UNIVERSITY OF VIRGINIA
JOURNAL *of* MEDICINE

Inside:

May 2009 • Volume 5

University of Virginia Health System

Information for Authors:

Purpose:

The mission of *the University of Virginia Journal of Medicine* is to provide residents, fellows, and faculty members the opportunity to publish original materials generated from their experiences in patient care or patient care related research. Broadly, each edition will include 5-10 case reports, 3-4 clinical reviews and updates on recent advances, and 1-2 clinical commentaries. **The journal will give UVA housestaff the opportunity to work with the faculty in writing medical case reports, thus providing a forum for learning about the process of journal article submission and revision.** In addition, the journal offers referring physicians in the state of Virginia, alumni of the medicine training programs, and healthcare providers associated with the University the opportunity to learn from the breadth of clinically based educational experiences generated from patient care at the University of Virginia.

Article Submission

Only original, unpublished materials will be considered for publication. Inclusion of housestaff on all articles is strongly recommended. Submissions should be made electronically to Joy Hilton, (njh3s@virginia.edu). Any images or figures accompanying the article should be emailed as separate .jpg files. When submitting a manuscript, authors should provide full disclosure of any duplicate publication of any content of the paper in a cover letter to the Editor.

Manuscript Format

- Authors are encouraged to follow the AMA writing style as outlined in *Writing and Publishing in Medicine*, 3rd Edition, Edward J. Huth, MD. Accepted manuscripts are edited in accordance with the *American Medical Association Manual of Style: A Guide for Authors and Editors*, 9th edition. All measurements should be expressed in SI units. Abbreviations that are nonstandard should be avoided; other abbreviations must be defined on first use. Generic drug names are preferred. The manuscripts must be free of any identifying patient information in order to respect confidentiality.

Images

- Any supporting images for an article must be submitted as .jpg files of at least 360 dpi. Files should be sent as separate attachments, and not imbedded within the article text. A placeholder such as <<image 1>> should be used within the text. Please take into consideration that all images will be converted to black and white for printing.

References

- All information not considered statements of common knowledge must be supported by citation of published articles in the medical scientific literature.

- Literature sources must be cited according to AMA guidelines.

  Examples of Reference Style:
  Journal Article
  1. Spock MR, McCoy D. Extraterrestrial transfusion methods. *J Interplanetary Med*. 2800;13:53-65.

  Book
  1. West H. *Reanimation in Theory and Practice*. Arkham, MA: Miskatonic University Press; 1923.

Guidelines for Article Review Process

Manuscripts will be blindly reviewed by two members of the review board. Decisions regarding acceptance for publication will be based on the strength of the paper compared with other papers in the literature, the need for *the University of Virginia Journal of Medicine* to represent a balanced picture of important advances in internal medicine, and the number of accepted papers in the paper's category and topic area. In addition, reviewers will score submissions based on the following criteria.

i. Originality of case presentation
ii. Clarity of teaching points
iii. Balanced and evidence-based representation of recommendations
iv. Quality of the writing

UVa Journal Article Categories:

Clinical Vignettes: *length - 800-1600 words*
- Clinical vignettes describe patients with classic presentations of rare diseases or common diseases with unusual or interesting aspects. Authors are encouraged to present a brief review of pertinent literature and discuss salient parts of the patient diagnosis. Clinical Vignettes are coauthored by the resident or fellow and the attending physician who supervised the care of the patient and focus on one or two teaching points related to diagnosis, management, or treatment.

UVa Images in Medicine: *length - maximum 250 words*
- Presentation of a radiographic image or digital photograph of an intriguing patient case accompanied by a brief case report. Authors should focus on the diagnosis and management of underlying pathophysiology related to the presented image and associated medical condition.

Medical Grand Rounds: *suggested length - 1600-3200 words*
- A review article written by an attending physician who recently presented during Medical Grand Rounds at the University of Virginia. Specifically, this article should provide readers a thorough overview of recent scientific and technologic advances, discussed during the Grand Rounds and developed at the University of Virginia, which have contributed to the overall understanding and management of specific conditions.

Clinical Review Article: *length - 1600-3200 words*
- A comprehensive review article written by an attending physician based on a thorough assessment of the literature with the goal of outlining the current understanding of the pathophysiology and up-to-date practice guidelines for specific clinical topics.

Clinical Commentary: *length - 1600-3200 words*
- The Clinical Commentary offers attending or resident physicians an opportunity to provide a unique clinical perspective on a component of patient care, education, or medical advancements. The scope of this submission is quite broad and may incorporate discussion of controversial issues in the practice of medicine, topics related to or examples of patient care that have affected the author's personal or professional outlook, and/or commentaries about health care policy or public health.

The Academic Hospitalist Corner: *length - 1600-3200 words*
- This section is dedicated to the emerging field of inpatient hospitalist medicine. Article submissions may be case reports, clinical reviews, perspective pieces, and/or commentaries on medical education and training as related to hospitalist medicine.

Chief Resident Clinical Medicine Conference: *length - 1600-3200 words*
- A report that describes a rare or unusual case, with an emphasis on processes of differential diagnosis, work-up, and management that are also applicable to commonly encountered medical conditions. The article should include a thorough discussion of several diagnostic dilemmas with the goal of addressing both the management of complex pathophysiology and the process of systematically arriving at difficult diagnoses.

Tutorials in Medicine: *length - 1600-3200 words*
- A classic presentation of a disease process with board-style questions about the case. This is followed by a discussion of one or more of the following: differential diagnosis, pathophysiology, management, or treatment. These should be authored by an attending physician with resident or fellow physician collaboration.

Clinical Research: *length - 1600-3200 words*
- Presentation of original data from clinical research conducted wholly or in part at the University of Virginia. Research accepted for publication must be current, well-executed, and applicable to patient care.

Burkitt Lymphoma, Lactic Acidosis, and Hypoglycemia in a 23-Year-Old Man: Literature Review and Treatment Strategy

Adam Zivony, MD, Postgraduate Year 3, Internal Medicine
Matthew M. Synan, MD, Postgraduate Year 3, Internal Medicine
John J. Densmore, MD, PhD, Associate Professor of Medicine, Division of Hematology/Oncology

Burkitt lymphoma is an aggressive lymphoma that very rarely presents with hypoglycemia and lactic acidosis. To date, only one such case has been described in the literature. We describe a young man with these complications, which were found to be the result of his underlying malignancy.

CASE REPORT

A 23 year-old white man without a significant medical history sought medical care because of weakness, fatigue, and dark stools that had been occurring for 1 week. A complete blood count revealed severe anemia and thrombocytopenia. A thorough gastrointestinal evaluation was performed, including an esophagogastroduodenoscopy, which revealed gastritis positive for *Helicobacter pylori*. A Hematology/Oncology consultation was obtained for evaluation of the patient's thrombocytopenia, which was initially believed to be secondary to thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. A peripheral blood smear revealed blasts, however, and this finding along with results of a subsequent bone marrow biopsy were diagnostic for Burkitt lymphoma.

On arrival at our institution from an outside facility, the patient was found to be somnolent. Laboratory findings revealed elevated blood urea nitrogen at 36 mg/dL and markedly elevated creatinine at 1.7 mg/dL. An anion gap of 36 was noted, with a corresponding bicarbonate gap of 12 indicative of an anion gap acidosis with concurrent metabolic alkalosis. Of note, the patient also had a glucose concentration of 28 mg/dL. A complete blood count revealed a white blood cell count of 13.62 k/μL, hemoglobin concentration of 10.5 g/dL, and hematocrit of 31.7%. The patient's platelet count was 29 k/μL. Lactate dehydrogenase, uric acid, and lactic acid were 9294 g/dL, 24.1 mg/dL, and 13.6 mmol/L, respectively, indicating ongoing tumor lysis. Because of the patient's profound hypoglycemia, a test for antiinsulin antibodies was performed, which was negative. Abnormally low levels of insulin-like growth factor (IGF) 51 ng/mL (reference interval 109-358 ng/mL); IGF-binding protein 3, 1.5 μg/mL (3.4-7.8 mg/mL); C-peptide, 0.25 ng/mL (0.5-2.0 ng/mL); and proinsulin, 1.5 pmol/L (3-20 pmol/L) were noted.

The patient was given ½ ampule of D50, after which he showed marked resolution of his altered mental status. His improvement was temporary, however, necessitating treatment with a D10 infusion. The patient required intermittent boluses of D50 to combat hypoglycemia during the next 24 hours. The patient's acute renal failure, which was believed to be attributable to both prerenal azotemia secondary to dehydration and tumor lysis, was treated with an infusion of 50% normal saline with 75 meq of sodium bicarbonate. Two doses of rasburicase were administered, and this treatment was followed by resolution of hyperuricemia. The patient was then started on induction chemotherapy with rituximab, cyclophosphamide, and intrathecal methotrexate, which resulted in improvement of his lactic acidosis and hypoglycemia. The patient's renal function initially improved, with a creatinine nadir of 1.2 mg/dL. With continued tumor lysis, however, his metabolic disarrary worsened, and the patient required transfer to the medical intensive care unit, where he underwent temporary hemodialysis.

DISCUSSION

Burkitt lymphoma, an aggressive form of non-Hodgkin B-cell lymphoma, is composed of small noncleaved cells. This disease is typically diagnosed in children and young adults but has been reported in middle-aged adults. It is a multivariant disease, with the endemic form, first described by Burkitt in 1958, predominantly seen in equatorial Africa.[1,2] The other subtypes include sporadic and immunodeficiency-related disease. All forms of this lymphoma have identical histological characteristics and chromosomal translocation involving the MYC onocogene.[2] Burkitt lymphoma

accounts for 40% to 50% of childhood non-Hodgkin lymphomas in nonendemic areas and 1% to 2% of all adult lymphomas in Western Europe and the United States.[3]

The clinical presentation of Burkitt lymphoma is largely dependant on the variant. The endemic form typically presents in young children, with involvement of the jaw, maxilla, and orbit.[4] This form has been associated with Epstein-Barr virus as well as concurrent malaria.

The sporadic form of Burkitt lymphoma is the most common form seen in developed countries. It has a propensity to invade the gut and the upper respiratory tract and can present with striking symptomatology of abdominal pain, bloating, and back pain. Bone marrow involvement is not typically seen at presentation, although it may develop as a complication of progressive disease. The sporadic form is associated with Epstein-Barr virus in approximately 30% of cases. The presence of circulating blasts is typical of advanced-stage disease. A variant associated with immuno-compromise is often seen in HIV and AIDS patients as well as posttransplantation patients on immunosuppressive therapy.

The first and only other reported case of Burkitt lymphoma presenting with lactic acidosis and hypoglycemia was reported in 2005 by Glashen and Sorensen. In this case, a 74-year-old patient with Burkitt lymphoma had symptomatic hypoglycemia unresponsive to glucose and glucagon as well as a severe anion gap acidosis secondary to a serum lactate of 15.8 mmol/L.[5] Our patient presented with a similar biochemical findings, but the 2 cases have multiple differences, particularly the age of the patients.

The mechanism of lactic acidosis in lymphoma is not clear. Sillos et al reviewed 28 cases of lymphoma and 25 cases of leukemia that presented with lactic acidosis through 2001. These investigators reported that 24 of 28 lymphoma cases and 18 of 24 leukemia cases had liver involvement.[6] This finding suggests that hepatic involvement of the underlying malignancy predisposes patients to lactic acidosis, which is likely secondary to decreased clearance of serum lactate. Our patient did not have obvious evidence to suggest lymphomatous involvement of the liver, but he did have rising total bilirubin throughout his hospital course. Another hypothesis is that IGFs produced by tumor cells may cause the overexpression of hexokinase, thus causing a decreased rate of glycolysis and an increased amount of serum lactate secondary to anaerobic metabolism.[7]

Our patient also presented with profound hypoglycemia (<40 mg/dL) refractory to therapy with intravenous glucose. Malignancy-associated hypoglycemia is thought to be secondary to increased tumor metabolism of glucose or elevated tumor release of IGF, which in turn causes increased use of serum glucose to maintain the high metabolic rate of tumor cells.[8] Many tumors are noted to produce IGF-like peptides, specifically IGF-II, that have 3- to 4-fold increased insulin-like bioactivity. When these growth factors combine with insulin-sensitive tissues, severe hypoglycemia may ensue that is not easily corrected with exogenous glucose or glucagon therapy. Often these patients have low inherent IGF, a state that corresponds to a probable negative feedback loop from overproduction of other unmeasured IGF molecules.[9]

The modality for therapy in a patient with Burkitt lymphoma presenting with hypoglycemia and severe lactic acidosis is treatment of the underlying tumor burden. During the past 10 years, the introduction of high-intensity clinical regimens has significantly improved outcomes for patients with Burkitt lymphoma. One initial mode of therapy, reported by Magrath et al, that showed excellent response rates in high-risk patients was the use of cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, and intrathecal therapy for 2 cycles each. Noted toxicities associated with this regimen include neurotoxicity from intrathecal therapy, hematological toxicity, and severe mucositis.[10] Modified regimens have been established to reduce the risk of toxicity, including a recent regimen established on the basis of a phase II study by Lacasce et al that demonstrated a decrease in neurotoxicity and mucositis with no treatment-related deaths. This treatment was effective in low-risk patients.[11] Other treatment modalities being explored include monoclonal antibody therapy such as rituximab, which has been shown to increase overall survival and disease-free survival when used with the regimen reported by Magrath et al.[12]

In summary, the patient we describe presented with lactic acidosis and hypoglycemia that were rare manifestations of Burkitt lymphoma. The only effective therapy for this condition is treatment of the underlying malignancy and supportive care. Further research into the mechanism of this aggressive disease is warranted to identify additional treatment modalities.

REFERENCES

1. Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. *Blood.* 2004;104:3009-3020.
2. Coakely D. Denis Burkitt and his contribution to haematolgoy/oncology. *Br J Haematol.* 2006;135:17-25.
3. Yustein JT, Dang CV. Biology and treatment of Burkitt's lymphoma. *Curr Opin Hematol.* 2007;14:375-381.
4. Wright DH. What is Burkitt's lymphoma and when is it endemic? *Blood.* 1999;93:758
5. Glasheen JJ, Sorensen MD. Burkitt's lymphoma presenting with lactic acidosis and hypoglycemia: a case presentation. *Leuk Lymphoma.* 2005;46:281-283.
6. Sillos EM, Shenep JL, Burghen GA, Pui CH, Behm FG, Sandlund JT. Lactic acidosis: a metabolic complication of hematologic malignancies. *Cancer.* 2001;92:2237-2246.
7. Mazurek S, Boschek CB, Eigenbrodt E. The role of phosphometabolites in cell proliferation, energy metabolism, and tumor therapy. *J Bioenerg Biomemb.* 1997; 29:315-330
8. Werner J, LeRoith D. The role of the insulin-like growth factor system in human cancer. *Adv Cancer Res*. 1996;68:183-223
9. Daughaday WH, Trivedi B, Baxter RC. Serum "big insulin-like growth factor II" from patients with tumor hypoglycemia lacks normal E-domain O-linked glycosylation, a possible determinant of normal polypeptide processing. *Proc Natl Acad Sci U S A.* 1993;90:5823-5827.
10. Magrath I, Adde M, Shad A, et al. Adults and children with small noncleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. *J Clin Oncol.* 1996; 14: 925-934.
11. Lacasce A, Howard O, Lib S, et al. Modified Magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. *Leuk Lymphoma.* 2004; 45:761-767.
12. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer* 2006;106:1569-1580.

Cardiac Sarcoidosis: A Case Report and Diagnostic Considerations

Kristen Gandee, BS, Medical Student
Robert Szeles, MD, Postgraduate Year 3, Internal Medicine
Gavin Slitt, MD, Postgraduate Year 2, Internal Medicine
Andrew Darby, MD, Fellow Physician, Department of Medicine, Division of Cardiovascular Medicine
James Bergin, MD, Professor of Medicine, Division of Cardiovascular Medicine

Sarcoidosis is a multisystem disease of unknown etiology. It is characterized by the cross-reactivity of antigen-presenting cells to a self-antigen that initiates a robust inflammatory response with $CD4^+$ T lymphocytes, which ultimately leads to the formation and maintenance of noncaeseating epithelioid cell granulomas.[1,2] Pulmonary involvement is the most common manifestation, but any organ can be affected. Cardiac involvement is rare and may be manifested by conduction abnormalities, congestive heart failure, ventricular arrhythmias, and sudden death.[3] Because of the relatively nonspecific presentation and inconsistent testing modalities for this condition, the diagnosis of cardiac sarcoidosis (CS) can be difficult and often is considered only after exclusion of a broad differential that includes malignancy, infection, and connective-tissue disorders. We report an unusual case of a 51-year-old man presenting with new-onset cardiomyopathy and complete heart block (CHB) caused by CS.

CASE REPORT

The patient, a 51-year-old man with a history of hypertension, diabetes, and obstructive sleep apnea, was admitted to an outside hospital with dyspnea on exertion, 2-pillow orthopnea, and lower-extremity edema of 1-month duration. The patient reported progressive shortness of breath for the past 6-8 months without chest pain/pressure or tightness, and review of other systems was positive only for diffuse, nonspecific arthralgias. The patient's medical history was also notable for a sinus infection 2 months prior to admission, exposure to occasional topical solvents during his work as a truck driver, and no known exposure to tuberculosis. The initial evaluation at the referring hospital included a transthoracic echocardiogram that demonstrated a systolic ejection fraction of 15%-20% with moderate mitral regurgitation. Lower-extremity Doppler ultrasound revealed a left superficial femoral vein thrombosis, and a computed tomography–pulmonary angiogram demonstrated cardiomegaly as well as bilateral mediastinal and hilar lymphadenopathy. Left and right heart catheterization revealed a 50%-60% stenosis of the left anterior descending artery and 75% stenosis of the posterior descending artery. An attempt at percutaneous coronary intervention was aborted after the patient became hypotensive and developed CHB. The patient was then transferred to the University of Virginia (UVA) Health System for possible pacemaker placement and further evaluation of this newly diagnosed cardiomyopathy and mediastinal lymphadenopathy.

The patient's physical exam upon arrival was notable for central obesity, distant heart sounds without murmurs or gallops, and equal but distant breath sounds without rales. Electrocardiogram readings showed fluctuation between accelerated junctional rhythm and sinus bradycardia with 2:1 atrioventricular block. Despite coronary artery disease revealed by catheterization, the patient's ischemic disease was not felt to fully account for the severity of left ventricular dysfunction seen on echocardiography. Alternative diagnoses that were considered included cardiac abnormalities attributable to familial mutations, infectious myocarditis, and infiltrative and autoimmune diseases. Lymphoma and infectious etiologies leading to the patient's diffuse lymphadenopathy were also considered. Results of blood cultures, serological tests for Lyme disease and troponin levels were negative. The patient subsequently underwent a mediastinoscopy with lymph-node biopsy, revealing noncaseating granulomatous inflammation most consistent with sarcoid. A gadolinium-enhanced cardiac magnetic resonance imaging (MRI) demonstrated full-thickness delayed enhancement of the inferior wall consistent with an infarct, left ventricular hypokinesis, and myocardial thinning as well as patchy and linear midmyocardial delayed enhancement involving the septum, anterior wall, apex, and lateral wall of the left ventricle (Figure 1). These findings were consistent with myocarditis or infiltrative disease. Given the combination of newly manifesting cardiomyopathy and conduction abnormality

along with noncaseating granulomas of the lymph node and myocardial infiltration visible on MRI, the patient's presentation was considered to be most consistent with the diagnosis of CS. He began treatment with 75 mg of prednisone daily, and trimethoprim/sulfamethoxazole was added for *Pneumocystis jiroveci* prophylaxis. The patient also successfully underwent dual-chamber permanent pacemaker implantation for his CHB and was discharged to home with close followup and continuation of his medical regimen.

DISCUSSION

CS is an infiltrative disease characterized pathologically by a patchy accumulation of noncaseating granulomas in the myocardium. CS can present prior to, in concordance with, or subsequent to sarcoidosis of other organs. Autopsy studies have shown that myocardial granulomas occur in 20%-30% of patients with sarcoidosis in the United States, but less than 5% of these cases demonstrated clinical evidence of CS, indicating that CS is often asymptomatic.[4]

Clinical manifestations of CS depend on the site of infiltration and the degree of scar formation. The most common location is the left ventricular free wall, followed by the intraventricular septum.[3] The myocardium is extremely vulnerable to insult by sarcoid granulomas. Electrocardiographic changes such as arrhythmias, conduction abnormalities, nonspecific repolarization, and pseudo-infarction patterns can be seen in up to half of patients with clinically evident involvement.[5] Conduction abnormalities ranging from first-degree atrioventricular block to CHB are the most common clinical manifestation.[3] CHB has been reported to affect 23%-30% of patients with CS.[3] Compared to cohorts who develop idiopathic CHB, patients with CHB due to sarcoidosis typically present at a younger age.[6] This clinical distinction can be important in the diagnostic evaluation of a patient with suspected CS. Ventricular arrhythmias are the second most common presentation of CS,[3] followed by valvular disorders, congestive heart failure, and sudden cardiac death.

Diagnosing CS is a difficult task that has yet to be definitively outlined. The Japanese Ministry of

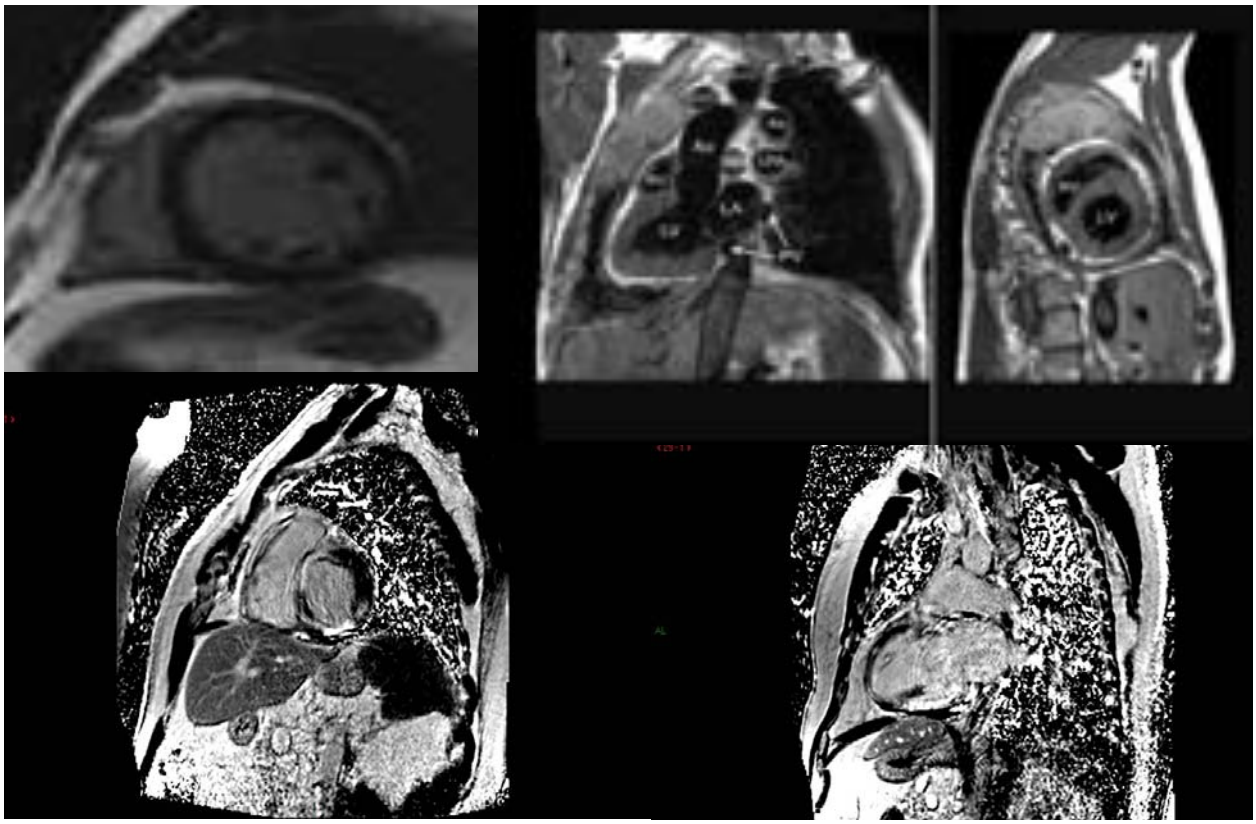


Figure 1. Cardiac magnetic resonance imaging (MRI) showing short-axis (left) and long-axis (right) views. Top, Normal MRI. Bottom, Patient MRI demonstrating areas of patchy midwall enhancement suggesting an infiltrative process.

Health and Welfare published guidelines[7] that have been used by other CS studies, but the criteria have not been prospectively validated. The guidelines, which are based on examination of CS from either a histologic or clinical perspective, are further elucidated in Table 1. In the hospital setting, endomyocardial biopsy showing noncaseating granulomas remains the gold standard, but this method is extremely limited in its utility. One study evaluated the diagnostic yield of endomyocardial biopsies in patients who were strongly suspected of having CS on the basis of a diagnosis of sarcoidosis in other organs according to the criteria in Table 1 (14 patients) and the presence of abnormalities on electrocardiogram, cardiac radionuclide images, or in left-ventricular wall motion (12 patients).[8] Only 5 (19.2%) of the 26 cases (9 of the 105 total biopsy specimens) were positive for granulomatous lesions. The inability to capture the granulomas is likely due to the patchy distribution of the disease as well as its tendency for basal locations, whereas biopsies tend to be from the apical septum. Recent clinical evidence has supported the use of gadolinium-enhanced cardiac MRI for its ability to detect nonviable tissue (focal scarring) associated with the inflammatory process. Smedema et al found the sensitivity and specificity of MRI to be 100% and 78%, respectively, with an overall accuracy of 83%.[9] In this study, however, CS was diagnosed based on the nonvalidated guidelines from the Japanese Ministry of Health and Welfare, and the investigators did not compare cardiac MRI findings to those from MRI-guided biopsy specimens.

Table 1. Guidelines for Diagnosing Cardiac Sarcoidosis from the Japanese Ministry of Health and Welfare[7]

1. **Histologic diagnosis**
   Endomyocardial biopsy demonstrating noncaseating epithelioid granulomas
2. **Clinical diagnosis**
   In patients with a histologic diagnosis of extra cardiac sarcoidosis, cardiac sarcoidosis should be suspected when item (a) and one or more of item (b) through (e) are present.
   (a) Complete right bundle branch block, left axial deviation, atrioventricular block, ventricular tachycardia, premature ventricular contraction, abnormal Q or ST change on the electrocardiogram.
   (b) Abnormal wall motion, regional wall thinning or dilation of the left ventricle on echocardiogram.
   (c) Perfusion defect on myocardial perfusion imaging or abnormal accumulation by gallium -67 or technetium -99m myocardial scintigraphy.
   (d) Abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed ejection fraction of the left ventricle on cardiac catheterization.
   (e) On endomyocardial biopsy, interstitial fibrosis or cellular infiltration over moderate grade, even if the findings are nonspecific.

Without a standard and dependable method to diagnose CS, there is a wide spectrum for misdiagnosis. Often a diagnosis is made only after exclusion of other possible diagnoses. Myocarditis, lymphoma, amyloidosis, hemochromatosis, and other infiltrative diseases can have presentations similar to CS.[10] Testing for these conditions can help narrow the possibilities. CS can closely mimic idiopathic dilated cardiomyopathy, and differentiation between the 2 requires attention to certain factors. For example, thoracic computed tomography can demonstrate significant mediastinal lymph-node swelling in CS patients, whereas mediastinal lymphadenopathy is usually absent in patients suffering from idiopathic dilated cardiomyopathy.[11] One study from Japan found that CS presenting as dilated cardiomyopathy was characterized by female predominance, a high incidence of advanced atrioventricular block, abnormal wall thickness, uneven wall motion abnormalities, and perfusion defects preferentially affecting the anteroseptal and apical regions.[12]

The standard treatment for CS is corticosteroids, which can slow the inflammatory process, halt the progression of cardiac disease, and improve survival. Dosages of 60-80 mg of prednisone per day are started initially, with close follow-up to determine efficacy and the potential for dose reduction pending disease control. Corticosteroids do not prevent ventricular arrhythmias,[13] thus antiarrhythmic agents and B-blockers may be warranted. Cyclophosphamide, azathioprine, and methotrexate can be substituted if corticosteroids are ineffective or produce intolerable side effects.[14,15] There has also been some success with the use of infliximab for refractory CS,[1] although this agent has been associated with an increase in mortality in patients with heart failure.[17] Although neither modality has been thoroughly evaluated, pacemaker placement for heart block or implantable cardioverter-defibrillator placement for those with ventricular arrhythmias and a risk of sudden death may be necessary. Surgery is also an

option, ranging from correction of damaged valves to cardiac transplantation for intractable damage and end-stage failure in young patients.[18]

The prognosis of systemic sarcoidosis is very good, with a 1% to 5% mortality rate per year.[19] The prognosis of CS, however, is quite poor. One early study noted a median survival of 2 years after the presentation of cardiac signs and symptoms, and another study noted a 5-year survival rate of 40%.[3,2] The use of corticosteroids, pacemakers, and implantable cardioverter-defibrillators are improving survival, a trend that should be enhanced by efforts toward earlier diagnosis and treatment initiation as well as consistent follow-up.

REFERENCES

1. Thomas PD, Hunninghake GW. Current concepts of the pathogenesis of sarcoidosis. *Am Rev Respir Dis*. 1987;135:747-760.
2. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *NEJM*. 2007;357:2153-2165.
3. Roberts WC, McAllister HA Jr, Ferrans VJ. Sarcoidosis of the heart: a clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy patients (group 11). *Am J Med*. 1977;63:86-108.
4. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation*. 1978;58:1204-11.
5. Stein E, Jackler I, Stimmel B, et al. Asymptomatic electrocardiographic alterations in sarcoidosis. *Am Heart J*. 1973;86:474-477.
6. Fleming HA. Cardiac sarcoidosis. *Semin Respir Med*. 1986;8:65-71.
7. Hiraga H, Yuwai K, Hiroe M, et al. *Guidelines for the Diagnosis of Cardiac Sarcoidosis: Study Report on Diffuse Pulmonary Disease*. Tokyo: Japanese Ministry of Health and Welfare; 1993:23-24.
8. Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. *Am Heart J*. 1999;138:299-302.
9. Smedema JP, Snoep G, van Kroonenburgh MP, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. *J Am Coll Cardiol.* 2005;45:1683-1690
10 Lubitz S, Goldbarg S, Mehta D. Sudden cardiac death in infiltrative cardiomyopathies: sarcoidosis, scleroderma, amyloidosis, hemachromatosis. *Prog Cardiovasc Dis*. 2008;51:58-73.
11. Otsuka K, Terasaki F, Eishi Y, et al. Cardiac sarcoidosis underlies idiopathic dilated cardiomyopathy: importance of mediastinal lymphadenopathy in differential diagnosis. *Circ J*. 2007;71:1937-1941.
12. Yazaki Y, Isobe M, Hiramitsu S, et al. Comparison of clinical features and prognosis of cardiac sarcoidosis and idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1998;82:537-540.
13. Le Guludec D, Menad F, Faraggi M, Weinmann P, Battesti J, Valeyre D. Myocardial sarcoidosis: clinical value of technetium-99m sestamibi tomoscintigraphy. *Chest*. 1994;106:1675–1682.
14. Lower EE, Baughman RP. The use of low dose methotrexate on refractory sarcoidosis. *Am J Med*. 1990;229:153-157.
15. Chapelon-Abric C, de Zuttere D, Duhaut P, et al. Cardiac sarcoidosis: a retrospective study of 41 cases. *Medicine (Baltimore)*. 2004;83(6):315-334.
16. Barnabe C, McMeekin J, Howarth A, Martin L. Successful treatment of cardiac sarcoidosis with Infliximab. *J Rheumatol.* 2008;35:1686-1687.
17. Chung E, Packer M, Lo K, Fasanmade A, Willerson J. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate to severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation*. 2003;107:3133-3140.
18. Valantine H, Tazelaar H, Macoviak J, et al. Cardiac sarcoidosis: response to steroids and transplantation. *J Heart Transplant*. 1987;6:244-250.
19. Gideon NM, Mannino DM. Sarcoidosis mortality in the United States 1979-1991: an analysis of multiple-cause mortality data. *Am J Med*. 1996;100:423-427.
20. Fleming H, Bailey S. The prognosis of sarcoid heart disease in the United Kingdom. *Ann N Y Acad Sci*. 1986;465:543-550.

Combination of Corticosteroids and Anidulafungin Associated with Acute Liver Injury and Hepatic Encephalopathy: Synergistic Toxicity

R. Christopher Harmon, MD, PhD, Fellow Physician, Department of Medicine, Division of Gastroenterology and Hepatology
Stephen H. Caldwell, MD, Professor of Medicine, Division of Gastroenterology and Hepatology
Michael G. Douvas, MD, Assistant Professor of Medicine, Division of Hematology/Oncology
Patrick G. Northup, MD, MHES, Associate Professor of Medicine, Division of Gastroenterology and Hepatology

Anidulafungin is a new antifungal agent used in the treatment of serious fungal infections due to *Candida* and *Aspergillus* species. The reported safety profile of this new agent favors its use over potentially more toxic antifungal agents, and no cases of acute liver failure (ALF) associated with this agent have been reported. The effect of the clinical use of anidulafungin in combination with corticosteroid treatment is unknown; however, animal studies have shown up to 100% mortality with anidulafungin in corticosteroid-pretreated mice.

We report a case of ALF occurring in a patient after treatment with dexamethasone and anidulafungin. This patient's ALF was associated with increased alanine aminotransferase (ALT) to nearly 2000 U/L, a peak international normalized ratio (INR) of 2.1, and altered mental status. Initial assessment included viral serologies, blood cultures, chest x-ray, abdominal ultrasound with Doppler exam of hepatic vasculature, an echocardiogram and consideration of other hepatotoxins. These investigations did not lead to discovery of the cause of the patient's ALF. Anidulafungin treatment was discontinued, and within 36 hours the patient's ALT began to decrease. Supportive care including the administration of lactulose resulted in improvement in his mental status within 12 hours and gradual return of normal liver function. Thus, anidulafungin may be associated with drug-induced liver injury and ALF and this risk may be increased with recent or concomitant treatment with corticosteroids. Immediate withdrawal of this agent if suspected as a cause of drug-induced liver injury may allow for return of normal liver function.

CASE REPORT

The patient was a 69-year-old man with a significant medical history of myelodysplastic syndrome and type II diabetes mellitus. The patient had recently been found to have progression to acute myelogenous leukemia, and he was admitted to the University of Virginia Health System for scheduled chemotherapy with a standard induction regimen with cytarabine and idarubacin. Prior to admission the patient had been in his normal state of health. His diabetes was well controlled with diet and metformin 500 mg twice daily (held on admission). He was otherwise healthy and had no history of liver disease, heavy alcohol consumption, or risk factors for blood borne pathogens. Prior to initiation of chemotherapy, the patient was evaluated with a multiple gated acquisition scan, which showed a left ventricular ejection fraction of 65%.

The patient received induction chemotherapy with cytarabine and idarubicin (idarubicin on days 0, 1, and 2 and cytarabine on days 0 through 6). Cytarabine was given at 100 mg/m^2 per day by continuous 24-hour infusion. The patient was also given 4 doses of dexamethasone at 20 mg daily on days 0 to 3 for prevention of chemotherapy-induced nausea. He tolerated administration of his chemotherapy regimen well. In response to his induction chemotherapy he became neutropenic and subsequently developed an apparent central venous catheter infection on day 6 as evidenced by erythema and induration around the catheter. Cultures were drawn from the catheter and catheter tip and multiple peripheral draws were obtained throughout his hospitalization, but cultures did not result in organism growth and speciation. Treatment for neutropenic fever was initiated with cefepime, ciprofloxacin, and vancomycin, and the patient's central line was removed. Despite this treatment, he continued to be febrile for several days. His fever was treated symptomatically with low doses of acetaminophen intermittently, with a maximum dose of 2.6 g in one day. Anidulafungin was initiated on day 10 as empiric treatment for persistent neutropenic fever. Prior to the administration of anidulafungin the patient reported feeling well and unchanged from his preadmission state of health.

On day 11 the patient's mental status significantly declined from baseline, and clinical assessment was consistent with encephalopathy. Initial laboratory values indicated acute liver injury, with an ALT of 1026 U/L. His INR was elevated to 2.0, and ammonia was determined to be 91. Total bilirubin was elevated at 2.9. The patient was determined to have grade III hepatic encephalopathy and thus ALF. The time course of laboratory data vs administration of potential hepatotoxic agents is shown in Figure 1.

DIAGNOSIS AND MANAGEMENT

The differential diagnosis for acute hepatic injury with aminotransferase elevations greater than 15 times the upper reference limits include toxic exposure; infection, including viral infection/ reactivation or fungal infection; vascular insufficiency, including hepatic venous thrombosis and shock liver; and autoimmune hepatitis.[1] Initial assessment in this case included blood cultures, a chest x-ray which showed bibasilar atelectasis, and right upper-quadrant ultrasound with Doppler exam of the hepatic vasculature which revealed normal liver size, mild fatty infiltration of the liver, a moderate amount of gallbladder sludge with a thickened gallbladder wall, no evidence of candidal lesions, and patent vasculature with appropriate directional flow. Echocardiogram showed decreased global left ventricular systolic function. Empiric treatment for the patient's ALF was initiated. First, all potential hepatotoxins were withdrawn, which included: acetaminophen, cefepime, ciprofloxacin, and anidulafungin. Given the new finding of global left ventricular dysfunction, fluid status was optimized and diuresis initiated with intravenous lasix. Initiation of empiric treatment for herpes simplex virus and Epstein-Barr virus hepatitis with acyclovir was considered, but deferred. Subsequent testing revealed negative Epstein-Barr virus antibodies, cytomegalovirus viral load, and viral hepatitis profile. Finally, the patient was given lactulose and the dose was titrated for effect.

The echocardiogram results indicated that the patient had global decreased left ventricular systolic function; however, right ventricular function was normal. There was no focal segmental

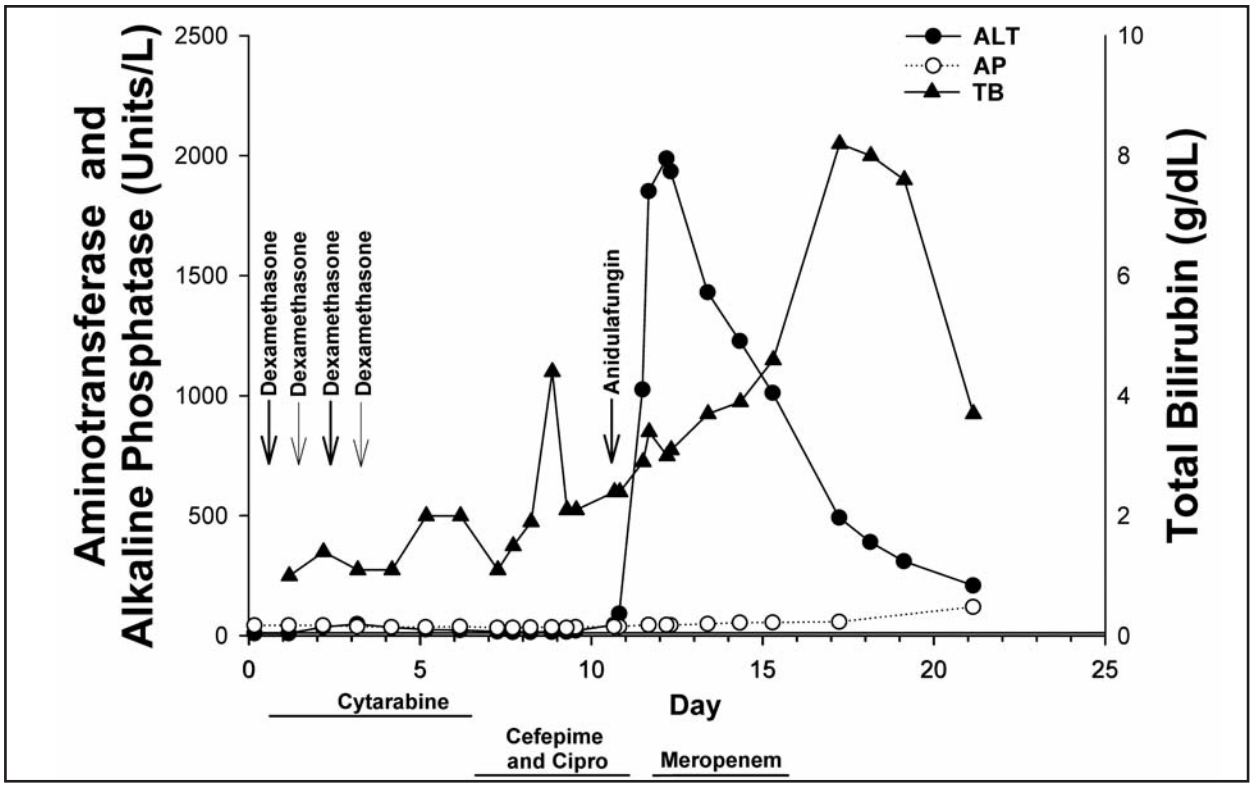


Figure 1. Clinical course timeline. Medications shown include all potentially hepatotoxic agents received by the patient. Arrows indicate single-dose administration. Lines indicate range of time during which the patient received medications. ALT indicates alanine aminotransferase; AP, alkaline phosphatase; TB, total bilirubin; APAP, acetaminophen; Cipro, ciprofloxacin.

dysfunction or preceding chest pain that would indicate occlusive coronary disease. Clinically, the patient was slightly volume overloaded with mild peripheral edema, but there was no jugular venous distention. Significantly, there was no hepato-jugular reflex to indicate hepatic congestion. There was also no ascites apparent on exam or on abdominal ultrasound, confirming the absence of hepatic congestion. The patient maintained good perfusion with warm extremities throughout his hospitalization and there were no episodes of hypotension. This decline in cardiac function was attributed to idarubacin-induced cardiotoxicity associated with intravenous fluid for prevention of tumor lysis syndrome. This mild volume overload responded well to medical management with diuresis and was not felt to be a major contributor to the patient's clinical picture of ALF.

After initial treatment the patient showed improvement clinically and in laboratory values. Within 12 hours of initiation of lactulose therapy the patient's mental status improved from stage III hepatic encephalopathy to stage II. He was conversant and appropriate, but somnolent. Lactulose treatment continued until there was significant evidence of improved liver function. Aminotransferases peaked within 36 hours of withdrawal of potential hepatotoxins. As expected, there was a delay in recovery of hepatic function, as indicated by peak INR of 2.1 on day 16 and total bilirubin of 8.2 on day 17. Prior to discharge on day 21 the patient's INR was within normal limits and total bilirubin was 1.9. There was no evidence of hepatic encephalopathy at the time of discharge.

DISCUSSION

Drug-induced liver injury (DILI) is the primary cause of ALF in the United States.[2] DILI is often a diagnosis of exclusion, but it must be strongly considered in the differential diagnosis of a patient with abnormal aminotransferase or bilirubin laboratory values. Studies of patients with jaundice from severe DILI demonstrate a short-term mortality as high as 10%.[3] In addition, patients with fulminant hepatitis from DILI have only a 20% likelihood of survival with supportive care.[4] In the case we report, the clinical time course and exclusion of other potential causes of ALF indicated that the patient had DILI. The mechanism of DILI can be classified as hepatocellular, cholestatic, or mixed injury. This classification is aided by calculating an R ratio (ALT divided by alkaline phosphatase). DILI can be characterized biochemically and clinically as predominantly hepatocellular when the R ratio at presentation > 5, cholestatic when R is <2, or mixed when 5 > R > 2. Most drugs have a signature profile with a characteristic pattern of liver injury and range of time to onset.[5] In this patient, calculation of the R ratio yields a value in excess of 40, indicating direct hepatocellular injury. There was no significant cholestasis, as evidenced by a normal alkaline phosphatase and no intra- or extrahepatic biliary ductal dilatation on ultrasound. There was, however, an elevation of total bilirubin, which was attributed to either cytarabine or hemolysis with subsequent hepatocelluar injury.

Potential hepatotoxic agents administered throughout the patient's hospitalization included acetaminophen, cefepime, ciprofloxacin, and cytarabine. Acetaminophen doses were well below therapeutically acceptable doses and the patient was not predisposed to toxicity by malnutrition or chronic alcohol ingestion, thus making acetaminophen toxicity improbable. Cefepime and ciprofloxacin cause a cholestatic pattern (R ratio <2) of injury and are unlikely to explain this patient's DILI.[6-8] Finally, cytarabine is known to be associated with hyperbilirubinemia and jaundice; however, acute DILI is less well characterized.[9] With the exception of venoocclusive disease, there have been no documented cases of ALF due to cytarabine. The R values of potential hepatotoxins are shown in Table 1.

Anidulafungin is an echinocandin antifungal medication that is generally considered a safe and effective treatment for systemic fungal infections due to *Aspergillus* and *Candida* species. This new

Table 1. R-values of Potential Hepatotoxicants*

Toxicant	R value
Acetaminophen	>5
Ciprofloxacin	<2
Cefepime	<2
Cytarabine	<2
Anidulafungin	Unknown to date
Case patient	41.2

*Drug-induced liver injury can be characterized biochemically as predominantly hepatocellular when the R ratio (alanine aminotransferase divided by alkaline phosphatase) at presentation > 5, cholestatic when R is <2, or mixed when 5> R >2. Most drugs have a signature profile with a characteristic pattern of liver injury and range of time to onset.[5]

intravenous agent is used in the treatment of candidemia, esophageal candidiasis, and other forms of invasive candidiasis.[10] One major benefit of anidulafungin is the absence of significant hepatic metabolism and renal excretion of the parent compound. At physiologic temperature and pH, anidulafungin undergoes slow chemical degradation to an inactive ring-opened peptide. After degradation, the ring-opened peptide is converted to peptide fragments and eliminated. The disposition of the nonpeptide metabolites has not been described, however. Anidulafungin has an elimination half-life of 26.5 hours, and there is no need to adjust the dose of this medication in either hepatic or renal disease.[10] Abnormal serum aminotransferase levels are known to occur with anidulafungin treatment, with an incidence of 2.3%.[10] To date, there have been no published reports of anidulafungin-induced hepatotoxicity and clinical ALF.

Our patient may have been predisposed to anidulafungin toxicity due to recent dexamethasone treatment, as suggested by animal studies indicating that corticosteroid pretreatment may predispose to anidulafungin toxicity. Pretreatment of rats with corticosteroids led to an increase in animal death associated with anidulafungin treatment. Animal models in the absence of infectious exposure receiving both corticosteroids and anidulafungin died at a rate of up to 100% vs 0% with anidulafingin alone, indicating a potentially toxic drug interaction with corticosteroids.[11] No causal relationship for the increased animal deaths in this study was reported. The safety of anidulafungin in corticosteroid-treated human patients has not been investigated. Further investigation into the possible interaction and toxicity associated with anidulafungin and corticosteroids is needed.

CONCLUSION

Abnormalities in serum aminotransferases are known to occur with anidulafungin, but to date there have been no reported cases of ALF associated with this agent. This is the first reported case of ALF that appears to be directly related to the new antifungal agent anidulafungin. Anidulafungin is likely safe in the general population; however, until more data are available, anidulafungin should be used with caution in patients who have recently received corticosteroids. Anidulafungin should also be considered as a potential cause of DILI and should be immediately withdrawn if suspected as a potential inciting agent. Early recognition of toxicity and withdrawal of this agent may allow for complete resolution of ALF and return to normal liver function.

REFERENCES

1. Polson J, Lee WM, and the American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology*. 2005;41:1179-1197
2. Watkins PB, Seeff LB. Drug-induced liver injury: summary of a single topic clinical research conference. *Hepatology.* 2006;43:618-631.
3. Bjornsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. *Dig Liver Dis.* 2006:38:33-38.
4. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med.* 2002;137:947-954.
5. Danan G, Benichou C. Causality assessment of adverse reactions to drugs, I: a novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J. Clin Epidemiol.* 1993;46:1323-1330.
6. Barbhaiya RH, Forgue ST, Gleason CR, et al. Safety, tolerance, and pharmacokinetic evaluation of cefepime after administration of single intravenous doses. *Antimicrob Agents Chemother.* 1990;34:1118-1122.
7. Van Poppel H, Wegge M, Dammekens H, Chysky V. Oral treatment of Pseudomonas-induced urinary tract infections with ciprofloxacin. *Chemotherapy.* 1986;32:83-87.
8. Villeneuve JP, Davies C, Cote J. Suspected ciprofloxacin-induced hepatotoxicity. *Ann Pharmacother.* 1995;29:257-259.
9. Kantarjian HM, Estey EH, Plunkett W, et al. Phase I-II clinical and pharmacologic studies of high-dose cytosine arabinoside in refractory leukemia. *Am J Med.* 1986;81:387-394.
10. Murdoch D, Plosker GL. Anidulafungin. *Drugs.* 2004;64:2249-2258; discussion 2259-2260.
11. Clemons KV, Sobel RA, Stevens DA. Toxicity of LY303366, an echinocandin antifungal, in mice pretreated with glucocorticoids. *Antimicrob Agents Chemother.* 2000;44:378-381.

Chest Pain and Dyspnea in a Patient with Cryoglobulinemia

Laura K. Moyer, MD, Postgraduate Year 3, Internal Medicine
Wael N. Jarjour, MD, Associate Professor of Medicine, Division of Clinical Rheumatology
Charles E. Hess, MD, Professor of Medicine, Division of Hematology/Oncology

Cryoglobulinemia most commonly presents with symptoms of purpura, peripheral neuropathy, arthralgias, or kidney and liver disease. Although the presentation can be heterogeneous, pulmonary and cardiac manifestations of cryoglobulinemia are rare. We describe a case of cryoglobulinemia in a 72-year-old woman who presented with symptoms of dyspnea and chest discomfort.

CASE REPORT

A 72-year-old woman with hypertension and hyperlipidemia was transported by emergency medical system to the emergency department after experiencing an episode of chest pressure with mild shortness of breath. She reported that the night before while in bed she had experienced a similar episode, which lasted only a few minutes before resolving. She also reported several months of dyspnea on exertion.

The patient's medical history was also notable for recently diagnosed cryoglobulinemia and an 8-year history of IgM-kappa monoclonal gammopathy and clonal B-cell lymphocytosis (lambda clonal), which were stable. The week before her presentation at the emergency department the patient had started treatment with prednisone 30 mg daily because of severe Raynaud phenomenon and a significantly elevated cryoglobulin level, both associated with her cryoglobulinemia. She had a remote history of tobacco use. Her family history was positive for cardiovascular disease in her father.

Electrocardiograms performed during emergency transport and at the emergency department on initial arrival of the patient showed a narrow-complex junctional rhythm with a rate around 50. Shortly after arrival in the emergency department, the patient converted to normal sinus rhythm with a rate in the 60s. Laboratory test results on presentation were notable for an initial troponin concentration of 0.02 ng/mL. Serial monitoring of the patient's troponin concentrations revealed a peak concentration of 1.61 ng/mL. Her white blood cell count was elevated at 18,000/μL. Serum electrolyte and thyroid-stimulating hormone concentrations were within reference intervals. The patient's cryoglobulin level was 0.33 ppt/mL after 48 hours at 4ºC (normal value is <0.01), with a negative hepatitis C antibody. Other diagnostic studies obtained included a chest x-ray, which showed pulmonary vascular congestion with mild interstitial edema. A transthoracic echocardiogram revealed mild concentric left ventricular (LV) hypertrophy and normal LV systolic function with an ejection fraction of 60%-65%.

The patient underwent an exercise stress test with Technetium-99m sestamibi (MIBI) imaging. She achieved 5.4 METS before the test was terminated early due to the onset of recurrent symptoms. At peak exercise, she became acutely dyspneic, dizzy, diaphoretic, and hypotensive, with her systolic blood pressure dropping to 50 mmHg. Nuclear imaging showed normal LV perfusion, wall motion, and function.

The acute hypotensive event experienced during the exercise stress test with a normal MIBI was suspected to be related to agglutination of cryoglobulins in the microvasculature. Similarly, her dyspnea on exertion was felt to be due to sludging secondary to cryoglobulins. The patient underwent plasmapheresis, with subsequent improvement in her dyspnea on exertion. She was started on immunosuppressive therapy with azathioprine in addition to prednisone. After initiation of this therapy, she did not develop recurrence of her dyspnea on exertion.

DISCUSSION

Cryoglobulins are plasma proteins that precipitate at temperatures lower than 37°C and redissolve at higher temperatures.[1-3] Cryoglobulinemia is a systemic vasculitis, involving small-to-medium vessels, due to the inflammatory response to cryoglobulin-containing immune complexes.[4] Cryoglobulinemias are classified into 3 types on the basis of components of the cryoprecipitate (Table 1). In type I cryoglobulinemia, the cryoprecipitate is composed of monoclonal Ig, typically IgM or IgG. Type II includes a mixture of polyclonal Ig, usually IgG, in association with a monoclonal Ig and, frequently, IgM with rheumatoid factor activity. Type III consists of polyclonal Ig. The term

"mixed cryoglobulinemia" refers to types II and III. [1-3] Type I disease is often associated with underlying lymphoproliferative disorders. Types II and III are more commonly related to autoimmune diseases or chronic infection, especially hepatitis C.[1,2]

The combined presence of arthralgias, purpura, and asthenia, termed "Meltzer's triad," has classically been considered to characterize symptomatic cryoglobulinemia.[5] Studies looking at the most frequent presentations of cryoglobulinemia reveal the most common to be purpura and other cutaneous lesions, peripheral neuropathy, arthralgias, and kidney and liver disease.[3,5-7] Alternatively, hyperviscosity syndrome with symptoms of bleeding, visual disturbances, or signs of central nervous system involvement (including dizziness, ataxia, and altered consciousness) can be a manifestation of monoclonal cryoglobulinemia.[8] This most often occurs with high levels of IgM, generally with high temperature amplitude (the highest temperature at which a particular cryoglobulin will start to precipitate).[9]

Pulmonary and cardiac manifestations of cryoglobulinemia are rare. Reported cases of symptomatic cardiac disease in patients with cryoglobulinemia have included myocardial infarction (including cases in patients without risk factors), pericarditis, and congestive heart failure.[3,6] Documented pulmonary symptoms include hemoptysis, pleural effusions, acute lung injury, and pulmonary fibrosis.[3,10-12] Bombardieri et al performed pulmonary function tests and chest x-rays in 23 patients with mixed cryoglobulinemia, about half of whom had mild pulmonary symptoms.[10] No trends of obstructive or restrictive lung disease were found, although chest x-rays revealed that most patients had mild-to-moderate pulmonary interstitial involvement. Postmortem studies have confirmed widespread vasculitis of small and medium-sized vessels, including involvement of the heart and lungs.[6]

Treatment of cryoglobulinemia requires addressing the underlying disorder or infection, if one is identifiable. Because of the variety of possible underlying conditions, the heterogeneity and multisystemic nature of the disease, and the lack of standardized therapeutic options, there is significant variability in treatment regimens.[7] In a study of 49 patients treated for type II cryoglobulinemia, 22 different treatments were used, the most common of which was corticosteroids.[7] Patients with more severe disease may benefit from adjuvant plasmapheresis or immunosuppressants, whereas a conservative approach is appropriate in patients with mild disease.[4] Patients suffering from hyperviscosity syndrome are generally treated with plasmapheresis.[8] Although the patient we describe did have an underlying biclonal low-grade lymphoproliferative disorder, this condition had been stable for 8 years and did not require treatment. Therefore, the patient received treatment with prednisone and azathioprine after undergoing plasmapheresis. Although serial cryoglobulin levels can be followed, their values often do not correlate with the severity or prognosis of the disease.[13]

The clinical presentation of this patient, along with symptomatic improvement after treatment with plasmapheresis and increased immunosuppression, suggest that the patient's dyspnea possibly was secondary to a cryoglobulin-induced hyperviscosity with decreased microvascular circulation, but more likely was due to a cryoglobulin-related vasculitis. Although the level of the patient's monoclonal protein had not increased over the years, her total IgM, including polyclonal IgM, had increased.

Table 1. Classification of Cryoglobulins

	Type 1	Type 2	Type 3
Associated immunoglobulin (Ig)	Monoclonal Ig, typically IgM or IgG	A mixture of polyclonal Ig, usually IgG, in association with a monoclonal Ig, often IgM with rheumatoid factor activity	Polyclonal Ig
Associated diseases	Lymphoproliferative disorders	Chronic infection, especially hepatitis C, autoimmune diseases	Chronic infection, especially hepatitis C, autoimmune diseases

This patient's serum viscosity was not measured, but it is possible that the intrinsic viscosity of the polyclonal IgM was high. Information on the 3 major properties of this patient's IgM protein that would have been useful includes intrinsic oncotic pressure, intrinsic viscosity, and plasma concentration. Cases of hyperviscosity syndrome usually occur with high levels of IgM with relative serum viscosity values above 4.0 in the absence of any cryoprecipitation. This patient's cryoglobulin may have had a temperature amplitude that allowed for precipitation at higher temperatures, including those found in central organs such as the heart. The temperature at which a particular cryoglobulin precipitates often correlates more with clinical symptoms than the amount of precipitate does. The laboratory at our institution, however, no longer performs tests to measure temperature amplitude of cryoglobulins or cold agglutinins.

Although anecdotal, this case adds to the evidence that cryoglobulinemia can present with a wide variety of clinical manifestations, including respiratory and cardiac symptoms. Clinicians should keep a high index of suspicion for cryoglobulinemia, especially in patients with hepatitis C, lymphoproliferative disorders, and autoimmune diseases. Treatment options for cryoglobulinemia are varied and can result in marked symptomatic improvement, as seen in this case.

REFERENCES

1. Chan A, Lau J, Chan CH, et al. Cryoglobulinaemia: clinical and laboratory perspectives. *Hong Kong Med J*. 2008;14:55-59.
2. Trendelenburg M, Schifferli J. Cryoglobulins are not essential. *Ann Rheum Dis*. 1998;57:3-5.
3. Rieu V, Cohen P, Andre M-H, et al. Characteristics and outcome of 49 patients with symptomatic cryoglobulinemia. *Rheumatology*. 2002;41:290-300.
4. Dispenzieri A. Symptomatic cryoglobulinemia. *Curr Treat Options Oncol*. 2000;2:105-118.
5. Meltzer M, Franklin EC, Elias K, et al. Cryoglobulinemia, a clinical and laboratory study; II: cryoglobulins with rheumatoid factor activity. *Am J Med*. 1966;40:837-56.
6. Gorevic PD, Kassab HJ, Levo Y, et al. Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. *Am J Med*. 1980;69:287-308.
7. Bryce A, Kyle R, Dispenzieri A, et al. Natural history and therapy of 66 patients with mixed cryoglobulinemia. *Am J Hem*. 2006;81:511-518.
8. Della Rosa A, Tavoni A, Bombardieri S. Hyperviscosity syndrome in cryoglobulinemia: clinical aspects and therapeutic considerations. *Semin Thromb Hemost*. 2003;29:473-477.
9. Petz LD, Garratty G. *Immune Hemolytic Anemias*. 2nd ed. Philadelphia, PA: Churchill Livingstone; 2003:72,182.
10. Bombardieri S, Paoletti P, Ferri C, et al. Lung involvement in essential mixed cryoglobulinemia. *Am J Med*. 1979;66:748-56.
11. Suzuki R, Morita H, Komuki D, et al. Mixed Cryoglobulinemia due to chronic hepatitis C with severe pulmonary involvement. *Intern Med*. 2003;42:1210-1214.
12. Konishi M, Ohosone Y, Matsumura M, et al. Mixed-cryoglobulinemia associated with cutaneous vasculitis and pulmonary symptoms. *Intern Med* 1997;36:62-67.
13. Ferri C, Zignego AL, Pileri SA. Cryoglobulins. *J Clin Pathol.* 2002;55:4-13.

Herpes Simplex Virus Type 2 Encephalitis in an Immunocompetent Elderly Man

Steven E. Bishop, BS, Medical Student
Gabriel B. Spring, MD, Postgraduate Year 1, Family Medicine
Mark E. Williams, MD, Ward K. Ensminger Distinguished Professor of Geriatrics, Division of General Medicine, Geriatrics and Palliative Care

Herpes simplex virus (HSV) is the most common agent causing fatal encephalitis in the United States, with mortality rates in untreated victims reaching 70%.[1] HSV often presents with subacute onset of fever, headache, focal neurological deficits, and altered mental status. Survivors are often left with neurologic, neuropsychiatric, and neurobehavioral sequelae. Nearly all reported cases in adults are due to HSV Type 1.[2] We describe a case of HSV-2 encephalitis in a 75-year-old man with an apparently intact immune system. To our knowledge, this is only the second reported description of HSV-2 encephalitis in an elderly immunocompetent individual.[3]

CASE REPORT

A 75-year-old man presented to a local emergency department with headache and malaise of 3 days duration. His medical history included diabetes mellitus type II, chronic kidney disease, atrial fibrillation treated with ablation, hypertension, hypothyroidism, and recent septic arthritis of the right knee treated with total knee arthroplasty and revision with insertion of an antibiotic spacer. At the emergency department where the patient was initially treated he was febrile with a temperature of 38.8°C, disoriented, and had difficulty speaking coherently. A head computed tomography (CT) scan ruled out acute hemorrhage, and he was transferred to University of Virginia (UVA) Health System for further evaluation and treatment.

On arrival in the UVA Emergency Department, the patient was noted to be persistently disoriented. Physical exam on admission revealed temperature 36.4°C orally, blood pressure 171/87 mmHg, pulse 81 beats/min, respiratory rate 24 breaths/min, and oxygen saturation 97% on 2 L of oxygen by nasal cannula. The patient's gaze was conjugate and his neck was supple; cardiovascular, respiratory, and abdominal examinations were unremarkable. The patient's right knee was warm and edematous but there was no pretibial edema. With the exception of a fluent aphasia, results of a neurologic examination were unremarkable. Admission laboratory test results were significant for serum sodium 133 mmol/L, serum creatinine 1.2 mg/dL, magnesium 1.5 mg/dL, hemoglobin 13.4 g/dL, and hematocrit 39.9%. The patient's serum thiamine level was within reference intervals. Magnetic resonance imaging (MRI) revealed a nonenhancing focus of increased signal in the left anteromedial temporal lobe on the FLAIR/T2-weighted images that was decreased in signal intensity in the T1-weighted images and did not demonstrate restricted diffusion on diffusion-weighted imaging (Figure 1); these findings argued against diagnosis of acute stroke. While in the emergency department, the patient began empiric therapy for meningitis with vancomycin, ceftriaxone, acyclovir, and trimethoprim/sulfamethoxazole.

The patient was admitted to the medical intensive care unit and while there suffered a generalized tonic-clonic seizure. An electroencephalogram showed background slowing. A lumbar puncture revealed normal opening pressure. Cerebrospinal fluid analysis showed 305 white blood cells, 10 red blood cells, and 94 lymphocytes in the fourth tube. Polymerase chain reaction testing of the cerebrospinal fluid yielded a positive result for HSV-

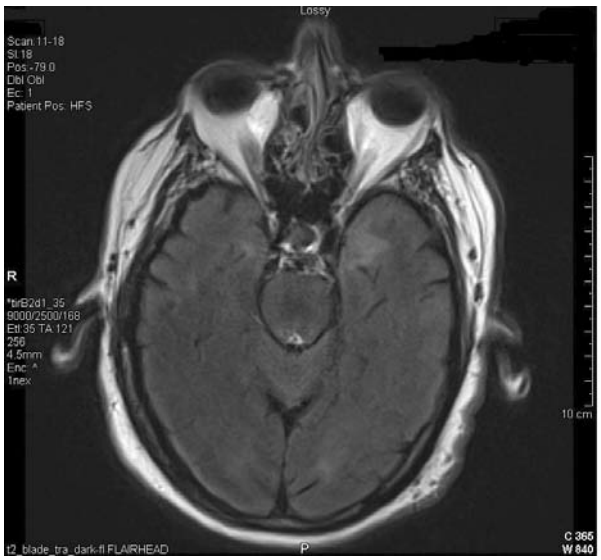


Figure 1. T1-weighted magnetic resonance image of the patient's brain showing a focus of abnormal signal in left anteromedial temporal lobe.

2. A cerebrospinal fluid cryptococcal antigen test was negative.

The patient's seizure was treated with phenytoin, and his acyclovir was continued for specific treatment of HSV-2. While in the medical intensive care unit, his serum sodium measurements began trending downward to a nadir of 122 mmol/L. At that time, his serum osmolality was 258 mOsm/kg, and his urine osmolality was 559 mOsm/kg, indicating a hypotonic hyponatremia that was believed to be due to the syndrome of inappropriate antidiuretic hormone. Measurements of serum cortisol and thyroid-stimulating hormone were within reference intervals. After 4 days of acyclovir therapy, the patient had not experienced any more seizures, his sodium was improved at 133 mmol/L, and he was transferred to the general medicine service.

While on the general medicine service, the patient showed no change in his mental status during the first 24 hours (day 4-5 of acyclovir), remaining oriented to person only; he continued to exhibit word-finding difficulties, paraphasias, repetition errors, and inability to follow complex commands. Over the following days, his orientation, language function and attention span gradually improved. Unfortunately, he continued to display short-term memory deficits as he was often unable to recall treatment plan conversations from the prior day.

DISCUSSION

Most incidents of HSV encephalitis are caused by HSV-1.[2] The few cases caused by HSV-2 are generally restricted to neonates and immunocompromised individuals. Although our patient had diabetes mellitus type 2, his disease was under relatively good management, as indicated by a hemoglobin A1C of 7.4%. He had no other medical history consistent with immunocompromise. The patient's social history, however, may have played a role in the natural history of his illness. Three days prior to his initial presentation, his son was killed by another family member. The family confirmed that the patient's understandably significant distress began prior to the onset of his symptoms. Psychological stress has been shown to be a factor in allowing HSV-1 to escape from T-cell control in vivo[4], and thus it is theoretically possible that this patient's social situation played a minor role in preventing his immune system from effectively thwarting the encephalitis in its nascent stages.

In immunocompromised patients HSV-2 infection of the central nervous system can cause aseptic meningitis, recurrent radiculopathy, and myelitis. When HSV-2 encephalitis occurs in immunocompetent individuals, its clinical presentation is usually similar to that of HSV-1 but can be of a less aggressive nature. In such cases disease presentation may also include altered mental status, focal neurologic deficits, and seizures.[2] This latter description mirrors the disease course in our patient, who developed variable mental status changes consistent with delirium, a seizure, and fluent aphasia during the course of his illness. Also consistent with other reported observations of HSV-2 encephalitis, our patient had no history of genital herpes and no confirmed lesions during the course of his illness.[2,5,6] Thus, in immunocompetent elderly patients the diagnosis of HSV-2 encephalitis should be considered in the right clinical setting as the tendency of this disease to show a less aggressive course in these patients could mislead clinicians into pursuing noninfectious diagnoses such as dementia or psychiatric pathology.

The generally accepted treatment for herpes simplex encephalitis is 14-21 days of intravenous acyclovir.[7] Although acyclovir has been shown to have in vitro activity against both HSV-1 and HSV-2, we know of no trials directly affirming this regimen specifically for HSV-2 encephalitis.[8] Even with treatment, a significant number of patients with HSV-1 encephalitis develop long-term sequelae. In one study, most patients treated for HSV-1 encephalitis displayed proper orientation but continued to have short-term memory deficits.[9] A limited study on 49 patients with HSV-2 central nervous system infections revealed that 4 of 6 patients with HSV-2 encephalitis had neurological sequelae 1 year after diagnosis.[5] These data are consistent with the course of our patient's illness. After treatment with acyclovir, he continued to show impaired short-term memory, having difficulty recalling recent conversations and events. Additionally, he had intermittent word-finding problems, paraphasias (for example, using "office" in place of "hospital"), and hesitancy when answering questions.

In summary, this elderly man without identifiable immune dysfunction presented with headache, fever, malaise, and focal neurological deficits consistent with an encephalitic process. After cerebrospinal fluid analysis, HSV-2 DNA was discovered via polymerase chain reaction. Additionally, MRI indicated an abnormal signal in

the left anteriomedial temporal lobe. Combining these results with the clinical picture, we diagnosed HSV-2 encephalitis in this patient, and he was treated with 14 days of intravenous acyclovir. On discharge, his clinical status was stable but with indications that he may have lingering sequelae from his infection.

REFERENCES

1. Kimberlin DW. Management of HSV encephalitis in adults and neonates: diagnosis, prognosis, and treatment. *Herpes*. 2007; 14:11-16.
2. Gilden DH, Mahalingam R, Cohrs RJ, Tyler KL. Herpesvirus infections of the nervous system. *Nat Clin Pract Neurol*. 2007;3:82-94.
3. Reuter MD, Manian FA, Kershaw MA, Alpert MA. Herpes simplex virus type 2 encephalitis in an elderly immunocompetent male. *South Med J*. 2007;100:1143-1146.
4. Freeman ML, Sheridan BS, Bonneau RH, Hendricks RL. Psychological stress compromises CD8+ T cell control of latent herpes simplex virus type 1 infections. *J Immunol*. 2007;179:322-328.
5. Omland LH, Vestergaard BF, Wandall JH. Herpes simplex virus type 2 infections of the central nervous system: a retrospective study of 49 patients. *Scand J Infect Dis*. 2008;40:59-62.
6. O'Sullivan CE, Aksamit AJ, Harrington JR, Harmsen WS, Mitchell PS, Patel R. Clinical spectrum and laboratory characteristics associated with detection of herpes simplex virus DNA in cerebrospinal fluid. *Mayo Clin Proc*. 2003;78:1347-1352.
7. Tyler K. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. herpes. 2004;11(Supplement 2):57A-64A.
8. Arvin A, Campadelli-Fiume G, Mocarski E, et al, eds *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge: Cambridge University Press; 2007:663.
9. McGrath N, Anderson NE, Croxson MC, Powell KF. Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. *J Neurol Neurosurg Psychiatry*. 1997;63:321-326.

Copper Deficiency and Excessive Soft-Drink Consumption: A Rare Cause of Neutropenia and Anemia

George J. Kannarkat MD, Fellow Physician, Department of Medicine, Division of Hematology/Oncology
John J. Densmore, MD, PhD, Associate Professor of Medicine, Division of Hematology/Oncology

Copper deficiency is a rare physiologic state resulting from unusual malabsorption syndromes, gastric or intestinal resections, parenteral nutrition lacking copper, or excessive zinc ingestion.[1] Copper deficiency typically leads to neutropenia and anemia, but this condition is rarely on the hematologist's differential diagnosis for pancytopenia. We report a case of copper deficiency causing neutropenia and anemia suspected to be attributable to excessive soft drink consumption.

CASE REPORT

A thin, healthy-appearing 28-year-old white female presented to her primary care physician's office for evaluation of generalized anxiety symptoms. Her physical exam was notable only for poor dentition. Results of thyroid function testing were within reference intervals. A complete blood count revealed a mild leukopenia with a total white blood cell count of 2400/μL, profound neutropenia with an absolute neutrophil count (ANC) of 700/μL (reference interval 1800-8000/μL), and mild normocytic anemia with hemoglobin (HGB) of 11.8 g/dL. The patient denied any ongoing herbal or prescription medication use, prior history of neutropenia, viral or bacterial infections, or any other constitutional symptoms. Initial hematology consultation led to further studies; results were within reference intervals for a hepatic panel, erythrocyte sedimentation rate, and concentrations of folate, iron, transferrin, ferritin, antinuclear antibody, and rheumatoid factor. The patient's serum vitamin B12 level was slightly low, at 211 pmol/L. Computed tomography of her chest, abdomen, and pelvis revealed no organomegaly or other abnormalities. Examination of bone marrow aspirate and biopsy tissue did not reveal any obvious increase in blasts or aplasia, myelodysplasia, plasma cell dyscrasia, iron deficiency, or fibrosis. Results of cytogenetic and flow cytometric studies on the marrow aspirate also revealed no abnormalities.

The patient was given 3 doses of 1000 μg vitamin B12 intramuscularly during a 3-month period and underwent close follow-up with weekly complete blood counts. During that period, her ANC and HGB decreased steadily. Her ANC fell as low as 100/μL, and her HGB decreased to 9.7 g/dL, but she did not show any signs of illness or report adverse events. A trial treatment with filgrastim 300 μg administered subcutaneously each day for 2 days resulted in an immediate correction of her neutropenia as evidenced by a return to an ANC of 6400/μL within 4 days. Within the following week, however, her ANC dropped below 1000/μL, and for the following month she continued to require weekly filgrastim to maintain an ANC greater than 500/μL. The patient did not require red blood cell transfusions or erythropoietin, and she remained free of serious infections.

A second opinion was sought from the Hematology division at the University of Virginia. In further interviews regarding her medical history the patient revealed that during the previous 6 months she had experienced parasthesias in all 4 distal extremities. A detailed social history also revealed excessive consumption of her soft drink of choice, Mr. Pibb®, amounting to at least twelve 12-oz aluminum cans daily during the previous year. Physical exam revealed a thin, healthy-appearing female with normal vital signs; normal sensation to light touch, pinprick, and vibration; no organomegaly; no focal arthritis; and no signs of infection or inflammation.

The patient's previous bone marrow biopsy from 3 months prior was also reviewed and revealed a normal blast percentage of 3.8% and grossly normal-appearing trilineage hematopoesis. The University of Virginia pathologist commented on 2 unusual but nondiagnostic findings, scattered plasma cells with coarse cytoplasmic granules staining positively for iron (Figure 1) and the presence of multiple large vacuoles within the cytoplasm of early erythroid precursors (Figure 2). No ringed sideroblasts or other myelodysplastic features were seen.

In summary, diagnostic findings for this patient were severe neutropenia, worsening normocytic anemia, mild diffuse parasthesias, and excessive soft drink consumption. Her bone marrow revealed plasma cells containing cytoplasmic iron granules and erythroid precursors containing large cytoplasmic vacuoles. Our differential diagnosis included atypical

myelodysplasia, evolving aplastic anemia, occult environmental exposures, and rare nutritional deficiencies. The role of excessive soft drink consumption in her disease process was unclear. We recommended that she decrease her soft drink consumption significantly over the next 2 months, and we continued to observe her blood counts. Her neutropenia and anemia did not resolve with an 80% reduction in soda consumption.

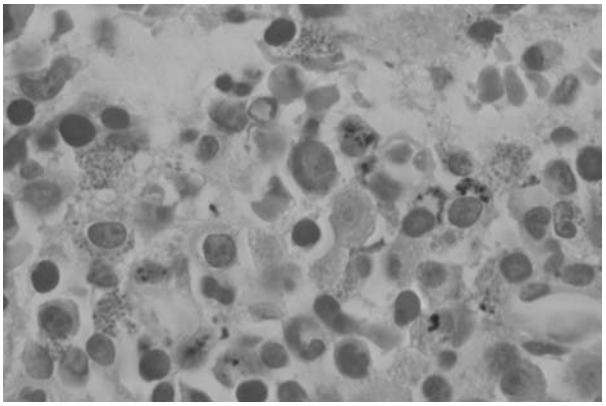


Figure 1. Plasma cell in marrow with cytoplasmic granules staining positively for iron. Iron stain.

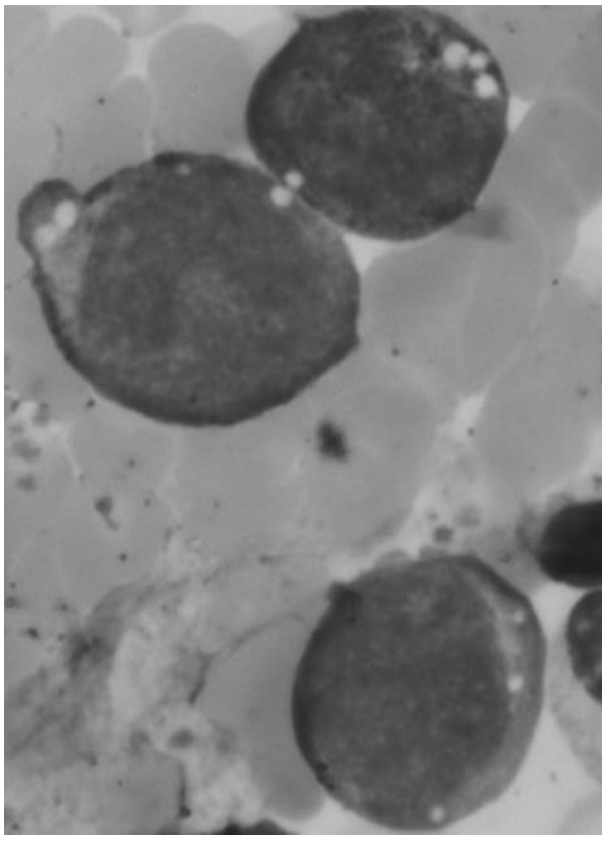


Figure 2. Erythroid precursors with large cytoplasmic vacuoles. Wright-Giemsa stain.

A literature search linking soft drink consumption to cytopenias revealed a single case series of 2 young women with a syndrome of copper deficiency associated with excessive soda consumption.[2] Further research led us to find small series of bone marrow profiles in patients with copper deficiency and myelosuppression with subtle findings consistent with those seen in our patient's marrow.[3-5] Given the inversely linked absorption of copper and zinc, serum levels of both were measured, and the results revealed a markedly low copper level of 5 µg/dL (reference interval 70-155 µg/dL) and a minimally elevated zinc level of 162 µg/dL (reference interval 70-150 µg/dL).[6-9]

Our patient had difficulty obtaining oral copper supplements in her rural locality. She was given intravenous cupric chloride, 2.5 mg weekly, and her neutropenia and anemia improved. After 3 doses, her ANC rose from 200/µL to 4200/µL, and her HGB rose from 9.7 g/dL to 12.5 g/dL. She then received 3 more weekly doses and had stable normalized blood counts. Subsequent measurement of her copper level showed an increase to 38 µg/dL, but it remained below the normal range. The patient returned to the clinic irregularly and received 3 more doses of intravenous cupric chloride during the next 4 months. While receiving this supplementation, she had unexplained complaints of polyuria, visual changes, and altered taste sensation. The patient continued to have stable but persistent peripheral neuropathy. She continued to drink approximately 20-30 oz of a different soft drink daily from a plastic bottle instead of cans. Results of blood counts measured 6 months after her last dose of cupric chloride remained within reference intervals, with an ANC of 2800/µL and HGB of 14.8 g/dL.

DISCUSSION

The etiology of our patient's copper deficiency is uncertain. She had no history of gastrointestinal resection, malabsorption syndrome, or nutritional deficiency. Her daily excess soft drink consumption and generally poor dietary habits were thought to be the most likely explanation for copper deficiency but the precise mechanism can only be hypothesized.

Copper deficiency has been causally linked to excessive zinc ingestion in animal models.[6-9] This patient may have been exposed to high levels of zinc through the soft drink or perhaps a component of the aluminum cans. Dietary zinc in excess of 50 mg/day causes intestinal cells to increase synthesis of

metallothionein, which in turn binds other metals in the gut mucosa and prevents their systemic absorption. Metallothionein has a preferential affinity for copper over zinc and prevents the systemic absorption of copper.[6-9] For this reason, the use of zinc preparations for treatment of Wilson disease has been investigated, with varying levels of success.[10,11]

An additional factor contributing to this case may have been the carbohydrate content in the soft drink. Consumption of fructose and sucrose as greater than 60% of total calories has been shown in rat and pig models to decrease the bioavailability of dietary copper and worsen preexisting copper deficiency.[12,13] Dietary carbohydrate in the form of starch did not have the same detrimental effect on copper metabolism.[12] Although this physiological effect has not been definitively demonstrated in adult humans, it is possible that in our patient a high-fructose diet exacerbated an already existing copper deficiency.

The essential biochemical role of copper was first recognized in 1928 when rats fed a milk-based diet were observed to develop anemia.[14] The anemia resolved with the addition of ash from animal and vegetable sources to their diet, later shown to contain copper sulfide. The function of copper in all living tissue largely revolves around its ability to accept or transfer electrons and thus change between its 3 states, Cu^0, Cu^{1+}, and Cu^{2+}. Copper acts as a cofactor or allosteric component of a group of cellular reduction-oxidation enzymes called cupro-enzymes.[15] This family includes but is not limited to cytochrome-c oxidase, superoxide dismutase, catechol oxidase, ceruloplasmin, and amine oxidases. Gene transcription is modulated by copper through the effects of transcription-factor proteins that act as metal-responsive genetic switches.

Copper and iron interact in several ways in the process of hematopoesis. Ceruloplasmin, the major transporter of copper, carries up to 6 copper atoms. Ceruloplasmin also oxidizes ferrous iron to its ferric state, Fe^{3+}, and binds to transferrin. Hephaestin, a copper-dependent transmembrane ferroxidase, is thought to facilitate iron uptake through enterocytes.[16] Decreased availability of copper and the resulting lack of cuproenzyme activity are hypothesized to impair hemoglobin synthesis and facilitate heme degradation. The precise pathophysiology behind the development of plasma cell iron granules and vacuolated erythroid precursors is unknown.

Our patient developed insidious severe neutropenia and anemia along with subtle pathologic findings consistent with previously reported marrow profiles of copper deficiency. She experienced very brief responses to filgrastim. Laboratory studies revealed severe copper deficiency and a mildly elevated zinc level. Her excessive soda consumption was suspected as the main contributory factor. Brief reduction in soda consumption did not alleviate her cytopenias. Immediate correction of her neutropenia and anemia occurred after 3 doses of intravenous cupric chloride, even though her serum copper level did not reach the normal range. Her peripheral blood counts remained normal 6 months after her last dose of cupric chloride.

In summary, copper deficiency is a rare but easily reversible cause of neutropenia and anemia. Classic but subtle pathologic findings of copper deficiency can be observed on marrow aspirate but are often overlooked. Copper deficiency may be caused by unusual dietary habits such as excessive soft drink consumption.

REFERENCES

1. Greer JP, Foerster J, Lukens J, et al. *Wintrobe's Clinical Hematology.* 11th ed. Philadelphia, PA: Lippincott Williams &Wilkins; 2004:1011-1033.
2. Harless W, Crowell E, Abraham J. Anemia and neutropenia associated with copper deficiency of unclear etiology. *Am J Hematol.* 2006; 81:546-9.
3. Chen CC, Takeshima F, Miyazaki T, et al. Clinicopathologic analysis of hematologic disorders in tube-fed patients with copper deficiency. *Intern Med (Japan)* 2007; 46(12):839-844.
4. Haddad AS, Subbiah V, Lichtin AE, et al. Hypocupremia and bone marrow failure. *Haematologica*. 2008;93:e1-5.
5. Huff J, Keung YK, Thakuri M, et al. Copper deficiency causes reversible myelodysplasia. *Am J Hematology*. 2007;82:625-630.
6. Fischer PW, Giroux A, L' Abbé MR, et al. The effect of dietary zinc on intestinal copper absorption. *Am J Clin Nutr*. 1981;34:1670-1675.
7. Oestreicher P, Cousins RJ. Copper and zinc absorption in the rat: mechanism of mutual antagonism. *J Nutr*. 1985;115:159-166.
8. Shils ME, Shike M, Ross AC, et al. *Modern Nutrition in Health and Disease*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:289-299.
9. Institute of Medicine, Panel on Micronutrients, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Copper. In: *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academy Press; 2001:224-257.
10. Marcellini M, Di Ciommo V, Callea F, et al. Treatment of Wilson's disease with zinc from the time of diagnosis in pediatric patients: a single-hospital, 10-year follow-up study. *J Lab Clin Med.* 2005;145:139-143.
11. Li M, Zhang YH, Qin J. Treatment of Wilson's disease with penicillamine and zinc salts: a follow- up study. *Zhonghua Er Ke Za Zhi.* 2003;41:119-122
12. O'Dell BL. Dietary carbohydrate source and copper availability. *Nutr Rev*. 1990;48:425-434.
13. Wapnir RA, Devas G. Copper deficiency: interaction with high-fructose and high-fat diets in rats. *Am J Clin Nutr*. 1995;61:105-110.
14. Hart EB, Steenbock H, Waddell J, et al. Copper is a supplement to iron for hemoglobin building in the rat. *J Biol Chem.* 1928;77:797-812.
15. Uauy R, Olivares M, Gonzalez M. Essentiality of copper in humans. *Am J Clin Nutr*. 1998;67(suppl):952s-959s.
16. Petrak J, Vyoral D. Hephaestin: a ferroxidase of cellular iron transport. *Int J Biochem Cell Biol*. 2005;37:1173-1178.

Septic Superior Sagittal Sinus Thrombosis after Face-Lift Surgery: A Case Report

Gavin T. Slitt, MD, Postgraduate Year 2, Internal Medicine
William G. Ogg, MD, Postgraduate Year 3, Internal Medicine
George Verghese, MD, Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine

Dural sinus thrombosis is a rare but serious and potentially life-threatening infection involving bacterial invasion and thrombosis within the cavernous sinus, lateral sinus, or superior sagittal sinus. Determination of the involved sinus can usually be established by assessment of clinical presentation, neurologic manifestations, and radiologic images.[1] In the preantibiotic era, septic dural sinus thromboses were almost uniformly fatal, and today these diagnoses still carry a significant risk. Cavernous sinus thrombosis (CST) has a morbidity rate of 60% and mortality rate of 20%-30%, and superior sagittal sinus thrombosis (SSST) leads to death in 78% of cases.[2-4]

We report a rare case of SSST complicated by subdural empyema due to infection with methicillin-resistant staphylococcus aureus (MRSA) in an otherwise healthy individual with a history of recent face-lift surgery.

CASE REPORT

A 53-year-old woman was brought to the emergency department via air transport after being found confused and minimally responsive on the floor of her house. Her medical history was significant only for hepatitis C. Four weeks prior to this presentation, the patient had undergone deep-plane rhytidectomy. The procedure was complicated by a recurrent postoperative wound infection that spontaneously drained purulent material from around the suture lines. The patient had completed a 5-day course of cephalexin and another 7-day course of the same antibiotic with gradual resolution of her symptoms. Unfortunately, no culture data were available. However, 3 days prior to presentation the patient developed a severe frontal headache. This headache persisted despite treatment with over-the-counter analgesics and was associated with nausea, vomiting, and photophobia. On the evening prior to admission, the patient was noted to be in her usual state of consciousness, although she was still nauseated and vomiting. She was found unresponsive the next day and brought to the emergency department.

On presentation, the patient was obtunded with a temperature of 41°C (105.8°F), heart rate of 120 beats/min, blood pressure of 140/70 mm Hg and a respiratory rate of 41 breaths/min. The patient was awake, but disoriented and did not follow commands. The findings on neurological examination included nuchal rigidity, slight anisocoria (right, 5-6 mm; left, 6-7 mm) with pupils reactive to light, and bilateral upgoing Babinski reflexes. Her exam was also notable for decreased lateral gaze in her left eye. She had spontaneous movement of all 4 extremities with normal tone and strength, and she withdrew and localized to pain. Deep tendon reflexes were equal and symmetric and she had no obvious clonus or frontal release signs. The remainder of the patient's physical exam revealed periorbital swelling (left greater than right), clean bilateral facial surgical scars with no evidence of skin or soft-tissue infection, no lymphadenopathy, and no notable murmurs on cardiac exam. Lung exam revealed bilateral diffuse inspiratory and expiratory rhonchi.

Laboratory results were significant for a white blood cell count of 14 k/μL with 80% neutrophils, platelets of 102 k/uL, and an arterial blood gas revealing pH 7.47/pCO2 32 mmHg/pO2 259 mmHg on 100% oxygen by nonrebreather. The patient's cerebrospinal fluid profile revealed protein 249 mg/dL, glucose 78 mg/dL, lactic acid 4.4 mmol/L, and white blood cell counts of 166 in tube 1 and 266 in tube 4, with 94% and 96% neutrophils, respectively. Cerebrospinal fluid gram stain was negative. Chest x-ray revealed bilateral patchy infiltrates, possibly secondary to multifocal pneumonia versus early acute respiratory distress syndrome. Noncontrast head computed tomography (CT) scan showed no evidence of intracranial hemorrhage, mass, or acute infarction. Transthoracic echocardiogram demonstrated no evidence of vegetation or findings suggestive of infective endocarditis.

On the basis of these findings, the patient was started on empiric broad-spectrum antibiotics including vancomycin, ceftriaxone, and ciprofloxacin. Magnetic resonance imaging/angiogram (MRI/MRA) of the brain revealed

venous infarcts involving bilateral anterior and paramedian frontal lobes secondary to an occluded superior sagittal sinus, with a shallow left subdural fluid collection and extensive left frontotemporal skin and subcutaneous soft tissue swelling suggestive of infection. Magnetic resonance venogram of the brain revealed a lack of normal flow-related signal within the superior sagittal sinus, consistent with an occluded anterior and superior sagittal sinus (Figure 1). Four of 4 cultures of blood samples (2 of 2 bottles) collected prior to the initiation of antibiotic treatment revealed MRSA that was resistant to penicillin and oxacillin but susceptible to erythromycin, clindamycin, trimethoprim/sulfamethoxazole, and vancomycin. No other antigen or virulence factor information was available.

The patient was transferred to the Neurology Intensive Care Unit, where anticoagulation with heparin was initiated and rifampin was added to the antimicrobial regimen. Electroencephalogram did not show seizure activity. Repeat MRI/MRA revealed progression of the venous infarcts into the left parietotemporal lobe as well as increase in size of the left subdural empyema. Despite anticoagulation and antibiotics, the patient's neurologic examination showed acute deterioration, with development of worsening anisocoria and a dilated left pupil. She was given mannitol, and a repeat emergent noncontrast head CT revealed progressive cerebral edema with evidence of bilateral uncal herniation and midline shift. Repeat MRI confirmed this new mass effect, with interval development of a right subdural empyema. The patient was taken to the operating room for bifrontal and bitemporal craniectomy. Bicoronal skin incisions incorporating her face-lift revealed subgaleal space abscesses. Her craniectomy revealed cortical vein thrombosis to the superior sagittal sinus and a large subdural empyema that evacuated immediately as the dura was opened. All cultures of skull, epidural, subdural, and intracerebral washings grew out MRSA. Repeat MRI several days later revealed resolution of the local mass-effect and midline shift, with interval development of new acute infarctions in the bilateral posterior cerebral artery territories and new intraparenchymal abscesses in the right inferior frontal lobe. The patient unfortunately remained comatose, and the family elected to transition to comfort care given her poor prognosis and neurologic devastation. She died 3 weeks after admission. An autopsy was not performed.

DISCUSSION

Young to middle-aged adults with septic CST typically present acutely with fever, headache, chemosis (swelling or edema of the conjunctiva), and ophthalmoplegia (paralysis or weakness of one or more muscles controlling eye movement).[1,5] This presentation leads to a fairly narrow differential that includes orbital cellulitis, allergic blepharitis,

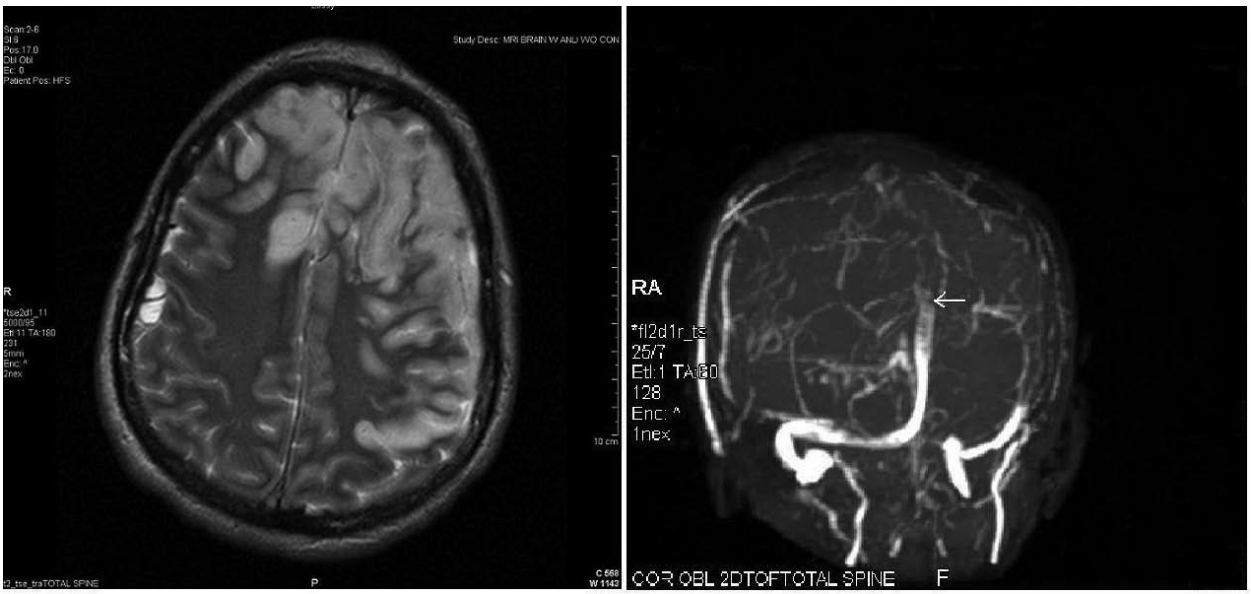


Figure 1. Magnetic resonance imaging reveals extensive venous infarcts involving the frontal and left parietotemporal lobes (left). Magnetic resonance venogram demonstrates extensive thrombosis of the anterior half of the superior sagittal sinus (right).

acute meningitis, and preseptal cellulitis. CST is most commonly associated with acute sinusitis within the ethmoid or sphenoid sinuses, although it can be secondary to soft tissue infections involving the face, nose, teeth, and soft palate.[2,6,7] Elderly patients with septic CST tend to present with depressed consciousness and altered mental status without headache, findings also observed in 50% of elderly patients presenting with meningitis.[8,9] Lateral sinus thrombosis patients usually present with headache, earache, nausea, and vomiting. This condition is almost always the result of infection spread via the mastoid air cells following otitis media. The rarest of these septic thromboses involves the superior sagittal sinus, which is the largest of the intracerebral venous sinuses. Septic SSST most often presents with severe headache associated with nausea and vomiting, usually followed by confusion with rapid progression to a comatose state. Meningitis has remained the primary risk factor for this disease, followed by infections of the ethmoid and maxillary sinuses.[2]

Treatment usually involves broad-spectrum antibiotics directed against the most commonly implicated pathogens. Additionally, anti-coagulation is considered a potential therapy, although given the rarity of the disease process the data are at best controversial.[10] Surgical debridement and decompression are also options, although these procedures are generally most beneficial in preventing septic thrombosis.

Sinusitis with extension to the cavernous sinus has become the most prevalent source for dural sinus thrombosis given the reduction in complicated facial infections in the antibiotic age.[2,5,11-13] The shift in source could be secondary to easily recognized soft tissue infections and early administration of antibiotics prior to the occurrence of complications.[10] Identification of the primary site of infection aids in the determination of the causative microorganism. In CST, the typical infecting organisms remain skin flora, *Staphylococcus aureus* being the predominant microbe, with streptococcal species, gram-negatives and anaerobic organisms less commonly isolated. Lateral sinus thrombosis has been associated with bacteria that are most commonly cultured in otitis media. Organisms associated with SSST are *Streptococcus pneumoniae*, other aerobic and anaerobic streptococci, *S. aureus, Haemophilus influenzae, and Klebsiella* sp.[2] With the recent emergence of MRSA, clinicians must strongly consider this organism when treating these diseases.

Surgical wound infections may increase susceptibility for developing septic dural sinus thrombosis. Rhytidectomy incorporates entry into the galea aponeurotica and the subgaleal spaces, and these scalp layers extend into the occipitofrontalis muscle. The subaponeurotic space lies beneath these muscles and extends anteriorly below the orbicularis oculi into the eyelids.[14] This area, which drains via the ophthalmic veins, is termed the "danger zone" for the development of infections such as dural sinus thrombosis and was the likely pathway of bacterial invasion in this patient. The initial presentation raised concerns for acute bacterial meningitis, and although consideration of this possibility did not delay initiation of treatment, it did highlight the subtleties involved in the diagnosis of septic SSST. Our patient presented with acute-onset headache and subsequently developed neck stiffness and photophobia, atypical for bacterial meningitis. Her lumbar puncture findings were also not consistent with bacterial meningitis, raising the possibility of an alternative diagnosis.

To our knowledge, this is the fifth documented case and the first documented fatal case of MRSA soft-tissue infection complicating rhytidectomy, and the first reported MRSA-associated septic superior sagittal sinus thrombosis. In a recent case series of postoperative surgical site infections after rhytidectomy, cultures from 4 of 5 patients (80%) were positive for MRSA, and 2 of 5 patients (40%) required hospitalization. Although postoperative wound infections after rhytidectomy are relatively rare (0.18% to 0.6%), they carry the risk of serious complications if not treated promptly.[15,16]

The decision to start anticoagulation in this patient was not taken lightly given the lack of sufficient evidence to support its use. Although several retrospective case series have shown benefit with anticoagulation, there have been no randomized controlled trials.[2,10] This treatment likely had no effect on the final outcome in this case, given that no acute hemorrhage was ever identified on CT, MRI, or during surgery.

Unfortunately for our patient, the increasing prevalence of MRSA involvement in postoperative wound infections and the inherent resistance of this pathogen to standard prophylaxis and treatment led to life-threatening complications.

The fact that she developed dural sinus thrombosis and subdural empyema from a subgaleal soft-tissue infection highlights this growing risk and makes physician awareness paramount.

REFERENCES

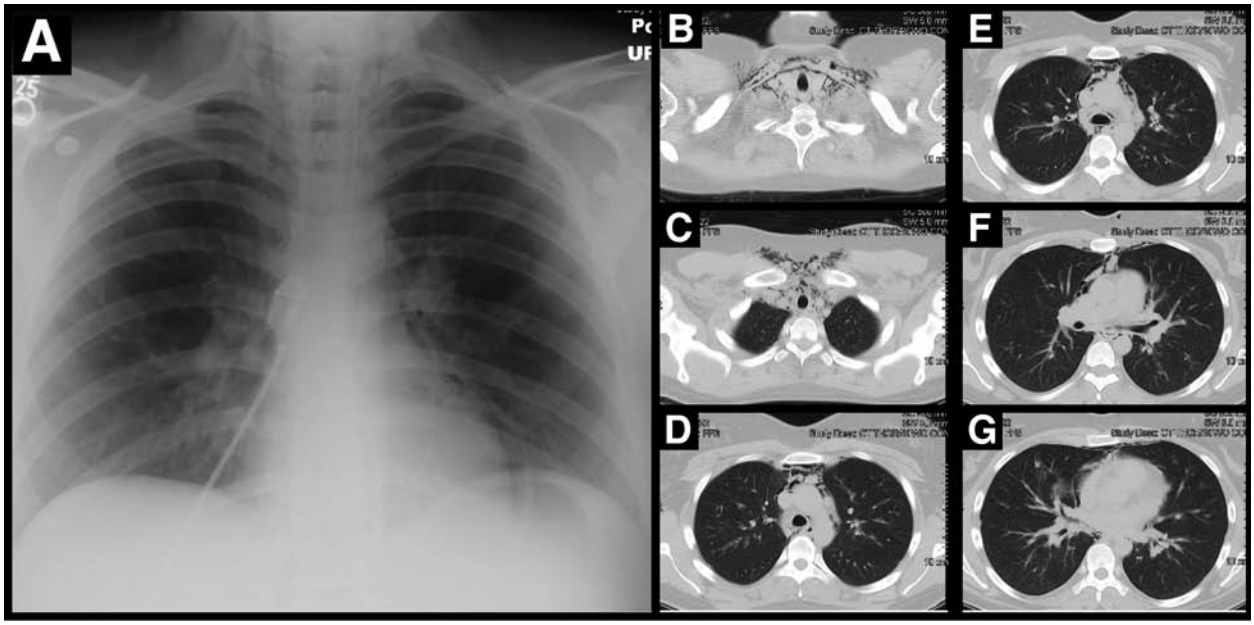
1. Ebright JR, Pace MT, Niazi, AF. Septic thrombosis of the cavernous sinuses. *Arch Intern Med.* 2001;161:2671-2676.
2. Southwick FS, Richardson EP, Swartz MN. Septic thrombosis of the dural venous sinuses. *Medicine.* 1986;65:82-106.
3. Clune JP. Septic thrombosis within the cavernous chamber. *Am J Ophthalmol.* 1963;56:33-39.
4. Yarington CT. Cavernous sinus thrombosis revisited. *Proc R Soc Med.* 1977;70:456-459.
5. Dinubile MJ. Septic thrombosis of the cavernous sinuses. *Arch Neurol.* 1998;45:567-572.
6. Westhout F, Hasso A, Jalili M, et al. Case report: Lemierre syndrome complicated by cavernous sinus thrombosis, the development of subdural empyemas, and internal carotid artery narrowing without cerebral infarction: case report *J Neurosurg.* 2007;106(1 Suppl):53-56
7. Sifri CD, Park J, Helm GA, Stemper ME, Shukla SK. Fatal brain abscess due to community-associated methicillin resistant Staphylococcus aureus strain USA300. *Clin Infec Dis.* 2007;45:e113-117.
8. Ferro JM, Canhão P, Bousser MG, Stam J, Barinagarrementeria F; ISCVT Investigators. Early seizures in cerebral vein and dural sinus thrombosis. *Stroke.* 2008; 39:1152-1158.
9. Ferro JM, Canhão P, Bousser MG, Stam J, Barinagarrementeria F; ISCVT Investigators. Cerebral vein and dural sinus thrombosis in elderly patients. *Stroke.* 2005;36:1927-1932.
10. Bhatia K, Jones NS. Septic cavernous sinus thrombosis secondary to sinusitis: are anticoagulants indicated? A review of the literature. *J Laryngol Otol.* 2002;116:667-676.
11. Murthy BV, Wenstone R. Cerebral venous thrombosis associated with inhalational drug abuse. *Rhinology.* 1996;34:188-190.
12. Kriss TC, Kriss VM, Warf BC. Cavernous sinus thrombophlebitis: case report. *Neurosurgery.* 1996;39:385-389.
13. Dale BAB, Mackenzie IJ. The complications of sphenoid sinusitis. *J Laryngol Otol.* 1983;97:661-670.
14. Unger W, Shapiro R. Editor's comments on Knudsen R, "Effect of medical therapy on surgical planning." in Unger WP, Shapiro R, eds. *Hair Transplantation.* 4th ed. New York: Marcel Dekker; 2004:148-151.
15. Zoumalan, RA and Rosenberg, DB. Methicillin-resistant Staphylococcus aureus-positive surgical site infections in face-lift surgery. *Arch Facial Plast Surg.* 2008;10:116-123.
16. LeRoy JL Jr, Rees TD, Nolan WB III. Infections requiring hospital readmission following face lift surgery: incidence, treatment, and sequelae. *Plast Reconstr Surg.* 1994;93:533-536.

Spontaneous Pneumomediastinum

Clay A. Cauthen, MD, Chief Resident, Internal Medicine
Mathew Goodman, MD, MPH, Associate Professor of Medicine, Division of General Medicine, Geriatrics, and Palliative Care

ABSTRACT

22 year-old previously healthy woman presented with acute onset of cough, shortness of breath as well as supraclavicular and neck fullness and pain. The patient experienced these symptoms shortly after taking a robust inhalation of marijuana. She described the episode as severe coughing followed by fullness in her neck. On examination, she was afebrile and in mild distress. Palpation demonstrated pronounced creptitus from below her right clavicle to the submandibular region of her neck. Chest radiograph (A) demonstrated subcutaneous air tracking from the mediastinum into the soft tissue of the neck. Chest CT (B-G) demonstrated moderate subcutaneous emphysema (B, C), moderate pneumomediastinum (D, E), and small pneumopericardium (F, G). The patient was diagnosed with a spontaneous pneumomediastinum, or Hamman's Syndrome. Hamman's Syndrome is an uncommon clinical entity that is benign and self-limited. Her clinical course was uncomplicated and she was discharged with close follow-up.



Control of the Onset of Puberty: Implications for the Evolution of Polycystic Ovary Syndrome

John Marshall, MD, PhD, Andrew D. Hart Professor of Medicine, Division of Endocrinology and Metabolism
Christopher McCartney, MD, Assistant Professor of Medicine, Division of Endocrinology and Metabolism
Susan Blank, MD, Fellow Physician, Department of Medicine, Division of Endocrinology and Metabolism
Kristin Helm, MD, Fellow Physician, Department of Medicine, Division of Endocrinology and Metabolism

Pulsatile gonadotropin-releasing hormone (GnRH) secretion is the primary driver of pubertal development. Pulsatile GnRH secretion stimulates pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn control ovarian sex steroid production and gametogenesis. Early puberty is marked by sleep-associated increases of GnRH pulse frequency, and in both older adolescents and cycling adults, GnRH frequency is intermittently suppressed by luteal progesterone concentrations. The ability to regulate GnRH pulse frequency is an important factor in producing cyclic ovulation. Polycystic ovary syndrome (PCOS) is marked by persistently rapid GnRH pulse secretion, which contributes to the hyperandrogenemia and ovulatory dysfunction that characterize this disorder. Persistently rapid GnRH frequencies in PCOS are partly related to an impaired ability of progesterone to suppress GnRH pulse secretion. Androgen-receptor blockade reverses this defect, suggesting that it is a result of hyperandrogenemia itself. Early data suggest the possibility that progesterone and testosterone direct diurnal and day-to-day patterns of GnRH secretion throughout puberty, and that peripubertal hyperandrogenemia disrupts this normal process. In this review we discuss the normal regulation of GnRH secretion during puberty and outline potential neuroendocrine mechanisms by which peripubertal hyperandrogenemia may contribute to the development of PCOS.

HYPOTHALAMIC–PITUITARY–GONADAL AXIS

GnRH is secreted by some 80-200 neurons into the hypophysial-portal circulation in a series of pulses. Pulsatile stimulation is essential to maintain synthesis and secretion of pituitary LH and FSH, and the frequency of secretion in part regulates LH vs FSH synthesis. LH acts on the gonads to produce testosterone in the male, which feeds back directly at the pituitary and the hypothalamus to inhibit GnRH pulse frequency and to reduce pituitary responsiveness. In females LH stimulates production of estradiol and progesterone, estradiol having a transient stimulatory feedback action at both the pituitary and hypothalamic level and progesterone being inhibitory on both GnRH frequency and LH release. FSH stimulates sperm production in the testes and follicular maturation in the ovary. Both organs produce inhibins (A and B), which feed back directly on the pituitary to reduce FSH release. Thus the system is regulated by GnRH pulse secretion. GnRH cannot be measured directly in humans, but because animal studies have shown that 1 pulse of GnRH stimulates release of 1 pulse of LH, in clinical studies pulsatile release of LH is used to assess GnRH secretion (Figure 1).[1]

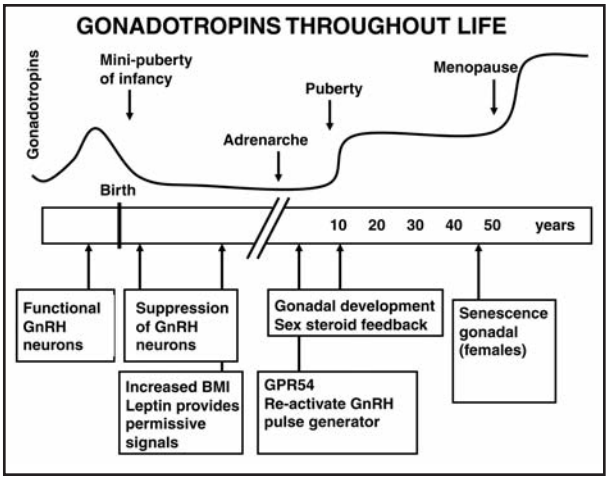


Figure 1. Phases in gonadotropin secretion throughout life. Gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are secreted in utero and achieve near adult levels toward term. Secretion continues for the first 6 to 9 months after birth, but gradually diminishes so that by the age of 1 year both LH and FSH levels are low and remain so for the next decade. Subsequently, activation of the hypothalamic GnRH pulse generator in the hypothalamus augments GnRH, LH/FSH steroid secretion, and the clinical signs of puberty become evident. BMI indicates body-mass index; GPR54, G protein–coupled receptor 54.

THE FIRST DECADE OF LIFE

In Utero

In the fetus GnRH neurons begin life in the nasal placode before migrating into the forebrain and taking a position in the hypothalamus. The factors regulating migration remain uncertain, but anosmin (a product of the *KAL-1* gene), fibroblast growth factor and its receptor (fibroblast growth factor receptor 1), and prokineticin-2 are known to be involved.[2] Mutations have been shown to be involved in the etiology of Kallmann syndrome (anosmia and hypogonadotropic hypogonadism).

By the end of the first trimester GnRH secretion is occurring; gonadotropins are synthesized and rise to adult levels prior to birth at the end of the third trimester. Gonadotropin secretion continues during the first 6 to 9 months of life, the "minipuberty" of infancy, but levels gradually fall so that by the end of the first year both LH and FSH levels are low.

Low levels of gonadotropins persist during the next 5 to 7 years, but some GnRH pulse activity occurs. This pulse activity is best observed during sleep, according to limited data indicating the occurrence of small pulses of LH (and by inference GnRH) activity. The mechanisms involved in suppressing GnRH secretion remain unknown, although children are exquisitely sensitive to steroid feedback.[3]

Toward the end of the first decade of life, 2 factors appear to be involved in facilitating initiation of GnRH secretion. It has been recognized for years that children who are significantly underweight owing to either calorie deprivation or severe illness do not undergo spontaneous puberty. The exact signaling systems by which the central nervous system (CNS) recognizes low body weight remain uncertain, but the process involves leptin, which is a product of the *Ob* gene and is secreted by fat cells. In rodents leptin is important in initiating the pubertal process, and leptin deficiency appears to be partly responsible for low gonadotropin secretion during starvation and anorexia nervosa in humans.

Adrenarche is the term used to describe increased adrenal androgen secretion, predominantly dehydroepiandrosterone sulfate. Values begin to rise at about the age of 7, some 2 years earlier in girls than in boys. The role that increased androgen secretion plays in the initiation of true hypothalamic puberty remains unclear. Individuals without adrenal function can still undergo puberty, but it seems likely that this initial exposure to increased androgens has a facilitory role in subsequent hypothalamic maturation.

The Pubertal Years/Adolescence

Clinical evidence of pubertal maturation is heralded by a marked augmentation in the amplitude and frequency of sleep-related GnRH secretion. The small nocturnal peaks mentioned earlier are augmented, a process that in turn gradually stimulates LH and gonadal steroid secretion.

Recent studies have provided insight into the mechanisms controlling GnRH secretion during this period of life. In 2003, groups in France and the United States showed a high incidence of hypogonadotropic hypogonadism in consanguineous families.[4,5] Affected individuals in these families had a mutation of the *GPR54* gene. GPR54 (G protein–coupled receptor 54) was an orphan receptor of unknown significance, but studies utilizing knock-out mice with loss-of-function mutations presented with low levels of gonadotropins and sex steroids and did not mature sexually.[6] Of interest no other abnormalities were apparent in these animals or in the children of consanguineous families. These findings focused interest on GPR54 as a central receptor in the regulation of reproduction, and subsequent investigations showed it was a member of the rhodopsin receptor family, with 85% homology between mice and humans. GPR54 receptors are expressed widely in the brain, but particularly in the hypothalamus and in GnRH neurons.

The ligand for the GPR54 receptor had been discovered 2 years earlier in 2001 and shown to be kisspeptin. Kisspeptin, a product of the *Kiss-1* gene, was originally identified in Hershey, Pennsylvania (hence the name). Study results of the Hershey groups, who were investigating cancer biology, indicated that the *Kiss1* gene was expressed only in malignant cells that were not metastatic. The gene encodes a 145 amino-acid protein, which is cleaved to a 54 amino-acid peptide, kisspeptin-54 or metastin, and to several smaller peptides, of which the shortest active form is kisspeptin-10.[7] The association of its receptor (GPR54) with GnRH deficiency stimulated major research efforts to establish the role of kisspeptin and GPR54 in pubertal maturation.[8] Kisspeptin was also found to be present in the hypothalamus (arcuate and median eminence), thus localizing both ligand and receptor to the area of GnRH production. Use of kisspeptin-10 in animal studies showed that both central and intravenous administration of kisspeptin

to animals produced dose-related increases in plasma LH and FSH in adult animals and humans. Proof of a critical link between kisspeptin and GPR54 was found when studies showed an absence of kisspeptin stimulation of gonadotropin secretion in GPR54 knock-out mice.[5] Subsequent work showed that kisspeptin stimulates gonadotropin secretion via activation of the GnRH neuron.[9] Kisspeptin stimulates GnRH release from hypothalamic explants and may have direct action on pituitary gonadotrope cells. Acyline (a GnRH antagonist) blocks the ability of kisspeptin to stimulate gonadotropin release, indicating the primary site of kisspeptin action is on GnRH release in the hypothalamus. Proof of this concept came from studies showing that kisspeptin increased Fos expression in GnRH neurons, an indication of neuron stimulation.[10] Thus kisspeptin acts directly on GPR54 in GnRH neurons to stimulate GnRH release. Subsequently, kisspeptin was proposed to be a central regulator in both steroid hormone feedback and in CNS recognition of body weight, androgen secretion, and other environmental and seasonal cues.[11]

As noted, pulsatile secretion of GnRH is essential to maintain LH and FSH gene expression, and continuous stimulation downregulates (desensitizes) gonadotropin secretion. The pulsatile nature of GnRH release probably reflects intermittent stimulation by kisspeptin and/or other CNS stimuli, and the frequency of pulsatile release is critical to determining whether the pituitary gonadotrope cell synthesizes LH or FSH. Rapid frequency GnRH pulses (every 15-30 minutes in rodents, 45-60 minutes in humans) preferentially stimulate LH production. Slower frequency pulses (less than every 60 minutes in rodents and every 3-4 hours in humans) stimulate only synthesis of FSH. A series of studies have shown that pulse frequency regulates several intracellular mechanisms, resulting in differential secretion of LH and FSH.[12,13] Steroid hormone feedback, either by progesterone in females or testosterone in males, is predominantly exerted by slowing the frequency of GnRH pulse secretion. Thus regulation of reproduction involves mechanisms to alter the frequency and amplitude of GnRH pulse secretion. In utero data are scanty, but pulses probably occur with a frequency of every 60 minutes. Before the onset of puberty, pulse frequency and amplitude are inhibited, with demonstrable pulses in children occurring approximately every 3 to 4 hours during the day. The initiation of puberty reflects increased GnRH pulse secretion, with frequency rising to about 1 pulse per hour during sleep; this increase is attributable to either new stimulatory events at this age or removal of prepubertal inhibitory factors. Few data are available on compounds that regulate kisspeptin and GnRH secretion in humans, but studies in rodents have provided insights. Excitatory stimuli include glutamate, whereas GABA (gamma-aminobutyric acid) and the enkephalins/endorphins are inhibitory.[14] Although the intrahypothalamic mechanisms remain obscure, once the ability to secrete GnRH at a frequency of 1 pulse per hour in humans has been achieved, subsequent regulation by sex steroids occurs mainly by slowing of the frequency of GnRH pulse secretion, thereby effecting differential synthesis of LH or FSH. During pubertal maturation the set points for regulation of GnRH secretion by steroids mature, and sensitivity to steroid inhibition is reduced. Testosterone slows GnRH pulse frequency to approximately 1 pulse every 1 to 2 hours in adult men, a frequency that is established during puberty and remains stable until later life. In adolescent girls however, the ability to change GnRH frequency and modulate LH and FSH production is essential to establishing normal cycles. During early puberty, rising GnRH (LH) pulse secretion at night increases secretion of progesterone and estradiol, albeit to low levels. By late puberty, daytime GnRH secretion has risen, further increasing steroid production. The 24-hour GnRH stimulus increases LH, leading to ovulation, after which higher concentrations of progesterone slow GnRH frequency, enhancing FSH production and follicular maturation, thus initiating cyclic regulation of GnRH secretion (Figure 2).[15,16]

Prepubertal children are very sensitive to steroid hormone feedback, and the patterns in Figure 2 suggest that a gradual progression of increased daytime GnRH secretion may reflect reduced sensitivity to the inhibitory action of estradiol and progesterone.

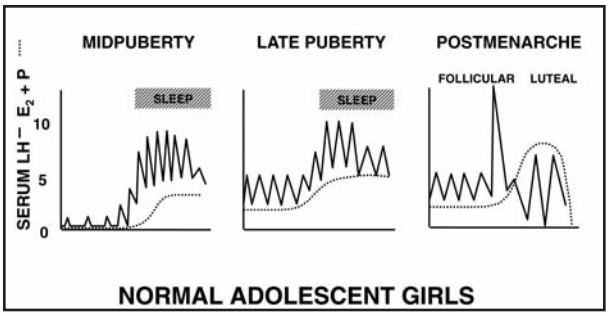


Figure 2. Evolution of day/night patterns of gonadotropin-releasing hormone, luteinizing hormone (LH), and ovarian steroid secretion through pubertal maturation in girls. E_2 indicates estradiol; P, progesterone.

Our own studies[17] showed that the initial increase in GnRH/LH during sleep is associated with a 2-fold rise in progesterone. We hypothesize that in early pubertal girls this nocturnal rise in progesterone plays a role in inhibiting GnRH secretion the following day. Testosterone also increases overnight, and plasma testosterone gradually increases during pubertal maturation in girls.[18] Indeed, by the time that pubertal maturation is first evident clinically (appearance of breast buds—Tanner stage 2) morning testosterone levels approximate those of adult women. Testosterone values exceed those of estradiol by approximately 100 fold, and thus the maturing hypothalamus exists in a milieu of increasing levels of androgen.

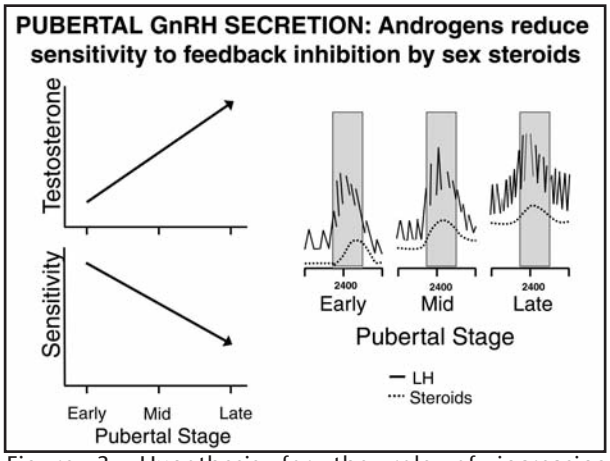


Figure 3. Hypothesis for the role of increasing testosterone to reduce the sensitivity of the gonadotropin-releasing hormone (GnRH) pulse generator to steroid-hormone feedback during normal pubertal maturation. LH, luteinizing hormone.

In women with elevated androgen levels the ability of sex steroids such as progesterone to inhibit GnRH pulse secretion is impaired[19] and can be restored to normal after blockade of androgen action by an androgen-receptor blockade (flutamide).[20] Thus elevated testosterone impairs progesterone feedback. The gradual increase in testosterone during normal puberty may reduce the ability of low concentrations of estradiol/progesterone to inhibit GnRH secretion during the day, allowing the gradual increase in GnRH and gonadotropin secretion to stimulate gonadal steroid production and effecting the clinical manifestations of puberty (Figure 3). Results of further studies support this thesis, and data show that administration of low doses of estradiol/progesterone are more effective in slowing GnRH/LH pulse frequency in early pubertal girls than in adults.[21]

The ability to regulate GnRH pulse frequency is an important factor in producing cyclic ovulation.[22] A

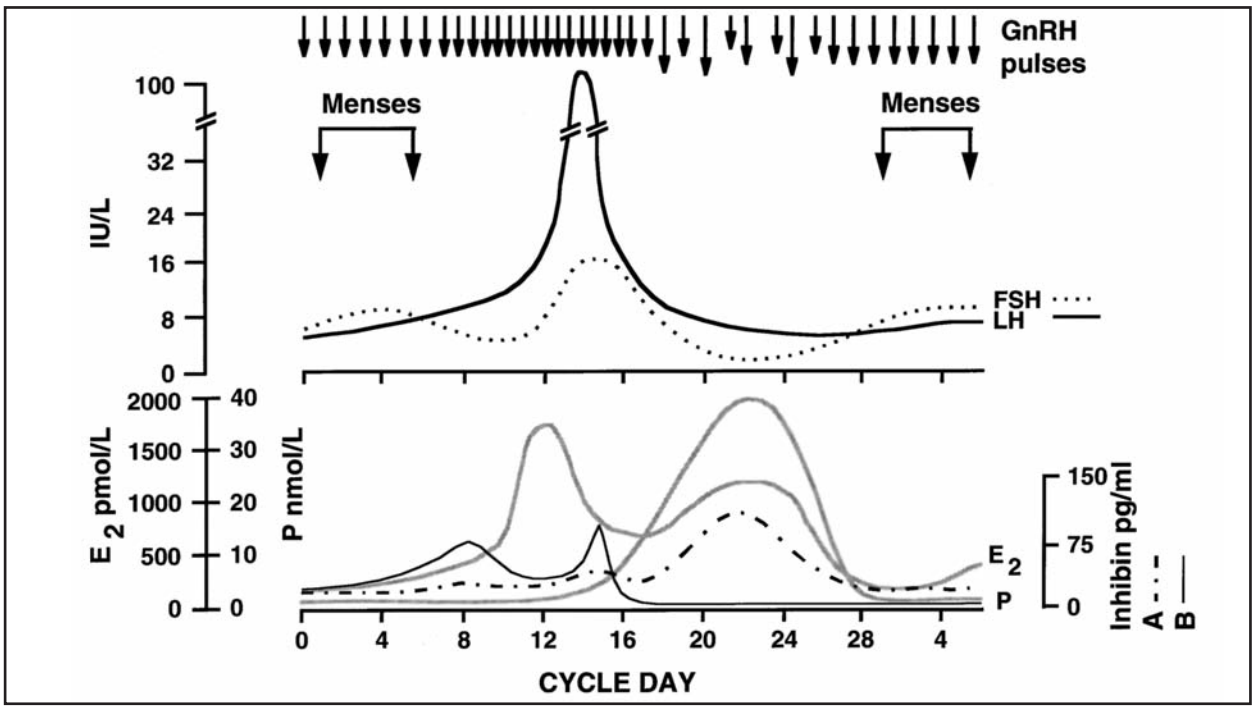


Figure 4. GnRH pulse secretion and hormone changes during an ovulatory menstrual cycle. Abbreviations are defined in the Figure 1 and 2 legends.

schematic of increasing frequency of GnRH pulses during the follicular phase, resulting in increase of LH and estradiol secretion and decreased FSH release, is shown in Figure 4.

Following ovulation, luteal progesterone slows GnRH frequency, which favors synthesis of FSH. The release of FSH from the pituitary, however, is directly blocked by inhibin A. With the demise of the corpus luteum, progesterone and inhibin A fall, and GnRH pulse frequency increases, releasing FSH to begin the next wave of ovarian follicular maturation.[23]

EVOLUTION OF ABNORMAL GnRH/LH SECRETION IN PCOS

PCOS, a disorder of uncertain etiology, results in excess production of androgen, anovulatory cycles and infertility, and development of multiple cysts in the ovaries. Women with PCOS have increased risk of obesity, diabetes, and the metabolic syndrome. PCOS is common, affecting some 6%-8% of women of reproductive age, and thus is a cause of significant morbidity in young women.[24]

In addition to elevated testosterone in plasma, LH pulse secretion is abnormal and is a consistent feature of women with PCOS, occurring in some 90%-95% of individuals who have not experienced recent spontaneous ovulation.[25] Patterns of pulsatile LH (GnRH) secretion in a woman with PCOS are shown in Figure 5.

In both lean and obese women with PCOS, LH pulses occur at a more rapid frequency that persists during the 24-hour cycle.[26] The amplitude of GnRH pulses is somewhat reduced in obese patients, reflecting reduced LH release to each GnRH pulse.[27] This persistently rapid GnRH pulse frequency is similar to that which occurs in normal women during the late follicular phase. In the absence of ovulation, progesterone secretion does not slow GnRH/LH pulses in women with PCOS, a phenomenon that may simply reflect the absence of ovulation, but other data suggest that it reflects elevated plasma androgen levels, which impair the ability of estradiol/progesterone to reduce the frequency of GnRH pulse secretion. The amplitude and frequency of LH pulse secretion in women with PCOS and during normal ovulatory cycles is shown in Figure 6.

Further support for the observation that the rapid GnRH frequency does not simply reflect the absence of ovulation is found in studies in

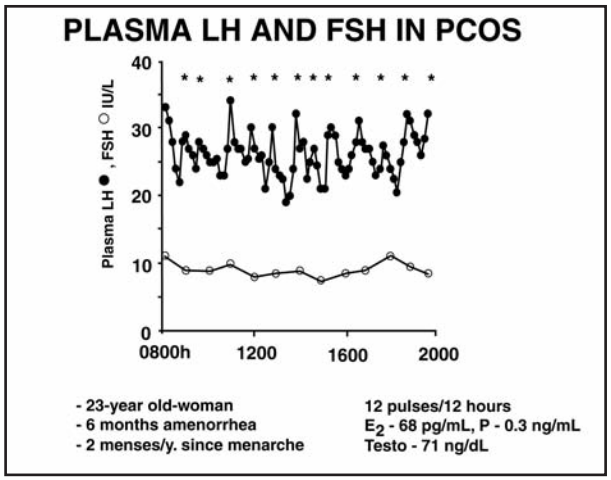


Figure 5. LH secretory pattern in a woman with polycystic ovary syndrome (PCOS). Testo indicates testosterone. Other abbreviations are defined in the Figure 1 and 2 legends.

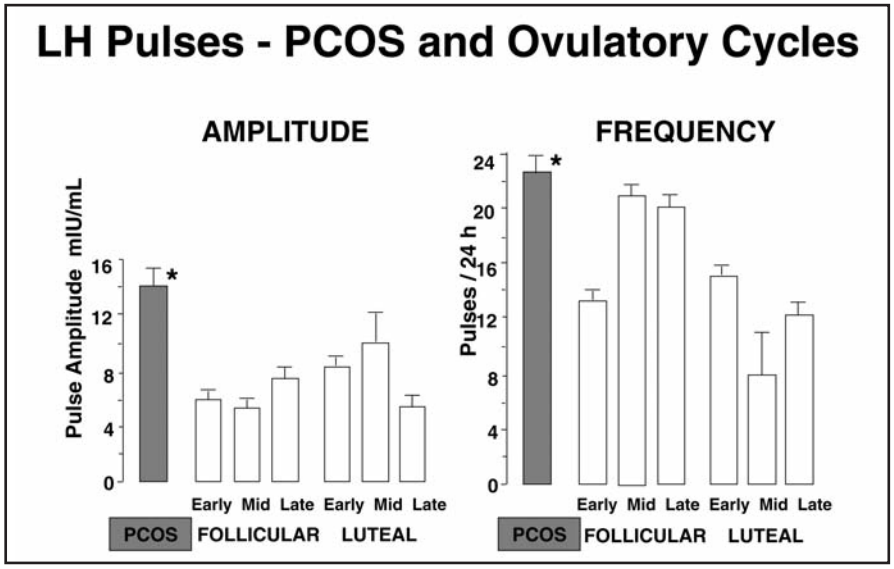


Figure 6 The amplitude of luteinizing hormone (LH) pulses is increased in women with polycystic ovary syndrome (PCOS), and the frequency is persistently elevated to a level similar to the fast frequency achieved by normal women prior to the ovulatory midcycle surge. Note the normal luteal slowing does not occur.

adolescent girls with hyperandrogenemia.[28,29] In girls prior to the onset of menarche a similar pattern of rapid frequency GnRH pulse secretion occurs, suggesting that the androgen per se may be impairing regulation GnRH pulse frequency.[28] Our own studies provided evidence that in adult women with PCOS, progesterone was less efficient in reducing GnRH pulse frequency than in normal controls.[19] Prior administration of the androgen receptor blocker flutamide for 4 weeks restored the ability of low concentrations of progesterone to reduce the frequency of GnRH pulse secretion, confirming the role of elevated androgens in impairing progesterone feedback (Figure 7).

Further evidence supporting a role for hyperandrogenemia in effecting abnormal regulation of GnRH secretion was seen in earlier studies. To compare the pattern of LH pulse secretion in normal premenarchal girls with those with elevated androgens, LH sampling was performed every 10 minutes during a 24-hour period, and studies were repeated after the onset of menarche. Premenarchal girls with elevated androgens exhibited 24-hour patterns of GnRH secretion, and the maturation of the pubertal GnRH pulse generator appeared to be advanced by about 2 years.[28] The rapid frequency LH/GnRH secretion persists, and postmenarchally a pattern similar to that seen in women with PCOS is present.

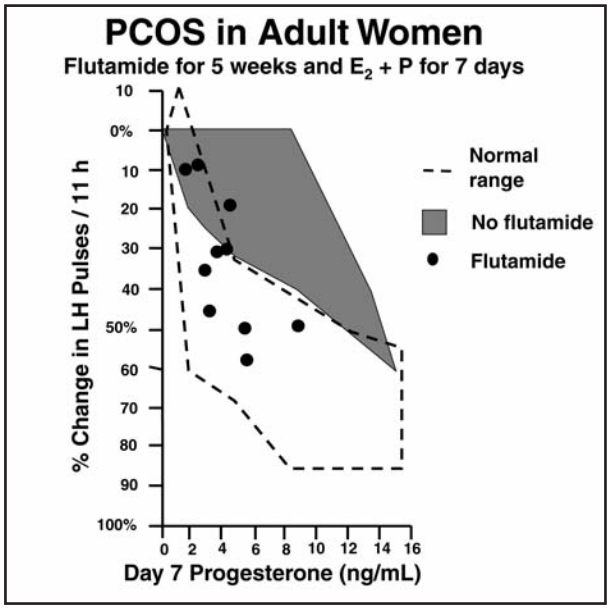


Figure 7. Suppression of luteinizing hormone (LH) (gonadotropin-releasing hormone [GnRH]) pulse frequency by progesterone. All subjects received estradiol (E_2) to achieve plasma concentrations of approximately 100 pg/mL and varied doses of oral progesterone (P) for 7 days. GnRH pulse frequency was measured before and after the 7 days. The change (reduction) in GnRH pulse frequency is shown on the vertical axis as a function of the plasma progesterone level in that subject. The range of suppression in normal subjects (hatched area) and in women with polycystic ovary syndrome (PCOS) (solid area) prior to flutamide treatment. Individual points represent pulse suppression after administration of flutamide. (Data were redrawn from previously reported studies.[19,20])

The origins of hyperandrogenemia during adolescence are also unclear, but recent work suggests they may be related to the epidemic of childhood obesity during the past 25-30 years. Data from the National Health and Nutrition Examination Survey studies showed that in adolescent girls between the age of 6-19 years the prevalence of obesity (>95% of ideal body weight) has risen from 4%-5% in 1970 to 17%-19% in 2004.[30] Our own investigations in obese girls in both early and late puberty showed that obesity is often associated with a marked increase in plasma testosterone and a decrease in sex-hormone–binding globulin (SHBG), so the free testosterone elevation is magnified. Insulin is known to act as a co-gonadotropin with LH in stimulating androgen secretion by the ovary. In addition insulin directly inhibits SHBG production by the liver. Thus the increase in hyperinsulinemia associated with obesity would be expected to increase androgen production. Data show that free testosterone concentrations are increased by some 3-7 fold throughout pubertal maturation in obese girls.[17,31]

The ability of progesterone to inhibit GnRH pulse secretion has also been tested in hyperandrogenic adolescent girls. Approximately half of the individuals with hyperandrogenemia showed impaired ability of progesterone to suppress GnRH pulse secretion.[32,33] Interestingly, other hyperandrogenemic girls with similar levels of free testosterone are not affected and appear to have normal sensitivity to progesterone feedback. The mechanisms of these differences remain obscure, but their occurrence suggests that individuals in whom testosterone impairs progesterone action may develop abnormalities of GnRH pulse secretion.

Earlier we proposed that in normal puberty the gradual increase in physiologic testosterone was a mechanism that reduced hypothalamic sensitivity

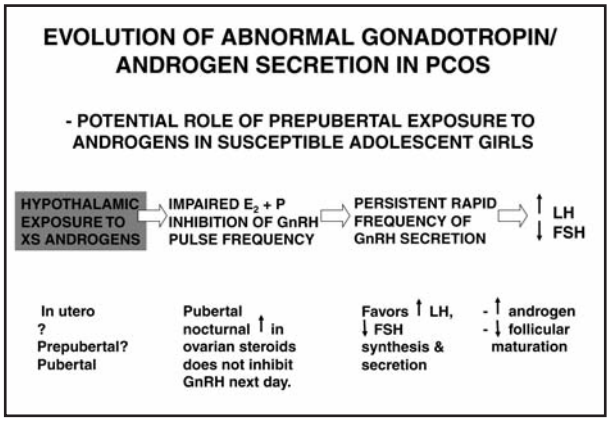


Figure 8. Hypothesized evolution of abnormal gonadotrophin/androgen secretion in polycystic ovary syndrome. Abbreviations are defined in the Figure 1 and 2 legends.

to estradiol/progesterone feedback, allowing increased daytime secretion of GnRH and LH. Thus it seems probable that in situations in which testosterone is elevated this process may be augmented, further impairing progesterone feedback leading to advancement of 24-hour GnRH secretory patterns.[28] Although aspects of this thesis remain to be proven, we propose that important factors in the evolution of adult PCOS include the recent marked increase in obesity and its associated hyperinsulinemia and androgen production, which in susceptible individuals impairs the normal maturation of ovarian steroid regulation of GnRH/LH pulse secretion. These concepts are summarized in Figure 8.

ACKNOWLEDGMENTS

Supported by Specialized Cooperative Centers Program for Research in Infertility and Reproduction (NICHD U-54 HD-28934)

These studies were performed in the General Clinical Research Center (GCRC) at the University of Virginia. We gratefully recognize the skilled assistance of nurses and staff of the GCRC for implementation of study protocols, and Lauren Lockhart, MPH, and Quinine Lamberts Okonkwo, MD, for subject recruitment, study scheduling, and maintenance of records. All assays were performed in the Ligand Assay Core of the Center for Research in Reproduction.

REFERENCES

1. Marshall JC, Kelch RP. Gonadotropin-releasing hormone: role of pulsatile secretion in the regulation of reproduction. *N Engl J Med*. 1986;315:1459-1468.
2. Tobet SA, Schwarting GA. Mini-review: recent progress in GnRH neuronal migration. *Endocrinology.* 2006;147:1159-1165.
3. Jakacki RI, Kelch RP, Sauder SE, et al. Pulsatile secretion of luteinizing hormone in children. *J Clin Endocr Metab.* 1982;55:453-459.
4. de Roux N, Genin E, Carel JC, et al. Hypogonadotropic hypogonadism due to loss of function of the KiSS-1 derived peptide receptor GPR54. *Proc Natl Acad Sci USA.* 2003;100:10972-10976.
5. Seminara SB, Messager S, Chatzidaki EE, et al. GPR54 gene as a regulator of puberty. *N Engl J Med*. 2003;349:1614-1627.
6. Funes S, Hedrick JA, Vassileva G. The KiSS-1 receptor GPR54 is essential for the development of the murine reproductive system. *Bio Chem Bio Phys Res Commun.* 2003;312:1357-1363.
7. Harms JF, Welch DR, Miele ME. KiSS-1 metastasis suppression and emergent pathways. *Clin Exp Metastasis*. 2003;20:11-18.
8. Ohtaki T, Shintani Y, Honda S, et al. Metastasis suppressor gene KiSS-1 encodes a peptide ligand of a G protein-coupled receptor. *Nature.* 2001;411:613-617.
9. Messager S, Chatzidaki EE, Ma D, et al. KiSS peptin directly stimulates GnRH release via G protein-coupled receptor 54. *Proc Natl Acad Sci USA.* 2005;102:1761-1766.
10. Irwig MF, Fraley GS, Smith JT, et al. Kisspeptin activation of GnRH neurons and regulation of KiSS-1 mRNA in the male rat. *Neuroendocrinology.* 2004;80:264-272.
11. Dungan HM, Clifton BK, Steiner RA. Mini review: KiSS peptin neurons as central processors in the regulation of GnRH secretion. *Endocrinology.* 2006;147:1154-1158.
12. Dalkin AC, Haisenleder DJ, Ortolano GA, et al. The frequency of gonadotropin-releasing hormone (GnRH) stimulation differentially regulates gonadotropin subunit mRNA expression. *Endocrinology.* 1989;125:917-924.
13. Burger LL, Haisenleder DJ, Dalkin AC, Marshall JC. Regulation of gonadotropin subunit gene transcription. *J Mol Endocrinol*. 2004;33:559-584.
14. Ojeda SR, Lomniczi A, Mastronardi C, et al. Mini review: the neuro endocrine regulation of puberty: is the time right for a systems biology approach? *J Endocrinol.* 2006;147:1166-1174.
15. Zhang K, Pollack S, Ghods A, et al. Onset of ovulation after menarche in girls: a longitudinal study. *J Clin Endocrinol Metab*. 2008;93:1186-1194.
16. McCartney CR, Gingrich MB, Hu Y, et al. Hypothalamic regulation of cyclic ovulation: evidence that the increase in GnRH pulse frequency during the follicular phase reflects the gradual loss of the restraining effects of progesterone. *J Clin Endocrinol Metab.* 2002;143:3243-3249.
17. McCartney CR, Blank SK, Prendergast KS, et al. Obesity and sex steroid changes across puberty: evidence for marked hyperandrogenemia in pre and early pubertal girls. *J Clin Endocrinol Metab.* 2007;92:430-436.
18. Mitamura R, Oyano K, Suzuki N, et al. Diurnal rhythms of LH, FSH, testosterone and estradiol secretion before the onset of female puberty in short children. *J Clin Endocrinol Metab.* 2000;85:1074-1080.
19. Pastor CL, Griffin-Korf ML, Aloi JA, et al. Polycystic ovarian syndrome: evidence for reduced sensitivity of the GnRH pulse generator to inhibition by estradiol and progesterone. *J Clin Endocrinol Metab.* 1988;83:582-590.
20. Eagleson CA, Gingrich MB, Pastor CL, et al. Polycystic ovarian syndrome: evidence that flutamide restores sensitivity of the GnRH pulse generator to inhibition by estradiol and progesterone. *J Clin Endocrinol Metab.* 2000;85:4047-4052.

21. Blank SK, Chhabra S, McCartney CR, et al. Reduced sensitivity of the hypothalamic GnRH pulse generator during pubertal maturation in adolescent girls with and without hyperandrogenemia. *Program and Abstracts Book Annual 88th Meeting 2006, Boston, MA.* Baltimore, Md: The Endocrine Society; 2006:555. AbsP2-622.
22. Reame N, Sauder SE, Kelch RP, Marshall JC. Pulsatile gonadotropin secretion during the human menstrual cycle: evidence for altered frequency of GnRH secretion. *J Clin Endocrinol Metab.* 1984;59:328-338.
23. Marshall JC. Hormonal regulation of the menstrual cycle and mechanisms of an ovulation. In: DeGroot LJ, Jameson JL, DeKretzer D, et al, eds. *Endocrinology*. 5th ed. Philadelphia, Pa: Elsevier; 2005:2911-2922.
24. Azziz R, Woods KS, Reyna R, et al. The prevalence and features of PCOS in an unselected population. *J Clin Endocrinol Metab*. 2004;89:2745-2749.
25. Taylor AE, McCourt B, Martin KA, et al. Determinants of abnormal gonadotropins secretion in clinically defined women with PCOS. *J Clin Endocrinol Metab.* 1997;82:2248-2256.
26. Waldstreicher J, Santoro NF, Hall JE, et al. Hyper function of the hypothalamic-pituitary axis in women with PCOS: indirect evidence for partial gonadotrope desensitization. *J Clin Endocrinol Metab*. 1997;66:165-172.
27. Pagain YL, Stouji SS, Jimenez Y, et al. Inverse relationship between LH and BM1 in PCOS: innovation of hypothalamic and pituitary contributions. *J Clin Endocrinol Metab.* 2006;91:1309-1316.
28. Apter D, Butzow T, Laughlin GA, et al. Accelerated 24 hour LH pulsatile activity in adolescent girls with ovarian hyperandrogenism: relevance to the developmental phase of PCOS. *J Clin Endocrinol Metab*. 1994;79:119-125.
29. McCartney CR, Prendergast KA, Blank SK, et al. Maturation of diurnal LH (GnRH) secretion across puberty: evidence for altered regulation in obese peri-pubertal girls. *J Clin Endocrinol Metab.* 2009;94:56-66.
30. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA.* 2006;295:1549-1555.
31. McCartney CR, Prendergast KA, Chhabra S. The association of obesity and hyperandrogenemia during the pubertal transition in girls: obesity as a potential factor in the genesis of post-pubertal hyperandrogenemia. *J Cin Endo Metab.* 2006;91:1714-1722.
32. Chhabra SK, McCartney CR, Yoo RY, et al. Progesterone inhibition of the hypothalamic pulse generator: evidence for varied effects of hyperandrogenemia in adolescent girls. *J Clin Endocrinol Metab*. 2005;90:2810-2815.
33. Blank SK, Chhabra S, McCartney CR, et al. Effects of androgens on hypothalamic GnRH pulse generator sensitivity: further evidence of variable sensitivity in hyperandrogenic adolescent girls. *Program and Abstracts Book Annual 90th Meeting 2008, San Francisco, CA.* Baltimore, Md: The Endocrine Society; 2008:334. Abs1-600.

Focus on Graduate Medical Education: Historical Perspectives and Future Pathways in Global Health Education in the University of Virginia Department of Medicine

Rebecca Dillingham, MD, MPH, Assistant Professor of Medicine, Division of Infectious Diseases and International Health
Gerald R. Donowitz, MD, Edward W. Hook Professor of Medicine, Division of Infectious Diseases and International Health

We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.
T. S. Eliot—*Little Gidding V*

In 1997, the Institute of Medicine articulated the foundations of US interest in global health. "[The United States has] a vital and direct stake in the health of people around the globe … this interest derives from a long and enduring tradition of humanitarian concerns and compelling reasons of self-enlightenment."[1]

A 2008 editorial in *Academic Medicine* introduced a theme issue on global health education in US medical schools by emphasizing the resonance of the concept of global health with today's technologically savvy medical students and residents. "[The] feeling of enhanced connectedness on a global scale—the sense of global community…is leading students and residents in record numbers to seek educational experiences that enrich their understanding of other cultures and health care systems."[2]

For decades the University of Virginia Department of Medicine (UVA DOM) has been committed to engaging in global health research of high relevance to international partners and providing meaningful global health experiences for trainees. This report describes the contemporary contexts in which global health has become so prominent, highlights the role of some of the important individuals from the UVA DOM involved in global health, and explains ongoing UVA DOM plans to optimize the education of future leaders in global health.

Why Global Health?

The switch in terminology from "international" to "global" health reflects an interest, which has become particularly prevalent during the past 20 years, in the promotion of the health of people around the globe rather than the promotion only of the health of the people in an individual nation.[3] Many factors spurred this change. Infectious diseases such as SARS (severe acute respiratory syndrome), pandemic influenza, and extensively drug-resistant tuberculosis easily traverse borders, highlighting mutual vulnerabilities. Chronic diseases, particularly those associated with obesity and metabolic syndrome, increasingly plague developing countries, even those where undernutrition remains a leading killer.[4]

During the past 28 years the human immunodeficiency virus (HIV) has exacted a horrible toll, and this pandemic and the global response to it have also played roles in changing the global health landscape. Paul Farmer, medical anthropologist and physician at the Department of Global Health and Social Medicine at Harvard Medical School, is an example of a prominent individual who has changed discourse about the provision of antiretroviral medications and other effective health interventions to the poor. Farmer pointed out that "The poor are doing their job—they're shouting as loud as they can. It's we who can't hear them. What the American public thinks is very important to the future of global health. Many people are moved by the idea that there is unnecessary suffering in the world, and we could do a lot to stop it. We have the technologies necessary to stop most of the suffering."[5]

This shift in thinking, articulated by Farmer and others, helped to catalyze the formation of powerful and sometimes unexpected alliances, such that of the rock star Bono and the former Senator from North Carolina Jesse Helms.[6] Their partnership, with US government assistance provided during President George W. Bush's administration, led to the President's Emergency Plan for AIDS Relief, an unprecedented $15 billion investment in measures to prevent the spread of HIV and to care for people affected by HIV in poor countries. Arguments in favor of addressing global health threats such as HIV have come not only from faith-based and human-rights organizations but also from other sectors, including the intelligence community.[7] During the

past 15 years prominent economists such as Jeffrey Sachs have sounded the alarm about the necessity of promoting global health to ensure military and economic security.[8]

In response to the compelling arguments to become involved in the cause of global health, new, generous funding has become available. The Bill and Melinda Gates Foundation, replete with a generous gift from Warren Buffett, holds the world's largest charitable endowment. These funds are to be used "until we reduce the burden on the poor, so that there is no real gap between us and them."[9] The availability of funds from the Bill and Melinda Gates Foundation has not stifled other giving, as some feared, but instead has promoted an increase, and in some cases a doubling, of multilateral, bilateral, and public-private aid.[9]

The combination of new imperatives and new funding opportunities has resulted in the development of "implementation science," a new approach to solving global health problems. This discipline makes note of the disparities between "innovations in health and their delivery to communities in the developing world."[10] Implementation scientists strive to "create generalizable knowledge" through the use of innovative techniques such as agent-based modeling, which helps policy-makers anticipate what effects small changes in policy or other factors may have on a population's health.

All of these factors make pursuing global health as a career an intriguing possibility for students of medicine. Indeed, as noted in a report in *Nature*, "international efforts to improve global health now offer a wide range of career opportunities." However, the same report laments that "despite the interest in global health and the intense need for skilled professionals, there is not yet a cohesive career path in developed or developing nations."[11] One suggested strategy is an "interdisciplinary, systems approach" to train leaders in this field.[10]

To meet the challenge of preparing students for careers in global health, some institutions, such as the Brigham and Women's Hospital in Boston, MA, and Duke University Hospital in Durham, NC, have developed pathways that allow trainees to gain experience overseas and to pursue academic curricula at their home institutions that are relevant to global health issues. Houpt et al worked with the American Society of Tropical Medicine and Hygiene and the Global Health Education Consortium to produce a report suggesting 3 core competencies in global health to be included in all medical school curricula: the burden of disease, traveler's medicine, and immigrant and refugee health.[12] The Global Health Education Consortium has also produced a resource for residency programs, *Developing Residency Training in Global Health: A Guidebook*.[13] No shared curriculum has been established, however, and institutions struggle to define best practices and ethical standards, particularly for global health electives that take trainees to foreign sites.[14]

Despite the lack of consensus about a unified curriculum, previous research has suggested that global health experiences result in a variety of positive outcomes for trainees that correlate to some degree with the core competencies defined by the Accreditation Council for Graduate Medical Education Core Competencies.[15] These include: (*a*) increased knowledge of "tropical diseases"; (*b*) improved clinical diagnostic skills; (*c*) greater appreciation for the "importance of public health, health service delivery, cross-cultural communication, and the challenges of health care in underserved communities;" and (*d*) greater likelihood to pursue a career that serves the disadvantaged.[16]

Global Health Education Leaders from UVA DOM

A look at the history of UVA DOM reveals 4 outstanding individuals who anticipated and helped to create the current opportunities in global health education. William Parson, an endocrinologist who first described the syndrome of pseudohypoparathyroidism, served as the Chair of the DOM from 1949 to 1966. In 1966 Parson, known as a master teacher, left UVA after receiving funding from the Rockefeller Foundation and subsequently became the Chair of Medicine at Makerere University in Kampala, Uganda. A colleague, Byrd Leavell, visited Parson in Uganda in 1970 and reported that Parson had "raised the standards of teaching…this has added to the prestige of the hospital, at home and abroad."[17] This commitment to providing excellent training to foreign medical personnel characterized the strategy for engagement in global health developed in the 1950s by leaders in internal medicine. Today, Michael Scheld and Chris Moore, both of the Division of Infectious Disease and International Health, continue Parson's proud tradition, working with and mentoring their research and clinical colleagues in hospitals in Uganda.

A contemporary of Parson, Thomas Hunter, was Dean of the School of Medicine from 1953 to 1965 and was an accomplished infectious disease specialist who first demonstrated the synergy of penicillin and streptomycin for the treatment of subacute bacterial endocarditis. Hunter, as president of the Association of American Medical Colleges, also championed the role of the US medical profession in the education of the global medical workforce, saying, "The United States should be the merchants of health, not the merchants of arms to the world."[18]

Edward Hook became Chair of Medicine in 1969 and held the position until 1990. An infectious disease specialist with expertise in the pathogenesis of *Salmonella* species, Hook dedicated significant time to developing a research collaboration with the Federal University of Ceará in Northeast Brazil, now the longest standing research collaboration in the UVA School of Medicine. In Hook's papers, housed in the historical collections at the UVA Claude Moore Health Sciences Library, one can read a 65-page account of his trip to Brazil to identify a research partner for UVA. In the travelogue, Hook documented the details of his trip, including astute case descriptions of acute Chagas disease, a mention of a dinner with Alvin Ailey, reflections on the health care payment system in the public hospitals in Brazil, and descriptions of the medical education system. He also carefully considered the merits of various potential partners and eventually settled on Ceará. Hook's commitment to the development of a bidirectional education and research collaboration based on trust and mutual respect is continued today by those he mentored. For example, William Petri has collaborated for the last 15 years with Rashidul Haque of the International Centre for Diarrhoeal Disease Research in Dhaka, Bangladesh. Their work is supported by grants to Petri from the Bill and Melinda Gates Foundation, the National Institutes of Health, and the US Centers for Disease Control and Prevention, and encompasses work on malnutrition and diarrheal and respiratory diseases in children. Many students and several medical residents and fellows have worked at this site under the supervision of Petri and Haque.

As a student and colleague of the leaders already described, Richard Guerrant (now the Thomas H. Hunter Professor of Medicine at UVA) traveled to Ceará with Hook and subsequently built the collaboration that has now thrived for 30 years. In addition to creating the research collaboration with Ceará, Guerrant has mentored dozens of students and young scientists from 4 continents. He has also expanded his vision through the development of the transuniversity Center for Global Health (CGH). Founded in 2001, CGH defines its mission this way: "to promote health in resource-limited settings by fostering the commitment of students, faculty, and partners from many disciplines to address the diseases of poverty." CGH provides scholarships to UVA students to participate in mentored global health projects, supports fellowships for the professional development of junior faculty from partner institutions in resource-limited settings, and coordinates global health curriculum development.[19] Partner CGH organizations have been founded by former CGH fellows in Ceará; Manila, the Philippines; and Thohoyandou, South Africa. For his visionary contributions to global health as a researcher and a mentor, Guerrant was recently awarded the 2008 Walter Reed Medal from the American Society of Tropical Medicine and Hygiene.

Continuing the Tradition of Global Health Leadership

In this rapidly evolving era of global health and with UVA DOM's rich history of engagement in global health, the residency program is piloting a new Global Health Leadership track beginning with the residency class of 2012. The goal of this track is to prepare young physicians to become leaders in global health practice, research, policy, and education. Two or 3 rising postgraduate-year 2 residents from both Internal Medicine and Family Medicine will be accepted into the track each year. The track will include a preparatory course for the Tropical Medicine Certification Examination, monthly global health didactic conferences, 2 month-long research rotations at one of the residency's target sites, a refugee health rotation, and the completion of a significant scholarly project related to a global health issue relevant to the resident's chosen target site. In addition, track residents will develop at least 2 global health teaching seminars to present at UVA and at their chosen partner site. With this intensive preparation, we expect that UVA residents will continue the tradition of UVA DOM's leadership in global health, a tradition characterized by a commitment to bidirectional research collaborations that develop leaders, build research capacity, and define solutions to the diseases of poverty in our partner countries and at home.

ACKNOWLEDGMENTS

The authors would like to thank Mrs. Jesse Hook for sharing her stories about her family's role in developing global health opportunities at the UVA School of Medicine and for her support of the global health leadership track. The authors would also like to acknowledge the close collaboration of Dr. Fern R. Hauck, MD/MS, Department of Family Medicine, in the development of the Global Health Leadership Track. The authors appreciate the support of HRSA grant D58HP10323 and the Framework Program in Global Health–NIH/Fogarty International Center Grant R25 TW007518.

REFERENCES

1. Board on International Health, Institute of Medicine. *America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests.* Washington, DC: Institute of Medicine; 1997.
2. Kanter S. Global health is more important in a smaller world. *Acad Med.* 2008;83:115-116.
3. Brown T, Cueto M, Fee E. 2006. The World Health Organization and the transition from "international' to "global" public health. *Am J Public Health.* 2006;96:62-72.
4. Caballero B. A nutrition paradox: underweight and obesity in developing countries. *N Engl J Med.* 2005.352:1514-1516.
5. PBS. Rx for survival, global health champions: Paul Farmer, MD, PhD. Available at: http://www.pbs.org/wgbh/rxforsurvival/series/champions/paul_farmer.html. Accessed December 10, 2008.
6. Helms J. Bono. Time. April 30, 2006. Available at: http://www.time.com/time/magazine/article/0,9171,1187308,00.html. Accessed April 1, 2009.
7. Frontline. The age of AIDS. Available at: http://www.pbs.org/wgbh/pages/frontline/aids/. Accessed December 10, 2008.
8. The New Security Beat. Jeffrey Sachs' memo to the next U.S. President. Available at: http://newsecuritybeat.blogspot.com/2008/04/jeffrey-sachs-memo-to-next-us-president.html. Accessed December 10, 2008.
9. Okie S. The Gates-Buffet effect. *N Engl J Med.* 2006;335:1084-1088.
10. Madon T, Hofman K, Kupfer L, Glass R. 2007. Implementation science. *Science.* 2007;318:1728-1729.
11. Gewin V. The global challenge. *Nature.* 2007;447:348-349.
12. Houpt E, Pearson R, Hall T. Three domains of competency in global health: recommendations for all medical students. Academic Medicine. 2007;82:222-225.
13. Global Health Education Consortium. *Developing Residency Training in Global Health: A Guidebook*. San Francisco, Calif: iUniverse.com; 2008.
14. Crump JA, Sugarman J. Ethical considerations for short-term experiences by trainees in global health. *JAMA.* 2008;300:1456-1458.
15. ACGME Outcome Project. General competencies. Available at: http://www.acgme.org/outcome/comp/compMin.asp. Accessed December 12, 2008.
16. Thompson MJ, Huntington MK, Hunt DD, et al. Educational effects of international health electives on U.S. and Canadian medical students and residents: a literature review. *Acad Med.* 2003;78:342-347.
17. *UVa School of Med Alumni Magazine*. Spring 1970.
18. Carey R. A Tribute to Dr. Thomas Harrison Hunter. *UVa School of Med Alumni Magazine.* Spring 1998.
19. Lorntz B, Boissevain J, Dillingham R, et al. Trans-university Center for Global Health. *Acad Med.* 2008;83:165-172.

The High Cost of Medical Care: Strategies for Delivering Cost-Effective Care in an Academic Environment

Karen A. Autio, MD Postgraduate Year 2, Internal Medicine
Margaret L. Plews-Ogan, MD, Associate Professor of Medicine and Chief, Division of General Medicine, Geriatrics, and Palliative Care
Carolyn L. Englehard, MPA, Assistant Professor and Health Policy Analyst, Department of Public Health Sciences

The United States spends more money per capita on health care than any industrialized nation, and this trend is increasing exponentially. The aging of the US population presents a challenge to the health system but does not account for the marked increase in costs. Although many believe that higher expenditures lead to better health outcomes, quality of medical care, and quality of life, data has shown this is inaccurate. In fact, on a population health basis, health outcomes in the United States are worse than those of all other developed nations, despite the fact that we outspend other countries by a factor of 2. The current health care economic crisis demands the attention of academic physicians committed to providing services for everyone who needs health care. It is crucial that the education of providers imparts an understanding of the current situation so that those entering health care professions can play a role in the creation of a sustainable health care system in the future.

CASE REPORT

In keeping with the spirit of the *UVA Journal of Medicine*, we include a case description that illustrates the problems we address. Unlike the subjects of most case reports, however, this patient was not affected by a rare disease manifestation or a widely aberrant phenomenon.

This patient, a 78-year-old man with profound vascular dementia, hypertension, and macular degeneration, was brought to the emergency room after having a near-syncopal event in the ophthalmology clinic. He had a history of syncopal events and had previously undergone evaluation for these at a nearby local hospital. Although his records were all at that hospital, the patient was taken to the emergency department of an academic medical center, where he promptly underwent a diagnostic evaluation that included a computed tomographic scan of his head, full laboratory panel, urinalysis, chest x-ray, and electrocardiogram and was placed on telemetry. In the emergency department the patient remained hemodynamically stable and at his mental-status baseline. Results of his laboratory tests were within reference intervals, and the computed tomographic scan revealed no acute changes. The patient was fortunate to have a 24-hour private home nurse, a primary care physician (PCP) who lived next door and made regular house calls, and a very attentive wife who rarely left his side. The patient's wife stated that because the patient had experienced prior episodes of near syncope and he always cognitively deteriorated in the hospital, she preferred he be allowed to go home. The patient's PCP agreed to see him that evening if he were released, but the emergency department staff were reluctant to release him. The general medicine team ultimately discharged him from the emergency room without ever having entered an admission order.

This patient's experience perhaps illustrates one of the better possible outcomes, but it still highlights a number of flaws in our chronically uncoordinated system of care, many of which result in high cost as well as suboptimal care. Had the patient's medical records been readily available in the emergency department, perhaps the initial and ensuing management would have differed. Or perhaps a concern for litigation was a partial driver in the decision-making. Nevertheless, if the family had not insisted, the patient surely would have been admitted, and one can imagine both the cost and the potential harm of that subsequent hospitalization.

SCOPE OF THE ECONOMIC PROBLEM

The United States currently spends significantly more on health care than any other developed nation. In 2006, $2.1 trillion was spent, which averages to approximately $7026 per person per year.[1,2] This amount contrasts strikingly with 1970 health care spending of $356 per person.[1] The Congressional Budget Office has identified federal spending on health care as the single most important factor influencing the government's long-term fiscal balance.[3] There are more uninsured persons today than at any time in recent history (46

million people), and the need for affordable health care and cost savings is urgent.[4]

WHERE HEALTH CARE DOLLARS ARE SPENT

To understand the factors influencing our high cost of health care, it is necessary to analyze how we spend our health care dollars. Personal health care accounts for 84% of national health expenditures, and approximately 52% goes toward hospital care and physician and clinical services (Figure 1).[5] The overutilization of clinical resources is often cited as a significant contributor to cost.[1,3,6,7] Indeed, the United States employs more costly care in the form of tests, procedures, specialty care, and new pharmaceuticals than any other wealthy nation.[6]

The shortcomings of the expensive US health care system suggest lack of efficiency in providing care. Newer technologies such as magnetic resonance imaging (MRI) are being widely implemented, particularly in areas where resources are abundant, such as large cities with multiple academic medical centers.[3,8] Compounding this problem, expensive testing may be done in addition to rather then in lieu of less costly alternatives.[9] Interestingly, Japan performs more MRI per capita than the United States, but because of Japan's universal health care system and the government's ability to negotiate prices, the technology has been built to accommodate the demand without driving up costs disproportionately. Cheaper, more compact MRI machines have been developed for physician offices in Japan (per 1 million people the United States has 27 MRI units versus Japan's 40.1 and Germany's 7.1).[10]

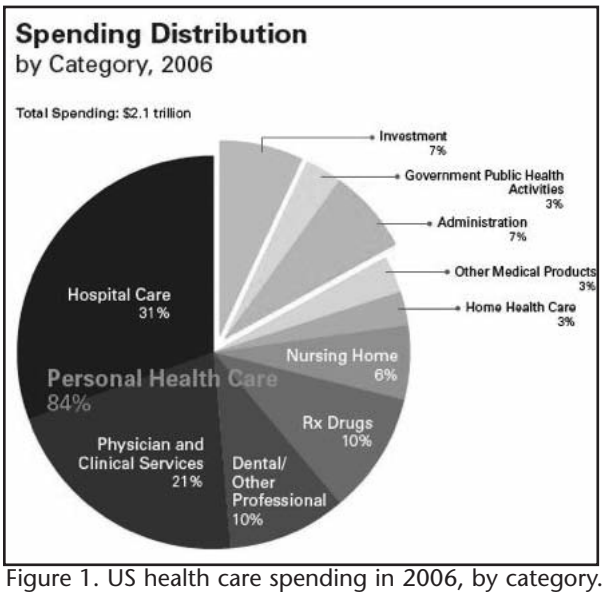


Figure 1. US health care spending in 2006, by category.

The cost of prescription drugs comprises 10% of health care costs.[1] In the United States, health care consumers pay 10%-30% more for the same pharmaceuticals than do individuals in other developed nations.[6] Furthermore, US physicians prescribe more newly available drugs than physicians in other countries. In 2005, the United States spent $752 per capita on drugs compared to Japan's $425 per capita.[6] Not surprisingly, pharmaceutical companies spend an extraordinary amount on marketing to physicians as well as directly to consumers. We've seen a 330% increase in direct-to-consumer advertising in the United States in 1996-2006 and a 300% increase in drug marketing delivered to physicians in 1998-2006.[2] Such advertising can be justified only by the higher prices in the United States, which contribute to overall higher drug costs.

Physician salaries are also 2 to 3 times higher in the United States than in other developed nations.[6] Higher physician salaries are thought by some to inappropriately contribute to the higher cost of medical care. On the other hand, US physicians have higher educational expenses and thus greater debt; therefore a portion of their salaries must be used to pay back the cost of their medical education.

US clinicians also order more tests and perform more procedures than physicians in other developed nations. One would hope this tendency is unrelated to physician salary. Unfortunately, however, the current US health care system and insurance companies continue to reward and pay more for

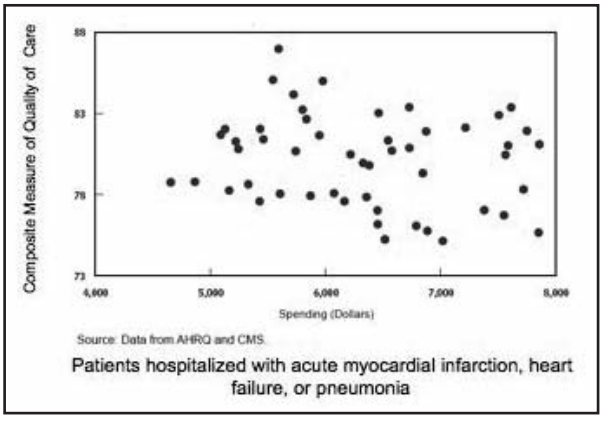


Figure 2. Relationship between quality of care and Medicare spending by state in the United States in 2004.

procedures and interventions than for preventive care. The emphasis on this system of reward begins early in medical training. As Emanuel and Fuchs have noted, "In medical training, meticulousness, not effectiveness, is rewarded."[6] Medical trainees are rewarded for excluding rare diagnoses with little if any attention to the cost needed to do so.

Despite highly thorough diagnostics and expensive treatment, a wealth of literature suggests that the increased cost of health care in the United States has resulted in minimal change in health outcomes. Little correlation exists between spending and quality of care (Figure 2)[3], largely owing to intensity and volume of practices. And despite expenditures that are 2-3 times higher, life expectancy in the United States does not compare favorably to that of other industrialized countries with similar resources and illness patterns.

High-Cost Health Care is under Scrutiny because it Does Not Correlate with Health Outcomes

Is it fair to target the medical care system for poor health outcomes? A variety of factors contribute to overall health (Figure 3).[11] We have little control over genetics. Behavioral factors contributing to poor health are largely modifiable, but little effort goes toward targeting behavior to improve outcomes and control costs, in part because of a "cultural reluctance to intervene on personal behavioral choices."[12]

Health is not the same as medical care, but data indicating poor outcomes despite high cost are difficult to ignore. Given the focus of medical care on overall health, there is a need to resolve the discrepancy between high cost and often poor health outcomes. Many cite the need for cost-effectiveness guidelines for practitioners as a means to resolve the discrepancy. A statement by the Congressional Budget Office reported in June 2008 highlighted the fact that variations in health care and health care costs are often more dramatic when there is the greatest clinical uncertainty.[3] This opinion has resonated with many professional medical societies, who have issued similar calls to action.[13]

The American College of Physicians has recommended the creation of an unbiased entity to compare both clinical outcomes and cost-effectiveness for different clinical management strategies.[13] There is debate within the medical community as to whether the goals of improved clinical outcomes and cost-effectiveness should be evaluated separately.[14] Britain's National Institute of Health and Clinical Excellence Program is one example of an evaluation program. This program

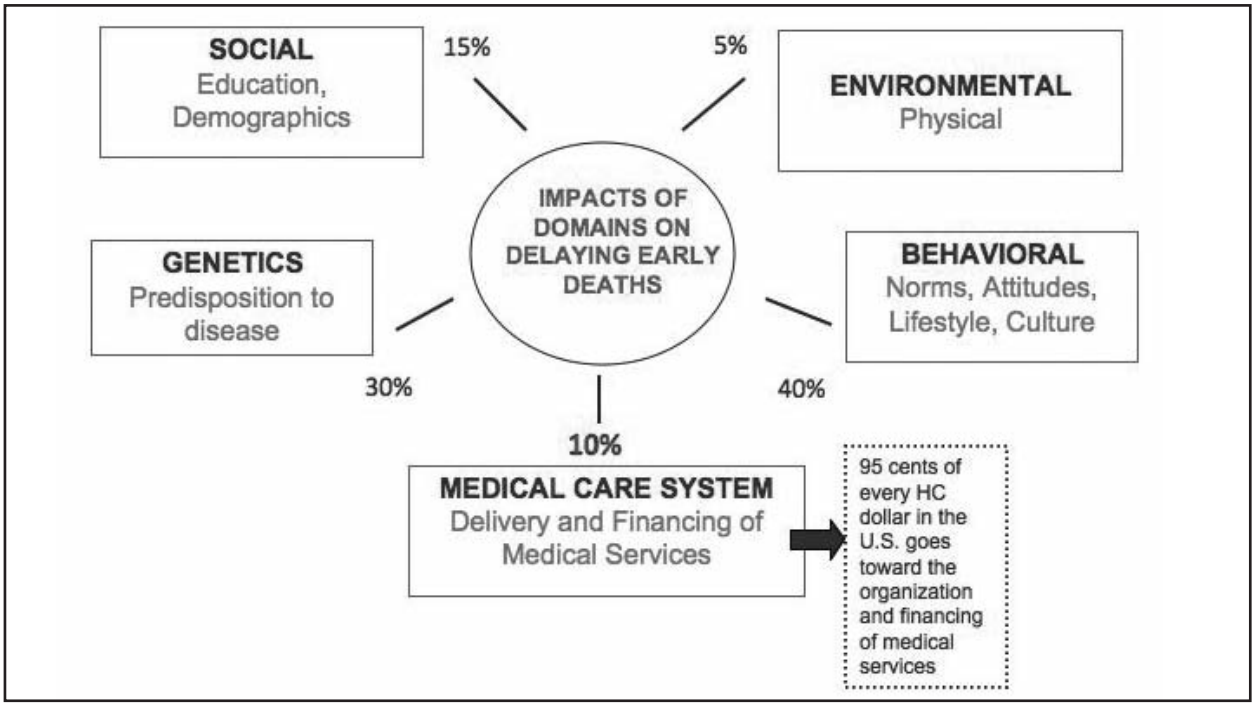


Figure 3. Factors other than medical spending that determine overall health.

takes on the challenging task of appraising drugs and assessing their cost-effectiveness as measured by QALY (cost per quality-adjusted life year).[15] In the United States, however, implementation of standardized cost-effective measures is often met with resistance, related in part to a culture that generally embraces a "do everything for the individual" attitude rather than approaching health care on a population basis.

Administrative Costs

A 2007 Congressional research report estimated that $465 billion dollars of our more than $2 trillion dollar health system go toward administration-related health care expenditures.[6] The current insurance system, with its innumerable claim forms and processes, drives up costs and contributes to a fragmented and cumbersome system of care.

Who Are the Largest Consumers of Medical Care in the United States?

Despite multiple payer systems such as Medicaid, Medicare, and employer-based and individual health care, there is agreement that in general the majority of health care costs are accrued by a relative minority of the population. Roughly 10%-20% of patients use 70%-80% of health care resources.[1,7]

As noted in Table 1, elderly persons and those with chronic illness are often recipients of expensive health care, although in these patients the clinical benefits are incremental.[13] Our medical system focuses on acute, episodic care with few rewards for delivering coordinated disease management. The decline in the number of medical trainees entering primary care is in part a reflection of frustrations with the current system.

Table 1. US Health Care Consumers: Who Consumes the Most Health Care Dollars?

- 5% of the Medicare population (frail, elderly, and chronically ill) account for 47% of Medicare expenditures.[1]
- The 4% of Medicaid enrollees consuming 50% of health care costs include preterm infants, spinal cord and traumatic brain injury patients, the mentally ill, foster care children, Alzheimer and dementia patients, and those with intellectual disabilities.[2]
- The average spending on those older than 65 years is $8647 annually compared to $1282 in those 18-24 years old.[1]
- Medicare spending in the last year of life was $23,047 per beneficiary compared to $6351 per Medicare patient who was not in the last year of life.[18]
- 75% of health care expenditures are spent on chronic disease.[19]

The lack of transparency of medical costs for the consumer is often seen as a contributing factor of the high cost of US health care. Given the small fraction of the population (10%-20%) generating health care expenses, however, the importance of transparency for the consumer becomes less obvious. For this relatively small percentage of people, Mongan et al noted, "Their ability and willingness to behave like shoppers who can make tradeoffs in cost and quality are uncertain at best."[7]

WHAT CAN BE DONE ABOUT THE HIGH COST OF HEALTH CARE?

Understanding where our health care dollars are spent can help us focus interventions for improving the system. We discuss specific strategies as they relate to the groups most likely to be involved with change. This includes physicians, consumers, insurance companies, pharmaceutical and medical equipment manufacturers, medical training centers, and the US government. A particular emphasis is placed on medical residents and trainees, who will be instrumental in implementing constructive change in the future.

Patients: Many policy analysts have advocated increasing the transparency of medical costs.[3,7] Demystifying new technologies and interventions that tend to be glamorized but are not associated with improved outcomes is another tactic. The role of patient advocates in the movement to educate about cost-effectiveness is important. Use of value-based copayments is another option that can be piloted.[3]

Pharmaceutical and medical device manufacturers: We need stipulations on direct-to-consumer marketing and restrictions on pharmaceutical company access to physicians and physicians in training because the modeling that occurs during training underscores future practice styles.[7] Manufacturers and physicians may be required, for example, to mention the existence of cheaper drug alternatives to consumers or to provide data to prove efficacy of devices.

Insurance companies: If payers are to collaborate with prescribing physicians, insurance personnel must be versed in clinical guidelines and effectiveness practices. Other strategies include payment reform such as financial incentives (rather than punishment) for cost-effective care and

coordination of primary care, value-based copayments, adoption of universal billing forms, investment in preventive care, and provision of useful financially oriented feedback to clinicians. Another strategy would be sharing the cost of electronic medical records. Insurance companies currently do not contribute to this service, yet they reap part of the benefit (such as cost saved from a reduction in duplication of orders). Physicians now pay for costly electronic medical records and receive roughly 20% of the return investment.[16,17]

Government: As mentioned previously, there is a need for an unbiased medical committee to assess cost-effective practices.[13] Greater funding for institutes such as the Agency for Healthcare Research and Quality and pilot programs in Medicaid/Medicare to investigate payment reform (eg, partial capitation) and comparative effectiveness would be helpful. Financial limitations on medical malpractice awards may also contribute a small cost savings.[7] The extent to which the US government is involved in legislating or mandating reform targeting the other key groups discussed in this report is debatable.

Physicians/clinicians: As the primary group ordering expensive medical care, clinicians must increase their awareness of evidence-based medicine and cost-effective strategies and dedicate efforts to decreasing costs. If physicians do not attempt to control resource utilization, they will be increasingly told to do so by third-party payers. Easier access to information that facilitates cost-effectiveness must be available, provided through widely accepted guidelines promulgated by professional specialty organizations or by a unified unbiased governmental body.[13] Coordination of point-of-care delivery of such information via electronic medical records is one option (as with clinical decision support systems). Another intervention that is associated with positive outcomes in the clinical setting is a greater emphasis on end-of-life care and earlier, appropriate referrals to hospice organizations.

Medical training centers: If the physician culture is to change, training programs must adopt a more proactive role in teaching the rudiments of cost-effective care and then rewarding physician efforts to provide it. Some feel that in an academic environment, ordering tests for the sake of learning or for "academic purposes" is appropriate, but this practice also establishes a norm of resource utilization that may perpetuate long after residency. Tertiary care centers must have electronic medical records, preferably with communication to community affiliates.[7] Ensuring that complete outside hospital records are provided for transferred or shared patients will also help to reduce duplication of tests and treatments. In addition, consensus must be reached among providers that conscious duplication of tests should be discouraged. Requiring that, prior to purchase, new equipment and devices are proven to improve care and to be fiscally responsible expenditures is critical. Medical centers might also invest in oversight personnel to monitor the volume of expensive procedures and investigate potential overutilization. Examples of costs of medical procedures and equipment are given in Table 2.

PHYSICIAN EDUCATION FOR COST-EFFECTIVE CARE

One strategy for changing physician culture and awareness to promote implemetation of cost-effective health care is to focus on educating physicians in training: medical students, residents, and fellows. Residents may learn cost-effective

Table 2. Sample Costs Based on Centers for Medicare and Medicaid

Radiology	
Abdominal ultrasound	$113 to $181*
Computed tomographic scan of abdomen with and without contrast	$331 to $660*
Magnetic resonance imaging of the abdomen with and without contrast	$677 to $1370*
Laboratory tests	
Vancomycin level	$18.93
Ammonia level	$20.36
Arterial blood gas with O_2 saturation	$39.65
Fecal lactoferrin	$27.42
Medical Equipment	
Power-operated vehicle/wheelchair	$2175
Driver pneumatic vehicle assist device	$79,750

*Range in radiology fees is based largely on geographic differences, 2008 Fee Schedule

practice from the attending physicians in the outpatient setting at resident training clinics. Such training is more difficult to put into practice in inpatient settings. General cognitive and system-change strategies applied at the individual and system level are listed below:

Cognitive Changes

- Recognize that the problem of high cost is real, it affects everyone in health care (not simply insurance companies), and you do not have to have a career interest in health policy or economics to be a part of the solution.
- When ordering a test, ask yourself whether the results will change your management of the patient. After this process you may still want or need the test results, but you will know exactly why you consider the test necessary.
- Try to resist the urge to order something for "academic purposes" or to duplicate only for convenience.
- Initiate dialogue about cost-effectiveness with attending physicians and your peers.
- Include important tests and procedures in dictation summaries so that this information will be available to patient PCPs and specialists who do not have access to hospital electronic medical records.

System Changes

- *Transparency of cost.* If the cost of a test were listed at the time you were ordering it (eg, in the electronic medical record), how would this affect your choice? Do you feel that this information would help or hinder your management of the patient? If there were a decision support tool that could identify a less costly alternative with a similar outcome, would that affect your choice of care?
- *Access to subspecialty services.* Are patients being admitted because they are trying to get into a specialty clinic and seek the advice of subspecialists? Is there a mechanism to expedite this process, such as arranging for an outpatient visit, to avoid admission? The use of early morning cardiology consults in the emergency department has led to reduced cardiology admissions at the University of Virginia Health System. For example, a patient with suspected noncardiogenic chest pain comes to the emergency department at 3 am. Results of initial troponin and electrocardiogram tests are unremarkable, and the patient remains in the emergency department for a second troponin to be drawn later in the morning. The cardiology consult team then sees the patient at approximately 7 am to advise and initiate management, which may entail outpatient echocardiogram and observation. Thus unnecessary admissions may be avoided.
- *Unnecessary admissions.* Can you have an open discussion with the emergency department regarding the appropriateness of admission? Is the emergency room concerned that outpatient follow-up may be inadequate, and are mechanisms in place to help with this situation? Does or should the emergency department receive feedback on admissions? Should the medicine department, as with other departments, have the right to refuse admissions?
- *Cost-effectiveness training:* "Cost awareness" is a component of systems-based practice, 1 of the 6 Accreditation Council for Graduate Medical Education competencies. At the University of Virginia, this component is a part of the evaluation for every attending physician. Avenues for expanding resident knowledge on these topics include dedicated conferences, integration of cost-effectiveness research with evidence-based medicine training, outpatient morning reports, and rounds devoted to this topic. Other opportunities may be institution specific. For example, "Thursday School," an initiative started by the 2008-2009 Internal Medicine chief residents, is a case-based clinical training program for medical residents. Part of this conference attempts to integrate cost considerations into decision-making (Table 3).

Although in this report we have focused on clinical trainees, an equally vital need exists to educate older clinicians and mentors who trained or practiced in very different environments and economic times. Strategies to educate these individuals include continuing medical education courses, grand rounds, and discussions during patient rounds. Trainees who are cognizant of cost-effectiveness issues should feel comfortable discussing these topics with mentors, particularly in an academic setting where attending physicians support the mission of continuous learning and adaption.

SUMMARY

The United States must reconcile its goals for providing excellent health care with affordability. Since many experts believe that up to 30% of all health care is either unnecessary or inappropriate, it suggests that a more efficient system will not

jeopardize patient care[5]. Identifying where our health care dollars are spent, focusing on inefficiencies, and engaging key groups of people will place the United States in a successful position to resolve our health care related fiscal challenges. Medical residents and academic medical centers are targeted intervention groups because medical trainees have potential to make a tremendous impact. Making cost-effectiveness education a routine part of physician residency training can have a positive effect on care while it is being delivered in a safe forum. Furthermore, if attention to cost-effective care is introduced early in the education of a physician, its practice is likely to endure as a ubiquitous skill rather than remaining an entity outside the realm of medicine.

Table 3. Specific Strategies for Residents

Transfer patients from community hospitals to tertiary care centers: These patients are at high risk of laboratory analysis/test duplications, which are often unnecessary. If patients are stable, repeating radiology studies is often unnecessary if scans can be transferred in a timely fashion. Strategies are needed to ensure records arrive with patients or before patients arrive. Furthermore, the need for a mechanism to reimburse radiology for reading outside films is critical in order to reduce test duplication.

The gratuitous or reflex laboratory test: During a patient's 4th admission for diabetic ketoacidosis in 1 year, is checking hemoglobin A1c on this admission necessary? Will a resident be considered less thorough if she does not order this test? For a hospitalized heart failure patient requiring lasix; after the first day, the clinician often has a sense as to the patient's potassium repletion requirements, so are BID laboratory tests necessary? A patient has diarrhea, and the physician is almost certain it is due to *Clostridium difficil*e. Is it necessary to determine the fecal lactoferrin as well?

Keeping up with evidence-based medicine while balancing the patient interest: An obese patient with chronic low back pain would like a magnetic resonance imaging examination, although the physician thinks this is unlikely to be revealing. Knowing the data necessary for an educated conversation about this decision will facilitate patient care and understanding. What percentage of asymptomatic patients have abnormal radiographic findings, and what are the implications? Would this patient be a candidate for surgery?

Shifting goals of care when appropriate: Perhaps one of the most difficult conversations to have with ill patients is the decision to begin palliative care. Providing the patient and their family with reasonable expectations is of paramount importance. The majority of Medicare dollars are spent on patients in their last month of life, and quality of life is often not improved by aggressive treatment when the anticipated outcome is poor.

REFERENCES

1. Kaiser Family Foundation. Health care costs, a primer. key information on health care costs and their impact. 2007;7670:1-14. Available at: http://www.kff.org/insurance/upload/7670.pdf. Accessed April 1, 2009.
2. Kaiser Family Foundation. Profiles of Medicaid's high cost populations. 2006;7565:1-57. Available at: http://www.kff.org/medicaid/7565.cfm. Accessed April 1, 2009.
3. Orszag PR. Opportunities to increase efficiency in health care. Congressional Budget Office; 2008. Available at: http://www.finance.senate.gov/healthsummit2008/Statements/Peter%20Orszag.pdf. Accessed April 1, 2009.
4. Kaiser Commission on Medicaid and the Uninsured. Approaches to covering the uninsured: a guide. 2008;7795:1-37. Available at: http://www.kff.org/uninsured/7795.cfm. Accessed April 1, 2009.
5. California Health Care Foundation, Health Care Costs 101, 2008. Available at: http://www.chcf.org/documents/insurance/HealthCareCosts08.pdf. Accessed April 8, 2009
6. Emanuel EJ, Fuchs VR. The perfect storm of overutilization. *JAMA.* 2008;299:2789-2791.
7. Mongan JJ, Ferris TG, Lee TH. Options for slowing the growth of health care costs. *N Engl J Med.* 2008;358:1509-1514.
8. Steinbrook R. The age of teleradiology. *N Engl J Med.* 2007:357:5-7.
9. Garber AM. A menu without prices. *Ann Intern Med.* 2008;148:964-965.
10. American College of Physicians. Achieving a high performance health care system with universal access: what the United States can learn from other countries. *Ann Intern Med.* 2008;148:55-75.
11. McGinnis JM, Williams-Russo P, Knickman JR. The case for more active policy attention to health promotion. Health Aff (Millwood). 2002;21:78-93.
12. Schroeder S. We can do better: improving the health of the American people. *N Engl J Med.* 2007; 357:1221-1228.
13. American College of Physicians. Information on cost-effectiveness: an essential product of a national comparative effectiveness program. *Ann Intern Med.* 2008;148:956-961.
14. Wilensky GR. Cost-effectiveness information: yes, its important, but keep it separate, please! *Ann Intern Med.* 2008;148:967.
15. Steinbrook R. Saying no isn't NICE: the travails of Britain's National Institute for Health and Clinical Excellence. *N Engl J Med.* 2008;359:1977-83.
16. The California Health Care Foundation. Report: insurers benefit most from health IT investment. *iHealthBeat*. 2007. Available at: http://www.ihealthbeat.org/Articles/2007/6/11/Report-Insurers-Benefit-Most-From-Health-IT-Investment.aspx. Accessed April 1, 2009.
17. Steele E. HER implementation: who benefits, who pays? *Health Manag Technol.* 2006:27:43-4.
18. Kaiser Family Foundation. Analysis of the CMS Medicare current beneficiary survey cost & use file, 2005. Available at: http://facts.kff.org/results.aspx?view=slides&topic=2&num=2. Accessed April 1, 2009.
19. Thorpe KE. The rise in health care spending and what to do about it. *Health Aff (Millwood).* 2005;24:1436-1445.

ABSTRACTS SELECTED FOR PRESENTATION AT

ASSOCIATES' DAY

VIRGINIA CHAPTER
AMERICAN COLLEGE OF PHYSICIANS

JANUARY 17, 2009

CHARLOTTESVILLE, VIRGINIA

UPPER EXTREMITY DEEP VENOUS THROMBOSIS (UEDVT): REASSESSING THE RISK OF SUBSEQUENT PULMONARY EMBOLISM

Christopher Bach, Ruth Fisher-Snowden, RN, RVT, Justin D. Pfeifer, MS, Gary Travis, RVT, Mark Levy, MD, Virginia Commonwealth University, Richmond, Virginia

The incidence of UEDVT diagnoses has increased with the increased use of peripherally inserted catheters, dialysis catheters, and defibrillator and pacemaker leads. Nevertheless, anticoagulation therapy is inconsistent and of variable duration. This study sought to analyze our institutions' current treatment practices for UEDVT and assess the risk for subsequent pulmonary embolism (PE).

Methods: Between 4/2005 and 7/2007, 200 consecutively encountered Peripheral Vascular Lab patients with UEDVTs were identified. UEDVT location and sonographic characteristics, patient demographics, anticoagulation treatment, and PE incidence and mortality were then examined from patients' medical records.

Results: Among the 200 patients, there was deep venous obstruction in the distal innominate (n=33), internal jugular (n=115), subclavian (n=114), axillary (n=69), and brachial veins (n=33). Forty one patients (21%) had UEDVTs identified as acute based upon sonographic appearance, and forty-nine patients (25%) had associated obstruction of UE superficial veins. Most patients with UEDVTs were symptomatic (n=188, 83%). Sixty-six patients had documented malignancy (33%), 58 were post-operative or trauma patients (29%), and 51 were obese (BMI>30, 26%). In addition, 152 patients had associated current or previous indwelling lines or leads (76%). Seventy-five patients (38%) had died at the time of the data-base analysis (07/08). Seventy-one patients (36%) were initially anticoagulated with heparin, while 62 patients were eventually converted to coumadin therapy (31%) for variable lengths of time.

Four patients (2%) suffered PE following or associated with their UEDVT diagnosis. However 2 of these were more likely attributable to more recently diagnosed lower extremity DVTs, having UEDVT diagnosed 10 and 16 months prior. Of the remaining 2 patients (1%), one had an asymptomatic PE diagnosed 6 months following a lovenox-treated brachial vein DVT; a second had a symptomatic PE diagnosed simultaneously with an axillosubclavian DVT, and was subsequently treated with lovenox and coumadin. An additional 2 UEDVT patients treated with coumadin died months after hospital discharge from intracranial bleeds following minor falls.

Conclusion: The incidence of PE attributable to previously documented UEDVT is very small (1%), regardless of anticoagulant therapy. Anticoagulation therapy for UEDVT is likely best suited to address the symptoms of UEDVT; its proposed use to decrease the very small risk of PE may be rarely indicated.

CHRONIC SALMONELLA SPLENIC ABSCESS IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA AFTER TRAVEL TO IRAQ

Daniel Bowers, MD, Eric Yeung, MD, Lisa Inouye, MD, Jason Maguire, MD, Naval Medical Center, Portsmouth, Virginia

Splenic abscess is a rare clinical condition. Autopsy reports have demonstrated a < 1% incidence, but clinically apparent splenic abscesses are even rarer, with less than 600 reported cases worldwide. We describe a 47 year old male with a five year history of chronic lymphocytic leukemia previously treated with one cycle of hydroxyurea and allopurinol and currently maintained on monthly intravenous IgG. Soon after an elective ventral hernia repair in Iraq, he began experiencing progressive fatigue and exertional dyspnea and was presumptively diagnosed with pneumonia complicated by a large left-sided pleural effusion that was drained by chest tube and treated with ceftriaxone and levofloxacin with improvement in his symptoms. Three weeks later, he presented with signs and symptoms of a small bowel obstruction and underwent exploratory laparotomy, lysis of adhesions and further hernia repair. Computed tomography (CT) performed at that time showed a persistent left pleural effusion and a hypodensity in the spleen, which was not investigated further. Three months later, the patient presented to his oncologist complaining of fatigue and fevers; blood cultures grew Salmonella enteritidis and he was treated with 7 weeks of intravenous ciprofloxacin. He continued to experience cough, fatigue, fevers and night sweats for several weeks after completing his course of antibiotics and was admitted to our facility for presumed left lower lobe pneumonia with a parapneumonic effusion. CT scan revealed a large splenic abscess, a large subdiaphragmatic fluid collection, as well as a left pleural effusion and left lower lobe consolidation. The patient was treated empirically with ceftriaxone and levofloxacin and the subdiaphragmatic fluid was drained percutaneously. Cultures from the fluid and sputum grew Salmonella enteritidis and the patient continues to slowly improve after 4 months of oral antibiotics with interval reduction in the fluid collections and pulmonary consolidation. This rare case of Salmonella enteritidissplenic abscess illustrates the importance of considering this diagnosis in immunocompromised patients with contiguous organ disease and bacteremia. Clinical manifestations of non-typhoidal salmonellosis, predisposing risk factors, diagnostic tools, and the benefits and disadvantages of percutaneous drainage and medical management vice partial or complete splenectomy are reviewed.

**The views expressed in these abstracts are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.*

A CASE OF NONUREMIC CALCIPHYLAXIS TREATED WITH SODIUM THIOSULFATE

Kristin Roussillon, MD, University of Virginia Health System, Charlottesville, Virginia

Calciphylaxis or calcific uremic arteriolopathy (CUA) is a small-vessel vasculopathy that is a rare but well described entity in end-stage renal disease and renal transplant patients. It is estimated to occur in approximately 1-4% of hemodialysis patients and mortality remains high, ranging from 60-80%. Calciphylaxis has been reported in nonuremic patients however little information is available on this entity and no prospective treatment trials have been conducted.

A 72-year-old Caucasian male presented to a local hospital because of non-healing lower extremity ulcers. The ulcers had gotten worse over a 6 month period despite treatment with Duoderm and an Unna boot. Physical exam revealed an extremely painful and near circumferential 8x5 cm left lower extremity lesion at the level of the mid-calf with areas of eschar and necrosis. The right lower extremity had a 2x2 cm small ulcer in the pretibial area with no eschar or necrosis. Popliteal pulses were 2+ bilaterally but dorsalis pedis and posterior tibialis pulses were difficult to appreciate. The patient had a history of peripheral vascular disease with a vascular stent graft in place in the proximal vessels of the left tibia/fibula region. Adequate blood flow to the bilateral lower extremities was confirmed by angiogram. Vasculitis was originally high on the differential although the lesions had a distinct lack of surrounding purpura and all vasculitis labs, other than an ESR of 103, were negative. A biopsy of the left lower extremity ulcer revealed calcifications within multiple medium and small caliber vessels in the deep dermis and subcutis adjacent to the ulcerated epidermis and consistent with calciphylaxis. The patient had no history of renal disease other than mild renal insufficiency with a baseline creatinine of 1.2. In addition, he denied exogenous calcium or vitamin D use and had normal calcium, parathyroid hormone, and calcium-phosphate product levels. Treatment for calciphylaxis was initiated with thrice weekly infusions of 25g of sodium thiosulfate infused over 60 minutes. Pain relief and healing of the ulcers were used as markers of clinical response to the intervention. After only three infusions, the patient no longer required analgesia prior to dressing changes. The patient had a PICC line placed and continued to receive sodium thiosulfate infusions after discharge from the hospital. At a follow-up with dermatology at 4 weeks there was significant improvement in the ulcers and at 4 months they had resolved completely, leaving only hyperpigmentation.

This case illustrates that calciphylaxis can be seen in patients without significant renal disease and should be considered in the differential of any patient with painful cutaneous ulceration. In addition, sodium thiosulfate in conjunction with aggressive wound care can be an effective treatment for calciphylaxis. However more research will need to be conducted to determine optimal dose and duration of treatment with sodium thiosulfate.

CLOSTRIDIUM DIFFICILE: ITS ROLE IN REFRACTORY AND WORSENING INFLAMMATORY BOWEL DISEASE

Laura Habelow, DO, John Smith, MD, Naval Medical Center Portsmouth, Virginia

Clostridium difficile (CD) is a toxin producing gut microbe which causes inflammatory changes in the colon when allowed to colonize the intestine. This over-colonization is often a result of antibiotic use which alters the normal gut flora. CD may also be a cause of refractory or worsening Inflammatory Bowel Disease (IBD) due to the inflammatory toxins.

We present the case of a 39 year-old male with a history of CD colitis and subsequent hospitalization in May 2006. Colonoscopy at that time revealed changes consistent with Crohn's Disease. However, he was found to have CD infection.

The patient was sent home on Asacol 800mg PO TID and Flagyl 500mg PO TID. His symptoms abated and he was lost to follow up. In April 2008 he was re-admitted with a two week history of diffuse, 10/10 abdominal pain. He reported nausea, vomiting, hematochezia and frequent bowel movements, but denied hematemesis, diarrhea or constipation. Physical exam revealed a diffusely tender abdomen with normal bowel sounds and no peritoneal signs. Diffuse colonic mucosal thickening, pnematosis coli and mesenteric fluid was seen on CT enterography. Colonoscopy revealed severely inflamed and ulcerated mucosa throughout the entire colon with normal terminal ileum. CD toxins A&B and stool culture were negative. Clinical presentation, colonoscopic findings, tissue findings and IBD serology lead to a final diagnosis of Ulcerative Colitis. He was treated with Methlyprednisone 60mg IV TID, Cipro 400mg IV BID and Flagyl 500mg IV QDay.

CD infections have become a common occurrence in the hospital. It is becoming more important in patients with IBD as they may not have the traditional risk factors. This case demonstrates the potential for CD overlap in IBD patients which may confuse the ultimate diagnosis. Clinicians should also be aware that up to one-fifth of hospitalized IBD patients may become infected within the first 48 hours of admission and if the patient worsens, CD infection should be ruled out. This case highlights that CD infection can complicate the presentation of IBD and close follow-up in these cases are important. A high suspicion for concurrent CD infection should be considered in cases of refractory IBD or in IBD patients with unexplained clinical deterioration who are on adequate therapy.

**The views expressed in these abstracts are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.*

A SUSPICIOUS PLOP: SYNCOPE IN A PATIENT WITH A DIASTOLIC MURMUR

Meghan Hughes, MD, Kevin Sumption, MD, FACP, Naval Medical Center Portsmouth, Virginia.

Introduction: In this patient, a diastolic murmur suggested a rare etiology of syncope, which was discovered incidentally while screening for a pulmonary disorder.

Case: A 51 year old female smoker presented with one week of exertional dyspnea and worsening orthopnea. These symptoms were preceded by a syncopal episode 6 weeks earlier. Cardiovascular exam revealed an early diastolic low frequency rumble. Abrupt onset of dyspnea, her 30 pack year tobacco history, and an elevated D-dimer (3.71 microgram/mL) prompted evaluation for pulmonary embolus with a spiral CT scan. The scan was negative for pulmonary embolus, but it identified a large mass filling the entire left atrium. Transthoracic and transesophageal echocardiogram further elucidated a 5 cm x 7 cm mass arising from the left atrial fossa ovalis which occupied the entire left atrium. By echocardiogram, it also appeared that the mass was causing "functional" mitral stenosis, with poor diastolic left ventricular filling. Excision of the mass revealed a mobile, pedunculated 6 cm x 10 cm mass, which was shown to be a myxoma by biopsy. Two months post operatively the patient had complete resolution of her dyspnea, and follow up echocardiogram showed only trace mitral regurgitation with no evidence of stenosis.

Discussion: Primary tumors of the heart are rare, but their symptomatology can mimic more common presentations of cardiovascular disease. In this case, the patient presented with exertional dyspnea, orthopnea, and syncope, which were suggestive of left heart failure. The diastolic murmur heard on physical exam has also been described as a "tumor plop," a low frequency sound in early or mid-diastole caused by impact of the tumor against the mitral valve or endocardium. Her worsening orthopnea as well as her diastolic murmur were clues to the functional mitral stenosis produced by positional changes, resulting in pulmonary edema and dyspnea. Progressive tumor growth resulted in diastolic dysfunction, producing decreased filling volumes and likely prompting her episode of syncope due to significantly decreased cardiac output. Though myxomas are considered to be "benign" tumors in terms of tissue histology, their mass effect and friable nature can produce arrhythmias, embolic phenomena, and mechanical heart failure. Increased use of noninvasive cardiovascular imaging techniques improves our sensitivity in the detection of cardiac tumors.

c-ANCA VASCULITIS WITH RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS SEEN IN A PATIENT WITH ULCERATIVE COLITIS AND PRIMARY SCLEROSING CHOLANGITIS

Susanne Francis, MD, John Smith, MD, Sam Gao, MD, Naval Medical Center, Portsmouth, Virginia

A majority of individuals diagnosed with primary sclerosing cholangitis have perinuclear antineutrophil cytoplasmic antibodies (p-ANCA). We present an uncommon case of cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) vasculitis and rapidly progressive glomerulonephritis in a patient with ulcerative colitis and primary sclerosing cholangitis.

A 21 year old female with a history of ulcerative colitis in remission with mesalamine therapy since 1998, was diagnosed with primary sclerosing cholangitis by ERCP in 2003. The patient developed a dominant stricture, which required serial stenting to maintain adequate biliary drainage, although her clinical course eventually progressed to end stage liver disease. She also developed chronic recurrent multifocal osteomyelitis of the right proximal clavicle and sternum, requiring debridement and an extended course of intravenous antibiotics. While at another facility for liver transplant work-up, the patient experienced an ulcerative colitis flare and Clostridium difficile infection. She received piperacillin-tazobactam, metronidazole, and vancomycin during her hospital course. The patient developed an acute rise in creatinine and her urine was positive for eosinophils. Out of concern for allergic interstitial nephritis, piperacillin-tazobactam was discontinued, and the patient was placed on ciprofloxacin.

A few months later, she was admitted for pyoderma gangrenosum on the bilateral lower extremities, anemia, and non-oliguric acute renal failure with nephrotic range proteinuria. The patient had been using NSAIDs daily as an outpatient to manage her pain. ANCA serologies showed positive c-ANCA, negative p-ANCA, but negative proteinase-3, making Wegener's granulomatosis unlikely. Serum complement levels were within normal limits and both ANA and anti-ds DNA were negative, excluding lupus nephritis from the differential diagnosis. A renal biopsy confirmed mesangial proliferative glomerulonephritis with focal crescents, moderate arteriolar sclerosis, and moderate patchy chronic tubulo-interstitial disease. There were no immune complexes seen on immunofluorescence, indicating a pauci-immune glomerulonephritis consistent with ANCA vasculitis. She was placed on high-dose prednisone (1mg/kg) and responded well to treatment. Her creatinine has returned to baseline, but she cont inues to have near nephrotic range proteinuria. Mycophenolate mofetil was added to deter relapse. Now controlled on low-dose prednisone and mycophenolate mofetil, the patient just received a liver transplant.

This is the first report of c-ANCA vasculitis leading to rapidly progressive glomerulonephritis in a patient with extensive autoimmune disease, including ulcerative colitis, primary sclerosing cholangitis, chronic recurrent multifocal osteomyelitis, and pyoderma gangrenosum.

A BUSINESS TRIP GONE SOUTH

Wendy Garlington, MD, Jennifer Ryal, MD, Eastern Virginia Medical School, Norfolk, Virginia

Abstract Text: Meningitis caused by Haemophilus Influenzae is primarily seen in children less than the age of five. Since the use of Hib vaccine, the cases of H. Influenzae meningitis have declined. It is an uncommon infection in adults because they have bactericidal and opsonization antibodies. Thus, it is important to determine if there is an underlying immunodeficiency in an adult who presents with H. Influenzae meningitis.

A sixty year old Caucasian male on a business trip from San Diego, California presented to a neighbouring community hospital with complaints of headache, nausea and confusion. His temperature was 99.5 Fahrenheit and he had a white blood count of 37,500/µL. A CT scan of the head showed pansinusitis without direct communication to the brain. A lumbar puncture (LP) showed a purulent fluid and an opening pressure greater than 550 mm H2O. Broad spectrum antibiotics were begun. Due to the increased opening pressure, the patient was transferred to our tertiary care hospital for possible ventriculostmy tube placement.

Upon arrival the patient was intubated, sedated and admitted to the ICU. By the third day of admission the spinal fluid culture grew H. Influenzae and the health department was notified. The antibiotics were narrowed and the patient was extubated the following day. Upon further questioning of the patient and his wife, a history of repeated sinus infections, several bouts of pneumonia, recurrent bronchiectasis and multiple ear infections as a child was discovered.

Due to the rarity of the infection, a serum IgG was measured to evaluate for an immunodeficiency. His level was less than 45 mg/dL (normal 700-1600 mg/dL). Further studies, including a serum protein electrophoresis, IgG subtype quantification, CD4/T cell differential, as well as antigen challenge testing, revealed the patient had common variable immunodeficiency. On day eight of admission, the patient was transfused with IgA reduced intravenous immunoglobulin (IVIG). The patient was discharged on day twelve back to San Diego where he would be admitted for further IVIG treatments and to finish his course of IV antibiotics.

Common variable immunodeficiency (CVID) has a peak onset in children aged 1-5 years, but can present at any age. The cause is currently unknown. We do know that it affects both humoral and cell-mediated responses, and has five distinct clinical phenotypes. While 10 percent of cases are familial, it has no definable pattern of inheritance. Most patients present with recurrent infections, usually affecting the upper and lower respiratory tracts. Patients with CVID are at increased risk for lymphomas, gastric carcinoma, and malignant melanomas. Once diagnosed, CVID is manageable with IVIG every 2 to 4 weeks to maintain adequate levels of IgG.

CONSTRICTIVE PERICARDITIS DUE TO ASBESTOS EXPOSURE

Ali Sharifian, MD, Mohit Bhasin, MD, Eastern Virginia Medical School, Norfolk, Virginia

Exposure to asbestos dust is associated with an increased incidence of pulmonary complications such as asbestosis, pleural mesothelioma and bronchogenic carcinoma1. Other localizations are exceptional, but exposure to asbestos occasionally causes benign pericardial effusion, thickening, and calcification. The pericardial thickening may result in constrictive pericarditis with functional consequences of impaired right ventricular filling2.

We present an 89 year old white male with symptoms of exertional shortness of breath. Past medical history suggested mild aortic stenosis with a valve area of 0.8 cm square, a prior negative nuclear stress test for ischemia, and exposure to asbestos. Physical exam revealed a nondisplaced PMI, a 2/6 crescendo-decrescendo systolic murmur, and normal JVP. High resolution chest CT showed extensive calcified and noncalcified pleural plaques throughout both hemithoraces in a pattern suggestive of asbestos associated pleural disease. Patient continued to have increasing exertional chest tightness. His symptoms suggested angina and potentially progression to symptomatic aortic stenosis so he was referred for right and left heart catheterization which showed angiographically normal coronary arteries. Left ventriculography showed left ventricular end-diastolic pressure of 17 to as high as 20 mmHg, notable pericardial calcification around the left ventricular chambers, calcified aortic valves with somewhat restricted leaflet movement, and an EF of 70%. Despite no equalization of pressures and concordant motion of the systolic peaks, constrictive physiology with Dip-and-Plateau was noted. At this point there was no strong convincing evidence of the pericardial disease causing his dyspnea so patient was referred for cardiac CT and MRI. Gated non-contrast 64 slice Cardiac CT showed heavily calcified pericardium over most of the left ventricle with only patchy areas of noncalcified pericardium visible at the base of the left ventricle, with extension of calcification along the pericardial reflection over the proximal great vessels and along the inferior interventricular groove Fig 1&2. Cardiac MRI showed normal cavity size with no evidence of regional wall motion abnormalities, a 3mm thick and calcified pericardium, and tethering of the distal lateral myocardium to pericardium on tagging sequences Fig 3.

Patient was diagnosed with severe constrictive pericarditis and had a pericardiectomy in April of 2008. After pericardiectomy, his CVP dropped from 21 down to 12 and his symptoms improved from NY class 3 to no dyspnea on exertion. Biopsy of pericardium showed fibrotic connective tissue with focal calcification and chronic calcification. Iron stain was negative for ferruginous bodies.

Asbestos exposure may cause calcification and tethering of the pericardium and eventually causing constrictive pericarditis in which gated non-contrast computer tomography and Cardiac MRI using tagging sequences together are the imaging modality of choice for diagnosis and follow up.

MACROPHAGES ADAPT TO OXIDATIVE TISSUE DAMAGE BY SENSING OXIDIZED PHOSPHOLIPIDS VIA TLR2 AND Nrf-2

Alexandra Kadl, MD, Florian Gruber, Monica Lee, Poonam Sharma, Michael R. Elliott, Brian Wamhoff, and Norbert Leitinger, University of Virginia Health System, Charlottesville, Virginia

Macrophages change their phenotype and biological functions depending on the microenvironment. Consequently, these cells can contribute to propagation as well as to resolution of inflammation. Oxidative tissue damage occurs in chronically inflamed tissues, however, it is not known how macrophages recognize and respond to oxidatively modified molecules. Using gene array analysis we show that macrophages develop a novel phenotype upon encountering oxidized phospholipids. This phenotype (M-ox) is strikingly different from the classically, Interferon gamma and LPS or TNF- activated M1 or the alternatively, IL-4- activated M2 macrophage. While it has been shown that M1 macrophages play a role in host-defense and promotion of Th1-responses, and M2 macrophages propagate immunregulation, promotion of tumor growth and promotion of Th2-response, the function of M-ox has yet not been recognized.

Here we describe in detail the characteristics of M-ox macrophages. Using gene array analysis and RT-PCR we identified a new macrophage phenotype, strikingly different from M1 and M2 macrophages. Bioinformatics analysis reveals 92 M-ox specific genes, 28 genes that are overlapping in M-ox and M1 macrophages, and.7 genes overlapping in M-ox and M2 genes. Furthermore, M-ox specific genes are mainly genes important in redox regulation, such as heme-oxygenase 1, thioredoxin reductase, and gluthathion reductase 1, but also VEGF, in contrast to M1/Mox overlapping genes, which are mainly proinflammatory genes, such as COX-2, IL1 beta, and MIP2. Using macrophages from knock-out mice, we demonstrate that the regulation of a subset of pro-inflammatory M1 markers such as COX-2, by oxidized phospholipids, and in particular by the long chain fraction of these lipids, is dependent on the expression of TLR2, but not on TLR4. Interestingly, the regulation of a subset of M-ox specific genes, such as heme-oxygenase 1 and glutathione reductase 1 are mediated by Nrf-2, a major transcription factor that regulates the expression of detoxifying and antioxidant genes. The upregulation of Nrf-2-dependent genes leads to an increased survival of M-ox. Moreover M-ox show impaired phagocytotic capacity as compared to M1 and M2 macrophages, when incubated with acetylated LDL, carboxylate beads or apoptotic cells, as a result of downregulation of scavenger receptors. Finally, using flow cytometry, immunofluorescence, and RT-PCR, we present evidence that M-ox are present at sites of chronic, lipid rich inflammation, such as atherosclerotic lesions and inflamed adipose tissue from mice on a high fat diet.

Taken together, these data show that oxidized phospholipids induce a novel macrophage phenotype that is present at sites of chronic metabolic inflammation.

CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF REFRACTORY TTP: WHERE ONCOLOGY MEETS HEMATOLOGY

Elisabeth Stronge, MD, Sami Tahhan, MD, Eastern Virginia Medical School, Norfolk, Virginia.

A 74-year-old African American female was transported to the Emergency Department (ED) after acutely developing slurred speech and generalized weakness. Upon arrival to the ED, she was found to have altered mental status, fever and the following initial pertinent studies: WBC 8.2, H/H 8.7/26.8, creatinine of 0.8, PT/INR of 10.3/0.96, platelet count of 29 and an unremarkable CT of the head. Subsequent lab work revealed the following: haptoglobin of 0, LDH of 725 and schistocytes on peripheral blood smear. She was diagnosed with thrombotic thrombocytopenic purpura (TTP) and plasmapheresis was initiated. Because the patient's platelet count continued to be low, plasmapheresis was increased to twice a day and high dose IV steroids were begun. The patient's mental status finally stabilized and, with continued twice a day plasmapheresis, her platelet count increased and LDH decreased. However, upon changing her plasmapheresis regimen to every other day, her platelets dramatically decreased. Vincristine was added to her treatment regimen and the patient initially responded to this therapy but after many days she again relapsed. At this point, rituximab was administered weekly for a total of four weeks. Following administration of the rituximab, the patient developed a stable platelet count, normal LDH and plasmapheresis was able to be discontinued. The patient was transferred to a nursing home and has had no return of her TTP.

Many cases of TTP are now thought to be caused by a deficiency or autoantibody against a von Willebrand cleaving protease, ADAMTS-13, and a decrease in its activity ultimately leads to increased platelet aggregation. Plasmapheresis is theorized to be an effective treatment for TTP because it decreases the autoantibody through exchange and supplies the enzyme via transfusion. Although most cases of TTP respond to plasmapheresis, 10-20% do not. This case illustrates the use of alternative therapies for TTP refractory to plasmapheresis alone including vincristine and rituximab. Because of the autoimmune nature of TTP, immunosuppressants such as vincristine and rituximab have been shown anecdotally to be helpful in the treatment of refractory TTP. While there are several case reports supporting the efficacy of vincristine because of its immunosuppressant capability, more evidence lies with rituximab. In available case reports, rituximab has been shown to induce clinical remission in more than 93% of patients with refractory TTP. Rituximab may be considered as first line treatment for refractory TTP in the future but randomized, controlled trials supporting its efficacy are needed.

GONE TO HELMINTH IN A HANDBASKET

Joseph Baltz, MD, University of Virginia Health System, Charlottesville, Virginia

A 33-year-old African American male was admitted with sharp and cramping upper abdominal pain of acute onset associated with poor appetite. Physical examination was positive for tenderness to palpation in the right upper quadrant with involuntary guarding and rebound tenderness. Laboratories were normal except for an elevated white blood count of 16.8 k/uL with 54% neutrophils and 29% eosinophils (absolute 4.65 k/uL). Computer tomography (CT) scan showed a normal appendix, wall thickening of the terminal ileum, and a possible closed loop obstruction. Surgical consultants recommended an emergent exploratory laparotomy, which was negative for a closed loop obstruction. A colonoscopy revealed erythema in the terminal ileum and a seven millimeter worm attached to the mucosa that was subsequently identified by a clinical laboratory scientist at Mayo Medical Laboratories as an adult female of the species Ancylostoma duodenale. Following removal of the worm, the patient was treated with mebendazole and discharged four days after admission with improved symptoms and an eosinophil count of 1.53 k/uL (15%).

The two main species of hookworms that infect and are transmitted by humans are Necator americanus and Ancylostoma duodenale, although other species found in dogs, cats, or pigs have been known to infect humans as a zoonosis[1]. Both of the above species are usually native to parts of Europe, Africa, India, China, Japan, and the Pacific, but N. americanus is the only one of the two found in the United States.[2] Hookworms infect humans by invading the skin, traveling through the blood circulation to the lungs, invading the lung parenchyma, continuing up the bronchial tree, and eventually being swallowed into the gastrointestinal tract where they cause symptoms such as cramping, abdominal pain, nausea, diarrhea, and flatulence. A prolonged infection often will cause anemia due to chronic blood loss. The preferred treatment of intestinal hookworm infection is with mebendazole, pyrantel pamoate, or albendazole[3].

The evidence suggests that helminthic infection was the most likely cause of this patient's acute abdominal presentation. The acuity of symptoms and identification of a hookworm species not endemic to the Unites States, despite the absence of recent patient travel history outside of Virginia, make this case of particular interest. Another consideration, given the patient's exposure to dogs, is a zoonotic infection with the dog hookworm A. caninum. This species, which is similar to A. duodenale, has been shown to cause similar eosinophilic enteritis in many patients in Australia[4]. This possibility could not be investigated in this case because the laboratory that identified the helminth does not normally identify canine hookworms. We recommend that, although it is rare in the United States, given similar symptoms and peripheral eosinophilia, parasitic gastrointestinal infections should be considered and evaluated more often.

MULTIPLE CULPRITS: A CASE SERIES OF PATIENTS PRESENTING WITH ST-ELEVATION MYOCARDIAL INFARCTION FROM ACUTE CLOSURE OF TWO VESSELS.

Peter Pollak, MD, Ellen Keeley, MD University of Virginia Health System, Charlottesville, Virginia

Introduction: Nearly every minute someone in the United States dies of a myocardial infarction. While most patients with acute myocardial infarction (AMI) involve a single vessel, some patients occlude multiple vessels simultaneously. Autopsy series have reported multivessel infarction rates of 10% to 50%; nevertheless, patients presenting with AMI stemming from multivessel thrombosis remain poorly understood. We report a series of 18 patients from two intuitions who presented with AMI due to thrombosis in multiple coronary arteries.

Methods: Retrospective analysis of prospectively collected data of 711 consecutive patients admitted with ST-elevation myocardial infarction (STEMI) and taken for PCI at two tertiary care academic hospitals. We reviewed the angiography films of patients with STEMI to identify cases where plaque rupture and thrombosis lead to acute vessel closure in multiple vessels. Determination of acute thrombus formation was made by angiographic appearance, and included films were independently reviewed and verified. Patients who had chronic occlusions were not included; however, patients who had acute in-stent thrombosis in the setting of acute thrombosis of a native coronary vessel were included.

Results: There were 18 cases of STEMI with multiple culprit vessels, nine from each institution. The incidence of STEMI with multiple culprits was 1.7% at one institution and 4.8% at the other with an overall rate of 2.5%. In our series, the majority of patients were white (61%) , male (89%), had hypertension (50%), and smoked (56%). We found no cases where multiple culprit lesions occurred in a patient with prior bypass grafting. Medication use included aspirin (27.8%), statin (27.8%), and beta blocker (27.8%). Only a single patient was taking clopidogrel., The two involved vessels were the right coronary (RCA) and left circumflex (LCX) arteries in 50.0% of cases, the RCA and left anterior descending (LAD) arteries were culprits in 27.8%, and the LCX and LAD were culprits in 22.2%. Clinical severity on presentation was high among patients with multiple culprit lesions. 27.8% were in cardiogenic shock, 22.2% had a life-threatening arrhythmia, and 22.2% needed a balloon bump. All patients received percutaneous coronary intervention, and all survived to hospital discharge.

Conclusion: This case series helps illuminate the details of a rare but serious phenomenon in patients presenting with STEMI. The low mortality rate in the face of high clinical severity on presentation emphasizes the therapeutic benefit of reperfusion and highlights the need to identify possible multiple culprits in patients with STEMI.

DIABETES MELLITUS ASSOCIATED EMPHYSEMATEOUS PYELONEPHRITIS

Andy Lee, MD, University of Virginia Health System, Charlottesville, Virginia

Emphysemateous pyelonephritis is a potential life threatening infection of the kidney that is characterized by gas formation within the kidney and its surround tissues. I describe a case of emphysemateous pyelonephritis in a poorly controlled diabetic and complement this with a brief review of current literature.

A 50 year old female with history of uncontrolled diabetes mellitus and diabetic foot ulcers presented with 3 day history of abdominal pain and vomiting. Patient denied any dysuria or urgency but noted of occasional fever and flank pain. Patient was found to have leukocytosis of 19.5 x 10^3/ul with neutrophilic predominance and thrombocytopenia of 36 x 10^3/ul. Metabolic panel also shows acute renal injury with elevated creatine of 2.1 mg/dl with hyperglycemia of 670 mg/dl. Patient's last hemoglobin A1c was noted to be 16.7. Patient was admitted to the hospital for urosepsis. Renal ultralsound preformed showed increase echogenicity in the right renal collecting with posterior shadowing. However, no hydronephrosis were noted. Follow up computer tomography of the abdomen with and without contrast showed right sided hydronephrosis with air and fluid in the collecting system. There was gas formation in the peri and pararenal spaces with extension posterior to the duodenum. In addition, a small amount of intraperitoneal air was also noted.

Emphysemateous pyelonephritis is a potentially life threatening infection commonly associated with diabetes mellitus. It is often caused by gas forming organisms such as Eschericia Coli and Klebsiella Pneumoniae. Emphysemateous pyelonephritis is categorized into type I and type II. Type I emphysemateous pyelonephritis is defined by gas patterns within the renal parenchyma whereas type II emphysemateous nephritis is defined by perirenal gas patterns. Type I emphysemateous pyelonephritis is associated with a poor outcomes due to extensive parenchymal necrosis and more fulminating course. While it remains a rare condition, untreated emphysemateous pyelonephritis is almost universally fatal. Meta-analysis studies show that treated emphysemateous pyelonephritis still has an overall mortality rate of 25%. Computer tomography remains the most reliable diagnostic tool with accuracy of nearly 100%. Increased echogenicity from the renal ultrasound can be mistaken for calculi or bowel gas and only has an accuracy of approximately 65% for diagnosing emphysemateous pyelonephritis. Initial management of emphysemateous pyelonephritis includes fluid resuscitation, antiobiotics, glycemic control, and elimination of obstruction if needed. Patients often will require percutaneous drainage or surgical nephrectomy for curative treatment. Patients with type I emphysemateous pyelonephritis, bilateral emphysemateous pyelonephritis, or thrombocytopenia tends to have higher mortality rates. Given that the patient did have thrombocytopenia, she was referred for nephrectomy.

Conclusion: Emphysematous pyelonephritis is a life threatening infection often associated with diabetes. Early diagnosis with percutaneous drainage or nephrectomy is often required.

MOLAR PREGNANCY-INDUCED THYROID STORM

Brett Montgomery, MD, Virginia Commonwealth University Health Systems, Richmond, VA.

A 50-year-old woman with hypertension and hepatitis C presented to the Emergency Department with five days of nausea, emesis, abdominal pain, and dyspnea. Pelvic examination revealed an 18-20 week uterus and right adnexal tenderness. Pelvic ultrasonography demonstrated the lack of an intrauterine pregnancy and many cystic structures with a "snowstorm" appearance. Her serum beta-HCG level was 1,062,859 mIU/mL (normal 1st trimester range 30,000-120,000). The patient was diagnosed with a molar pregnancy and underwent an urgent total abdominal hysterectomy. Post-operatively her blood pressure was 190/110 mm Hg, and she developed substernal chest tightness, headache, and increased dyspnea. She was transferred to the Coronary Care Unit (CCU). On physical examination she was tachycardic (99 bpm) and in mild distress. Her lungs were clear to auscultation bilaterally, and she had no heart murmurs. She had normal peripheral pulses. Laboratory investigation revealed a mild anemia (Hgb 10.5 g/dL). Her renal function and liver function were normal, and she had no coagulation abnormalities. Her thyroid-stimulating hormone (TSH) was <0.01uIU/mL (normal range 0.35-5.5), free T4 was 3.0 ng/dL (normal range 0.8-1.8) and T3 of 659 ng/dL (normal range 60-181). An ECG showed sinus tachycardia and left ventricular hypertrophy without ischemic changes. Transthoracic echocardiography demonstrated normal ventricular size and function. Nicardipine and esmolol continuous infusions were begun in addition to methimazole 30 mg daily. The patient's symptoms resolved quickly, and the next day she was transitioned to oral metoprolol and transferred from the CCU to the Obstetrics service for further care. Her beta-HCG decreased to 449,608 mIU/mL 24 hours post-operatively and was 36,082 mIU/mL by discharge four days later. At follow-up 11 days later her TSH was 0.13 uIU/mL and beta-HCG was 3455 mIU/mL. Her beta-HCG level remained detectable until 3 months after her initial presentation.

Thyrotoxicosis is a rare but clinically significant complication of molar pregnancy. The biochemical similarity of beta-HCG and TSH (same alpha, different beta subunits) provides the mechanism for cross-reactivity in the setting of very high beta-HCG levels, such as those produced in molar pregnancies. Treatment is removal of the molar pregnancy, after which beta-HCG levels fall precipitously. Molar pregnancies occur in about 1 in 1500 pregnancies, and biochemical hyperthyroidism occurs in 25-64% of patients. Despite this frequency, only 5% of patients with molar-induced hyperthyroidism have clinical manifestations. Thyroid storm is the most serious consequence of molar-induced hyperthyroidism but is very rare. This infrequent manifestation of an uncommon disease may lead to diagnostic error when it occurs. Clinicians should be aware of this possibility and consider it when evaluating the pregnant patient with symptoms of hyperthyroidism.

DYNAMIC NON-LINEAR ANALYSIS OF HEART RATE SERIES CAN BE USED TO DISTINGUISH ATRIAL FIBRILLATION FROM NORMAL SINUS RHYTHM

Deeptankar DeMazumder, MD, Paul C. Iazzetti, Yuping Xiao, MS, Doug Lake, PhD, J. Randall Moorman, MD, University of Virginia Health System, Charlottesville, Virginia

BACKGROUND: Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance. An accurate estimation of the "AF burden" (proportion of time spent in AF) can help guide treatment decisions (e.g., need for anticoagulation), and is available from dual chamber implanted pacemakers and ICDs. No single lead device reports the AF burden because only RR intervals are measured. AF is especially common in patients receiving ICDs, and 25% of ICD shocks are delivered inappropriately for AF. Thus, there is a need to improve upon current automated methods for AF detection in short segments of RR intervals.

INTRODUCTION: Sample entropy, deduced from approximating the Kolmogorov entropy of a process, has its roots in nonlinear dynamics and Chaos theory. Our hypothesis is that the coefficient of sample entropy (COSEn), a parameter optimized for AF detection, discriminates between normal sinus rhythm (NSR) and AF in very short segments of RR intervals. Our specific goals are to develop improved AF detection algorithms, and to develop and to make public a large database of 24-hour Holter ECG records with clinical correlates for further study.

METHODS: 200 consecutive 24-hour Holter ECG recordings, each from a different patient were manually read (gold standard) for comparison with COSEn analysis (diagnostic test). Sample entropy is the conditional probability (CP) that 2 sequences of heart beat intervals of a certain length that match within a certain tolerance will also match at the next point, and is the negative natural logarithm of the CP that a short epoch of data, or template, is repeated during the time series. COSEn is a form of sample entropy that is optimized for AF detection in that it is independent of the tolerance and the heart rate.

RESULTS: 21 recordings showed AF alone. COSEn values were normally distributed for AF and NSR data; as expected, the mean COSEn value was higher in AF (-0.345) compared to NSR (-2.43, $p<0.001$). COSEn had ROC curve area >0.99 for diagnosing AF, and episodes of AF were detected with 97% sensitivity and positive predictive accuracy.

CONCLUSIONS: COSEn is a robust strategy for classifying AF with high accuracy from very short records of RR intervals available in implanted pacemakers and ICDs. It might be used to diagnose AF, to improve ICD therapy, to estimate AF burden to guide treatment, and to explore important clinical questions about AF. The UVA AF ECG and clinical database will be an important resource for future work on detecting other arrhythmias.

SEPTIC EMBOLUS TREATED WITH THROMBOLYSIS

Matthew Huffman MD, University of Virginia Health System, Charlottesville, Virginia

Thrombolysis is commonly used in the treatment of myocardial infarction, stroke, and massive pulmonary embolism. Here, we describe a case where it is utilized as an adjunctive therapy for a patient with a massive septic embolus.

A 48 year-old woman with a past medical history significant for hepatitis C, bipolar disorder, and recurrent urinary tract infections presented to the Emergency Department with fevers, chills, severe fatigue, generalized malaise, and diffuse pain. Her vital signs showed that she was febrile, hypotensive, tachycardic, and hypoxic. On physical examination, she was severely distressed, had dry mucus membranes, and had crackles in the right lower lung field. No murmurs were appreciated. Chest x-ray revealed a right lower lobe pneumonia. A transthoracic echocardiogram discovered a large mobile mass on the tricuspid valve consistent with a vegetation. The right ventricle was dilated and had severe systolic dysfunction. The left heart system had normal structure and function. Chest CT with contrast illustrated a large mass in the proximal right pulmonary artery, causing near occlusion of the vessel, as well as a ground glass appearance of the right lower lobe. Blood cultures returned with growth of methicillin-sensitive staphylococcus aureus. The diagnosis of infectious endocarditis with a massive septic embolus was made. Additional history revealed that she had used intravenous drugs in the past. She was started on appropriate antibiotics, IV fluids, and a heparin infusion. Despite these measures, she clinically declined. She was transferred to the intensive care unit, intubated, and started on vasopressors. Because of the extreme proximal location of the septic embolus in the right pulmonary artery, surgical intervention was not possible. Similarly, because of the location and the setting of an active infection, stenting of the vessel was not a viable option. The patient had worsening hemodynamic compromise. Catheter-guided tissue plasminogen activator (tPA) infusion was initiated and continued for 72 hours. She had a great response to this therapy. There were no signs of bleeding. Her vital signs rebounded relatively quickly, and she was weaned off of vasopressors. Several days later, she was successfully extubated. Her hospital course was complicated by nosocomial infections, but she made a complete recovery. Eventually, she was discharged home with oral antibiotics.

This case illustrates the efficacy of thrombolytic therapy for the management of hemodynamically unstable patients with septic emboli. While associated with a risk of hemorrhage, thrombolysis clearly can lead to immediate improvement in some patients. In addition to the current accepted indications for thrombolysis, there are other clinical scenarios where its use could be beneficial.

MEDIASTINAL MASS CAUSING COMPLETE ATRIOVENTRICULAR CONDUCTION BLOCK AND ASYSTOLIC PAUSES

Chetan Patel, MD, University of Virginia Health System, Charlottesville, Virginia

Third degree heart block and asystolic pauses secondary to metastatic malignancy to the heart have been reported. Given the rarity of this entity it requires a high degree of clinical suspicion to initiate close cardiac monitoring. This may especially be beneficial in patients with thoracic malignancies because they are at risk for both hematogenous and direct spread of the cancer to the heart.

A 79 year old female presented to her primary care physician complaining of 3 to 4 weeks of progressive fatigue, shortness of breath with exertion, and some minimal night sweats. Her past medical history is significant for stage III chronic kidney disease and hypertension. She has a minimal history of tobacco use in the remote past. Family history is significant lung cancer and leukemia. Her initial exam was only notable for a grade 2/6 systolic murmur at the right upper sternal border that also had a diastolic component. Initial laboratory analysis revealed anemia with a hematocrit of 26.6 and a normal MCV. Chest radiograph demonstrated a large left pleural effusion with concern of a mediastinal mass. Subsequent thoracentesis of 800 milliliters of serous fluid was consistent with an exudative process with 1283 white blood cells. No malignant cells were identified in the pleural fluid. Computed tomography of the chest demonstrated a large infiltrating mass in the central mediastinum surrounding the aortic root, SVC, right and left coronary arteries, and likely involving the left ventricular wall. There was an additional large, left hilar mass with confluent extension to the anterolateral chest wall. Other significant findings included proximal occlusion of the superior vena cava as well as pulmonary nodules and liver hypodensities. Upon admission, an electrocardiogram showed a bradycardic ventricular rhythm consistent with third degree heart block. Physical exam was notable for a palpable right anterior cervical lymph node and supraclavicular node. A biopsy was obtained. The patient's hospital course was complicated by a symptomatic pause of 12 seconds that spontaneously resolved. In the cardiac intensive care unit, she continued to have pauses which were now associated with seizure activity. An echocardiogram revealed a mediastinal mass infiltrating numerous cardiac structures including the aortic root, myocardium, and interatrial septum. The pathology from the biopsy demonstrated poorly differentiated non-small cell carcinoma favoring squamous cell carcinoma.

The above case highlights a potential cardiac complication of mediastinal malignancies via direct extension of the tumor as opposed to hematogenous spread of disease. Although the extent of cardiac invasion by the malignancy in this case is rare, it illustrates that these patients may benefit from close cardiac monitoring and may require temporary pacing if aggressive treatment is pursued.

ACUTE KIDNEY INJURY DUE TO MASSIVE RENAL LEUKEMIC INFILTRATES

Joshua King, MD, University of Virginia Health System, Charlottesville, Virginia

Malignant lymphoproliferative diseases, both leukemia and lymphoma, commonly infiltrate the kidneys, but rarely cause acute kidney injury as a result of renal involvement. In cases where acute kidney injury precedes overt hematologic evidence of malignancy, diagnosis may be considerably obscured.

A 44 year-old man with a history of hypertension diagnosed several years prior and no history of prior renal disease presented to his primary physician with a complaint of blurry vision. He was found to be quite hypertensive, started on olmesartan, hydrochlorothiazide, and metoprolol, and referred to an ophthalmologist. In the ensuing several weeks, the patient presented to the emergency room twice with hypertensive urgency manifesting as headaches; his blood urea nitrogen and creatinine rose from 40 mg/dL and 1.8 mg/dL to 85 mg/dL and 4.4 mg/dL respectively in the space of eleven days. His peripheral white blood cell count was modestly elevated to 15,100/microliter. Urinalysis was notable for 2+ protein without a significant amount of red blood cells, white blood cells, or casts visible on urine microscopy. A renal ultrasound revealed bilaterally enlarged kidneys. His 24-hour urine protein was 0.69 g per 24 hours.

The patient was initially treated with amlodipine, minoxidil, and labetalol, as well as withholding his olmesartan. His creatinine rose within two days to 8.4, at which point a renal biopsy was performed and hemodialysis was initiated. Renal pathology revealed a massive monomorphic lymphoid infiltrate which stained diffusely positive for CD3 without substantial evidence of glomerular damage or immune complex disease. Concomitantly, the patient's white blood cell count began to rise after several days in the hospital to 35,000/microliter. Peripheral blood flow cytometry performed after the preliminary renal biopsy result revealed a T-cell acute lymphoblastic leukemia. Subsequent treatment with chemotherapy under the HyperCVAD protocol yielded an eventual return to normal renal function, despite substantial tumor lysis syndrome in the setting of established acute kidney injury. After a prolonged hospital course, the patient was discharged to home with plans to continue his chemotherapy.

The value of this case rests in recognizing acute kidney injury as an uncommon manifestation of lymphoproliferative disease. Unusual and frequently unapparent in both leukemia and lymphoma, renal failure as a direct result of malignant infiltration of the kidneys is often very responsive to treatment of the malignancy. Bilateral renal enlargement may be the most distinguishing clue to the presence of an infiltrative disorder, and may lead to earlier detection and treatment of a serious disease.

HEART FAILURE IN CANCER SURVIVORS: A CASE OF DOXORUBICIN-INDUCED CARDIOMYOPATHY

Roshanak Robati, MD, Virginia Commonwealth University Health Systems, Richmond, Virginia

Doxorubicin is a potent antineoplastic medications. One indication of the success of this drug is that young patients treated with Doxorubicin survive long enough that chronic cardiotoxicity of this drug is now a clinical problem.
.
KH is a 31 year old male with history of acute lymphocytic leukemia at age 15 (1991), who received chemotherapy with Doxorubicin, Vincristine, DM26 and Prednisone for two years. He remained asymptomatic in remission for 9 years before he presented with shortness of breath and was diagnosed with heart failure. He quickly worsened with three admissions in the past year for heart failure exacerbation requiring home Dobutamine infusion in spite of conventional therapy including Carvedilol, Lisinopril, Spironolactone, Furosemide, and Amiodarone. Subsequently he underwent successful cardiac transplantation and is currently doing well.

Doxorubicin-induced heart failure is common and associated with a poor prognosis. Patients treated with Doxorubicin should undergo a lifelong screening for Doxorubicin-induced heart failure with echocardiogram as this can be a late manifestation of drug adverse effect. Clinical Doxorubicin-induced cardiomyopathy can progress rapidly and irreversibly to congestive heart failure with little or no response to conventional therapy. Although there have been reports of cardioprotection with Dexrazoxane and risk reduction with Carvedilol and ACE inhibitor, currently the only successful treatment option in Doxorubicin-induced end-stage heart failure is cardiac transplantation. The potential risk of tumor recurrence and post transplant lymphoproliferative disease using long-term immunosuppression in recipients of cardiac transplant raises considerable concern about the long-term prognosis of survivors of childhood cancer. There have been reports of patients who remain cancer-free post cardiac transplant although further studies on the outcome of patients post cardiac transplant and their risk of tumor recurrence are warranted.

NOT ALL ST SEGMENT ELEVATIONS MEAN ACUTE MYOCARDIAL INFARCTION

Christopher Hayes, MD, Virginia Commonwealth University Health Systems, Richmond, Virginia

In the majority of cases, ST segment elevation on an electrocardiogram (EKG) indicates an acute myocardial infarction (AMI), but it has been estimated that from 9% to 14% of the cases this is not the correct diagnosis.

A 73yo African-American woman presents with acute onset of chest pain and shortness of breath that began suddenly while she was walking down stairs. EMS personnel noted ST segment elevation on cardiac monitoring, a blood pressure of 88/68, and a heart rate of 140. Upon arrival in the ED, she remained in cardiogenic shock, with ST segment elevations in leads II and III, q-waves in leads III and aVF, with no prior EKG for comparison. The patient was somnolent and a poor historian so no other history was obtainable. The cardiology team took her emergently to the coronary angiography suite where they identified severe 3-vessel disease but no culprit lesion. During the procedure the patient had an intra-aortic balloon pump inserted because of persistent shock. Laboratory data was only significant for troponin I levels that were not elevated at the time of admission or six hours. Due to persistent shock a transthoracic echo (TTE) was obtained and revealed a moderately dilated right ventricle (RV), moderately reduced RV systolic function, flattening of the septum, and elevated pulmonary artery systolic pressure of 55 mmHg. All findings were consistent with acute RV pressure overload. Lower extremity venous doppler ultrasound revealed acute thrombosis of the superficial femoral, popiteal, posterior tibial and peroneal veins. A chest CT revealed a large clot burden in the distal aspects of the right pulmonary artery, left pulmonary artery, and filling defects in all the segmental and subsegmental branches of all lobes of the lungs. There was evidence of reflux of contrast media into the inferior vena cava and hepatic veins. Cardiothoracic surgery was consulted and took the patient emergently to the operating room where they performed a bilateral pulmonary artery embolectomy, coronary artery bypass surgery, and placement of an IVC filter.

Early recognition and treatment of ST-segment elevation AMI is proven to reduce mortality. A recent retrospective analysis revealed that in patients undergoing emergent cardiac angiography for suspected AMI that 9.5% of the patients did not have significant coronary artery disease and that 14% of the patients did not have a culprit lesion. Other possible diagnoses include pulmonary embolism, pericarditis, and aortic dissection. The clinician must be aware that not all ST segment elevations on EKG indicate an AMI. If the clinical picture is not supported by the angiography then the clinician should have a low threshold for ordering additional testing to rule out other potentially fatal causes.

ENDOSCOPIC DRAINAGE OF PANCREATIC FLUID COLLECTIONS WITH FULLY COVERED SELF-EXPANDABLE METALLIC STENTS (CSEMS). HOW DOES IT COMPARE TO CONVENTIONAL DRAINAGE WITH PLASTIC STENTS?

Jayant P. Talreja, MD, Vanessa M. Shami, MD, Jennifer Ku, Kristi Ellen, Michel Kahaleh, MD,
University of Virginia Health System, Charlottesville, Virginia

Introduction: Transenteric drainage of pancreatic fluid collections (PFC) using covered self-expandable metallic stents (CSEMS) offers the option of providing a larger diameter access fistula for drainage when compared to conventional plastic stents. Our aim was to evaluate the efficacy and safety of transenteric CSEMS placement in the drainage of PFC and compare this technique to conventional drainage using plastic stents.

Materials and Methods: Between January 2007 and September 2007, 18 patients (51 ± 18 years old, 12 male) underwent placement of CSEMS for the drainage of PFC. All but two patients were drained using endoscopic ultrasound (EUS) guidance. A double pigtail was placed along side (4 cases) or into the CSEMS (14 cases) to prevent migration. Follow-up and final results were prospectively recorded until May 2008. These results were then compared to a group of 18 patients matched by age, gender, and size of PFC, who underwent placement of plastic stents for the drainage of PFC. The chi-squared test was used to analyze between-group differences in categorical variables, and Student's t test to analyze differences between the means of continuous parameters. A p value of <0.05 was considered significant.

Results: Etiologies of PFC were gallstone (9), alcohol (5), and other (4). Mean size was 10 ± 4 cm (range: 4-16 cm). A median of 1 session was required to achieve drainage (range: 1-4 sessions). Mean time of follow-up until final evaluation was 66 ± 56 days (range: 15-240 days). Complications included superinfection (5), bleeding (2) and inner migration (1). One patient experienced migration of CSEMS with resolution of the collection and spontaneous expulsion. A total of 17/18 (95%) patients responded successfully with 14 (78%) patients achieving complete resolution of their PFC. The patient who failed required multiple endoscopic sessions and surgical drainage of infected necrosis. When compared to conventional drainage with plastic stents (66 ± 56 days vs. 138 ± 118 days, $p < 0.05$), patients who underwent CSEMS drainage had a statistically significant shorter time to final outcome (see table).

Conclusion: Placement of a CSEMS seems to offer a faster alternative for the drainage of PFC when compared to conventional drainage with a plastic stent. A prospective and randomized study should be performed comparing the two techniques to confirm these data.

POEMS SYNDROME - NEUROLOGY MEETS HEMATOLOGY

James Thompson, MD, Virginia Commonwealth University Health Systems, Richmond, Virginia

A 67-year-old woman with diabetes and hypothyroidism was admitted from neuro-opthalmology clinic after presenting with recent onset of visual disturbance in the setting of progressive weakness and sensory loss. Her symptoms began approximately one year prior to her visit with stocking-glove numbness and tingling in the legs and hands. She developed progressive weakness in her legs with unsteadiness of gait requiring the use of a walker, and progressive weakness in the hands making it difficult to even sign her name. She also reported increasing fatigue, dyspnea on exertion, fever, ankle swelling, abdominal swelling, right hip pain, increased thirst, cold intolerance and hirsuitism but no rash. Symptoms did not improve with adjustment of her levothyroxine by her endocrinologist. The general physical exam was notable for mild hypertension, a pre-existing heart murmur, hepatosplenomegaly, and severe lower extremity edema to the level of the hips. She had no lymphadenopathy and her thyroid gland was mobile and without nodules. The neurological portion of the exam revealed 4/5 strength in her upper extremities, and 3/5 strength in her lower extremities, slightly weaker in her right hip flexor. Deep tendon reflexes were universally diminished. There was near complete sensory loss in a stocking and glove distribution including all modalities of sensation: light touch, pinprick, temperature, vibration and proprioception. Visual acuity was not significantly impaired and visual fields were intact. Optic fundoscopy revealed severe, diffuse disc edema with peripapillary nerve fiber layer hemorrhages and exudates. Initial lab-work for electrolyte disturbance, hematologic abnormalities nutritional deficiencies and hypothyroidism were unremarkable. CSF was obtained and revealed an elevated protein level but no cells. MRI, MRA and MRV ruled out the presence of brain tumor or other mass lesion, vascular pathology, central demyelination and hydrocephalus. A plain film of her right hip led to the discovery of a lytic lesion in her right ischium. Further skeletal survey and bone scan discovered similar lesions in the skull and spine. SPEP and UPEP confirmed the presence of monoclonal gammopathy and a biopsy revealed of the right hip lesion to be a plasma cell tumor. The diagnosis, POEMS Syndrome, was thus confirmed and the patient was referred to Hematology-Oncology for further evaluation and treatment.

The acronym POEMS stands for polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes. It is a syndrome with wide ranging manifestations but by definition includes monoclonal plasma cell disorder and peripheral neuropathy. The secondary manifestations, including papilledema, peripheral edema, endocrinopathies and skin changes, are thought to be related to the chronic overproduction of pro-inflammatory cytokines. The prominent neurological symptoms in this patient, ultimately explained by a paraneoplastic syndrome, are fascinating and highlight the value to the diagnostician of fluency in a wide range of medical disciplines.

METHYL BINDING DOMAIN PROTEIN 2 (MBD2) MAINTAINS EPITHELIAL DEDIFFERENTIATION IN BREAST CANCER

Omar Y. Mian, Shou Zhen Wang, Sheng Zu Zhu, Merlin N. Gnanapragasam, Gordon D. Ginder,
Virginia Commonwealth University, Richmond, Virginia

Purpose: Methyl-CpG Binding Proteins (MCBPs) function as interpreters of epigenetic signals encoded in the genome. However, their role during normal development and in disease remains largely undefined. We have studied the function of Methyl-Binding Domain Proteins (MBDs) in human mammary epithelial cancers, where repatterning of CpG methylation is common.

Results: We find Methyl Binding Domain Protein 2 (MBD2) promotes the abnormal multi-cellular morphology characteristic of tumor cells grown in extracellular matrix extracts. Stable MBD2 knockdown in MCF7 cells leads to an increased proportion of differentiated epithelial structures (e.g. acinii, 70%, [CI=0.55-0.83]) when compared with untransfected (46%, [CI=0.39-0.53], p≤0.038) and scrambled shRNA transfected (37%, [CI=0.29-0.45], p≤0.012) control cells. To identify the genes underlying this MBD2 dependant phenotype, high throughput quantitative PCR data were probed using self organizing map (SOM) analysis. We found a small subset of the breast cancer specific tumor suppressors known to be silenced by promoter hypermethylation were regulated by MBD2 (n=7, 15%). Several genes previously shown to be MBD2 bound by chromatin immunoprecipitation (ChIP) were not induced by MBD2 knockdown, suggesting MBD2 exhibits tumor and tissue-type specificity. Moreover, gene sets activated by the DNA methylation inhibitor, 2-deoxy-5-aza-cytidine (4uM, n=30, 67%), and MBD2 knockdown (n=18, 40%) were not mutually exclusive and many genes exhibit additive induction (n=11, 24%). The MBD2 dependant genes were rapidly re-suppressed upon rescue with a shRNA binding site variant MBD2 and ChIP studies confirmed binding of MBD2 at all genes examined within the MBD2 dependant cluster. Transient siRNA mediated knockdown of individual MBD2 dependant genes did not restore the dedifferentiated phenotype, suggesting coordinate regulation by multiple downstream targets of MBD2.

Conclusion: Our studies show MBD2 maintains pathologic dedifferentiation in breast cancer and intimates a role for MBD2 in establishing epithelial morphology during development as well as in the progression of neoplastic disease.

This work was supported by NIH-2R01DK029902-26A2

LYMPHOMATOID GRANULOMATOSIS

Rupali Roy, MD, University of Virginia Health System, Charlottesville, Virginia

Lymphomatoid granulomatosis (LG) is an uncommon angiocentric and angiodestructive lymphoproliferative disorder of extranodal lymphoid tissue that predominantly involves the lungs and less frequently involves the skin, kidney, liver, central nervous system, and gastrointestinal tract. The majority of cases are Epstein-Barr virus (EBV) associated. Here, we describe a case that is not.

A 45 year-old female was admitted with a history that started three years prior to admission when she developed facial numbness and was found to have multiple white matter lesions on brain MRI. Her symptoms partially resolved without treatment. Later, she developed a cough and dyspnea and was found on chest CT to have bilateral diffuse nodular pulmonary infiltrates. Biopsy revealed an EBV-negative, nodular angiocentric lymphohistiocytic infiltrate. A definitive diagnosis was not made. The patient was started on prednisone to which she responded clinically and radiographically. After her prednisone was tapered and azathioprine was added, her dyspnea returned and she began experiencing lower extremity weakness, frequent falls, and occasional bowel and bladder incontinence prompting hospital admission.

Physical exam on admission was significant for bilateral arm tremor, spasticity at the knees, clonus at the ankles, and decreased sensation from the right breast to foot. Gait was wide-based. Basic labs, quantitative immunoglobulins, cerebral spinal fluid analysis, bone marrow biopsy, and flow cytometry were normal. An HIV test was negative. A brain and spine MRI revealed widespread areas of enhancement in the cerebrum, cerebellum, pons, medulla, and cervical cord. Review of pathology from her previous lung and gastric biopsies revealed nodules with a T cell predominant angiocentric lymphohistiocytic infiltrate some of which had areas of central necrosis. No granulomas were noted. AFB stains were negative. This pathology prompted a diagnosis of lymphomatoid granulomatosis. The patient was treated with iv dexamethasone followed by oral prednisone and within a week had no cough, dyspnea, bowel or bladder incontinence and had a decrease in the size and number of the previously noted brain and spinal cord lesions on MRI. She continued to report some sensory loss and weakness in her right leg. As an outpatient, the patient was maintained on prednisone and azathioprine without change in her symptoms from discharge.

Lymphomatoid granulomatosis is a difficult diagnosis to make because it can mimic infectious diseases, vasculitis, or metastatic malignancies. Its prognosis varies, and there is no standard of care for treatment. Corticosteroids, chemotherapy, interferon alpha-2b, radiotherapy, and stem cell transplantation have all been attempted, but there have been no randomized prospective studies. In this case, a patient with LG with pulmonary, central nervous system, and gastrointestinal involvement remains clinically stable on prednisone and azathioprine three years after first presenting with symptoms.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME DUE TO HISTOPLASMA CAPSULATUM: AN UNCOMMON PRESENTATION FOR A COMMON YEAST

Tushar Sinha, MD, Brian Wispelwey, MD, University of Virginia Health System, Charlottesville, Virginia

A 36-year-old male immigrant from El Salvador with AIDS (Acquired Immunodeficiency Syndrome) and a history of disseminated histoplasmosis presented with complaints of pain and swelling in his left neck for the previous week. He also endorsed subjective fevers and sweats over this course. He denied photophobia, neck stiffness or headaches. His AIDS defining illness was disseminated histoplasmosis in April 2007. He had since started ART (Antiretroviral Therapy) in May 2007. His past medical history included acute kidney injury due to amphotericin B, a gunshot wound to the leg as a teenager when he required blood products, and a stab wound to the chest. His medical regimen on admission was Atripla (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg), Trimethoprim/Sulfamethoxazole prophylaxis, itraconazole, and azithromycin.

Physical examination showed a temperature of 36.8°C, BP 136/93mmHg, pulse 74bpm, respiratory rate 20, oxygen saturation 97% on room air. Exam of his neck revealed a 1.5 by 2 cm node over the mandible, a 2 by 3 cm submandibular node and a 1 cm node in the posterior cervical chain. All were very tender, hard, mobile and non-fluctuant. Laboratory studies showed a WBC count of 9800/µL with 45% neutrophils/18.7% lymphocytes & BUN/Cr 14/0.9. His CD4 count trend over the prior 9 months was 82 (5/07)  316 (7/07)  358/µL (admission). HIV viral load trend was >1,000,000 (5/07)  343 (7/07)  <50 copies/mL (admission). Urine histoplasma antigen was non-detectable on two occasions. An EBV assay showed positive VCA IgG & nuclear Ab but negative VCA IgM. A CMV viral load was non-detectable. Itraconazole/hydroxyitraconazole levels were <0.3 µg/mL.

The patient was febrile on the first hospital day. Blood cultures, urinalysis and chest x ray were performed and all found to be non-revealing. A lymph node aspirate revealed marked acute inflammation in the left submandibular node. A silver stain was negative for microorganisms and flow cytometry showed no evidence of malignancy. As results from the above tests returned the patient spontaneously defervesced and was discharged in stable condition. An excisional lymph node biopsy was performed 2 weeks later. This showed necrotizing granulomas and suppurative abscess, and a silver stain showed yeast forms consistent with Histoplasma. Given the treatment failure with itraconazole, the patient's regimen was changed to posaconazole 400mg twice daily. He was followed in clinic thereafter and was given a 3 month course of prednisone to relieve his painful lymphadenopathy. He did well with this regimen and has had significant regression of his lymphadenopathy.

While Mycobacteria have been well described to be associated with lymphadenitis, Histoplasma has not. Immune Reconstitution Inflammatory Syndrome (IRIS) due to mycobacteria is well described in several case reports and series. However, Histoplasma has rarely been associated with this syndrome. This case report serves as an example of IRIS due to Histoplasma capsulatum.

COMPARING SECONDARY ISCHEMIC STROKE PREVENTION PRACTICE WITH ESTABLISHED GUIDELINES IN A LARGE TEACHING HOSPITAL: DO WE MEASURE UP?

Jeff Neal, MD, Richard Wardrop, MD, PhD, Carilion Health System, Roanoke, Virginia

Introduction: The incidence of ischemic stroke in the United States approaches 700,000/year. Of these 200,000 are recurrent. Multiple high quality clinical trials aimed at secondary prevention have been described and have evaluated anti-platelet agents, the use of statin therapy, and inhibition of the RAAS with ACE-I. The most recent American Heart Association Guidelines for the Prevention of Secondary Stroke incorporate treatment recommendations based on these trials that show clear benefit. Literature evaluating institutional compliance with these guidelines is sparse. We hypothesized that in a large teaching institution with neurology consultative services, compliance with published guidelines would be near unity.

Methods: Using ICD-9 codes, we retrospectively analyzed data from a cohort of 440 patients who presented to our institution with a primary diagnosis of stroke. Baseline characteristics were collected including demographics, admitting service, presence of neurological consultation, co-morbidities, admission medications, smoking history, length of hospitalization, diagnostic tests performed, discharge medications and final diagnoses.

Results: There were 440 patients who presented with stroke from January 1 thru July 31, 2007. One hundred thirty-three patients were excluded because of hemorrhagic stroke. Of the 307 patients reviewed, 176 (59%) presented with ischemic stroke and 131 (41%) with TIA. These patients were further analyzed to exclude pre-existing atrial fibrillation, coagulopathy, or coronary artery disease.

The remaining 185 patients were analyzed with specific attention to secondary prevention. Antiplatelet agents were prescribed to 148(80%) of these patients on discharge. Antiplatelet agents prescribed were ASA 74(40%), ASA/clopidogrel 27(14.6%), ASA/dipyridamole 25(13.5%), clopidogrel 13(7%), ASA along with ASA/dipyridamole 8(4.3%), and 1(<1%) clopidogrel plus ASA/dipyridamole. Interestingly we identified 11(5.9%) patients prescribed warfarin, warfarin/clopidogrel 3(1.6%) and 1(<1%) warfarin/ASA with no evidence of atrial fibrillation.

Seventy-four patients (40%) received statin therapy at discharge. A total of 138(74.6%) patients received some type of antihypertensive therapy at discharge; of these, 83(60%) were prescribed an ACEI or ARB.

Finally, there were 104(56.2%) neurology consults documented. Patients were no more likely to receive the combination of ASA/dipyridamole or clopidogrel alone than those without a neurology consult

Conclusion: Adherence to clinical guidelines for secondary stroke prevention is proving to be a challenging target. Our analysis utilized strict exclusion criteria to minimize clinical variability, yet of the 185 patients studied only 80% were prescribed anti-platelet agents. Of these, 20% received optimal therapy. Similarly, 40% were placed on statin therapy, and of the 138 patients on antihypertensive therapy only 60% were on an ACEI/ARB. Based on these results, we intend to create a novel pre-determined order set for those patients who present with stroke to optimize secondary prevention of stroke in our population.

URINARY ASCITES PRESENTING AS AN OVARIAN MALIGNANCY

Anishka Rolle, MD, Carilion Health System; Roanoke, Virginia

A 52 year old female was admitted to our hospital with a one month history of increasingly painful abdominal distension. She also reported having three weeks of intermittent anorexia, nausea and vomiting associated with generalized weakness and malaise. She was seen in the Emergency department at an outlying hospital one week prior, and was sent home to complete a two week course of antibiotics for pyelonephritis with a non-obstructing left ureteropelvic kidney stone. Her medical history was remarkable only for type 2 Diabetes mellitus. On admission, her temperature was 100.4 F, blood pressure 98/43 mmHg and pulse 86 beats per minute. Examination revealed a thin female with no peripheral edema or lymphadenopathy. Her abdomen was grossly distended and tender throughout with diminished bowel sounds. Other systems were normal. Laboratory workup revealed normal renal function and a white blood cell count of 27,000 cells per microlitre and hemoglobin of 8 mg/dl. Serum CA-125 was 180. Urinalysis was positive for leukocyte esterase and urine culture had a heavy growth of proteus mirabilis, for which she was given Ciprofloxacin. A paracentesis was done and ascitic fluid white blood cell count was 9,046, protein was 2.6, LDH 3,800 and glucose 10. An abdominopelvic CT revealed a low anterior abdominal wall mass with possible omental caking and free fluid in the pelvis. We made a presumptive diagnosis of ascites secondary to ovarian malignancy. A transvaginal ultrasound showed no abnormalities. By the second hospital day, the patient admitted to having been beaten about the body prior to admission. A repeat abdominal CT scan was done and showed a left perinephric retroperitoneal fluid collection and irregular renal collecting system contours. A new diagnosis of urinary ascites from blunt abdominal trauma was entertained and confirmed by an ascitic fluid creatinine of 13.1 and BUN of 16. The patient remained on antibiotics and had CT guided posterior percutaneous fluid drainage and left nephrostomy for urinoma drainage.

A urinoma is an encapsulated collection of chronically extravasated urine. It is rare and also difficult to diagnose. It can be traumatic or non-traumatic caused by a ureteral stone. Our patient had cause for both. In this case, urine appeared to have tracked under the pelvic peritoneum giving the appearance of omental caking and an ovarian tumor, which ultimately delayed treatment. This case highlights the importance of radiographic imaging in diagnosis and image-guided intervention in treatment. It also emphasizes an atypical presentation for ascites and the need for a high index of suspicion in patients presenting with blunt abdominal trauma.

DERMATOLOGICAL DISEASES IN THE PERUVIAN AMAZONIA

Alex G. Ortega-Loayza, MD, Ericson L. Gutierrez, MD, Willy Ramos, MD, Carlos Galarza, MD, Virginia Commonwealth University, Richmond, Virginia, Clinical Research Institute of San Marcos University, Lima, Peru

Background: The dermatologic diseases vary widely due to geographic location and may be influenced by ethnic and environmental factors. In developing countries, the dermatological diseases are a considerable problem in public health. Additionally, the exponential increase of tourist activity in the jungle of Peru imparts a serious health risk as these ailments can affect travelers in the area. Aim: To determine the epidemiology of dermatological diseases in three different regions of the Peruvian Amazonia. Patients and Methods: Transversal and multicentric study, which was carried out during February of 2006, 2007 and 2008 in three regional hospitals in the Peruvian Amazonia. All new patients who were looking for a dermatological attention were included. Diagnoses were based on clinician's criteria and skin biopsy. The information was recorded in a survey and analyzed using SPSS version 15.0. Univariate analysis based on frequencies, percentages, central tendency and dispersion measures and bivariate analysis with chi square for qualitative variables were used. The variables that were statically significant were analyzed by multinomial logistic regression. All the calculations were made with a confidence interval of 95 %. Results: 1602 patients were included in the study. By group, the infectious and parasitic dermatoses were the most prevalent (31.5%). There was a statically significant association between infections of the skin and subcutaneous tissue and children ($p<0.001$). The presence of parasitic dermatoses such as scabiosis, pediculosis, and miasis was associated with an altitude less than 700 meters above sea level ($p=0.003$, OR=3.1, IC: 1.5-6.7). On the other hand, radiation-related disorders of the skin and subcutaneous tissue were associated with an altitude more than 700 meters above sea level. By groups, the dermatophytoses were the most common diagnosis (8.4%). The most frequent endemic dermatoses were leishmaniasis (1.7%) and classical dengue (0.9%). Conclusions: Infectious dermatological diseases were the most common diagnoses in the Peruvian Amazonia, which has similar climatic conditions with other tropical regions worldwide. Additionally, radiation related disorders of the skin and subcutaneous tissue should be addressed for people living/traveling in the rainforest area. These findings may assist in the training of general doctors in diagnosis and treatment of the most common dermatoses in tropical areas. This is especially relevant in regards to the physicians' shortage in the Amazonia region. Moreover, the present study would be helpful for any physician from developed countries when giving medical advice and attention to travelers or immigrants of tropical environments. Skin lesions may be useful clues to systemic/localized diseases in immigrants, short and long-term residents.

BACILLUS CEREUS MENINGOENCEPHALITIS

J. Peter Heyboer II, MD, Virginia Commonwealth University, Richmond, Virginia,

Bacillus cereus is a spore-forming, Gram-positive bacillus that is well known to cause benign, self-limited gastroenteritis. When detected in clinical specimens, it is often dismissed as a laboratory contaminant. Rarely, however, it can cause highly fatal systemic disease in neutropenic or immunocompromised hosts - notably in low birth weight neonates and adults with leukemia undergoing chemotherapy.

A 73 year old woman has been followed closely by her oncologist for chronic myelogenous leukemia. After previous therapies had caused intolerable side effects and had failed to adequately suppress blood counts, she was enrolled in a phase I trail with bosutinib (SKI-606), a tyrosine kinase inhibitor similar to imatinib. She seemed to be responding well until a few months ago, when she developed an abrupt onset headache and was found to have leukemic meningitis. She had an Ommaya reservoir placed and began bi-weekly courses of intrathecal methotrexate and hydrocortisone, resulting in resolution of headache and clearing of cells from the cerebrospinal fluid.

The patient recently returned to her oncologist for scheduled administration of methotrexate/hydocortisone via Ommaya reservoir. At the visit, she was feeling well and her cerebrospinal fluid was devoid of cells. The medications were administered using sterile technique, and she returned home without significant event. Two days later, she presented to the emergency room with acute onset altered mental status, headache, and nuchal rigidity.

At arrival to the hospital, she was tachycardic, febrile to 38.7 °C, and lethargic. She had a 3/6 systolic murmur over the right upper sternal border, which had been noted on previous records, but no other clinical stigmata of endocarditis. Cerebrospinal fluid analysis revealed pleocytosis (4020 WBC, 99% polys), protein 121 mg/dL, glucose 88 mg/dL, and gram-variable rods on gram stain. Her CBC was significant for a leukocytosis of 19.2 10e9 cells/L with 96% neutrophils and a left shift. Samples of blood and cerebrospinal fluid were sent for culture, and patient was started empirically on cefepime and vancomycin.

She responded well to antibiotic therapy. By the second day of hospitalization, her headache had improved and she was significantly more alert. Her blood and cerebrospinal fluid cultures both grew Bacillus cereus, sensitive to vancomycin. She was tapered to vancomycin monotherapy, and neurosurgery removed the Ommaya reservoir. Her hospital course was complicated by oral candidiasis and oral herpes simplex virus outbreak, which were treated with fluconazole and acyclovir, respectively. Echocardiogram revealed no evidence of endocarditis, and the patient was discharged home to complete a 2-week course of vancomycin.

This case demonstrates that Bacillus cereus can be highly pathogenic in certain clinical circumstances, such as patients with leukemia. Since it is associated with a high mortality rate in this context, its presence should not be summarily disregarded in patients with similar conditions.

ALL THAT GLITTERS. FALSE POSITIVE PET SCAN IN PATIENTS TREATED FOR HODGKIN'S LYMPHOMA: TWO CASES

LT Joseph Gresens, MC, USN (MD), CDR Michael Hopkins, MC, USN. Naval Medical Center Portsmouth, VA

Positron Emission Tomography (PET) Scans, have found increased use in hematologic malignancies. Fluorodeoxyglucose (FDG) PET scans have replaced gallium scans in the evaluation and staging of Hodgkins Lymphoma (HL) and appear to have utility in predicting response to treatment. PET scans are increasingly showing false positives when used in routine post-therapy follow-up. The two cases presented highlight false positive results in patients after completing chemotherapy for Hodgkin's Lymphoma.

The first patient was a 35 year old male who presented with a large mass on his left neck that had been growing for the past several months. CT/PET scan was done showing a solitary mass in the left neck, which had increased uptake of 8.5-9 SUV. Biopsy confirmed that the patient had nodular sclerosing Hodgkin's Lymphoma. The patient was treated with 4 cycles of ABVD chemotherapy and upon completion of treatment was rescanned. The scan showed metabolically active lymph nodes in the supraclavicular region bilaterally. The patient had an upper respiratory infection at the time. A lymph node dissection, looking for relapsing disease was negative for malignancy.

The second patient was a 29 year old male who had three weeks of coughing, shortness of breath, back pain and night sweats. PET scan revealed diffuse lymph node involvement both above and below the diaphragm and bony involvement. Patient was treated with 6 cycles of ABVD. Imaging at the end of two cycles showed a complete remission. A few weeks after completing therapy, a PET scan showed evidence of recurrence. The ensuing biopsy of two lymph nodes revealed granulomatous change with giant cells and no evidence of Hodgkin's disease. Follow-up imaging has shown complete resolution of PET active adenopathy.

Both of these patients had scans at the conclusion of therapy with false positive results. FDG scans have shown good utility in detection and early response to treatment as researched by Brepoels et al. However there can be a high false positive rate in post-therapy scans: 16% according to a study by Levine et al. Both studies suggest that high false positive rates could be the result of fibrosis, inflammation, or thymic hyperplasia especially in younger patients, among other possibilities. Caution should be taken when interpreting a positive PET scan and toxic salvage therapy should only be considered of biopsy confirmed metabolically active centers. Consideration of follow-up imaging with standard CT has been suggested to avoid biopsy of false positive PET findings.

**The views expressed in these abstracts are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.*

THE POTENTIAL RISKS OF DAILY EXERCISE: A CASE REPORT OF CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Christopher Gelwix, MD, Gautham Kalahasty MD, and George W. Vetrovec MD, Virginia Commonwealth University, Richmond, Virginia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but potentially fatal disease characterized by exercise-induced syncope or sudden cardiac death. Ventricular arrhythmias are provoked through adrenergic surges brought about by exercise or emotional stress in the absence of structural heart disease.

A 55 year old African-American man with controlled diabetes, anemia, and hepatitis C presented to his primary care physician with a chief complaint of dyspnea on exertion. The patient reported progressive worsening shortness of breath with daily activity beginning several months prior to presentation. His symptoms became more apparent with heavy exertion, sighting examples of walking up two flights stairs and while carrying objects up a steep hill. He reported, however, no such symptoms while walking on level terrain and stated he could walk several miles without having symptoms. He also noted palpitations during these episodes. His symptoms were relieved with rest. He denied any syncope, paroxysmal nocturnal dyspnea, orthopnea, weight gain, swelling, or associated chest pain. His family history is significant for sudden cardiac death in his brother, paternal grandparents and aunt. His physical exam showed no signs of JVD, S3, murmurs, rubs or gallops, lower extremity edema and was overall unremarkable. Baseline ECG showed no electrical abnormalities. Routine CBC revealed stable hemoglobin at the patient's baseline of 11.5 g/dL. He was referred for exercise stress testing to further evaluate his symptoms.

During the administration of his stress test the patient reached a target heart rate and developed palpitations and shortness of breath. ECG tracing revealed polymorphic ventricular tachycardia. Additionally, the patient also reported anginal symptoms. He was taken for urgent cardiac catheterization. Cardiac angiography showed no significant coronary lesions. Cardiac MRI was performed and showed no structural abnormalities. Electrophysiology testing failed to evoke ventricular tachycardia. The patient was started on a beta-blocker and the diagnosis of catecholaminergic polymorphic ventricular tachycardia was made.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially fatal disease caused by adrenergic induced ventricular arrhythmias. The pathognomonic feature is polymorphic exercise-induced ventricular tachycardia in the absence of structural cardiac abnormalities. Patients with CPVT typically present with syncope exacerbated by physical or emotional stress, however variable clinical presentations have been reported. CPVT has a strong genetic predisposition with variable penetrance. Identification of patients at risk may help to guide treatment modalities in reducing the risk of sudden cardiac death. Beta-blocker therapy with or without implantation of a cardiac defibrillator remain the treatment strategies of choice. Given the patient's strong family history of sudden cardiac death he was consented to undergo genetic testing and these results are pending at the time of submission.

ANTI-GBM DISEASE: ANTIBODIES CAN BE DECEIVING

Pratima Thotakura, MD, Virginia Commonwealth University, Richmond, Virginia

Anti-glomerular basement membrane (GBM) disease is a diagnosis that is readily made with the presence of circulating anti-GBM antibodies in the serum. Goodpasture's disease is more specifically the findings of glomerulonephritis, pulmonary hemorrhage and anti-GBM antibodies. However, there are rare cases in which the diagnosis is not as straightforward.

A 55 year old African-American man presented with a 3 week history of shortness of breath and hemoptysis. He denied night sweats, fevers, weight loss, chest pain, orthopnea, rash, arthralgias, hematuria and dysuria. On examination, the patient's vital signs were notable for an oxygen saturation of 99% on 2 liters of oxygen. Examination was also notable for decreased bibasilar breath sounds without egophany, wheezes or rhonchi. The lower lung fields were not dull to percussion. The remainder of the physical examination was unremarkable. Laboratory evaluation revealed a BUN and creatinine of 15 and 1.43, respectively, white blood cell count of 16.6, hemoglobin of 12.8, and a urinalysis significant for proteinuria. Chest X-ray showed bilateral perihilar infiltrates. Multiple sputums were sent to rule out tuberculosis and treatment was begun for community acquired pneumonia. The patient, however, did not respond to antibiotics; hemoptysis persisted. Chest CT revealed extensive pulmonary disease, prompting a bronchoscopy which showed diffuse alveolar hemorrhage.

Over the hospital course, the patient's renal function did not improve, prompting the consideration of a pulmonary-renal syndrome. A renal biopsy was scheduled to further investigate an etiology for the patient's renal function. The immunologic results were notable for a positive p-ANCA, but otherwise negative c-ANCA and anti-GBM. The patient was presumed to have small vessel vasculitis and treatment for such was initiated. However, the pathology report from the renal biopsy revealed the patient had "immunofluorescence microscopy features of anti-GBM disease." The report continued with comment that this patient was notable for having features of anti-GBM disease without the serologic presence of anti-GBM immune complexes. Other microscopic features suggest the diagnosis of pauci-immune glomerulonephritis as well.

Though this case may represent a false negative regarding the absence of circulating anti-GBM antibodies, the consensus among our nephrologists was that this patient had a combination of pauci-immune glomerulonephritis as well as anti-GBM disease. Given the patient's clinical picture, a more thorough way of testing for etiology in this case included a renal biopsy in addition to immunochemistries. Serisier et al describes case reports of patients with alveolar hemorrhage only and reports that, though documented cases are rare, "alveolar hemorrhage in anti-GBM disease that is seronegative . . . may be more common than previously appreciated . . . evidence of even minimal renal involvement should point to a strong consideration of renal biopsy."

FULLY COVERED REMOVABLE SELF EXPANDABLE METAL STENT IN BENIGN ESOPHAGEAL DISEASES: A MULTICENTER ANALYSIS

Basil S Al-Awabdy,MD, Mohamad Eloubeidi, MD, Michel Kahaleh, MD, Jayant Talreja, MD, Tercio Lope, MD, Vanessa Shami, MD, University of Virginia Health System, Charlottesville, Virginia, University of Alabama, Birmingham, Alabama

BACKGROUND: Fully covered esophageal stents are thought to induce less mucosal hyperplasia and are potentially removable, and therefore have been considered as an attractive alternative for the treatment of benign esophageal diseases. However, large scale studies with long-term data on their effectiveness, safety and removability are lacking.

AIM: To evaluate the efficacy and safety of fully covered removable Nitinol esophageal SEMS in the treatment of benign esophageal diseases.

MATERIALS AND METHODS: Between January 06 and September 07, 35 patients (18 males with mean age 61 years, range 20-85 years) underwent SEMS placement (ALIMAXX, Alveolus) (18 or 22 x 70, 100 or 120 mm) for benign esophageal strictures at two tertiary academic medical centers. Response to treatment as well as short and long-term complications were documented.

RESULTS: Indication for stent placement was: Esophageal leak/fistulae (n=12), refractory benign strictures (including reflux disease, pill and lye induced) (n=10), anastomotic strictures (n=7), perforations (n=4), and radiation-induced strictures (n=2). All SEMS placements were successful. Technical problems encountered during deployment included 4 partial invaginations (11%). Immediate complications were chest pain (2), stent migration (2) dysphagia (1), respiratory compromise (1) and arrhythmia (1). Long-term complications included recurrent dysphagia (6), aspiration pneumonia (2), globus sensation (2), abdominal pain (2) and fever (1). Stent migration was observed in 12 patients (34%), and was more frequent in distal (5/9, 56%) and upper (4/11, 36%) compared with mid esophageal (3/15, 20%) stents. Migration was more frequent in stents placed for strictures (7/19 stents, 37%), and fistulae/leak (4/12 stents, 33%) compared with perforation (1/4 stents, 25%) with p values of 0.614 and 0.339 respectively.

Post placement, dysphagia scores at one month improved significantly from 3.1 ± 1.0 (range: 0-4) to 1.2 ± 1.3 (range: 0-4), p value < 0.0001. A total of 11/35 patients (31%) had successful treatment defined as resolution of presenting symptoms with sustained response after stent removal. All stents were retrieved successfully. One stent was fractured and retrieved completely in two pieces

CONCLUSION: Use of SEMS for benign esophageal conditions resulted in frequent stent migration and long-term improvement in a third of patients. Further investigation is required before universally recommending SEMS in the treatment of benign diseases of the esophagus. The subset of patients that can benefit from stent placement for benign esophageal disorders requires further investigation and definition.

SWALLOW INDUCED SYMPTOMATIC ATRIOVENTRICULAR BLOCK

Jason Foreman, DO, Alexander Vigh, DO, Richard M. Wardrop III, MD, Carilion Health System, Roanoke, Virginia.

Introduction: Syncope is a commonly encountered problem for internists and cardiologists and often results in hospital admission and a large diagnostic work-up. Unfortunately a cause is only discovered in ~30-40% of cases when vagal mechanisms are considered. Deglutition or swallow syncope is a rare cause of syncope associated with the loss of consciousness while swallowing certain objects. Here we report a case of swallow syncope uncovered during an inpatient admission for chest pain.

Case Presentation: A 52 year-old female was admitted for the evaluation of recurrent atypical chest pain. Outpatient nuclear stress testing had suggested modest but reversible ischemia. Past medical history includes PTSD, depression, anxiety, GERD, hypertension, and hyperlipidemia. Her medications on admission included aripiprazole, furosemide, zolpidem, venlafaxine, ibuprofen, amitriptyline, hydrocodone-acetaminophen, hydrochlorothiazide, metoprolol, and potassium chloride. Review of systems was positive for dyspnea on exertion, chest pain, heartburn, anxiety, depression, and near syncope. Blood pressure was 159/84 mmHg, pulse 69 bpm, and 20 respirations per minute. Exam was normal. Complete blood count, comprehensive metabolic panel, and cardiac enzymes were negative. An admission electrocardiogram showed normal sinus rhythm. Coronary angiography showed no evidence of coronary artery disease with an ejection fraction of 60%. Prior to the patients' transfer to psychiatry, the patient began to have episodes of transient second degree, Type II heart block and near syncope. On further questioning, these episodes occurred only while the patient was swallowing foods of a substantial consistency such as steak or chicken at the time of the telemetry changes. The symptoms were reproducible and the episodes lasted 4-5 seconds each. During these episodes, her blood pressure was 86/59 mmHg, pulse of 65 bpm, oxygen saturation of 95% on room air. The patient reported that she had been having similar episodes while swallowing similar foods at home for some time. Amitriptyline was discontinued and the patient was started on a full liquid diet and symptoms resolved.

Discussion: Discovering a unique etiology to a commonly encountered medical condition such as syncope requires obtaining a good history and physical examination. In this case, telemetry monitoring lead directly to the diagnosis of swallow syncope. An exact mechanism behind swallow syncope is not defined but an exaggerated vagal response leading to cardiovascular inhibition is felt to be largely responsible. Most cases reported have shown some type of esophageal or cardiac abnormality upon further testing. Moreover, the consistency and temperature of the swallowed food appears important. While syncope is a common presenting complaint, swallow syncope is a rare condition that may be discovered with a thorough examination, proper diagnostic work-up, and high level of clinical suspicion.

AN UNUSAL PRESENTATION OF PLATYPNEA-ORTHODEOXIA

Sean Enkiri, MD, University of Virginia Health System, Charlottesville, Virginia

Platypnea-orthodeoxia syndrome is rare and frequently unrecognized. Platypnea refers to dyspnea upon sitting up from a supine position, while orthodeoxia is hypoxemia caused by this same maneuver. The underlying cause is commonly the presence of a shunt whereby deoxygenated blood is introduced into the systemic circulation.

An 87 year-old woman with a history of chronic obstructive pulmonary disease, a stroke and atrial fibrillation presented to her primary care physician complaining of increasingly frequent falls and dyspnea with minimal exertion over the preceding two weeks. The patient was in moderate distress, dyspneic and light-headed. She had an oxygen saturation of 87% on room air while sitting and was subsequently directly admitted to the hospital. When seen by the admitting team however, the patient was in no apparent distress, lying comfortably in bed, with an oxygen saturation of 100% on 2 liters nasal cannula and 99% on room air. Relevant features of her exam included: an irregularly irregular rhythm with a normal rate; lungs that were clear to auscultation; no clubbing or peripheral edema; and a normal neurological exam except for moderate dysmetria, consistent with her prior stroke. When the patient was asked to sit up, she became visibly short of breath and desaturated to 91%. Upon lying supine, her symptoms and hypoxemia abated. The patient was diagnosed with platypnea-othrodeoxia syndrome after standing prompted further desaturation to 80%. Initial work-up was unrevealing except for a chest X-ray that showed a markedly tortuous and ectatic aorta. Eventually a contrasted echocardiogram revealed an intracardiac versus intrapulmonary shunt, present when the patient was standing. A subsequent TEE confirmed the presence of bi-directional shunting across an atrial septal defect in the setting of normal PA pressures. The patient underwent device occlusion of the patent foramen ovale, with lack of residual shunting confirmed during the procedure. The floor team noted resolution of the patient's platypnea-orthodeoxia the following day. She was then discharged and reported no falls or complaints of dyspnea at a follow-up appointment one month later.

It is unusual for a patient to present with a symptomatic intracardiac shunt at such an elderly age. It is even more unusual in a patient without elevated pulmonary arterial pressures to drive blood flow in a right-to-left pattern. Our theory is that the patient's tortuous and dilated aorta was responsible. Upon standing, an abnormally tortuous aorta could conceivably fail to hold the atrial septum in its appropriate anatomical position, causing or permitting inflow turbulence that could allow for a right-to-left shunt without pulmonary arterial hypertension. A literature search revealed that this has never been described in a patient this old, confirming the importance of suspecting an intracardiac shunt for platypnea-orthodeoxia in the elderly - even without pulmonary hypertension.

BRINGING BACK MORE THAN JUST MEMORIES AND PHOTOGRAPHS

Howard Malpass, MD, University of Virginia Health System, Charlottesville, Virginia

A 30-year old female nursing student presented to the student health clinic with two weeks of symptoms including low grade fever, fatigue, daily nausea and emesis, diarrhea, and anorexia resulting in a 10 pound weight loss. Lab tests from that initial visit showed peripheral eosinophilia of 7.7%. Pertinent history included travel six months ago to South Africa and Mozambique for 6 weeks and Spain for one week. She previously had a negative HIV ELISA testing one year ago and since then had been with one partner and had used barrier protection. In addition, she had recently been under a lot of stress associated with her graduate work. Her medications included birth control and she did not take herbal or OTC medications. At that time, the clinic treated her supportively for a viral illness and GERD with a PPI. Over the course of one month, her progressive gastrointestinal symptoms prompted two further visits to student health. Laboratory testing with the first of these two visits showed peripheral eosinophilia of 27.7%, ova and parasite stool testing was negative, H. pylori antibody negative, beta HCG was negative, a comprehensive metabolic panel and lipase were normal, and ascaris antigen was negative. She was referred to a gastroenterologist for presumed eosinophilic esophagitis who preformed an EGD with biopsies which were normal. She continued to have symptoms of daily fevers, nausea, diarrhea, anorexia and weight loss. At her next student health visit tests included a negative Schistosomiasis antibody, stool ova and parasites which was negative, and a Strongyloides IgG antibody which was positive at 2.19. Treatment with Ivermectin was initiated and the patient noted a rapid response with her fever dissipating after 48-hours. Over the next week, the vomiting, diarrhea, and abdominal pain resolved but the patient still had nausea, and anorexia. Due to these persistent symptoms the patient under went a second course of treatment with Ivermectin which resulted in resolution of all symptoms
.
This case illustrates the clinical course of an infection with Strongyloidies stercoralis. The patient most likely acquired the infection while in Africa and through autoinfection the helminth continued to replicate until a period relative immunosuppression through severe stress facilitated a symptomatic infection. Another feature shown by this case is the commonly negative O and P exam of the stool and that this diagnosis must always be considered when a patient has elevated peripheral eosinophilia.

AUTOPSY OF HEART TRANSPLANT RECIPIENTS: WHAT DID WE MISS CLINICALLY?

Nadew S. Sebro, MD, John M. Herre, MD, James F. Paulson, Ph.D, Eastern Virginia Medical School, Norfolk, VA

Background: There is a lack of published post-mortem results in patients who have undergone Orthotopic Heart transplant (OHT)

Objective: Describe post-mortem pathologies after OHT and correlate with clinical data.

Design and method: Retrospective chart review of all OHT recipients, who had post-mortem exams done, at Sentara Norfolk General Hospital.

Results: Subjects: Since 1989, 272 OHT have been performed. To date, 130 (47.8%) have died and 29 (22.3%) had autopsies. The mean age at transplantation was 46.4 +/- SD 12.7yrs; and 49.7 +/- SD 12.6 yrs at the time of death. The average days of survival were 1418.1 +/- SD 1401 days. Twenty-one (72.4%) were Male. The ethnic/racial mix included; white 15 (51.7%), Black 13 (44.8%), and Asian 1(3.4%). Seven (24.1%) were out-of-hospital deaths.

Causes of death: The five most commonly identified causes of death were acute cellular rejection 6 (20.7%), coagulopathy 4(13.8%), pulmonary emboli 3 (10.3 %), graft failure 3 (10.3%), infection 3(10.3 %) and vasculopathy 3(10.3%). The immediate cause of death was correctly identified, before the post-mortem exam, in 15 (51.7%), wrongly assigned in 5 (17.2%) and unknown in 9 (31.0%) of cases.

Of note, the most frequently, 5 (17.2%), misdiagnosed or unknown cause of death was acute cellular rejection, per se or in combination with antibody-mediated.

Rejection: Seventeen patients (58.6%) had rejection of some degree: 6 (20.7%) grade IR, 3 (10.3%) Grade II R and 4 (13.8%) Grade III R. The reported degree of rejection from autopsy and the last endomyocardial biopsy (EMB) before death was congruent in only13 (44.8%) and didn't match in 11 (37.9%) of subjects. The last EMB was taken on average 82.5 days +/- SD 169.2 days prior to death.

Although graft rejection is assumed to be a systemic process and samples are, by default, taken from the right ventricle only, Our autopsy data shows that the degree of rejection found on the left and right ventricle/septum was different,hence underdiagnosed, in 4 (13.8%) of subjects.

Cardiac Allograft Vasculopathy: Fifteen (51.7%) patients had some degree of atherosclerotic lesion in the Epicardial Coronary arteries: 7 (24.1%) mild, 2 (6.9%) Moderate, and 6 (20.7 %) Severe. However, Myocardial ischemia was present only in 9 (31.0%) subjects. Patients who survived beyond 2700 days (7.4 yrs) Post OHT had coronary artery lesion invariably.

Conclusions: Acute cellular rejection remains to be the most frequent immediate cause of death in OHT, and, clinically, the most frequently misdiagnosed pathology. Right ventricular biopsy, current standard of care for detecting rejection, may miss rejection in a significant number of cases

SPINAL CORD BLASTOMYCOSIS IN AN IMMUNOCOMPETENT HOST

Sajid Melvin George, MD, Stephanie Nagy-Agren, MD, Chris Durando, DO, Deepa Lala, MD
VA Medical Center - Salem and Carilion Health System, Roanoke, VA.

Introduction: Blastomycosis is a potentially serious disease caused by dimorphic fungus Blastomyces dermatitidis. We report a case of blastomycosis involving the spinal cord treated successfully with Amphotericin B followed by oral treatment with voriconazole.

Case: A 60 year old caucasian male presented with complaints of bilateral lower extremity weakness and inability to walk. He was recently diagnosed with pulmonary blastomycosis but had not initiated his oral itraconazole. Symptom complex consisted of constipation followed by pain in the inner left thighs and bilateral lower extremity weakness for 2 weeks. Medical history was significant for bilateral lung nodules since 2004, COPD, DM, HTN and Hep C. Worsening of lung nodules on CT scan led to biopsy which showed yeast consistent with blastomycosis on cytology. Pt had a 60 pack year smoking history and marijuana and alcohol use. He worked in fiberglass and golf business, participating in courses of sand excavation in 1970-1990s in Kansas City, Chicago and St Louis. Exam was noted for neurologic deficits including left lower extremity strength 4/5 at hip flexion and knee extension, and 3/5 at plantar flexion bilaterally, decreased sensation to light touch in anterior thighs left > right, absent bilateral ankle jerks. The following assays were negative: cryptococcal antigen, HIV Ab, ANA, RPR, Aspergillus titers, and C-ANCA, P-ANCA and Atypical P-ANCA. Blastomycosis titers were 1:8. Spinal fluid showed protein 30 mg/dL, glucose 49 mg/dl and WBC 1/cmm; fungal cultures, india ink, IgG index, monoclonal band and cytology were all negative. MRI of spine demonstrated 1cm intramedullary and intradural lesions at T10 and T11 levels, respectively. Repeat spinal tap showed no malignant cells. Repeat Ct guided biopsy of lung confirmed blastomycosis on cytology but did not grow the fungus. Neurosurgery suggested that the spinal cord lesions resembled infectious etiology and deferred operative biopsy. The patient was initiated on IV amphotericin B lipid complex. He improved dramatically and gained strength enough to walk with walker. Pt completed one month of IV amphotericin B and was discharged on PO voriconazole 200mg twice daily with complete resolution of symptoms. Pts serial MRI showed regression of size of lesions. Serial CT scan showed mild improvement in lung nodules without complete resolution.

Discussion: CNS involvement of blastomycosis occurs in <5% of immunocompetent individuals, and is most commonly manifested as abscess or meningitis. Focal intramedullary spinal blastomycosis, without surrounding vertebral involvement, is exceedingly rare - only two cases have previously been reported. All CNS Blastomycosis should be initially treated with lipid formulation amphotericin B followed by stepdown therapy with azoles. Voriconazole has excellent CSF penetration and activity against B. dermatiditis. Our patient had spinal cord blastomycosis successfully treated with 4 weeks of lipid Amphotericin B followed by oral voriconazole. Clinical follow-up is ongoing.

TRANSIENT GESTATIONAL DIABETES INSIPIDUS

Olga Kuchmak, MD, James S.Cain, MD, Carilion Health System, Roanoke, Virginia

Gestational Diabetes Insipidus (GDI) is a rare endocrinopathy complicating about 4:100,000 deliveries. Here we describe a case of the patient transferred initially to our hospital for suspected pre-eclamsia.

A 19- year-old AA female G1P0 with past medical history of Asthma and Chlamydia was admitted at 34 wks of pregnancy. On admission patient had vaginal spotting, contractions, +1 proteinuria, her BP was 186/79.She was given magnesium sulfate as a treatment for possible pre-eclamsia. The patient was found to have polydipsia (oral fluid intake about 5,769 cc/day) and polyuria (urine output 8,200 cc/day). Review of systems was remarkable for excessive thirst started early in her pregnancy. Patient's serum osmolality and urine osmolality were 286 mOsm/k (Normal range is 280-295mOsm/k) and 184 mOsm/k (Normal range is 300-1000mOsm/k) respectively. Arginine Vasopressin level was 1.5 pg/ml (Normal range is 1.0- 13.3 pg/ml). She was started on DDAVP with daily monitoring of urine osmolality, which increased to 400-600 mOsm/k in response to the treatment. Patient's daily urinary output diminished as well. On hospital day eight, the patient delivered a live female infant. After delivery, urine osmolality was checked and was normal. DDAVP was discontinued. On a day of discharge oral intake was 980 cc with urine output 1,300cc.

Gestational Diabetes Insipidus (GDI) is a rare transient syndrome presented with polydipsia, polyuria and persistent thirst manifesting in the third trimester of pregnancy. The etiology for GDI is the production and release of vasopressinases (the other name is placental cysteine aminopeptidase) from the placenta causing increased catabolism of ADH. The level of the vasopressinase increases 1,000 fold during pregnancy and its role is not clear. The GDI also might be associated with acute fatty liver of pregnancy and HELPP syndrome when degradation of vasopressinase in liver diminished. Primary polydipsia and head trauma should be excluded. Ingestion of medications such as lithium, mannitol, diuretics and anticholinergics should be questioned. The treatment of choice for GDI is DDAVP. Symptoms usually resolve after delivery. Awareness of the syndrome of transient Gestational Diabetic Insipidus may lead to early diagnosis and appropriate treatment that will reduce the risks of maternal and fetal morbidity.

HUMAN MONOCYTOTROPIC EHRLICHIOSIS: AN ELUSIVE PREDATOR OF WOODLAND AMERICA

Andrew Munro, MD, Rachel Villavicencio, MD, Virginia Commonwealth University, Richmond, Virginia,

Introduction: Human monocytotropic ehrlichiosis (HME) is a rare disease with an incidence of 0.1% in the United States. Symptoms are nonspecific and mimic an acute viral syndrome, presenting a significant diagnostic challenge to the physician. A high index of suspicion should be maintained in endemic areas and in peak seasons for this evasive pathogen and empiric treatment initiated when the clinical presentation is suggestive of infection. Left untreated, HME can cause severe complications and may even be fatal.

Case Presentation: A 59 year-old Caucasian male with no significant previous medical history was admitted for 6 days of chills, fever, drenching night sweats, fatigue, myalgias and arthralgias, nonproductive cough, anorexia, and diarrhea. On admission, the patient's vital signs were 94/67 mmHg, heart rate 100 bpm, respirations 20 per minute, and a temperature of 100.0° F. The patient reported living in a wooded area southwest of Richmond. Notable findings included pancytopenia, elevated transaminases, serum sodium at 127 mmol/L, and the absence of a rash. The patient was started on empiric doxycycline therapy and IV fluids. Overnight, the patient was febrile to 102.8° F concurrent with hypotension (88/52 mmHg), tachycardia, and a new oxygen requirement. Morning labs revealed acute renal failure (creatinine 2.1 mg/dL), leukopenia (2,200, 1% lymphocytes, 39% bands), thombocytopenia (19,000), and elevated transaminases. On physical exam, the patient had a new central maculopapular rash and newly distant heart sounds. His hospitalization was further complicated by bradycardia and infectious cardiomyopathy. A trans-thoracic echocardiogram (TTE) revealed an ejection fraction (EF) of 40% with global hypokinesis. Over the next 48 hours the patient recovered on doxycycline, with vitals stabilizing and normalization of CBC, BMP, and LFT assays. Repeat TTE showed an EF of 55% with normal motility. Several weeks later lab results returned positive for Ehrlichia chaffeensis IgG and IgM antibody titers, confirming the diagnosis of HME.

Discussion: Human monocytotropic ehrlichiosis is caused by Ehrlichia chaffeensis, a tick-borne illness with Amblyomma americanum (the "Lone Star tick") as its specific vector. Infection typically occurs during April through September in the Mid-Atlantic, Southeastern, and southern Midwestern regions of the United States. HME presents with fever, malaise, headache, myalgias, and a maculopapular rash involving the truck and extremities. Laboratory findings may include elevated transaminases, lymphopenia, and thrombocytopenia. In the case presented, definitive diagnosis of HME was not made until after doxycycline was completed; however, had empiric therapy not been started, potential complications might have included toxic shock-like or septic shock-like syndrome, respiratory insufficiency, acute respiratory distress syndrome, and/or meningoencephalitis. The astute clinician will be able to recognize this clinical presentation and act aggressively to avoid complications of this evasive pathogen,
thus avoiding severe complications including death.

University of Virginia Internal Medicine Offices

Cancer Center
434-982-4194

Cardiology Clinic
434-924-5004

Digestive Health Clinic
434-243-6169

Endocrinology Clinic
434-924-0211

Endoscopy Clinic
434-243-6169

Infectious Diseases Clinic
434-924-3627

Infusion Center
434-982-4194

General Medicine, University Medical Associates
434-924-1931

General Medicine, University Physicians
434-924-2472

Geriatrics Clinic, CMA
434-924-1212

Geriatrics Clinic, JABA
434-964-1333

Kidney Center
434-924-1984

Pulmonary Clinic
434-924-5219

Rheumatology Clinic
434-243-0223

Traveler's Clinic
Center for Global Health
434-924-9677

Save the date!

October 28-30, 2009

The 36th Annual

EDWARD W. HOOK. JR., M.D.

Recent Advances in Clinical Medicine Conference

Omni Charlottesville Hotel
Charlottesville, Virginia

Visit: www.cmevillage.com for more information

University of Virginia Health System
University of Virginia
Department of Medicine
P.O. Box 800466
Charlottesville, VA 22908-0466