This issue of the Pitt Quarterly Digest reflects exciting developments and programs within the Division of Gastroenterology, Hepatology and Nutrition at the University of Pittsburgh. Robert Schoen, MD, MPH published a major article on screening sigmoidoscopy in JAMA [2003 Jul 2;290(1):41-8] that was highlighted on CNN’s Wolf Blitzer Reports and NBC’s The Today Show. Miguel Regueiro, MD and Christianna Kreiss, MD each won Research Excellence in GI and Liver (REGAL) awards, and Michael Pezzone, MD, PhD obtained major funding to advance his IBD-chronic interstitial cystitis program. Upcoming CME programs include GI & Hepatology: What’s New and What to Do scheduled for November 1, 2003 in Pittsburgh, and the 4th International Symposium on Inherited Diseases of the Pancreas will follow the American Pancreas Association’s annual meeting in Chicago on November 7–9, 2003. Visit http://ccehs.upmc.edu/CCEHS/cme/formal_courses.asp for details about both of these programs.

Inside, you will find interesting clinical case presentations by two of our senior fellows – Gary Payman, MD and Tina Yu, MD – related to diverticular disease and Churg-Strauss syndrome. These case materials were presented at our weekly UPMC Digestive Disease Center Grand Rounds and are highly relevant to the practice of gastroenterology.

On page four you will find a snapshot of work by Asif Khalid, MD and Sydney Finkelstein, MD concerning an innovative and highly accurate technique to solve the dilemma of what to do when initial biopsies or fine needle aspiration biopsies are “indeterminate” or negative in a suspected malignant tumor of the pancreas or biliary tract.

Of special note, the Division has embarked on two new programs, one directed at intestinal rehabilitation and the other a joint effort with Magee-Womens Hospital focusing on women’s GI health issues, immune-related diseases, motility and functional disorders. The first program is presented by Stephen J.D. O’Keefe, MD, MSc, professor of medicine and the director of the Center of Intestinal Health and Nutrition Support. Dr. O’Keefe was just elected to the AGA Council and is serving as vice-chair of the Nutrition and Obesity Section of the AGA. The second program is directed and presented by Steven Abo, MD. Read more about these programs on page five.

Finally, the Division continues to enhance its outstanding fellowship program, and the new fellows are introduced on page six. Keep your eye on them – they are destined for future excellence!

In good health,

David C. Whitcomb, MD, PhD
Professor of Medicine, Cell Biology & Physiology and Human Genetics
Chief, Division of Gastroenterology, Hepatology and Nutrition
An Unusual Presentation of a Common Disease  
by Gary H. Payman, MD  
Fellow, Division of Gastroenterology, Hepatology and Nutrition  

Case Presentation

An 82-year-old woman with a six month history of constipation (thin caliber, small volume stools), abdominal pain, increased abdominal girth and a seven pound weight loss over one month, was hospitalized with increasing severity of abdominal pain awakening her from sleep. Two years earlier she had been seen in the Digestive Disease Center for long-standing crampy abdominal pain where evaluation revealed a hematocrit of 35%, mean corpuscular volume of 82 fl, serum iron 67 mcg/dl, iron saturation of 15% and a normal red cell distribution width. Colonoscopy revealed two 0.5cm tubular adenomas in the right colon and a 2 cm submucosal mass in the sigmoid colon felt to be a lipoma.

Current laboratory studies were unchanged, abdominal xray showed stool in the rectum consistent with fecal impaction, and a single contrast barium enema revealed narrowing in the sigmoid colon with the appearance of an “apple core lesion.” CT scan of the abdomen and pelvis (Figure 1) showed a 6 cm long segmental stricture of the sigmoid colon with mural thickening; partial bowel obstruction with dilation of the colon and adjacent diverticula with no inflammation of the sigmoid mesentery.

What is the differential diagnosis and how would you proceed with workup? The differential diagnosis includes both colon carcinoma and non-malignant processes such as a benign stricture. Colonoscopy to the cecum showed a tight stricture in the sigmoid colon 12 to 20cm from the anal verge, sigmoid diverticula and a small submucosal mass, possible lipoma, at 40cm unrelated to the area of obstruction. Subsequent exploratory laparoscopy confirmed a firm region in the sigmoid colon corresponding with the area of obstruction. A sigmoid colectomy with side-to-end colorectal anastomosis was performed. The pathologic specimen (Figure 2) revealed diverticulosis-associated muscularis propria hypertrophy, pericolonic fibrosis and acute inflammation with focal crypt abscesses in mucosa adjacent to diverticula (peridiverticulitis). No tumor was identified.

Discussion: Diverticular disease is age-related with a prevalence of 5% in those under age 40, 30% by age 60 and 65% by age 85. The majority of patients (75%) remain asymptomatic. Differences in prevalence across populations have been associated with decreased fiber intake. Diverticula occur when the mucosa and submucosa herniate through the muscular wall. This occurs at the point of greatest structural weakness where the intramural vasa recta penetrate the circular muscle layer. Colonic wall thickening is associated with shortening of the teniae (myochosis) which narrows the colonic lumen. Complications of diverticular disease include diverticulitis (15-20%), bleeding (5-15%), fistula, obstruction and perforation. Diverticulitis occurs when there is micro- or macroscopic perforation of a diverticulum. Erosion of the diverticular wall is caused by increased luminal pressure or inspissated food particles which leads to hyperplasia of the lymphoid tissue within the mucosa. After repeated attacks, fibrosis may produce narrowing, stricture or obstruction. If a patient presents with acute obstruction, diverticular stricture must be distinguished from stenosing neoplasm as both may have similar clinical presentations. Colonoscopy has been shown to distinguish a benign stricture from stenosing neoplasm in two out of three patients. If malignancy cannot be excluded despite endoscopic and radiographic examinations, or if obstruction cannot be medically managed, surgical resection is indicated. In cases of malignant stricture, colonoscopy is also useful to evaluate for metachronous lesions in the colon.

Summary: A diverticular stricture may mimic colon cancer, whereas colon cancer may be masked by diverticulosis. Radiographic and colonoscopic evaluation may aid in the diagnosis, but high grade obstruction necessitates surgery if there are no contraindications.

References
A Gastrointestinal Catastrophe Averted

Tina Yu, MD
Fellow, Division of Gastroenterology, Hepatology and Nutrition

Case Presentation

A 55-year-old man presented with the recent onset of severe chest pain following a several week history of vague postprandial abdominal pain, hematochezia, and unintentional weight loss of 20 pounds. Past medical history was that of adult-onset asthma. Medications on admission included albuterol and Advair. Two months prior, he was tapered off prednisone after an asthma exacerbation, and was briefly on the leukotriene inhibitor, Montelukast. On admission, he was afebrile with normal vital signs and mild wheezes on chest exam. Heart exam was unremarkable and abdominal exam revealed mild periumbilical tenderness.

Laboratory studies included a white blood cell count of 32 thous./mcl with 60% eosinophils, mildly elevated liver transaminases, and elevated cardiac enzymes with a CPK of 362 and a troponin of 12.7. Hepatitis B and C serologies were negative and rheumatoid factor was elevated at 174 IU/mL. Stool studies, blood and urine cultures were negative. No coronary artery disease was found on cardiac catheterization. Mural thickening of the distal colon was seen on CT scan. EGD revealed multiple shallow duodenal ulcerations, and flexible sigmoidoscopy showed patchy ulceration of mucosa in the sigmoid colon with biopsies revealing eosinophils and microthrombi.

During hospitalization, the patient developed fever, vomiting and a tender, distended abdomen. Dilated loops of small and large bowel were seen on abdominal X-ray and a subsequent CT scan showed pneumatosis affecting the large and small bowels (Figure 3).

What is the provisional diagnosis?
The patient had multi-organ involvement, with asthma, myocarditis, ischemic bowel, peripheral eosinophilia, elevated liver transaminases, and mononeuritis multiplex. A systemic disorder was likely the cause. Mucosal biopsies revealed eosinophils and microthrombi (Figure 4) suggesting a vasculitis. Vasculitides known to involve the gastrointestinal tract include: polyarteritis nodosa, Henoch-Schönlein purpura, rheumatoid arteritis, Kawasaki disease, SLE, Churg-Strauss syndrome, and Wegener’s granulomatosis.

Of these, the Churg-Strauss syndrome is closely associated with asthma, particularly adult-onset asthma, prior to the onset of vasculitic symptoms.

Hospital Course: A nasogastric tube was placed for decompression and surgery was consulted. Intravenous fluids, TPN and broad spectrum antibiotics were given. A mesenteric angiogram was normal. Solumedrol 1g QD was started with rapid clinical improvement. Episodic bradycardia prompted consideration of transcutaneous pacemaker. Pulse cyclophosphamide was administered with resolution of bradycardia, eosinophilia, and GI symptoms. Oral feedings were re-instituted over the ensuing weeks, and the patient was discharged on Prednisone 60mg po QD.

Discussion: Churg-Strauss syndrome (CSS) is a rare disorder characterized by asthma peripheral eosinophilia and vasculitis involving two or more extrapulmonary organs. A necrotizing vasculitis affecting small to medium sized vessels, it develops usually in middle-aged individuals with adult-onset asthma. Biopsies may show fibrinoid necrosis, infiltration with eosinophils, and extra-vascular granulomas. The gastrointestinal tract is the third most common site of involvement (behind lung and skin) and 50% of patients have GI manifestations which include perforation of the bowel, ileus, ischemic bowel, ulcers, cholecystitis, and pancreatitis. Etiology remains unknown and controversy exists regarding an association with anti-leukotriene drugs. It is unclear whether such drugs cause CSS or whether withdrawal of steroids after institution of these drugs unmasks forme frustes CSS. CSS is generally responsive to corticosteroids; however, immunosuppressive agents such as cyclophosphamide may be required for induction of remission, especially when poor prognostic indicators such as cardiac or GI involvement are present. With treatment, prognosis is good with a 73–83% survival after 7 years.

Summary: The association of vasculitis and asthma, known as Churg-Strauss syndrome, is an important entity to recognize, as it may have devastating consequences if left untreated, and has a high rate of remission if treated aggressively and promptly.

References
Molecular Analysis of Biliary Brush Cytology

by Asif Khalid, MD and Sydney Finkelstein, MD

The pancreatobiliary group, in collaboration with the Department of Pathology has been involved in studying techniques to improve the ability to accurately diagnose malignant biliary strictures.

A definitive diagnosis of malignancy related to biliary strictures requires the objective demonstration of cancer-associated alterations in representative cells collected by brushing of the stricture during endoscopic retrograde cholangiography. This time-honored approach has recognized limitations, since the diagnosis of malignancy can be expected to remain indeterminate in a significant proportion of patients following cytologic examination (sensitivity <60%). Since treatment in these circumstances is often multimodality with major morbidity risks, it is vital that the diagnosis of malignancy be achieved in a prompt, objective and highly reliable manner.

Recent work involving human and animal models of pancreatic neoplasia – and, to a lesser extent, biliary cancer – has identified and characterized predictable molecular alterations closely associated with tumorigenesis in these tissues. For example, the vast majority of pancreatic adenocarcinoma of ductal cell origin manifest k-ras-2 point mutational change as one of many cumulative mutational alterations generally acquired early in tumor development. Mutational damage affecting tumor suppressor genes, including P53, p21, p16Ink4a/CDKN2A and DPC4/SMAD4, also occurs with common frequency in pancreatobiliary tumors. It is generally accepted that no single gene alteration is completely reliable for or universally present in any given cancer. Rather a cumulative accounting of mutational damage appears to serve as a more reliable indicator of the malignant state providing a potential independent and objective parameter to diagnose malignancy.

We hypothesized that representative cells from malignant strictures would manifest a high level of accumulated mutational damage that would not be seen in reactive strictures. Recognizing that malignant strictures could be derived from pancreatic or biliary epithelial origin, the profile of mutational change would not necessarily be the same but, in any case, significantly different from that seen in non-neoplastic state.

Eighteen patients were studied to test this hypothesis. Seventeen patients had surgically proven cancer. One patient had an inflammatory process. Eight patients had positive cytology; nine had suspicious cytology; and one had atypical cytology. Representative cytopathology and surgical pathology slides were selected for microdissection genotyping that included analysis for loss of heterozygosity (LOH) in a panel of selected microsatellite markers as well as k-ras-2 point mutation determination. For cytology specimens, clusters of neoplastic cells were identified and manually microdissected from the slides. For surgical pathology slides, normal biliary tissue (negative control) and neoplastic areas were manually microdissected. In order to afford sufficient DNA substrate for broad panel genotyping, genome-wide amplification was performed.

The overall genotyping analysis represented a combination of point mutational and allelic loss damage. Genetic targets consisted of sequencing for k-ras-2 point mutation and 15 allelic imbalance assessments using polymorphic microsatellites.

Non-neoplastic tissue targets adjacent to neoplasia showed no evidence of allelic loss. All patients (17/17) with cancer manifested high levels of allelic loss damage with or without k-ras-2 point mutational change. In one subject without cancer, microdissected cytologic and tissue samples were without mutational damage.

Irrespective of the reasons for indeterminate status, the resulting profile of accumulated mutated markers was sufficiently precise to firmly correlate with malignancy based on a cumulative mutational profile. We are now investigating the utility of this technique in indeterminate specimens acquired from pancreatic tumors by endoscopic ultrasound guided fine needle aspiration.
Gastroenterology and Magee: A Winning Combination
by Steven R. Abo, MD

The Magee-Womens Hospital, affiliated with the University of Pittsburgh Medical Center, has recently expanded its services to fulfill its mission as a hospital devoted to women’s health. The Division of Gastroenterology, Hepatology and Nutrition has taken a leading role in this effort, recognizing that many gastrointestinal disorders are more common or manifest differently in women.

Some of the most common disorders seen by gastroenterologists are the functional bowel disorders. These include irritable bowel syndrome (IBS), dyspepsia and disorders of defecation and incontinence. At Magee, we offer a multi-disciplinary approach to these problems. Our Division is known for its interest and expertise in gastrointestinal motility, and the Digestive Disorders Center at Magee has a modern laboratory to evaluate these disorders. Available tests include esophageal, intestinal and anorectal manometry, anal ultrasonography, colonic transit, breath hydrogen test for carbohydrate malabsorption and bacterial overgrowth and ambulatory esophageal pH monitoring by conventional and advanced (BRAVO) technology.

Although we are based at Magee, both men and women are seen for gastrointestinal complaints. We work closely with the minimally invasive (laparoscopic) surgical group for treatment of gastroesophageal reflux and morbid obesity. The pleasant atmosphere at Magee has provided an excellent home for the Immune Mediated Inflammatory Disease (IMID) Treatment Center, which specializes in the most current immunologic treatments for inflammatory bowel disease.

For more information about the GI Services at Magee-Womens Hospital or to make an appointment, call (412) 641-2135.

Dr. Abo is an assistant professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition at the University of Pittsburgh and is the director of GI Services for the Digestive Disorders Center at Magee-Womens Hospital.

Concepts of Intestinal Rehabilitation
by Stephen J.D. O’Keefe, MD, MSc

The Center for Intestinal Health and Nutrition Support specializes in the evaluation and treatment of all conditions which disrupt nutrient processing. Advanced support is provided for nutrition delivery, intestinal rehabilitation and intestinal transplant evaluation and support. This Center also collaborates with the weight reduction program and other institutional programs related to patient nutritional needs.

Many of our patients suffer from intestinal damage or loss, and intestinal rehabilitation is therefore one of the major priority areas of the Center for Intestinal Health and Nutrition Support. Our Center concentrates on the innate ability of the bowel to heal itself and to adapt to loss of digestive capacity.

Key Concepts in the Promotion of Rehabilitation
Intestinal adaptation involves an increase in the mucosal surface area (villous and microvillus hyperplasia), an increase in brush-border and pancreatic enzyme activities, upregulation of epithelial nutrient and electrolyte transporters, increased mucosal blood flow and reduced motility. Successful net results include enhanced digestive efficiency, enhanced nutrient transport, prolonged nutrient mucosal contact time and increased absorption per unit of mucosal mass. Although most of the adaptation occurs within the first three months, continued improvement can be expected for up to two years.

In the absence of residual mucosal disease, independence from IV supplements is possible only if the colon is lost, or if more than 200cm of small intestine is preserved. IV fluids will be needed if less than 200cm remains. IV fluids and nutrition (i.e., TPN) will be required if less than 50cm of intestine remains.

We have found that normal food is the most powerful stimulant of intestinal adaptation. Intestinal rehabilitation patients need to change their eating habits. They need to avoid large meals and learn to nibble! Patient with colons should increase their intake of complex carbohydrates to promote colonic bacterial metabolism as well as nutrient and salt salvage. Water is a no-no, and the consumption of fluids containing salt and carbs should be encouraged.

Antisecretory agents are useful for a short time (e.g., PPIs). Prolonged use of somatostatin analogues should be avoided, as they counteract adaptation. Imodium can be used in large doses, and can enhance absorption. Trophic hormones (e.g., GH or GLP-2) can be helpful and can help patients with borderline gut failure become independent of IV fluids. Surgical reconstruction should be considered in post surgical patients with chronic anorexia and subacute obstruction. Lastly, if home TPN fails, consider intestinal transplantation.

For more information about the Center for Intestinal Health & Nutrition Support, call toll-free, 1-866-4GASTRO (1-866-442-7876).

Dr. O’Keefe is a professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition at the University of Pittsburgh and directs the Division’s Center for Intestinal Health & Nutrition Support.
The University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition was pleased to welcome the following new Fellow recruits this summer.

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<th>NAME</th>
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<tr>
<td>Gaëtan Beinari, MD</td>
<td>University of Massachusetts</td>
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<tr>
<td>Yasser Bhat, MD</td>
<td>Cleveland Clinic Foundation</td>
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<tr>
<td>Daniel Chung, MD</td>
<td>University of Pittsburgh Medical Center</td>
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<tr>
<td>Niraj Jani, MD</td>
<td>Mt. Sinai, NY</td>
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<td>Ajay Pabby, MD MPH</td>
<td>Boston Medical Center</td>
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**Gastroenterology Fellows**

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<th>NAME</th>
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<tr>
<td>Shahid Habib, MD</td>
<td>UPMC Shadyside</td>
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<td>Paul Kim, DO</td>
<td>West Penn Hospital</td>
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**Hepatology Fellows**

An 82-year-old woman presented with a one week history of pruritus, darkening of urine and clay colored stools and was found to have elevated liver enzymes of a cholestatic pattern. A right upper quadrant ultrasound (top) and an endoscopic retrograde cholangiography (ERC) (bottom) were performed.

Compare your answer to Dr. Rastogi’s answer on page four.

Questions or information related to Pitt Quarterly Digest may be directed to Joy Jenko Merusi at merusij@msx.dept-med.pitt.edu or by calling, toll-free, 1-866-4-GASTRO (1-866-442-7876). Visit our website at http://gi.medicine.pitt.edu