Bi-weekly Hepatitis Grand Rounds

CME—Live and Online—Enhances Understanding of Hepatitis and its Treatment

RAJENDER REDDY, MD

At Penn, Rajender Reddy, MD, has initiated a program called Viral Hepatitis Grand Rounds to increase physician access to vital information about hepatitis, its diagnosis and treatment. Director of Hepatology at the University of Pennsylvania, Dr. Reddy has published more than 200 articles on the subject of hepatitis, its treatment and effects.

Viral Hepatitis Grand Rounds is a CME event hosted by the Perelman School of Medicine and ViralEd, an online physician-directed medical education company. The event occurs on the fourth Wednesday of each month at noon (12 PM) eastern time and is available for on-demand viewing immediately following the live broadcast at **www.viraled.com/ hepatitisgrandrounds**. Dr Reddy and Mark Sulkowski, MD, Medical Director of the Viral Hepatitis Center at Johns Hopkins University School of Medicine, serve as course directors.

Presentations cover important and current topics in hepatitis therapy and are conducted by specialists with expertise in the field. Recent and future speakers include John W. Ward, MD, Director of the Division of Viral Hepatitis at the Centers for Disease Control and Prevention, and Nezam H. Afdhal, MD, Chief of Hepatology and Director of the Liver Center at Beth Israel Deaconess Medical Center. Presentations are designed to be immediately relevant to clinicians treating hepatitis; many are case-based.

The concluding ten minutes of each presentation consists of a live question and answer period, with the presenting faculty member available to answer questions from both attendees and participants using the webinar interface.

Viral Hepatitis Grand Rounds is designed for all hepatitis specialists, hematology/ oncologists, HIV/AIDS practitioners dealing with co-infection, infectious disease specialists, internal medicine specialists, family practice physicians, dermatologists, nephrologists, psychiatrists, public health professionals, OB/GYNs and other clinicians interested and involved in the care of patients with hepatitis.

The Penn Pancreatic Cyst Program *(con't from pg. 4)*

involve patient and family education about pancreatic cyst management, regular and prompt communication with referring providers and long-term surveillance of patients with pancreatic disease. Physicians are also introduced to information about new translational and clinical research studies to discover new avenues for diagnosis and treatment.

Referrals

Individuals who may benefit from evaluation at the Penn Pancreatic Cyst Program include patients with newly diagnosed or suspected pancreatic cysts, including:

- Intraductal Papillary Mucinous Neoplasms (IPMN)– both main duct and side branch variants
- Serous cystadenomas (SCA)
- Mucinous cystic neoplasms (MCN)
- Pseudopapillary tumors (AKA Frantz tumor, Hamoudi tumor)
- Cystic neuroendocrine tumors
- Pseudocysts secondary to pancreatitis
- Cysts for which the cause is unknown
- Family history of von-Hippel Landau syndrome

The program also welcomes patients seeking second opinions regarding diagnosis or therapy as well as those interested in participating in clinical research studies for pancreatic cysts.

Access

Ruth and Raymond Perelman Center for Advanced Medicine
Gastroenterology, Hepatology and Endoscopy Center

4th Floor, West Pavilion
3400 Civic Center Boulevard
Philadelphia, PA 19104
215-349-8222

ANIL K. RUSTGI, MD
T. Grier Miller Professor of Medicine and Genetics, Chief, Division of Gastroenterology

Chief's CORNER

The gastroenterology team at the Perelman School of Medicine and Penn Medicine is nationally recognized for clinical research and superlative care for its patients. I am pleased to announce the following recent honors and awards accorded our faculty.

Gary Falk, MD, MS, was co-director of the AGA/ASGE Clinical Congress, convened in San Diego, CA. from January 17-19, 2013. The meeting covered GI and liver topics by national experts, and also had a "hands-on" endoscopy course.

Penn has outstanding CME courses coming up, and we encourage your participation:

The 8th IBD Symposium
March 8-9, 2013 | Four Seasons Hotel | Philadelphia, PA
To register, visit cme.med.upenn.edu/eventinfo_9374.html

The 6th Annual Penn Live: GI Endoscopy and Liver Disease 2013
April 19-20, 2013 | University of Pennsylvania | Philadelphia, PA
To register, visit: cme.med.upenn.edu/eventinfo_9384.html

David Kaplan, MD, MS, and his group have received an NIH/NCI R01 grant on liver cancer and immunology/immunotherapy.

David Jaffe, MD, has won a teaching award given by Penn's medical students.

Octavia Pickett-Blakely, MD, MHS, was promoted to Assistant Professor of Medicine at Penn. As an expert in small bowel disorders (including celiac sprue), nutrition and obesity, she directs these programs at Penn GI.

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GASTROENTEROLOGY NEWSLETTER 2013

Penn Digestive & Liver Center
Penn Medicine

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Research in Pancreatic Cancer & Cystic Disease

GASTROENTEROLOGY NEWSLETTER

Translational Research in Pancreatic Cancer

This edition of the Gastroenterology Newsletter features a selection of the groundbreaking research examining the pathophysiology, genetics, diagnostics and treatment of pancreatic cancer and cystic disease. These studies represent a cooperative effort between the Divisions of Gastroenterology and Hematology-Oncology, the Abramson Cancer Center and the Departments of Medicine, Surgery, Pathology and Laboratory Medicine, and Oncology and Clinical Pharmacology at Penn Medicine.

Tumor-Derived Granulocyte-Macrophage Colony-Stimulating Factor Regulates Myeloid Inflammation and T Cell Immunity in Pancreatic Cancer

The tumor microenvironment of pancreatic ductal adenocarcinoma (PDA) is defined by active suppression of the immune response concomitant to inflammatory cell-associated tumor development and progression. Recently, a team of researchers at Penn Medicine identified granulocyte-macrophage colony-stimulating factor (GM-CSF) as an important regulator of inflammation and immune suppression in PDA. The team, comprised of specialists from the Abramson Cancer Center, the Divisions of Hematology-Oncology and Gastroenterology, and the Departments of Medicine and Pathology and Laboratory Medicine, was led by Robert H. Vonderheide, MD, DPhil, with contributions from Ben Z. Stanger MD PhD.

The GM-CSF finding was the result of a wider investigation into the role of the antigens Gr-1 and CD11b in PDA. Both antigens are expressed as markers on myeloid-derived suppressor cells (MDSCs), which contribute to immunosuppression in PDA. Numerous in vitro studies have reported the expansion of Gr-1+ CD11b+ cells in implantable tumor models. However, the in vivo relevance of the T cell suppressive qualities remains controversial.

The Penn researchers focused on the KPC mouse model of spontaneous PDA to evaluate a mechanism of tumor-induced immune modulation critical to maintaining the local immune suppressive network characteristic of the disease. KPC mice develop primary PDA lesions that faithfully recapitulate features of the human disease, including progression from preinvasive pancreatic intraepithelial neoplasia (PanIN) to invasive cancer to metastatic disease.

(con't pg. 2)

LOCATIONS

Ruth and Raymond Perelman Center for Advanced Medicine
3400 Civic Center Boulevard
Philadelphia, PA 19104
215.349.8222

Penn Presbyterian Medical Center
38th and Market Streets
218 Wright-Saunders Building
Philadelphia, PA 19104
215.662.8900

Penn Medicine at Radnor
250 King of Prussia Road
Module B
Radnor, PA 19087
610.902.1500

(con't from pg. 1)

The Penn researchers found that the dense desmoplasia and leukocytic infiltration classically observed in the tumor stroma of patients with PDA is reproduced in tumors of KPC mice. In addition, Gr-1+ CD11b+ cells were shown to accumulate in the spleen as well as the tumor in this model, where these cells maintained a close proximity to tumor cells and were prominently associated with metastatic lesions.

The authors noted that Gr-1+ CD11b+cells derived from tumor-bearing KPC mice suppressed the proliferation of splenic T cells from normal mice and that the cells exhibited high levels of arginase activity and nitrite, suggesting expression of inducible nitric oxide synthase (iNOS); both arginase and iNOS have been previously linked to immunosuppression by Gr-1+ CD11b+ cells in tumor-bearing mice.

Splenic cells proved to be the link to the potential origin of Gr-1+ CD11b+ cells in PDA. In the KPC murine model, splenocytes from tumor-bearing KPC mice exhibited a c-kit+ population similar in percentage to that of c-kit+ precursors found in bone marrow and higher than that found in splenocytes from normal mice. C-kit is a cell surface marker used to identify some types of hematopoietic progenitors in bone marrow.

When the researchers isolated c-kit+ Gr-1+ CD11b+ lineage cells from the spleens of tumor-bearing KPC mice and incubated them with conditioned media obtained from previously isolated cultured PDA tumor cells, c-kit+ cells expressed high levels of Gr-1 and CD11b, exhibited arginase and iNOS activity, and potently suppressed T cell proliferation in the OT-1 T cell suppression assay.

The Penn researchers hypothesized that a tumor-derived factor might drive the generation of Gr-1+ CD11b+ cells from c-kit+ cells in the spleen. To identify this factor, a set of secreted proteins from a panel of PDA tumor cell lines was measured in conditioned media and the results compared to those for conditioned media from benign pancreatic ductal cells from normal control mice. Conditioned media from every PDA line supported proliferation of c-kit+ cells into Gr-1+ CD11b+ cells, whereas media from none of the normal pancreatic ductal cells supported c-kit+ cell proliferation. Among 11 proteins examined, only granulocyte-macrophage colony-stimulating factor was expressed at high levels by every PDA line but by none of the normal pancreatic ductal lines, suggesting that tumor-derived GM-CSF might be linked to Gr-1+ CD11b+ cell generation.

When recombinant GM-CSF was tested in in vitro assays, the researchers found that GM-CSF drove proliferation and differentiation of c-kit+ Gr-1+ CD11b+ splenocytes isolated from tumor-bearing mice into functional myeloid-derived suppressor cells. Further investigation concluded that GMCSF is both necessary and sufficient for in vitro generation of functional, immunosuppressive Gr-1+ CD11b+cells, and that in vivo GM-CSF secreted by transformed pancreatic epithelial cells is critically involved in the regulation of inflammation associated with PDA. When tumor-derived GM-CSF was abrogated in vivo, tumors failed to grow, rejected by an T cell response. Importantly, the investigators showed that GM-CSF is expressed by more than 95% of pancreatic tumors from patients, providing further rationale for novel strategies to inhibit GM-CSF in clinical trials.

This study was published in Cancer Cell.

Bayne LJ, Beatty GL, Jhala N, Clark CE, Rhim AD, Stanger BZ, Vonderheide RH. Tumor-Derived Granulocyte-Macrophage Colony-Stimulating Factor Regulates Myeloid Inflammation and T Cell Immunity in Pancreatic Cancer. Cancer Cell. 2012 Jun 12;21(6):822-35.

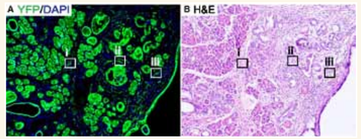
Pancreatitis Research

The Rustgi lab is investigating the ways in which pancreatic development and regeneration and pancreatitis and cancer overlap. Funded by the NIH, the group pioneered the use of 3-dimensional cell culture model systems, and uses these with animal models and human tissues to identify key genes and pathways that drive these processes. A recent report from the group that explored the regulatory processes that overlap ductal development, acinar-ductal metaplasia and the progression of normal cells to pancreatic intraepithelial neoplasia appeared in Genes and Development.

Reichert M, Takano S, von Burstin J, Kim SB, Lee JS, hida-Stansbury K, Hahn C, Heeg S, Schneider G, Rhim AD, Stanger BZ, Rustgi AK. The Prrx1 homeodomain transcription factor plays a central role in pancreatic regeneration and carcinogenesis. Genes Dev. 2013; Jan 25.

EMT and Dissemination Precede Pancreatic Tumor Formation

Currently, two major paradigms have been proposed to explain the metastatic process. The first, or classical model, sees metastasis as the final step in a progressive sequence in which tumors acquire mutations that promote invasive behavior and dissemination late in tumor evolution. The alternative model envisions metastasis as an inherent feature of a tumor very early in its natural history. This model is consistent with recent investigations in the field of breast cancer that suggest that cellular dissemination leading to metastasis (or metastatic seeding) may occur prior to the formation of an identifiable primary tumor among cells that would not meet a standard definition of cancer.



Hematogenous Spread and Liver Seeding Precede Tumor Formation

(A and B) images showing individual YFP$^+$ cells (green) intermingles with stromal cells prior to tumor formation in 10-week-old PKCY PanIN mouse (A). Delaminated YFP$^+$ cells have a spindle-shaped morphology and express Zeb1 (boxes i-iii); they are indistinguishable from surrounding Zeb1$^+$YFP stromal cells by H&E staining of an adjacent section (B).

Recently, this alternative model has evoked the concept that pancreatic cancer cells precede the formation of tumors. Among the mysteries of pancreatic adenocarcinoma is that while it is often discovered after the cancer has matured and metastasized, it is rarely found in its nascent stages.

To examine the early events leading to pancreatic tumor formation, a team of researchers at Penn Medicine led by Ben Z. Stanger, MD, and Andrew Rhim, MD, developed a sensitive lineage-labeling system to tag (detect and isolate) cells of pancreatic epithelial origin during stochastic tumor progression in a mouse model. An advantage of the labeling system was that it allowed the team to determine the kinetics of the epithelial-to-mesenchymal transition (EMT) and hematogenous dissemination during the natural evolution of pancreatic ductal adenocarcinoma (PDAC). It has been proposed that carcinoma cells undergo EMT, losing epithelial characteristics and acquiring invasive properties and stem-like features in the process.

Results

The Penn team discovered that tagged cells invaded and entered the bloodstream unexpectedly early, before frank malignancy could be detected by rigorous histologic analysis; this behavior was widely associated with epithelial-to-mesenchymal transition (EMT).

Circulating pancreatic cells maintained a mesenchymal phenotype, exhibited stem cell properties, and seeded the liver. EMT and invasiveness were most abundant at inflammatory foci, and induction of pancreatitis increased the number of circulating pancreatic cells. Conversely, treatment with the immunosuppressive agent dexamethasone abolished dissemination. These results provide insight into the earliest events of cellular invasion *in situ* and suggest that inflammation enhances cancer progression in part by facilitating EMT and entry into the circulation.

This study was published in Cell.

Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, Reichert M, Beatty GL, Rustgi AK, Vonderheide RH, Leach SD, Stanger BZ. EMT and dissemination precede pancreatic tumor formation. Cell. 2012 Jan 20;148(1-2):349-61.

PENN GASTROENTEROLOGY RESOURCES

- GI Division patient website: PennMedicine.org/GI
- GI Division academic website: www.med.upenn.edu/gastro
- GI Division Research: www.med.upenn.edu/gastro/research.shtml

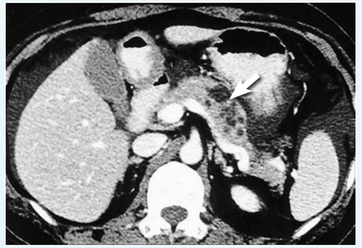
PENN CANCER RESOURCES

- Abramson Center patient website: www.penncancer.org
- Abramson Cancer Center Research website: www.oncolink.org
- Roberts Proton Therapy Center: www.pennmedicine.org/perelman/proton

The Penn Pancreatic Cyst Program

The Penn Pancreatic Cyst Program offers a single point of access to a collaborative, multidisciplinary team of experts in pancreatic cyst management whose goal is to optimize clinical care, propel research and enhance the collective education and expertise of the field.

Pancreatic neoplasms are classified as benign pseudocysts or lesions with pre-malignant or malignant potential. Of the three, pseudocysts are by far the most common, representing up to 80% of pancreatic lesions and an incidence of roughly 1 per 1000 persons per year. Relatively uncommon by contrast, premalignant and malignant pancreatic neoplasms represent a profound risk to well-being. The majority of pancreatic cancers are discovered at an advanced stage, when treatment is ineffective. When discovered early, premalignant lesions can be resected with an excellent prognosis, but their diagnosis is often confounded by their radiological and symptomatic resemblance to harmless pseudocysts.



Chronic pancreatitis with pseudocysts in the body of the pancreas (arrow).

Practitioners faced with a pancreatic lesion are often in need of a resource to evaluate the patient and identify next steps. More importantly, the diagnosis of a pancreatic cyst can be stressful and confusing for patients so it is critical that when appropriate they receive timely assessment, treatment and long-term surveillance for their condition.

These concerns, and the specter of under-treatment for evolving premalignant neoplasms, were among the driving forces for the creation of the multidisciplinary Penn Pancreatic Cyst Program.

Under the co-direction of Nuzhat A. Ahmad, MD, associate Director of the Penn endoscopy program and Charles M. Vollmer, MD, Director of pancreatic surgery, the Program has the goal of improving clinical care for patients with pancreatic disease, as well as promoting research and enhancing the collective education and expertise of specialists in the field.

A component of the Program, the Pancreatic Cyst Management Conference meets every other week to offer to offer physicians in the region a single point of access to a collaborative, multidisciplinary team of experts in pancreatic cyst management.

At each meeting, physicians from gastrointestinal surgery, gastroenterology, radiology and pathology/cytopathology collaborate on the care of individual patients.

In explaining the Conference, Dr. Ahmad emphasizes its integrative and collaborative processes. "Each week, physicians submit cases to the Conference for review," Dr Ahmad says. "A team made up of specialists in gastroenterology, radiology and pathology/cytopathology then arrives at a consensus for diagnosis. This, in turn, leads to the development of a comprehensive treatment plan in consultation with surgeons and others involved in the patient's care."

Given that a substantial proportion of pancreatic cysts are overtly malignant, or at least premalignant at the time of diagnosis, surgical removal plays a significant role in the management of this problem. Often surgery offers an early intervention to an otherwise lethal entity – pancreatic cancer. However, many patients can be safely observed, and therefore avoid the short- and long-term complications of an unnecessary pancreatic resection. The multidisciplinary clinic allows for pancreatic surgical specialists Charles Vollmer, MD, (Director of Pancreatic Surgery) and Jeffrey Drebin, MD, (Chairman of Surgery) to select an optimal approach for each patient. Penn Medicine ranks among the top 10 in the country for volume of pancreatic resections at close to 150/year. When surgery is necessary, outcomes at Penn for major pancreatic surgery are among the best in the nation.

The comprehensive treatment plans developed at the Pancreatic Cyst Program extend into the community to

(con't pg. 5)