As the third installment of a multi-part series, the Pitt Quarterly Digest features the Division of Gastroenterology, Hepatology and Nutrition’s Inflammatory Bowel Disease Center this fall. We hope you will enjoy reading about the comprehensive clinical and research innovations of this group.

Inflammatory Bowel Disease Center

by Miguel D. Regueiro, MD

The UPMC Inflammatory Bowel Disease (IBD) Center provides specialized care for patients with ulcerative colitis and Crohn’s disease, contributes to the advancement of IBD research and educates patients and health care professionals about IBD.

The IBD Center utilizes a cohesive team of physicians and surgeons, who are recognized as experts in their respective specialties. Directed by gastroenterologists who unite surgeons, nutritionists, radiologists and pathologists, the Center is designed to attract and care for a large volume of patients with IBD. In addition to providing comprehensive primary care to these patients, specific attention is also directed to cancer surveillance, women’s health, intestinal rehabilitation and transplantation medicine, mental health and the transition of care from the pediatric to adult gastroenterologist.

As such, care of IBD patients is integrated with the Pittsburgh Cancer Institute, Magee-Womens Hospital, The Thomas E. Starzl Transplantation Institute, Western Psychiatric Institute and Clinic and Children’s Hospital of Pittsburgh. By coordinating care across a variety of specialties and by providing IBD patients with “one stop shopping” for expert consultations and excellent diagnostic techniques, the Center continues to attract increasingly larger numbers of patients from the tri-state area.

The success of the IBD Center is defined by individual achievements and team effort. The Center physicians direct several multi-center, international research trials on novel IBD treatments and are respected as authorities in genetics, immunology and clinical research. Dr. Duerr, Dr. Plevy and I have each been recognized as Crohn’s and Colitis

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Significant advancements in IBD research, education and comprehensive patient care have established the UPMC IBD Center as one of the top IBD programs in the country. The IBD Center’s genetic, immunological and translational research programs are possible because of the large and diverse patient base as well as the Center’s internationally known physician-scientists: Drs. Duerr, Plevy and Regueiro.

Clinical advancements are highlighted by the IMID (Immune Mediated Inflammatory Disease) Center based at the Magee-Womens Hospital of the University of Pittsburgh Medical Center. Under the direction of Dr. Plevy, the IMID Center welcomes both men and women and treats IBD and other immunological and inflammatory diseases using new immunomodulating therapies.

The physicians and scientists within our Division are also committed to updating and educating physicians and other healthcare professionals about advancements in IBD. While traditional classroom training remains available (e.g., join us for our annual accredited course, *Updates in GI & Hepatology: What's New & What To Do*, November 13, 2004, at the Sheraton Station Square Hotel in Pittsburgh), technology has enabled us to expand IBD educational efforts to the world. Led by Dr. James B. McGee, GI Rounds Online is a highly interactive online course, and four one-hour IBD courses are currently available for physician and healthcare professional participation by visiting [http://girounds.pitt.edu](http://girounds.pitt.edu). GI Rounds Online has won two Medicine on the Net awards and is an excellent way to obtain CME credits while working a busy practice schedule.

I hope that this issue of *Pitt Quarterly Digest* provides a useful overview of the outstanding IBD programs being offered in Pittsburgh.

In good health,

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

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**Hospitalists Join GI and Hepatology Faculty**

*by Gauri Agarwal, MD*

The University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition launched a GI hospitalist service at the beginning of the July 2004 academic year. The hospitalist program has been designed to provide exceptional and consolidated inpatient GI care.

This program is currently being staffed by three hospitalist attendings: Gauri Agarwal, MD, Scott Cooper, MD and Christine Lee Gulati, MD. These physicians each have a housestaff team consisting of residents, interns and medical students.

GI hospitalist service patients are primarily GI patients known to the division faculty or those who have been referred from outside institutions with primary gastrointestinal or liver diseases. These patients are hospitalized under one comprehensive service, and the hospitalists consult with appropriate subspecialty gastroenterologists as needed (e.g., general gastroenterology, hepatology, pancreaticobiliary, nutrition, etc.). This process has centralized the care of GI patients, in contrast to the previous system of placing patients with multiple, disparate medical teams. Patients on the GI service can now be managed by physicians, nurses and support staff who have specific knowledge and expertise in the management of GI illnesses.

This model also functions as an invaluable teaching opportunity for housestaff and fellows and will enable them to manage a great variety of cases – from routine cases to extremely complex and often unusual disorders. GI focused lectures, conferences and opportunities to observe procedures are all available to housestaff while on service. The hospitalist program also enables the rotating GI faculty to focus on teaching and other academic activities. To date, the experience has been embraced by all involved and has enhanced the quality of patient care.

Dr. Agarwal joined the faculty of the Division of Gastroenterology, Hepatology and Nutrition this past summer and coordinates the GI hospitalist service in partnership with Dr. Scott Cooper and Dr. Christine Lee Gulati. The hospitalist program is supervised by David Sass, MD, assistant professor of medicine with the Division.
Unexplained Diarrhea and Weight Loss in a Middle-Aged Female

by Niraj Jani, MD
Fellow, Division of Gastroenterology, Hepatology and Nutrition

Case Presentation

A 48-year-old white female with a past medical history of diabetes mellitus, hypertension and mild mental retardation was referred from an outside institution with a nine-month history of profuse watery diarrhea, weight loss and fatigue. Prior to the onset of her symptoms, she had one normal bowel movement per day. Gradually, she developed worsening diarrhea, characterized by three to five watery bowel movements per day with urgency. Nocturnal diarrhea was also present, and her symptoms did not improve with fasting. Despite maintaining her appetite and caloric intake, she lost 50 pounds. She denied having fevers, abdominal pain, hematochezia, melena, joint pain or history of diarrhea in the past.

The patient had undergone an extensive work-up consisting of blood tests, stool studies and multiple endoscopies. She was initially given a diagnosis of microscopic colitis, then Crohn’s disease, and finally ulcerative colitis. Despite treatment with corticosteroids and mesalamine, she only had limited improvement. She was hospitalized twice for severe diarrhea and electrolyte abnormalities with renal failure.

Physical examination revealed an obese woman who appeared fatigued. She was normotensive with a height of 64 inches and weight of 240 pounds. Her heart, lung and abdominal examinations were normal. Liquid stool was found in the rectal vault which was hemoccult negative. There was no lymphadenopathy, skin rashes or joint tenderness or swelling. There was pedal edema bilaterally. Laboratory tests showed hemoglobin of 34.3%, white blood cell count 8700/mm³, albumin 2.7 g/dL, thyroid stimulating hormone 2.2 IU/mL, and HbA1C 6.2%. Calcium level, alkaline phosphate and electrolytes were normal. Other normal laboratory tests included anti-endomysial Ab, total serum IgA, cortisol, VIP, 5-HIAA and gastrin levels. A 24-hour stool collection showed a total weight of 275 grams and an osmolar gap less than 50. Her vitamin B12 and 25-hydroxy D levels were low.

Evaluation and Management

Upon admission to UPMC, the patient underwent upper endoscopy and colonoscopy. Endoscopy revealed mild edema in the antrum, but an otherwise normal appearing duodenum. Biopsies showed chronic inactive gastritis and complete villous atrophy with thickened subepithelial collagen deposition (> 15 µm) and increased subepithelial lymphocytes in the duodenum (Figure 1). Colonoscopy revealed mild to moderate colitis with a normal appearing terminal ileum. Biopsies of the colon showed markedly increased lamina propria inflammation with lymphocytes, plasma cells and eosinophils and subepithelial collagen deposition, but no architectural distortion. The terminal ileum exhibited atrophy with subepithelial collagen deposition (Figure 2). These findings were suggestive of collagenous sprue. The patient was placed on corticosteroids, loperamide and cholestyramine. One month later, the patient’s bowel movement frequency had decreased, and weight was maintained.

Collagenous sprue is a rare disorder, characterized by both the loss of normal villi in the small intestine and collagen deposition of greater than 10-15 µm in small bowel and colon. The age of affected patients ranges from 20 to 60 years old with equal sex distribution. Clinically, patients have significant watery diarrhea, moderate to severe weight loss, weakness, fatigue and lack of abdominal pain.

Discussion of Management Issues

Patients typically have an incomplete or poor response to a gluten-free diet. Abnormal laboratory findings may include hypoalbuminemia, decreased mineral and vitamin levels, steatorrhea, abnormal D-Xylose and celiac antibodies. Additional histologic findings include elongated hyperplastic crypts and lymphoplasmocytic lamina propria. It has been suggested that the depth and extent of collagen deposition may be the main factor in determining the severity of symptoms. In a review of 146 adult celiac patients, Bossert et al. documented a zone of subepithelial collagen deposition.
Inflammatory Bowel Disease Center
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Foundation of America (CCFA) Physicians of the year. The IBD “team” consists of the collective efforts of the following health care professionals:

- **Richard Duerr, MD**, Co-Director of the IBD Center and Head of the IBD Genetics Program, directs a research group that seeks to understand the complex genetic basis of Crohn’s disease and ulcerative colitis. His group participated in a collaboration that identified the first Crohn’s disease gene and is working to identify other IBD genes. Dr. Duerr has co-authored multiple abstracts and manuscripts on the genetics of inflammatory bowel disease and has been an invited speaker on inflammatory bowel disease topics in several national and international forums. He has chaired sessions on the genetics of IBD at Digestive Disease Week meetings, serves as a Genetics Section Editor for the *Inflammatory Bowel Diseases* journal and is a founding member of the IBD International Genetics Consortium.

- **Scott Plevy, MD**, Co-Director of the IBD Center and Head of the IBD Immunology Program, is a nationally known IBD immunologist and is a recognized thought leader in the field. Dr. Plevy is involved in research directed at understanding the immunologic basis of IBD. He is the director of the University of Pittsburgh’s Immune Mediated Inflammatory Disease (IMID) Center, which is located at Magee-Womens Hospital. This world-class Center delivers immune based therapies to both male and female Crohn’s disease and ulcerative colitis patients as well as patients afflicted with other immune mediated diseases.

I am the Co-Director of the IBD Center and Head of the IBD Clinical Program and work as the principal investigator for several international clinical trials. I also serve on the national medical advisory board of the Crohn’s and Colitis Foundation of America. By directing the clinical operations for the IBD program and coordinating clinical trials, we have recently developed an IBD research registry that phenotypes and prospectively collects clinical information on environmental factors and the natural course of diseases from IBD patients. In the first year, we have enrolled more than 500 patients and their families.

- **Krista Gray, CRNP** is the research nurse practitioner in the IBD Center. Ms. Gray provides direct patient care, assists the physicians in the clinic, participates in educational activities for patients and their families and is a co-investigator on several clinical research trials.

- **Beth Rothert, RN** and **Kim Morgan-Waugh, RN** are the research nurse coordinators for the IBD Clinical Program. They coordinate patient care, participate in national educational conferences and serve as “point persons” for IBD patients entering UPMC.

- **Kim Jones, RN** and **Katie Keller, RN** are the research nurse coordinators for the IBD Clinical Program. They are responsible for coordinating the clinical research trials and for the delivery of novel therapeutic agents to IBD patients.

This is an exciting time in the field of inflammatory bowel disease. The available medications and surgical procedures for IBD treatment are better than ever. The research advances in the fields of genetics and immunology have rendered a better understanding of the disease and offer hope to one day find a cure. The UPMC IBD Center is a nationally recognized program that provides unparalleled clinical care, offers the latest in cutting-edge research and promises to remain a leader in the field of IBD for decades to come.

To consult with a physician or schedule IBD patients, call the UPMC Digestive Disorders Center, toll-free, at 1-866-4 GASTRO (1-866-442-7876).

Dr. Regueiro is an Assistant Professor of Medicine, Co-Director of the Inflammatory Bowel Disease Clinical Center and Head of the Inflammatory Bowel Disease Clinical Program at the University of Pittsburgh.
IBD Genetics Research
by Richard H. Duerr, MD

A large body of evidence suggests that the inflammatory bowel diseases (IBD), Crohn’s disease and ulcerative colitis, result from interplay of genetic and environmental factors, triggering an overactive immune response in intestinal tissues. Observations in animal models of chronic intestinal inflammation suggest that intestinal bacteria are important environmental triggers of the inflammation.

The IBD Genetics Research Program at the University of Pittsburgh works to identify genes that predispose to IBD and to understand how these genes interact with each other and with environmental factors such as intestinal bacteria to cause IBD. Starting several years ago, we have collected DNA samples from hundreds of families with multiple IBD-affected members. Our team systematically searched the human genome to identify chromosome regions shared by IBD-affected relative pairs more often than expected by chance. Our studies and similar studies by other IBD genetics research groups have identified several chromosome regions that are linked to IBD.

Collaboration among researchers from various academic institutions including the University of Pittsburgh has yielded the identification of the first Crohn’s disease gene, NOD2/CARD15, which is located on chromosome 16 within one of the IBD-linked regions. The Crohn’s disease-associated genetic variants in NOD2/CARD15 appear to link environmental triggers (intestinal bacteria), the immune system (the innate immune system) and the development of Crohn’s disease. However, only 25 percent of Crohn’s disease can be attributed to the major NOD2/CARD15 genetic variants, and these NOD2/CARD15 genetic variants are not associated with ulcerative colitis. Therefore, more work needs to be done to fully understand the complex genetics of IBD.

Our research group is currently working to identify IBD genes on chromosome 2, 3 and 12. We also continue to collaborate with other IBD genetics research groups as one of the founding members of the IBD International Genetics Consortium and the NIDDK IBD Genetics Consortium.

Dr. Duerr is an Associate Professor of Medicine and Human Genetics, Co-Director of the Inflammatory Bowel Disease Center and Head of the Inflammatory Bowel Disease Genetics Program at the University of Pittsburgh.

IBD Immunology Research
by Scott E. Plevy, MD

My laboratory looks to understand how interactions between the immune system and the environment lead to the initiation and perpetuation of inflammation in inflammatory bowel disease (IBD). To accomplish this, we utilize mouse models of IBD and by using cells and tissue from IBD patients.

The environmental factor that has attracted the most attention in the pathogenesis of IBD is the enteric microbial flora. Bacteria and other microbes that reside in the intestinal tract outnumber mammalian cells in the human body by 10 to 1. These cells are separated by a single epithelial cell layer from the largest collection of immune cells in the body. The intestinal epithelium, both as an immunologically active cell type and as a barrier, serves to keep this abundant microbial mass from directly activating the immune cells that reside in the intestinal tract (the mucosal immune system). If bacteria gain access to the mucosal immune system, they must be rapidly eradicated. If, through defects in the epithelial cell or in the immune response, there is persistent stimulation of inflammation by intestinal bacteria, IBD may result.

Our laboratory is actively involved in many studies to determine how bacteria activate immune responses in the intestinal epithelium at the molecular level and, in important cells of the innate immune system, macrophages. We study the regulation of pro-inflammatory and anti-inflammatory cytokine gene expression. Understanding how bacteria activate pro-inflammatory pathways in the intestine and understanding mechanisms through which these pathways can be inhibited will lead to new insights into the pathogenesis of IBD as well as new therapeutic targets.

We are also interested in a second environmental factor that influences the course of IBD. In studies from numerous geographic populations, cigarette smoking has been well described as protective against the development of ulcerative colitis. We have been studying the potent anti-inflammatory effects of a component of cigarette smoke, carbon monoxide (CO), in mouse models of IBD.

Dr. Plevy is an Associate Professor of Medicine and Immunology, Co-Director of the Inflammatory Bowel Disease Center and Head of the Inflammatory Bowel Disease Immunology Program at the University of Pittsburgh.
A 19-year-old male was admitted with a two day history of hematochezia and presyncope. Initial hemoglobin was 12.7 g/dl. EGD showed no source of bleeding, and colonoscopy showed residual blood in the terminal ileum and no colonic sources of bleeding. His hemoglobin decreased to 7.7 g/dl with continued bleeding. Tc-99m pertechnetate scintigraphy was obtained (Figure 1).

Figure 1

Collagen deposition in 36 percent of patients compared to none of 20 controls. In most patients, collagen deposition did not correlate with clinical symptoms, response to a gluten free diet or long-term prognosis. However, clinical improvement and the normalization of biopsies took longer in those patients with extensive collagen deposition.

The etiology of collagenous sprue is unknown. Several pathogenetic mechanisms have been proposed, including a primary defect in collagen turnover, an underlying inflammatory process or toxicity from luminal factors leading to increased collagen deposition. Treatment for collagenous sprue is limited, and the response is variable. Corticosteroids, sulphasalazine, and metronidazole have been used in the literature with modest success.

Summary

The patient described above had severe villous flattening in the small intestine and collagen deposition throughout her gastrointestinal tract. Similar to patients with celiac sprue, there is an association with lymphoma, and she will need to be followed closely. Further management will include tapering steroids with an introduction of an immunomodulator as well as repeating small intestinal biopsies to determine histologic improvement.

References


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