of congenital esophageal atresia presented with a two-week history of progressive left neck swelling and pain, fever and difficulty swallowing. She had undergone colonic interposition during childhood. A barium esophagram was performed (*Figure 1*). The patient underwent an emergent neck exploration which revealed a large perforated diverticulum in the main segment of the colonic graft. After surgical repair and drainage, she was treated with IV antibiotics and clinically improved. Five years earlier, the patient had presented with progressive dysphagia to solids. At that time, barium swallow and EGD demonstrated diverticulosis in the transplanted colonic graft (*Figure 2).*

Discussion

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) are common congenital conditions, affecting one in 3,000 to 4,500 live births. Based on the type of atresia and presence of tracheoesophageal fistula, five common anatomic patterns are described. The pathogenesis of EA-TEF is uncertain. Approximately 50 to 70 percent of these patients have other associated congenital anomalies such as vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal malformation, renal anomalies and limb defects (VACTREL). Over the past 60 years, infant survival has increased from zero to 95 percent due to early diagnosis, ICU and neonatal care, nutrition support and improvement in surgical repair techniques. With increased survival, a number of patients reach adulthood. Surgical repair includes early or delayed primary esophageal anastomosis, lengthening procedures with or without esophagomyotomy or esophageal replacement with gastric, jejunal or colonic interposition. Until recently, the colon was the preferred esophageal replacement in children due to fewer acid reflux complications and more durability.

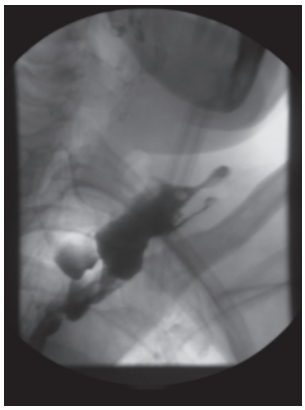


Figure 1 – Esophagram: perforated diverticula

The use of the colon as an esophageal substitute was first introduced by Kelling and Vuillet in 1911. Colonic interposition is also indicated in other conditions such as peptic and caustic strictures, severe reflux disease, esophageal cancer, end-stage achalasia and iatrogenic esophageal fistula. Interposition of the left colon is the most popular procedure, providing long-term graft function, an isoperistaltic segment and predictable vascular anatomy. Common long-term colonic interposition complications include anastomotic leaks (16 percent), strictures (40 percent), dysphagia (up to 75 percent), gastroesophageal reflux (up to 70 percent), tracheomalacia, altered peristalsis with delayed gastric emptying, colon redundancy and, rarely, colonic adenocarcinoma.

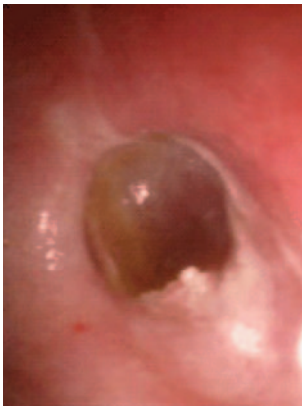


Figure 2 – EGD: diverticulosis transplanted colon

Summary

There are only three previously reported cases of newly developed diverticulosis in a transposed colon. All three cases occurred in adults with colonic interposition during adulthood. There are no reports of patients undergoing the procedure during childhood, when, theoretically, the colon should be free of diverticulosis. The mechanism of diverticular formation in the graft is unclear, and the incidence may be under-recognized or under-reported. There is no literature to support screening for diverticulosis in this population.

References upon request.

Proximal Crohn's and Pancreatitis

by Mark Lazarev, MD
Gastroenterology Fellow

Case Presentation

A 57-year-old woman with no significant past medical history presented with intermittent nausea, vomiting and abdominal pain. Notable labs were a lipase of 2000 U/L, amylase of 300 U/L; liver function tests were normal. She was diagnosed with acute pancreatitis. An upper endoscopy showed duodenitis, aphthous ulcers, diffuse ulceration through D_3 and a stricture between D_2 and D_3 (*Figure 1).* Biopsies were negative for *H pylori* but were notable for gastritis and duodenitis (*Figure 2*). An ERCP was attempted; there was periampullary inflammation, and the papilla could not be cannulated (*Figure 3*). She denied diarrhea, and colonoscopy was normal.

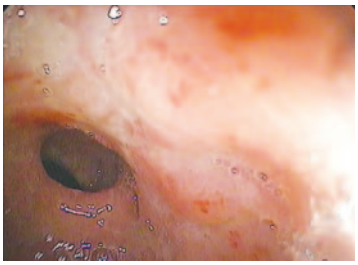


Figure 1 – Stricture between D_2 and D_3

The patient was diagnosed with proximal Crohn's disease. Her pancreatitis and symptoms resolved after a one-month steroid taper. Weekly methotrexate was initiated, and she remained symptom free. She has yet to manifest any significant lower GI symptoms, and a colonoscopy was unremarkable. Repeat upper endoscopy showed decreased inflammation and stricturing.

Twenty to 40 percent of documented Crohn's disease patients will have endoscopic and/or pathologic evidence of proximal disease, though only a minority will be symptomatic. Common presentations include epigastric pain, weight loss, nausea and vomiting. The antrum and duodenum are typically involved, and endoscopic findings vary from mucosal friability and ulceration to stricture formation. Biopsies are often nonspecific, and only ten percent of patients will be *H pylori* positive. Granulomas are seen in only 15 to 45 percent of patients. It is unusual to see proximal Crohn's disease without first having distal disease in the small bowel or colon.

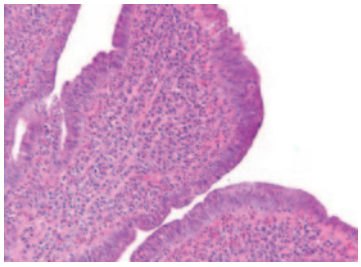


Figure 2 – Chronic active duodenitis

Pancreatitis related to Crohn's disease is linked often to medications (azathioprine, 6-mercaptopurine) and has been theorized to be an extra-intestinal manifestation. Rarely, as in this case, Crohn's disease involving the ampulla and duodenum with duodenal stricturing can lead to pancreatitis.

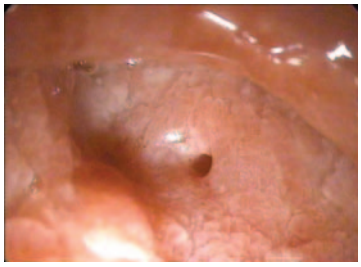


Figure 3 – Ampullary inflammation, edema

There have been no large studies examining treatment for proximal Crohn's disease. Steroids are considered first line therapy for flares, and proton pump inhibitors are associated with improved symptoms and healing of Crohn's-related ulcers. Case reports suggest that immunomodulators can maintain remission. Up to one third of patients with Crohn's-related duodenal strictures will require surgery, with gastroenterostomy and strictureplasty being the most frequently performed procedures.

References upon request.

Answer to ***What Is This*** *photo on page six: Diverticular Colitis/Segmental Colitis Associated with Diverticulosis*

Flexible sigmoidoscopy revealed an erythematous, 9 cm stricture with submucosal hemorrhage in the sigmoid colon associated with diverticulosis. The patient underwent a left hemicolectomy, and pathologic examination revealed diverticulosis with acute and chronic inflammation.

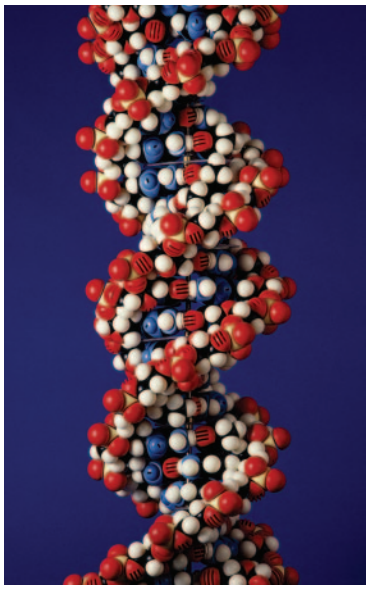
The pathogenesis of this entity is poorly understood but is postulated to be multifactorial related to mucosal prolapse, fecal stasis with changes in bacterial flora and localized ischemia. Patients may be asymptomatic or have symptoms including hematochezia, abdominal pain, diarrhea or constipation, resembling those seen in patients with segmental colitis. Differential diagnoses include inflammatory bowel disease, infectious colitis, NSAIDS induced colitis and ischemic colitis. Diagnosis is made endoscopically and histologically usually distinguished based upon clinical context. However distinction from IBD may be difficult as the histologic features of IBD (neutrophilic cryptitis, crypt abscesses, distorted crypt architecture) may all be present. The natural history of diverticular colitis is unknown, but affected patients appear to be at risk for complications related to diverticulosis (such as stricture). Case reports describe successful treatment with antibiotics and/or aminosalicylates, although surgery may be required in severe cases.

References upon request.

Pancreatic Cyst DNA Analysis

by Asif Khalid, MD
Assistant Professor of Medicine
Chief GI Section, VA Pittsburgh Health Care
University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition

Previously felt to represent only a small percentage of pancreatic neoplasms, recent studies suggest that a quarter of the population may harbor a pancreatic cyst at the time of death. The increased recognition of pancreatic cysts is due to the wide use of body imaging. Most cystic neoplasms are benign, but more than half resected at a tertiary care facility were pre-malignant, including mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN). Key, therefore is distinguishing premalignant from benign pancreatic cysts; and accurately detecting malignant degeneration in premalignant cysts.



Unfortunately, the clinical presentation and imaging of pancreatic cysts with CT and EUS cannot differentiate among benign, premalignant and malignant cysts. As such, EUS-guided fine needle aspiration (EUS-FNA) is nearly always required. Cytology of the aspirated fluid yields a diagnosis in approximately 50 percent of cases, but the fluid is often acellular. Aspirated fluid is tested also for pancreatic enzyme content (amylase and lipase) and tumor markers (CEA, CA 19-9). Aspirate CEA level best differentiates mucinous (premalignant) from non-mucinous (benign) pancreatic cysts, but a shortcoming of these tests is the inability to detect malignant change.

Our group at the University of Pittsburgh in collaboration with Dr. Sydney Finkelstein, formerly with the University of Pittsburgh Department of Pathology, has been interested in developing a genetic test for differentiating premalignant and malignant cysts. We investigated the DNA content and mutations in pancreatic cyst aspirates and found mutations similar to those found in pancreatic ductal carcinoma including k-ras, p16, p53, APC, PTEN, etc. The k-ras mutation is directly sequenced, while allelic loss analysis is utilized for the other genes. This method detects a mutated copy of the gene and loss of the chromosomal segment containing the normal, non-mutated copy. Our preliminary study enrolled 36 patients with confirmed histology. The cyst pathology was compared to cyst aspirate cytology, CEA and DNA analysis. The DNA analysis included aspirate DNA amount, DNA quality, and the number of mutations and sequence of mutations (*Clin Gastro Hepatol* 2005). DNA analysis was the most accurate test to detect malignancy (carcinoma-in-situ or invasive cancer). Higher DNA amount, better DNA quality, more mutations and the specific sequence of a k-ras mutation followed by allelic loss all correlated with malignant cysts with mutation sequence being the most predictive (*see Table 1*).

Funded by an ASGE Career Development Award, a prospective multicenter study, PANDA (Pancreatic Cyst DNA Analysis), was begun in July 2004. Seven U.S. centers are actively enrolling study patients.

I presented an interim analysis (July 2004 to Sept. 2005) of PANDA at this year's DDW meetings. In the first 14 months, PANDA enrolled 187 patients who underwent EUS-guided pancreatic cyst aspiration for cytology, CEA and DNA analysis.

continued on page six

Cyst pathology	# of cases	DNA quantity (OD)	DNA quality (CT)	Mean # Mutations	Mutation sequence- k-ras followed by allelic loss
Malignant	11	16.5 ± 15.7	24.5 ± 4.5	2.8 ± 1.3	10/11
Premalignant	15	3.6 ± 2.5	30.9 ± 5	0.9 ± 1.2	1/15
P-value		0.008	0.009	0.002	<0.001

Table 1: OD – optical density reflects DNA amount; a higher value suggests more DNA. CT – cycle threshold: A lower value suggests higher quality DNA.

Pancreatic Cyst DNA Analysis *continued from page five*

Cyst Pathology	# of cases	CEA	OD	CT	Mean # of mutations	K-ras mutation	K-ras followed by allelic loss
Malignant	20	1299+/-1358	170+/-381	26.5+/-2.9	1.3	11/20	9/20
Premalignant	21	3318+/-9692	5.6+/-10.7	29.9+/-2.4	1.24	9/21	1/21
P-value			<0.001	<0.001	NS	NS	0.004

Table 2: CEA: Carcinoembryonic Antigen. OD-optical density reflects DNA amount; a higher value suggests more DNA. CT-cycle threshold: A lower value suggests higher quality DNA.

Of 187 enrolled patients with cysts, 58 had confirmed histology. Of these, 41 were MCN or IPMN (20 malignant and 21 premalignant). CEA level was unavailable in 15/41 cases due to insufficient aspirate volume. Malignant cysts could be differentiated from premalignant cysts on the basis of DNA quantification and specific mutation sequence of a k-ras mutation followed by allelic loss. The mean number of mutations was not different for the two categories (*see Table 2*).

To date, the most accurate predictor of malignancy in MCN and IPMN appears to be aspirate DNA quantity and quality. Occurrence of a first hit k-ras mutation followed by allelic loss is highly specific for a malignant cyst. These findings will need to be validated upon completion of the PANDA study.

What Is This?

Presentation: A 40-year-old male with diverticulosis presented with a two week history of left lower quadrant pain, bilious emesis, abdominal bloating and constipation. For the previous two years, he reported similar less severe episodes which resolved with passage of a bowel movement. Abdominal imaging and flexible sigmoidoscopy were performed.

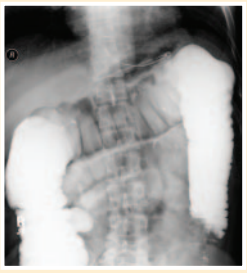


Figure 1
Gastrografin enema

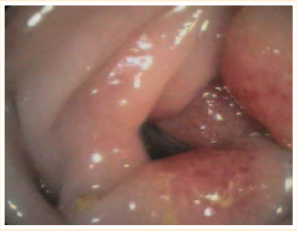


Figure 2
Flexible sigmoidoscopy

Images and explanation provided by John Lyons, MD, Gastroenterology Fellow. Compare your answer to Dr. Lyon's answer on page four.

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