The UPMC Center for Liver Diseases offers a convenient, responsive point of access to a full range of liver disease treatments. The Center features care by experienced hepatology specialists and coordinates this care with a number of subspecialists, including experts in hepatobiliary and transplant surgery, hemochromatosis, therapeutic endoscopy, pathology and oncology.

The reputation of the Center for Liver Diseases has been built on its ability to provide cutting edge therapies. Expertise is available in transplant and liver surgery, liver oncology and abdominal imaging, as well as the promising new discipline of living donor liver transplantation. The Center also specializes in viral hepatitis, particularly hepatitis C, as well as cirrhosis and its complications, including hepatocellular carcinoma.

We are pleased to welcome David Sass, MD to the Center of Liver Diseases faculty in July 2004. Dr. Sass was the 2002-2003 chief GI fellow and is currently completing a fourth year of hepatology training in the Center for Liver Diseases supported by his AASLD/Schering Advanced Hepatology Fellowship Award. His research interest is adult hepatology, with a focus on primary biliary cirrhosis (PBC).

The Center for Liver Diseases currently operates in the Falk Medical Building on Fifth Avenue in Oakland. Within the coming year, the Center will move to the ninth floor of UPMC Kaufmann Building in close proximity to the Thomas E. Starzl Transplantation Institute.

To consult with a physician or schedule patients, call the Center for Liver Diseases directly at 412-647-1770 or, toll free, 1-866-4GASTRO (1-866-442-7876). (See Liver Disease Research article on page five)
The University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition is emerging as one of the most effective and innovative academic divisions in the nation. Our group is also becoming one of the largest GI divisions in the U.S., with more than 30 faculty members currently employed and with anticipation of over 40 faculty members by the end of next year.

This Division is effective because it is carefully divided into six centers of excellence which will be presented sequentially over subsequent issues of Pitt Quarterly Digest. The importance of a Center of Excellence is that it allows a physician-scientist with an interest in a specific disease process to work with other professionals to better understand every aspect of a complex medical problem.

Chronic gastrointestinal diseases have been especially difficult to understand and treat, because they represent the interaction of multiple factors contributing to an overall pathologic process. Our Centers of Excellence, working from bedside to bench and back to bedside, are effective in providing new insights into disease processes leading to major breakthroughs in gastrointestinal, liver and nutritional diseases.

I hope this issue provides a glimpse of the outstanding hepatology programs which are being developed in Pittsburgh. Your interest and support are vital to the continued success of such programs, and, as always, we look forward to hearing from you.

In good health,

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

Academic Health Centers: Condition Guarded

by Barry Kisloff, MD and Charles Dizard

The current medical care environment features increasing numbers of uninsured, demand for unfettered access to high tech medicine and – in the wake of our recent economic slowdown – a decrease in public funds available for health care. In this climate, the economic health and viability of Academic Health Centers (ACH) is both guarded and challenged.

ACH, composed of the union of a medical school, an affiliated hospital with house staff and a faculty practice plan, have missions and funding sources which are enormously diverse. The missions of AHC are teaching, research and patient care. Patient care includes:

- the need to provide a disproportionately large amount of uncompensated care;
- standby capacity to render highly specialized and unique care to a region; and
- the research and teaching functions which are the ultimate defining role of this type of facility. As with any enterprise, dollars are the life blood of an AHC, and its revenue consists of a complex, intricate web of cross subsidies including:
  - Patient care revenue which includes indirect medical education compensation provided to the AHC based upon intensity of teaching as measured by interns and residents per bed.
  - Direct medical education compensation for house staff and faculty salaries. This revenue source is explicit with Medicare and implicit in contracts negotiated with non-governmental payors.
  - Disproportionate hospital share payments from Medicaid.
  - Research grants.
  - Endowments and gifts to the medical school and hospital.

With the obligations and goals of the AHC, costs per inpatient case exceed those of other hospitals. What may surprise many is that despite the higher reimbursements received by an AHC, their collective profit margins are substantially less than non-AHC institutions as demonstrated using 1998 values.

References


continued on page six
Acute Liver Failure

by Yasser M. Bhat, MD
Fellow, Division of Gastroenterology, Hepatology and Nutrition
University of Pittsburgh Medical Center

Case Presentation

A 65-year-old retired insurance agent presented to his primary care physician with a three week history of jaundice with associated fevers, chills, nausea, vomiting and fatigue for five days. Fifteen years prior, he was diagnosed with sarcoidosis when he presented with massive splenomegaly, hypercalcemia and retroperitoneal lymphadenopathy. Non-caseating epitheloid granulomas were seen in the liver and spleen, and he was treated with prednisone for two years with good results. On current presentation, he denied weight loss, loss of appetite or recent travel history. He was a non-smoker and had worked in a plastics manufacturing factory with exposure to vinyl chloride for seventeen years, from age 27-44. Family history was non-contributory.

On examination he was icteric but in no acute distress. Abdominal exam revealed a tender liver edge 3cm below the costal margin. No stigmata of chronic liver disease or ascites were appreciated. Laboratory data included creatinine 1.7mg/dl, corrected calcium 9.2 mg/dl, hemoglobin 9.9 gm/dl, albumin 2.3 gm/dl, bilirubin 12.9 mg/dl, ALT 179 IU/L, AST 416 IU/L, ALP 394 IU/L and INR 1.6. Right upper quadrant sonography showed a coarse, heterogeneous liver with patent hepatic vessels. MR abdomen (Figure 1) revealed a liver replaced by innumerable nodules. Serologies for acute and chronic liver disease were negative.

Evaluation

Differential diagnoses for this case include angiosarcoma and hepatic sarcoidosis as well as infectious causes including mycobacteria, disseminated mycoses and Q fever. Percutaneous liver biopsy (Figure 2) confirmed the diagnosis of angiosarcoma. A single granuloma was seen on biopsy as well. The patient’s condition deteriorated over the next week. As he was not a candidate for chemotherapy, palliative measures were instituted, and he died eight days after admission.

Discussion

Hepatic angiosarcoma or hemangioendothelial sarcoma is a rare tumor of mesenchymal origin. It comprises less than two percent of all primary liver tumors, and about 25 cases are diagnosed annually in the United States. It is strongly associated with exposure to gaseous vinyl chloride monomer during its polymerization to polyvinyl chloride. First noted by Creech et al in 1974, there is a latency period of 19-22 years after exposure prior to development of tumor.

Other agents associated with angiosarcoma are thorotrast (a contrast agent last used in 1955), arsenic, cyclophosphamide, anabolic steroids, Von Recklinghausen’s disease and hemochromatosis.

Clinical features are generally non-specific. There is a 3:1 male preponderance, and the average age at diagnosis is 50 to 59. Symptoms include fever, sometimes of “unknown origin,” right upper quadrant abdominal pain, fatigue and weight loss. Physical examination may reveal jaundice, hepatomegaly, ascites and spontaneous hemoperitoneum (17 to 27 percent). Radiologic evaluation is generally not diagnostic. Abdominal films may show thorotrast in the periphery of the liver in those patients with a history of exposure. CT and MR scanning may show a single large mass or multifocal lesions of vascular origins. Diagnosis is made with liver biopsy, though on one-third of patients may develop a traumatic hemoperitoneum.

Established treatment protocols do not exist currently. Adriamycin-based chemotherapy has been tried with poor results. Rarely a tumor, if localized, may be amenable to surgical therapy. Liver transplantation has been attempted but carries a high rate of recurrence (65 percent in one study) and is therefore contraindicated. Median survival is about six months without treatment. Our patient appeared to have had a more aggressive form of the disease, since he presented with severe liver dysfunction leading to death.

Summary

Hepatic angiosarcoma is a rare primary hepatic tumor with a poor prognosis despite current therapy. It presents with a non-specific clinical picture but should be suspected in patients with a history of exposure to arsenic, vinyl chloride, thorotrast or the presence of spontaneous hemoperitoneum.

References

Edema in a Pediatric Patient
by Feras Alissa, MD
Fellow, Division of Pediatric Gastroenterology
Children’s Hospital of Pittsburgh

Case Presentation
A previously healthy three-year-old girl presented with a one-week history of periorbital edema. Over the next few days preceding admission, the edema progressed to involve both lower extremities and her abdomen. There was no history of fever, vomiting, diarrhea, urinary complaints or failure to thrive. Her physical examination was significant for periorbital edema, ascites and pitting edema of both lower extremities. Basic laboratories were significant for a total protein 3.7 g/dL and albumin 1.3 g/dL. CBC with differential was normal, and total lymphocyte count was 6624 cells/mm3 (normal for age). Urinalysis was normal without proteinuria. Chest X-ray showed small bilateral pleural effusions, and CT scan of the abdomen and pelvis showed free pelvic fluid and no masses.

Differential Diagnosis and Evaluation
In childhood, nephrotic syndrome is the most common cause for severe hypoalbuminemia, but this was excluded by the negative urinalysis. Although gastrointestinal symptoms were not present in this patient, gastrointestinal protein loss must also be considered. Common pediatric causes of GI protein loss include Menetrier’s disease, intestinal lymphangiectasia, celiac disease, and cystic fibrosis with malnutrition. Further workup revealed normal IgM and IgA, low IgG of 225 mg/dL (normal for age 505-1280), negative antiendomysial antibody, normal sweat chloride test and negative fecal elastase. The low IgG was compatible with GI protein loss. These studies excluded cystic fibrosis, pancreatic insufficiency and celiac disease. Elevated fecal alpha-1 antitrypsin levels of 1.33 mg/gm stool (normal 0-0.63 mg/gram stool) confirmed that the gut was the source of protein loss. An EGD showed a normal esophagus and stomach with multiple superficial aphthoid ulcerations in the duodenum. Biopsies from the esophagus and stomach were normal. Duodenal biopsies showed preserved villous architecture, dilated lymphatics and bowel wall edema consistent with intestinal lymphangiectasia (Figure 1: low power image, Figure 2: high power image).

The patient was given albumin and lasix for symptomatic relief. Then she was begun on a high protein, low fat and medium chain triglyceride (MCT) oil supplemental diet and was discharged home in good condition. Two weeks later, while still on dietary restrictions, she weighed 2.3 kg less than her admission weight, and her physical exam was unremarkable.

Discussion
Intestinal lymphangiectasia is characterized by diffuse localized dilation of the lymphatic channels extending into the small bowel villi, resulting from obstruction of lymph flow. Loss of lymph constituents may lead to lymphopenia, low albumin and IgG levels. Primary disease is generally rare, and it can be either isolated or part of a generalized syndrome that involves abnormal development of lymphatic vessels (e.g., Turner, Noonan syndromes). Secondary causes, such as intra-abdominal tumors, post radiation therapy, connective tissue diseases and cardiac diseases should be ruled out.

Dietary management is a lifelong therapy and is achieved by increasing protein intake and restricting dietary fat. The diet is supplemented with MCT oil, which is absorbed by the enterocytes by simple diffusion. Long term follow up studies show relapse if patients become noncompliant with dietary restriction. Other therapeutic options which have been evaluated include corticosteroids for connective tissue diseases and cardiac diseases should be ruled out.

Studies have shown promising results with heparin use, especially following surgery for congenital cardiac disease. Small intestinal B-cell lymphoma has been described as a complication, often five to 15 years from disease onset.

References:
Post-Transplant Hepatitis C: from Bench to Bedside

by A. Obaid Shakil, MD

A major interest of the Center for Liver Diseases, a hub of liver clinical research activity at the University of Pittsburgh Medical Center, is hepatitis C. This virus affects 1.8 percent of the American adult population. Among patients chronically infected, about 30 percent develop end-stage liver disease requiring liver transplantation. Compounding the problem is recurrent infection in the transplanted liver, which causes accelerated graft damage and high likelihood of graft failure and death.

To address these issues, I have initiated prospective follow up of liver transplant recipients with hepatitis C. In addition to the evaluation of demographic, clinical, virologic, histologic and donor variables, I will examine hepatitis C quasispecies as a predictor of disease severity. This study is funded by a grant from the National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDK).

Hepatitis C is an RNA virus that belongs to the family flaviviridae and genus hepacivirus. It has a positive single strand that encodes for a ~3000 amino acid viral polyprotein through a cap-independent mechanism. Because of an ineffective proofreading ability, the viral polymerase incorporates a high degree of nucleotide diversity. The virus thus exists as a mix of highly variable but closely related strains, thus the “quasispecies” terminology. My research focuses on the highly variable envelope glycoprotein which has multiple immunodominant epitopes.

The aim of my study is to examine the relationship between viral genetic features and the severity of recurrent hepatitis following transplantation by a) assessing HCV diversity prior to transplantation in a group of individuals with known transplantation outcomes; b) assessing HCV diversity following transplantation in a group of individuals; and c) tracking changes in cloned viral sequences by analyzing multiple sequences samples at frequent intervals prior to and following transplantation in a small number of individuals enrolled in prospective studies.

Immune suppression following liver transplantation diminishes the role played by host immune responses in graft survival. The presence of an association between genetic features of HCV and transplant survival may help screen individuals prior to transplantation to ensure higher graft survival as well as closer monitoring and stronger intervention following transplantation. We hypothesize that viral genetic features, rather than host factors, play a more important role in determining the disease course and outcome following liver transplantation. In other words, immunosuppressed transplant recipients with high levels of viral replication experience viral factors as the predominant drivers of disease activity.

When completed by the end of this year, this project should provide a better understanding of the pathogenesis of hepatitis C, particularly in the transplant recipient. Such knowledge will help us develop strategies to ensure a more favorable outcome through prevention and treatment of HCV infection.
Academic Health Centers (continued from page two)

In analyzing the disparity between AHC and non-AHC costs per case, the differential resides in wages and case mix costs (higher in AHC) and, most significantly, in indirect medical education and mission related costs. Of the mission related costs, the standby capacity constitutes the largest cost component. It is this facet of the AHC – allowing for clinical services such as specialized units and transplants – which the public most expects and faculty most demands.

The current tenuous finances of AHC are a product of attempts by public payors to:

- Decrease indirect medical education payments as per the Balanced Budget Act of 1997; and
- Decrease the disproportionate hospital share payments by State Medicaid agencies.

Private payors have attempted to seek coverage for their insured at less costly non-AHC facilities and to narrow margins for per-diem payments contracted at AHC hospitals. Recent attempts to slow the growth of health care spending, if successful, are likely to limit the dollars available for standby capacity.

The public must ultimately decide whether it will permit AHC to continue to fulfill their mission to provide advanced specialty care, teaching and research. AHC must, in turn, discriminate useful from redundant technology, translate useful technology into more cost effective ways to prevent and treat disease and enhance information transfer mechanisms which ultimately lessen costs.

Dr. Kisloff (left) is the Director of Clinical Services for the Division of Gastroenterology, Hepatology and Nutrition at the University of Pittsburgh. Mr. Dizard (right) is the Division Administrator.

What Is This?

A 78-year-old male with iron deficiency anemia presents for further evaluation. A colonoscopy is performed and the following findings are noted throughout the colon (Figures #1 and #2).

Compare your answer to Dr. Pabby’s answer on page five.