UPMC Liver and Pancreas Institute (LPI)

by David A. Geller, MD

The UPMC Liver and Pancreas Institute (LPI) was established in 2006 to coordinate efforts among the clinical physicians and scientists managing patients with liver and pancreatic diseases. Flagship LPI programs include the Liver Cancer Center (LCC) and the Pancreatic Cancer Center (PCC). The LCC and PCC function as multidisciplinary health care teams at the forefront of providing clinical services, innovative treatment strategies, and cutting-edge research for patients with liver and pancreatic cancer.

The LPI, directed by Dr. Adam Slivka (see related article on page 3 of this issue) and Dr. David Geller, has the following specific goals:

✔ Establishment of an organizational structure implementing efficient delivery of healthcare services for patients with liver and pancreatic cancer within the UPMC Health System;

✔ Coordination and cross-fertilization of the established liver and pancreas centers of excellence at UPMC Presbyterian, Montefiore, Shadyside, and Passavant hospitals;

✔ A system-wide increase in overall clinic visits, admissions, operative procedures, regional therapies and transplant referrals; and

✔ Promotion of clinical and basic research activities for liver and pancreatic diseases.

The UPMC Liver Cancer Center (LCC) was launched five years ago as a division of the Starzl Transplant Institute, and evaluates over 500 new liver cancer patients per year. The physicians and staff at the LCC specialize in the management of HCC, cholangiocarcinoma, gallbladder cancer, neuroendocrine cancer, and metastatic colorectal cancer to the liver. Treatment options for liver cancer include surgical resection, liver transplantation, regional chemotherapy, Yttrium-90 internal radiation, radiofrequency ablation (RFA), systemic chemotherapy and novel gene therapy approaches. LCC surgeons, pioneers in laparoscopic liver resection surgery for cancer, have performed more than 200 of these minimally invasive hepatic resections.

The UPMC Pancreatic Cancer Center (PCC) was established in 2006 and is co-directed by Drs. Herbert Zeh and James Moser. The PCC provides state-of-the-art treatment for patients with pancreatic cancer, pancreatic cysts, and chronic pancreatitis. The PCC evaluates more than 300 patients with pancreatic cancer or pancreatic lesions each year.

Dr. Geller is Director of the UPMC Liver & Pancreas Institute and is the Co-Director of the Liver Cancer Center. He is the Richard L. Simmons Professor of Surgery at the University of Pittsburgh.
Pittsburgh, in the minds of many physicians, is synonymous with liver transplantation. The pioneering efforts of Thomas Starzl MD, recent recipient of the prestigious National Medal of Science, made organ transplantation a modern-day miracle. New developments in the care of patients with liver disease are featured in this Pitt Digest. Dr. David Geller’s cover page feature on the new multidisciplinary UPMC Liver Pancreas Institute (LPI) is complemented by articles by Drs. Adam Slivka and Kapil Chopra, who share leadership roles in the LPI.

UMPC liver and pancreas teams have been highly effective in providing innovative patient care and in advancing medical and surgical knowledge. Recently, LPI’s multidisciplinary pancreas team authored the June, 2007 issue of Gastroenterology Clinics of North America, entitled Advances in the Diagnosis and Treatment of Pancreatic Diseases. Thirty-three faculty and advanced fellows from the University of Pittsburgh contributed to this state-of-the-art update, covering both malignant and non-malignant diseases.

In this Digest, Dr. Jaideep Behari focuses on complex liver disease research, highlighting the clinical problems of fatty liver diseases. Having completed our group’s NIDDK T-32 training program under the mentorship of Dr. Satdarshan Paul Monga, Dr. Behari joined our faculty in June, 2006 and is a promising physician scientist in our Division.

Two of our clinical fellows, Drs. Carmen Meier and Scott Cooper (who also contributed to the production of another GI Rounds Online physician education program on chronic pancreatitis http://girounds.pitt.edu), provide the teaching cases in this issue. Our annual live physician education program, What’s New in GI and Hepatology will feature the Management of Female-Predominant GI Diseases and will be held on November 15 and 16, 2007.

We look forward to future opportunities to address your questions about UPMC’s digestive disease programs, patient collaborations and research breakthroughs. Join us for Pitt GI’s educational offerings — either in person or online!

In good health,

David C. Whitcomb, MD, PhD

Giant Eagle Foundation Professor of Cancer Genetics
Professor of Medicine, Cell Biology & Physiology and Human Genetics
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Understanding the Molecular Mechanisms of Fatty Liver Disease

by Jaideep Behari, MD, PhD

Nonalcoholic fatty liver disease, characterized by the accumulation of fat in the liver in the absence of significant alcohol intake, is an increasingly common reason for referral to hepatology clinics. NASH (for nonalcoholic steatohepatitis) is a progressive form of fatty liver disease that can lead to cirrhosis and liver cancer. Molecular signaling pathways in the liver cell play an important role in the development of this disease.

Compared with normal mice (panel A), knockout mice lacking β-catenin protein in the liver (panel B) show increased steatohepatitis when exposed to a steatogenic diet.

Research in my laboratory is focused on understanding the role of one such molecular signaling pathway, called the Wnt/β-catenin pathway, in the development of fatty liver disease. We use genetically engineered mice lacking the β-catenin protein in the liver (called “knockout” mice) and experimentally induce hepatic steatosis to study alterations in molecular processes within liver cells. Recently, we found that our knockout mice, when exposed to a steatogenic diet, have a striking increase in hepatic steatosis, in some cases approaching 100 percent. Knockout mice also have disturbances in several important metabolic pathways in the liver and show more hepatic fibrosis. We are currently dissecting the molecular interactions that underlie these results, and future research plans include developing strategies which utilize these observations to design therapeutic interventions for this disease.

Dr. Behari is an assistant professor of medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition. He practices in the Division’s Center for Liver Diseases.
The State of Pancreaticobiliary Cancer Diagnosis

by Adam Slivka, MD, PhD

With the unique dedication and expertise existing among faculty members of the Division of Gastroenterology, Hepatology and Nutrition and UPMC’s Oncologic Surgery and Transplant Surgery groups, along with the creation of the Liver and Pancreas Institute (LPI), UPMC is making major advances to improve the early diagnosis and care of patients afflicted with diseases of the pancreas and biliary system. The article which follows highlights our current knowledge and practice in the early diagnosis and management of two potentially devastating diseases, cancer of the pancreas and cholangiocarcinoma.

Pancreas Cancer

Of the 32,180 people in the United States diagnosed with pancreatic cancer every year, 31,800 will die from their disease. Pancreas cancer is the most lethal of all cancers and is the fourth highest cancer killer in the United States among both men and women. Early diagnosis of pancreas cancer is problematic, since there are no specific symptoms, and work-up for other conditions results in delayed diagnosis. Typical symptoms are midline abdominal pain radiating to the back associated with weight loss. Cancers in the head of the pancreas cause bile duct obstruction which is usually painless. New onset of diabetes in an older adult, new onset depression and upper back pain may also herald the development of pancreas cancer.

Recent studies investigating pancreatic cancer (PC) risk factors have determined that older age, male gender, African ethnicity, smoking, obesity and chronic pancreatitis may be linked to its development. A subgroup of PC has genetic components, and familial clustering may be seen. Diets, exposure to chemicals and pesticides as well as gingivitis and periodontal disease have been linked to pancreas cancers.

While there are no specific blood tests for PC diagnosis, elevated liver injury tests may indicate malignant obstruction of the bile duct, and tumor markers carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) may be elevated. Diagnostic imaging studies include CT scans and endoscopic ultrasound (EUS). CT scans using helical reconstruction and IV contrast equipment can detect tumors up to 1cm in size, provide information about spread to distant organs, most commonly the liver and regional lymph nodes, and confirm invasion of blood vessels making the tumor inoperable. EUS can detect even smaller tumors and has the added advantage of allowing safe fine needle aspiration with high diagnostic accuracy. Although more than 90 percent of pancreatic cancers are adenocarcinomas, there is an increasing recognition of precancerous conditions in both solid and cystic pancreas tumors. Pioneering work at UPMC and other institutes has examined the role of molecular derangements in early diagnosis in susceptible individuals and the recognition of precancerous lesions. DNA from individual cells can be examined for oncogenic mutations.

The only treatment offering a potential pancreatic cancer cure is surgical resection with the operative approach depending on the location of the tumor. Although the vast majority of patients will succumb to their disease, 20 percent of early-stage cancers may be cured with a surgical resection. In other patients undergoing surgery for curative intent but in whom the cancer recurs, survival is significantly improved compared to those who undergo medical treatment alone with chemotherapy and radiation.

Cholangiocarcinoma

Cholangiocarcinoma, a cancer of the biliary tree, is rare and affects 2,000 to 3,000 patients each year in the United States. Common symptoms are obstructive jaundice, itching, abdominal pain and weight loss. Blood tests show elevated liver injury, and tumor markers, CEA and CA19-9, may be variably elevated.

In the United States, the most commonly associated risk factor for cholangiocarcinoma is primary sclerosing cholangitis (PSC), an inflammatory disease involving the bile ducts. The risk of developing cholangiocarcinoma in PSC...
A Rare Complication of Pregnancy

by Carmen B. Meier, MD
Gastroenterology Fellow

Case Presentation

A 33-year-old woman, 36 weeks into her third pregnancy, presented with ten days of jaundice. She noticed dark urine and profound fatigue during the past week, and her husband reported that she fell asleep during conversations over the past two days. During the few hours prior to presentation, she had increasing uterine contractions. On physician exam, she was jaundiced and drowsy but was easily aroused with verbal stimulation. She had asterixis. Her abdominal exam was significant for mild bilateral upper quadrant tenderness and a gravid abdomen.

The patient’s preceding pregnancy occurred three years ago. She became jaundiced during this previous pregnancy, but this resolved spontaneously after delivery. Her only medication was a prenatal vitamin. She was married with two healthy children and denied use of any tobacco, alcohol or illicit drugs. Her family history was not remarkable.

Laboratory studies were significant for the following: total bilirubin 24 mg/dL, direct bilirubin 20 mg/dL, ALT 75 U/L, AST 127 U/L, ALP 324 U/L, INR 3 and WBC 20,000/mm^3 with a left shift. An abdominal ultrasound with Doppler evaluation was essentially normal.

Acute fatty liver disease of pregnancy (AFLP) was suspected. Fortunately, as the patient’s contractions became more frequent, her membranes ruptured, and she delivered a healthy baby boy. Following delivery, her mental status deteriorated further. She was intubated, and transferred to an ICU shortly thereafter.

A CT scan of the abdomen revealed a markedly enlarged liver with extensive hepatic steatosis (Figure 1). A liver biopsy was performed on day two of her hospitalization, showing severe microvesicular steatosis (Figure 2), confirming the diagnosis of AFLP. The woman eventually suffered seizures, and increased intracranial pressure was confirmed by jugular bulb catheter placement. She was listed for liver transplantation and received a cadaveric transplant seven days after initial presentation to the hospital. Her mental status improved rapidly after transplantation, and she made a full recovery. The pathology of the native explanted liver showed massive hepatic steatosis (3995 grams) with severe microvesicular and macrovesicular steatosis.

AFLP occurs in one out of 7,000 to 13,000 deliveries, most frequently during the third trimester and in multiparous women. Presenting symptoms are often nonspecific, such as nausea, vomiting and abdominal pain. Elevated aminotransferases, hyperbilirubinemia, leukocytosis, thrombocytopenia and coagulopathy are often present. Patients can worsen rapidly with hypoglycemia, pancreatitis and hepatic encephalopathy. Imaging, such as ultrasound or MRI, is often performed but is rarely helpful with diagnosis. The diagnostic gold standard is liver biopsy which shows microvesicular hepatic steatosis. Severe HELLP syndrome as well as viral hepatitis should be considered in the differential diagnosis.

The pathogenesis of AFLP remains unclear. Current evidence implicates disorders of lipid metabolism in the fetus with defects of mitochondrial fatty acid oxidation, specifically long-chain 3-hydroxyl-CoA dehydrogenase.

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Weight Loss and a Sunless Tan

Case Presentation

A 26-year-old woman with a past medical history significant for depression and hypothyroidism presented to the emergency room 24 hours after a laparoscopic cholecystectomy complaining of severe persistent nausea and vomiting. A CT scan (figure 1) showed the presence of water density fluid in the peripancreatic and right pericolic space. The pancreaticobiliary service was consulted to evaluate for a bile leak.

Four months prior to the cholecystectomy, the patient experienced progressively severe and frequent episodes of nausea and vomiting associated with a 45-pound weight loss. No exacerbating or relieving factors were found for the nausea. The patient reported intermittent watery diarrhea, anorexia, postural lightheadedness, and progressive generalized weakness and fatigue. She denied abdominal pain, fevers, chills, melena or hematochezia. Her complexion darkened with little exposure to the sun. Three months prior to her cholecystectomy, she had an extensive workup showing the following findings: two normal upper endoscopies with normal small bowel biopsies, a normal colonoscopy, normal abdominal and head CT scans and a normal TSH. Stool studies for cultures, c. diff. toxins, ova and parasites and fecal leukocytes were normal.

One week prior to presentation, her symptoms worsened, and the patient had a right upper quadrant ultrasound showing possible biliary sludge without evidence of biliary obstruction or cholecystitis. Due to these findings on the ultrasound the patient underwent an uneventful elective cholecystectomy without any known complications.

The patient’s physical examination was remarkable for hypotension with blood pressure of 94/54 pulse 88 and mild diffuse abdominal tenderness to deep palpation without signs of peritonitis. Laboratory evaluation was remarkable for serum sodium of 133, potassium of 5.2, hemoglobin of 11.9 with a normal MCV. CT scan findings were thought to be consistent with a normal postoperative state due to the lack of peritoneal signs. Further workup included an AM cortisol level, which was undetectable, and a plasma corticotropin level of 143 picograms per milliliter, which was consistent with chronic primary adrenal insufficiency or Addison’s disease.

Chronic primary adrenal insufficiency was first described by Thomas Addison in 1849 and has a prevalence of 39 to 60 per million people. The mean age of diagnosis is 40 years. Seventy to 90 percent of chronic primary adrenal insufficiency cases are due to autoimmune adrenalitis. The remainder of cases are caused by infections (e.g., tuberculosis, systemic fungal infections or AIDS), malignancy or hereditary causes. The common presenting signs and symptoms may be found in the lower left table. Hyperpigmentation is the most common physical finding and is usually more prominent in areas exposed to light and chronic friction. The hyperpigmentation is due to increased melanin in the skin due to elevated levels of adrenocorticotropic hormone (ACTH).

An AM cortisol reading of less than three micrograms per deciliter is diagnostic of adrenal insufficiency. A value greater than 19 micrograms excludes the diagnosis. Intermediate values require further testing, such as a cosyntropin stimulation test. Further testing with a serum ACTH level greater than 100 picograms per milliliter is diagnostic of primary adrenal insufficiency.

Treatment replaces insufficient steroids with 15mg hydrocortisone in the morning and 10mg in the afternoon along with 50 to 200 micrograms of oral fludrocortisone as a replacement for aldosterone.

The patient was started on hydrocortisone and fludrocortisone. Her nausea and vomiting resolved significantly within 24 hours, when she could consume a normal diet. Within one month, her energy returned to normal levels, she began regaining weight and her diarrhea resolved.
is approximately 15 percent. Approximately 80 percent of PSC patients have inflammatory bowel disease, more often ulcerative colitis than Crohn’s disease. Patients with chronic viral hepatitis and immune cholestatic liver disease are at increased risk for cholangiocarcinoma as are those with rare congenital abnormalities of the biliary tree called choledochal cysts. The incidence of cholangiocarcinoma appears to be increasing in North America, Europe, Asia and Australia. Reasons for these increases are unclear but may be related to improvements in diagnostic modalities.

Bile duct cancers may be located peripherally in the small bile ducts inside the liver or may be more centrally located in the main biliary tree as it leaves the liver and descends through the head of the pancreas into the duodenum. Bile duct cancers are adenocarcinomas by histology. They are slow growing tumors, and the cells surround themselves with fibrous tissue making their diagnosis difficult. These tumors may be diagnosed by CT scan. Using Endoscopic Retrograde Cholangio-Pancreatography (ERCP), catheters can be advanced into the bile duct with dye injected to visualize characteristic bile duct cancer blockages. Tissue may be obtained by brushing or biopsy. Most recently, the therapeutic endoscopy team of our Division has been chosen to test a new miniature scope that can be passed through the standard ERCP scope directly into the bile duct. Physicians at UPMC have used this new device, called the Spyglass, to improve diagnostic yield in patients with cholangiocarcinoma.

Pancreas cancer is the most lethal of all cancers and is the fourth highest cancer killer in the United States among both men and women.

Like pancreatic cancer, surgery is the only curative modality. Small tumors in the periphery of the liver may be cured in up to 40 percent of cases through resection of the involved segment of the liver. For tumors involving the main bile duct outside of the liver, cure rates of up to 40 percent may be expected with early disease and early diagnosis.

Unfortunately, the majority of patients with cancers of the pancreas and bile duct present too late to be offered a curative operation. In these instances, palliative surgery may improve survival and prevent suffering. ERCP can be used to place temporary or permanent stents to relieve bile duct and digestive tract obstructions. Endoscopic ultrasound can be used to provide nerve blocks for patients with unrelenting pain. Certain pancreas tumors and premalignant lesions located in the body and tail of the pancreas may be amenable to laparoscopic resection, with surgeons at UPMC having the world’s largest published experience in laparoscopic resection for pancreas tail tumors.

Dr. Slivka is a Professor of Medicine and is the Associate Chief for Clinical Care with the Division of Gastroenterology, Hepatology and Nutrition. He is also Co-Director for UPMC’s Liver Pancreas Institute.

References upon request.

What Is This photo on page eight:

The mucosa in the fundus and antrum was pale with loss of rugal folds. Submucosal vessels were visible under the thinned mucosa. This is the classic appearance of atrophic gastritis. There are three subtypes of atrophic gastritis: autoimmune metaplastic, environmental metaplastic (associated with Helicobacter pylori infection), and non-metaplastic (associated with gastric atrophy). The above patient had gastric fundic biopsies demonstrating chronic, inactive gastritis with intestinal metaplasia. He had a positive serum antibody to gastric parietal cells and was diagnosed with autoimmune gastritis. He has been cured of his pernicious anemia by regular monthly injections of vitamin B12. The above patient has autoimmune gastritis with prominent intestinal metaplasia and pernicious anemia. He has autoimmune thyroiditis, adrenal insufficiency and Type I diabetes mellitus.

What Is This?
Expanded Hepatology Services with the Liver Pancreas Institute

by Kapil B. Chopra, MD, FACP

The Comprehensive Liver Program at the Liver Pancreas Institute (LPI) is responsible for the medical management of patients with chronic liver disease. While based at the Center for Liver Diseases at the UPMC Presbyterian Hospital, liver clinical services are also offered at the UPMC Passavant and UPMC Shadyside hospitals.

LPI liver team members are liaisons for the management of complex liver disorders among the regional gastroenterologists, primary care physicians and the multidisciplinary medicine and surgery team of the UPMC Liver Pancreas Institute.

Areas of clinical expertise and emphasis for the Comprehensive Liver Program focus on the following disease presentations:

- Management of diverse chronic liver diseases including viral hepatitis B and C, autoimmune diseases, and genetic hemochromatosis;
- Complications of cirrhosis of the liver, including management of portal hypertension, ascites and hepatic encephalopathy;
- Screening and surveillance for hepatocellular carcinoma and cholangiocarcinoma; and
- Evaluation and selection of patients who may be appropriate liver transplantation candidates.

LPI’s Comprehensive Liver Program facilitates an organized and efficient way of delivering cutting-edge health care to patients with complex liver disorders.

Dr. Chopra is an Associate Professor of Medicine with the Division of Gastroenterology, Hepatology and Nutrition and is the Co-Medical Director for Liver Transplantation. Dr. Chopra is also Medical Director for the Comprehensive Liver Program with the Liver Pancreas Institute.

--- Faculty Focus ---

Randall Brand, MD, an internationally recognized expert on familial pancreatic cancer and early detection of pancreatic cancer and GI malignancies, joined the Division this autumn.

Dr. Brand directs the GI Malignancy Early Detection, Diagnosis and Prevention Program at UPMC and is academic director for the UPMC Shadyside GI Division (the hospital associated with the Hillman Cancer Center and University of Pittsburgh Cancer Institute).

Dr. Brand’s work will be featured in an upcoming issue of Pitt Digest.

--- Fellow News ---

The University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition is pleased to announce its new Gastroenterology Fellows.

Joining the Division of Gastroenterology, Hepatology and Nutrition as Year I Gastroenterology Fellows are:

**Elie Aoun, MD** – American University of Beirut (M), University of Pittsburgh Medical Center (R)

**Sandra El-Hachem, MD** – American University of Beirut (M), Cleveland Clinic, Lerner College of Medicine (R)

**David Lo, MD** – Northwestern University, Feinberg School of Medicine (M), Barnes-Jewish Hospital (R)

**Shahid Malik, MD** – Drexel University College of Medicine (M), University of Pittsburgh Medical Center (R)

Joseph Rodemann, MD – Loyola University Chicago, Stritch School of Medicine (M), Barnes-Jewish Hospital (R)

Vinay Sundaram, MD – New York University School of Medicine (M), University of Virginia Health System (R)

**Hepatology Fellow:**

**Anastasios Mavrakis, MD** – University of Athens Greece Medical School (M), Caritas St. Elizabeth’s Medical Center (Tufts) (R)

(M) = Medical School
(R) = Residency

Additional information about the University of Pittsburgh Fellowship program may be found at http://www.dom.pitt.edu/gi/fellowship/index.asp
What Is This?  Presentation: A 35-year-old African-American male with a past medical history significant for insulin-dependent diabetes mellitus presented with fatigue, shortness of breath and anemia (initial hemoglobin = 5.9 g/dL with an MCV = 126.0). An upper endoscopy was performed.

Compare your answer to Dr. Ng’s answer on page 6.

A Rare Complication of Pregnancy
continued from page 4

(LCHAD) deficiency found in some cases. Authorities recommend screening all infants born to a mother with AFLP for such disorders.

Treatment involves expedited delivery of the fetus and is otherwise largely supportive. The prognosis for AFLP is good with appropriate treatment, since most patients recover spontaneously after delivery. Yet, in some series, maternal mortality approaches 18 percent. Liver disease severity rarely progresses to necessitate transplantation. Fetal outcome data is sparse, but fetal mortality has been quoted at zero to 66 percent, with varying data related to the quality of perinatal care. Typically, this disease does not recur in subsequent pregnancies.