The Medicine Forum
To Friends of the Department of Medicine:

The Thomas Jefferson University Hospital Internal Medicine Residency Program was informed this past February by the RRC that it has received Continued Accreditation with a 5 year cycle length – the longest cycle length awarded for compliance with essential elements of training in Internal Medicine as mandated by the ACGME. The program’s next visit will be in 2015. This is the third straight highly successful accreditation review for the program and the third straight 5 year cycle awarded.

The success of the recent visit should be attributed to our wonderful housestaff and superb educational organization including:

Our amazing office staff: Joanne Gotto (Education Manager), Debbie Richards (Program Coordinator), Fortune Medeiros (Dr. Kane’s Assistant), and Brenda Merlino.

Our committed Associate and Assistant Program Directors: Drs. Gretchen Diemer, Mark Graham, Sal Mangione, Elisabeth Carr, Jessica Salt, and Donna Williams.

Our talented Chief Residents: Drs. Assis, Moleski, Fisicaro (2008-2009), & Drs. Hess, Patel, Serper, and Nolt (2009-2010), as well as those of prior years.

While those elements are vital; the commitment of our Chairman, Arthur M. Feldman, MD PhD, to the educational mission at Jefferson is the essential ingredient to the training of gifted Internists for careers in academics and patient care. Under his leadership, our clinical programs and research activity have expanded and excelled; creating a fertile environment to support the growth of our students, residents, and fellows. All of our faculty are to be congratulated for their contributions to the education of our trainees, as their work, day in and day out, provides the daily attention necessary for the health of all of our programs.

While accreditation itself is an important goal; the main objective of our program is to train outstanding physicians for practice, research, and education. Achieving full accreditation allows us to pursue many of the innovative programs and projects that truly define the excellence of our Department and our Residents. One such project is the publication of this journal. Our Editors should be proud indeed of the work of their contributors and of their own effort in organizing and editing this edition. It is yet one more way we enhance the educational and academic environment at Jefferson!

Of all the important things we do as academic physicians – the discovery of new scientific knowledge, the conduct of important clinical trials, service to national medical organizations, or the delivery of advanced patient care; contributing to the knowledge and skill of the Internists of Tomorrow is among the most satisfying; given the personal connections we have with our trainees and the future impact of these young physicians in the years ahead. Jefferson’s reputation as a leader in research, patient care, and education continues to grow. The success of our training programs reflects the excellence of the institution and of our human capital.

We hope you’ll enjoy this issue of the Forum and congratulate each of the contributors as they cross your path.

Gregory C. Kane MD, FACP, FCCP
Professor of Medicine
Residency Program Director and Vice-Chairman
Interim Chief, Division of Pulmonary and Critical Care
Department of Medicine
As the Jefferson Forum embarks on its 11th issue a number of additions have been instituted. First, we are proud to announce new faculty collaborators with Dr. Steven Herrine, Dr. Danielle Duffy, Dr. Daniel Frisch, Dr. Anjali Avadhani, Dr. Joseph Desimone and Dr. Edward Ruby.

Our faculty has helped us with creating a new section of outstanding articles that we introduce in this issue. The “Best Of” designation allows us to highlight articles that were chosen by peer and faculty review as the best example of academic work submitted in each field of medicine. We hope that this addition will inspire more residents and faculty to get involved with the journal.

In addition, as residents graduate and embark on their individual academic journeys, we hope they remain connected to the forum by contributing their knowledge and expertise. We believe that in this issue a new level of excellence has been achieved and that could not be accomplished without our outstanding residents. We hope you enjoy this issue and look forward to the next one!
The Jefferson Medicine Forum
The Journal of Thomas Jefferson University Hospital
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*“Jefferson” photograph by Cecilia Kelly, MD*
ACUTE PANCREATITIS WITH NORMAL AMYLASE AND LIPASE

Kichul Ko, MD, Luz Catherine Tello, MD, Jessica Salt, MD

Introduction
Acute pancreatitis is diagnosed by clinical history and physical examination with concurrent elevations in serum amylase and lipase levels; occasionally radiographic findings are of further assistance. We report a case of radiographically proven acute pancreatitis with normal serum amylase and lipase levels.

Case Report
A 35 year old male patient was in his usual state of health until four days prior to presentation when he began experiencing severe epigastric abdominal pain accompanied by nausea and vomiting. On Day 2 of his symptoms, he reported to the emergency department and was discharged home with a diagnosis of viral gastroenteritis. His symptoms worsened causing his return to the emergency department the following day for re-evaluation. The patient’s past medical history included recently diagnosed diabetes mellitus type 2 and gastroesophageal reflux disease (GERD). His medications included metformin and esomeprazole which he took for the first time on Day 1 of symptom onset and did not continue taking secondary to severe nausea and vomiting. He had no known drug allergies. He reported occasional use of alcohol with the last use about two months prior to this presentation. He smoked one and a half packs of cigarettes per day for 14 years. He denied any past or present illicit substance use. He reported no personal or family history of pancreatitis.

His admission laboratory findings were: WBC count 19.8 x 10^9/L with 11% bands, hemoglobin 13.3 g/dL, platelets 282 x 10^9/L, creatinine 1.1 mg/dL, aspartate aminotransferase 16 IU/L, alanine aminotransferase 24 IU/L, alkaline phosphatase 78 IU/L, lactate 23.1 mg/dL, triglyceride 1195 mg/dL, amylase 17 IU/L (normal <132) and lipase 25 IU/dL (normal <52). A CT scan of the abdomen revealed diffuse fatty liver infiltration, homogenously enhancing pancreas and significant peripancreatic infiltration with surrounding fluid consistent with a diagnosis of acute pancreatitis. The patient was diagnosed with acute pancreatitis secondary to chronic pancreatitis. It also showed gallstones with no ductal dilation. The abdominal ultrasound showed cholelithiasis with no evidence of cholecystitis.

Based on the clinical presentation and radiographic findings, the patient was diagnosed with acute pancreatitis secondary to hypertriglyceridemia. He was treated with bowel rest, hydration, and pain control. The patient was also found to have pneumonia which was treated with moxifloxacin. Gemfibrozil and simvastatin were added for his dyslipidemia. His symptoms continued to improve during the hospital course and he was discharged on Day 7 with medications for pain control, dyslipidemia, diabetes, GERD and pneumonia.

Discussion
The diagnosis of acute pancreatitis is made based on relevant clinical features including severe abdominal pain, nausea, vomiting and elevation of pancreatic enzymes with serum amylase and/or lipase levels usually three times the upper limit of normal. Abdominal imaging with CT, magnetic resonance imaging (MRI), or transabdominal ultrasonograph (US) can be helpful in confirming the diagnosis of pancreatitis or ruling out other etiologies of acute abdominal pain that may cause mild elevations of serum pancreatic enzymes.

Lipase is a 48 kD pancreatic enzyme that is involved in digestion. Lipase level increases within four to eight hours of acute pancreatitis, peaks at 24 hours, and remains elevated for one to two weeks, typically longer than amylase levels. Lipase is more sensitive and specific than amylase in diagnosing acute pancreatitis, with a negative predictive value of 94% to 100%. Therefore, normal lipase level in the setting of acute abdominal pain is often used to rule out a diagnosis of acute pancreatitis. Our patient was admitted with a clinical picture and radiographic findings consistent with acute pancreatitis despite normal lipase and amylase levels throughout the hospital course. In the case of our patient, the etiology of acute pancreatitis was hypertriglyceridemia. Previous studies suggested that the hyperlipemic serum may interfere with the amylase assay in vitro leading to false negative results. However, there have been no previous reports on the effect of serum triglyceride on lipase level analysis. A literature search yielded two cases of symptomatic acute pancreatitis with normal lipase levels similar to our patient, however, neither reported the likely etiology for acute pancreatitis. While it is possible that this presentation was an acute-on-chronic attack secondary to longstanding pancreatitis caused by hypertriglyceridemia, this is an unlikely explanation based on clinical and radiographic findings. This was the first reported symptomatic occurrence of pancreatitis in this patient and the radiographic findings did not reveal calcifications or fibrosis in the pancreas that is commonly associated with chronic pancreatitis.

This is an unusual case of acute pancreatitis with normal amylase and lipase levels in the setting of hypertriglyceridemia. This case highlights that while laboratory findings are useful diagnostic criteria, the absence of such findings should not replace clinical judgment used in formulating most appropriate diagnosis.

References
Perioperative Beta-Blockers: Where do we stand?
Li Shien Low, MD, Jennifer Heckman, MS III, Matthew DeCaro, MD

Introduction
Cardiovascular disease is a significant cause of morbidity and the leading cause of mortality in both the United States and worldwide.1,2 Given the considerable burden of disease, cardiac risk assessment is an especially important element of preoperative evaluation prior to noncardiac general surgery.3 Globally, an estimated 100 million adults undergo noncardiac surgery each year,4 more than one third of whom have underlying coronary artery disease (CAD).5 Cardiac complications, including cardiac death, nonfatal myocardial infarction (MI), and nonfatal cardiac arrest, represent major causes of peri- and postoperative morbidity and mortality.6 The incidence of such cardiac complications is an estimated 1.4% in relatively unselected patients,7 with an even greater incidence (2.4 – 5.8%) among those with or at risk of cardiac disease.8,9,10,11,12,13 Annually, more than one million patients are likely to experience such a complication.6 The magnitude of this problem can be measured not only in patient health outcomes and illness burden, but also in terms of the large cost subsequently imposed upon the healthcare system, especially as the number of noncardiac surgical patients at risk for adverse cardiac outcomes continues to increase.14

A common underlying pathophysiology posited to mediate perioperative myocardial infarctions is atherosclerotic plaque disruption, which leads to coronary vessel obstruction,15 as well as prolonged ischemia.16 Perioperative myocardial ischemia is a consequence of an exaggerated sympathetic response, evidenced by increased myocardial oxygen demand and decreased coronary diastolic filling time (secondary to increases in heart rate and contractility caused by physiologic stress and elevated catecholamine levels).17

The exact mechanism by which beta-blockers reduce perioperative cardiac complications remains unclear. It has been proposed that through attenuation of the sympathetic response, with the major effects of reduction in heart rate (leading to increased perfusion time) and contractility (leading to decreased oxygen demand), perioperative beta-blockade results in a reduction in both cardiac caused mortality and the incidence of cardiovascular complications.18 Another hypothesis is that it is optimal heart rate control, rather than a specific agent, that is associated with a decline in ischemic events, as cardiac damage often results from inadequate myocardial blood flow.16 Additional potential cardiovascular effects of perioperative beta blockade include “vulnerable” coronary plaque stabilization and dysrhythmia prophylaxis.19

Perioperative Beta-Blockade: Evolution of the Evidence
Initial randomized trials, including the landmark study on which the original 1996 American College of Cardiology/American Heart Association (ACC/AHA) recommendations20 were based, suggested that beta-blockers reduce perioperative ischemia in patients with underlying arterial disease.18 Mangano et al18 performed a randomized, double-blind, placebo-controlled study comparing the effects of atenolol with those of a placebo on overall survival and cardiovascular morbidity in individuals undergoing noncardiac surgery with coronary artery disease (history of MI, typical angina, or atypical angina with positive stress test result) or risk factors for coronary artery disease (≥2 of the following: age >65 years, hypertension, current smoker, cholesterol level >240 mg/dL, or diabetes). Results of this study of 200 patients demonstrated that, in this population, perioperative atenolol (administered intravenously 30 minutes prior to surgery and continued by mouth throughout the hospital stay for up to 7 days) significantly reduced overall mortality and incidence of cardiovascular complications for as long as two years following discharge, with the primary effect identified as a decrease in mortality from cardiac causes during the first six to eight months. Atenolol administration, however, did not significantly reduce cardiac causes of mortality during hospitalization or incidence of perioperative MI. This lack of effect of atenolol in the perioperative period, however, may have been a result of the low incidence of significant perioperative cardiac events among study population patients, thus demonstrating a potential limitation of the study.

Subsequent research continued to contribute to a mounting body of evidence supporting perioperative beta-blockade in patients undergoing noncardiac surgery at high risk for adverse cardiac outcomes. In 1999, the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) Study Group21 reported a randomized, non-blinded, placebo-controlled, multi-center trial examining the effect of bisoprolol on perioperative mortality and myocardial infarction in a subgroup of high-risk patients undergoing vascular surgery. High-risk patients were identified by the presence of both clinical risk factors and dobutamine stress echocardiography results positive for ischemia. Subjects were randomized and treatment group patients received standard perioperative care plus bisoprolol (initial dose at least one week prior to surgery and continued for thirty days postoperatively, with subsequent dosing individually adjusted by physician based on heart rate). Study endpoints were defined as cardiac death and myocardial infarction. A majority of the adverse cardiac events in both groups occurred during the first seven days following surgery. Overall study findings indicated a reduction in perioperative incidence of cardiac causes of mortality and nonfatal MI with the perioperative administration of bisoprolol. Despite the lack of significant clinical and echocardiogram differences between the standard care and treatment groups, the combined incidence of cardiac events in the standard care group was 34%, compared to 3.4% in the bisoprolol group. This striking difference demonstrated a substantial benefit to treatment,
significant enough to cause the investigation safety committee to suspend the study.

Based on investigation results, the DECREASE Study Group recommended that high-risk surgical patients receive beta-blockers perioperatively, with initiation one to two weeks preoperatively and continuation for at least two weeks postoperatively, with a goal of heart rate reduction to <70 beats/minute preoperatively and <80 beats/minute in the immediate postoperative period. Investigators also suggested a potential alternative approach to standard preoperative management, proposing exclusion of preoperative non-invasive cardiac testing and replacement with prescription of perioperative beta-blockade for all patients with clinical risk factors undergoing high-risk surgery. Major limitations of this study were the fact that it was not blinded, thus allowing for potential bias and reporting error, and its focus only on a specific subpopulation.

Prevention of perioperative morbidity and mortality is not the only consideration in the initial preoperative evaluation of a patient. Also important is the assurance of long-term future survival. As such, a related, follow-up study by the DECREASE Study Group assessed the long-term cardioprotective effects of perioperative and prolonged postoperative beta-adrenergic blockade with bisoprolol in the same, randomized cohort of high-risk patients following successful major noncardiac vascular surgery. Again, study treatment dosage was adjusted by physicians based on prescribed heart rate guidelines. Two-year follow-up was complete in all patients, monitoring for the occurrence of late cardiac events, including cardiac death and myocardial infarction. With no significant differences in clinical characteristic between the treatment and control groups, combined perioperative and long-term postoperative bisoprolol administration resulted in a significant, three-fold decrease in the incidence of late cardiac death and MI among high-risk patients after surviving major vascular surgery. However, similar to the previous study, patients and physicians were not blinded to the treatment. In addition, pre-trial risk of cardiac events in the two study groups may not have been comparable; the standard treatment group included survivors of perioperative MI, who may have consequently been at increased risk of late cardiac events during follow-up, and elevated incidence of perioperative mortality in the standard treatment group may also have eliminated the highest risk patients in this group.

Further trials evaluating the use of perioperative beta-blockers in patients undergoing noncardiac surgery did not produce favorable results, which challenges their efficacy and safety. Randomized controlled trials, including the Diabetic Postoperative Mortality and Morbidity (DIPOM) trial and the Metoprolol after Vascular Surgery (MaVS) study, demonstrated a lack of benefit of perioperative beta-blockade among specific patient populations, though there were limitations in the designs of these trials. More notably, the recent POISE trial, a large, multinational, multicenter, randomized, double-blind, placebo-controlled trial, was conducted to investigate the effects of perioperative beta-blockers in patients with risks for atherosclerosis or known atherosclerosis undergoing noncardiac surgery. Patients were randomized to receive either placebo or extended-release metoprolol succinate, which was initiated two to four hours prior to surgery and continued for 30 days postoperatively. Intention to treat analysis was conducted on a population of 8351 patients, and the primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest. At follow-up 30 days postoperatively, while significantly fewer treatment group patients reached the primary endpoint (an outcome driven entirely by a significant reduction in MI among treated patients), the incidences of both death and stroke were significantly greater in the metoprolol group. Though other factors may be responsible, investigators associated these findings primarily to the clinically significant hypotension and bradyarrhythmia associated with beta-blockade. Subsequent meta-analyses of trials of perioperative beta-blockers including POISE revealed some similarities in results and consistency with POISE findings. Meta-analyses demonstrated a risk reduction in non-fatal MI with beta-blockade, but also suggested an increased risk of death and non-fatal stroke with use of perioperative beta-blockers.

The POISE study represents the largest trial conducted to date addressing perioperative beta-blockers in patients undergoing noncardiac surgery. It is important to recognize, however, that this study too has its limitations. This trial utilized a very high and fixed dose of metoprolol (initial dose 2-8 times the commonly prescribed dose with no adjustment for heart rate). Additionally, therapy was initiated shortly (only hours) before surgery. Also of note is that in all of the meta-analyses conducted, POISE data accounted for approximately 80% of the patients. Results do, however, underscore the potential risks underlying the assumption that perioperative beta-blockade is beneficial and without harm.

Evidence Limitations
The role of beta-blockers in the perioperative setting is not yet clearly defined. Few randomized trials of medical therapy to prevent major perioperative adverse cardiac events have been performed, and most trials do not have sufficient power. Despite evidence from some trials demonstrating the potential benefit of perioperative beta-blockade in high-risk patients, much controversy still surrounds their use, especially given the methodological limitations of prior studies. No single agent, dose, route of administration, dosing schedule, or duration of treatment has been shown to be most effective. In addition, few studies have examined the effect of titration of therapy (i.e., to a target heart rate). Other controversial issues include the use of long- versus short-acting agents, effects of beta-blockade in patients on chronic beta-blocker therapy prior to surgery versus...
beta-blocker naive patients, and genetic variability in response to beta-blockade. Future research should aim to identify the optimal beta-blocking agent as well as define the role of perioperative beta-blockade in intermediate- and low-risk populations. To date, no literature has addressed the important topic of care-delivery mechanisms in the perioperative setting, identifying how, when, and by whom perioperative beta-blocker therapy should be implemented and monitored. More evidence is needed to corroborate the findings of previous studies and provide future direction. Further study will contribute to improved understanding, elucidation of these issues, and better clinical application of the available data.

Current Guidelines
While POISE trial investigators concluded a need for revision of the approach to the use of perioperative beta-blockers, current ACC/AHA guidelines, published in 2006, which include a focused update on perioperative beta-blocker therapy, still endorse a relatively wide indication for perioperative beta-blockade. Class I recommendations include: 1) continuation of beta-blockers in patients undergoing surgery who are prescribed beta-blocker therapy for angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications, and 2) administration of beta-blockers to patients undergoing vascular surgery at high cardiac risk with ischemia on preoperative testing. In addition, based on Class Ila recommendations, beta-blockers are probably recommended for 1) patients undergoing vascular surgery with evidence of coronary heart disease on preoperative testing, 2) patients in whom preoperative evaluation for vascular surgery identifies high cardiac risk, and 3) patients in whom preoperative assessment identifies coronary heart disease or high cardiac risk and who are undergoing intermediate- to high-risk procedures. According to Class IIb recommendations, beta-blockade may also be considered for 1) patients who are undergoing intermediate- or high-risk procedures in whom a single clinical cardiac risk factor is identified preoperatively, and 2) patients undergoing vascular surgery with low cardiac risk not currently on beta-blockers.

Though an approach to documenting cardiac risk different from the AHA/ACC guidelines, the Revised Cardiac Risk Index (RCRI)7 is another extensively tested and accurate estimate of risk that can be utilized to guide care. The RCRI accounts for six variables: 1) high risk type of surgery, 2) ischemic heart disease, 3) history of congestive heart failure, 4) history of cerebrovascular disease, 5) insulin-dependent diabetes mellitus, and 6) chronic renal insufficiency (preoperative serum creatinine >2.0 mg/dL). Based on this method of preoperative risk stratification, subsequent risk of major cardiac complications with noncardiac surgery is estimated as illustrated in Figure 1, with and without beta-blocker therapy.28

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Where Do We Go From Here?
What, then, are the consequences of the results of the POISE trial for the use of perioperative beta-blockers in clinical practice? In using the treatment regimen outlined by the DECREASE Study Group, a low-dose, long-acting agent titrated to effect at least 7 days prior to surgery, a greater overall benefit to perioperative beta-blockade is seen as compared to risk. The POISE trial, however, demonstrates that acute administration of high-dose beta-blocker therapy may be associated with greater risk than benefit. Given all of the data, we do not believe that the evidence supports the initiation of prophylactic perioperative beta-blocker therapy in low- to intermediate risk patients (RCRI <2) undergoing noncardiac surgery. While beta-blockers do appear to decrease the risk of perioperative MI, the observed increases in the rates of stroke and mortality likely outweigh this benefit. A majority of the myocardial infarctions will be asymptomatic, but a few will result in serious complications in the perioperative period. In contrast, most strokes will be seriously disabling or incapacitating. However, perioperative beta-blockade still likely has significant cardioprotective effects in high-risk patients (RCRI ≥3) or patients with evidence of significant ischemia by preoperative evaluation. In these patients, use of a beta-blocker perioperatively, with possible continuation in the postoperative period seems most prudent, with additional consideration for whether the patient is on chronic beta-blocker therapy prior to surgery or is beta-blocker naive. Beta-blockers should be started orally, if possible even weeks prior to the scheduled date of surgery to allow gradual up-titration of the dosage to achieve optimal heart rate and blood pressure control.

Conclusion
Cardiac complications of noncardiac surgery result in substantial morbidity and mortality, posing a serious health problem, whose magnitude only threatens to increase as the incidence of CAD rises and the population ages. As such, an accurate tool for cardiac risk assessment as well as sound guidelines for the subsequent prevention of such adverse outcomes is essential in moving forward. In select patients, perioperative beta-blockade may provide a safe and effective method of cardioprotection. However, it is crucial to highlight that as per the POISE trial, initiating perioperative beta-blockade is not without its own set of complications. Therefore, identification of the appropriate target population, avoidance of the adverse outcomes of such drugs, and future research aimed at characterizing the
appropriate therapeutic regimen are needed in order to achieve the goal of reduced morbidity and mortality.

References
A Case of an Atypical, Community Acquired Pneumonia: A Case Summary and Topic Review

David P. Cork MS IV, Joanne Kim MD, Jie Cui, MD

Case Report
A 59 year old gentleman with a past medical history of hypertension, hyperlipidemia, anxiety, depression, arthritis, and hypothyroidism presented with a five day history of fever to 102º F. He complained of a three-day history of nausea, vomiting, and non-bloody, loose diarrhea, all of which had been persistent and worsening over the past week. Over the past two days, the patient had felt short of breath, and presented in a state of severe dyspnea. He had experienced an indolent course of illness, but was now concerned with his tachynpea and wheezing, and he had developed a productive cough with a small amount of yellow-brown sputum. He denied any hemoptysis as well as recent travel or sick contacts. On admission, the patient was taking hydrochlorothiazide, lisinopril, atorvastatin, levothyroxine and fluoxetine. He was also using over-the-counter ibuprofen for arthritic pain.

The patient was a smoker with a ten pack-year history. He denied intravenous drug use and occasionally drank alcohol. Family history was significant for paternal obstructive lung disease and coronary artery disease. On review of systems, the patient denied having a sore throat or any nasal congestion.

Vital signs upon presentation were temperature 101.0º F, pulse 110 beats per minute, respiratory rate 40 breaths per minute, blood pressure 125/68 mmHg, and pulse oximetry of 86% on a non-rebreather mask. Upon physical examination, the patient was in moderate respiratory distress and unable to talk in complete sentences. He appeared mildly confused, but was awake, alert, and oriented. Jugular venous distention was not recognized. His cardiovascular exam was significant for tachycardia, but was without murmurs, rubs, or gallops. His pulmonary exam demonstrated coarse breath sounds bilaterally with diffuse, rhonchi throughout all lung fields. His abdomen was soft, mildly distended with moderate obesity, and was without hepatosplenomegaly. He had no lower extremity edema and his musculoskeletal exam was grossly normal. His skin was warm and moist, with good capillary refill (<2 sec).

Laboratory studies upon admission demonstrated electrolyte abnormalities, including a sodium of 125 mmol/L, chloride of 91 mmol/L, blood urea nitrogen of 83 mmol/L and creatinine of 5.6 mmol/L. His complete blood count was within normal limits. Blood gas demonstrated a pH of 7.22 carbon dioxide pressure of 45 mmHg, and oxygen pressure of 69 mmHg. Cardiac enzymes were negative and brain natriuretic peptide was 43.9 ng/L. His coagulation studies were within normal limits, as was his thyroid stimulating hormone. A urinalysis showed a slightly cloudy specimen with mild proteinuria. Clostridium difficile antigen was negative.

Figure 1. Imaging upon admission
Chest x-ray – A bilateral infiltrative process is seen consuming the majority of the right lung.

Figure 2. CT Chest without contrast – As the images move superiorly to inferiorly, note the dense consolidation of the right upper and lower lobes, as well as the groundglass appearance to the infiltrative process of the left upper lobe.
The patient was intubated in the Emergency Department due to severe dyspnea, hypoxia, and respiratory failure. Blood, urine and stool cultures were obtained. The patient was started on empiric antibiotic coverage for signs of possible systemic inflammatory response system with consolidative pneumonia with piperccillin-tazobactam, vancomycin, and azithromycin. Given the patient’s history of diarrhea, dyspnea, mild confusion, and hyponatremia, a Legionella urine antigen was also sent. The patient was admitted to the medical Intensive Care Unit, and nephrology and infectious disease services were consulted.

The patient’s urine Legionella antibody assay returned positive, and antibiotic coverage was then narrowed to azithromycin. Treatment was planned for 21 days. After nine days of ventilatory support, the patient was weaned and extubated without complication. Upon questioning, the patient explained that he had recently been working to remodel his bathroom, including removing a finished bath tub which was designed to lay a top the previous tub. The oldest tub was full of stagnate water which had been pooled there for approximately six months before this planned bathroom remodel. This added a potential source of Legionella infection to the overall clinical story.

Introduction to Legionella and Legionnaire’s Disease

Background
First identified in Philadelphia in 1976, Legionella has become recognized as a common atypical pathogen. Legionella is ubiquitous and classified as a fastidious gram-negative coccobacilli, representing a genus with over fifty subgroups. L. pneumophila comprises at least sixteen different subgroups, many of which require very specific culture growth media. Legionellosis refers to two clinical syndromes caused by the genus Legionella: 1) Legionnaire’s disease, a syndrome of pneumonia, and 2) Pontiac fever, an acute febrile illness that tends to be self-limited in nature.

Epidemiology
Legionella is noted as one of the top four causes of community acquired pneumonia (CAP) amongst the immunocompromised population, and is a common culprit of hospital-associated pneumonia. In fact, the incidence of Legionella as a cause of sporadic community-acquired pneumonia ranges from 2-15% of all cases requiring admission to a hospital.

Transmission of Disease
Transmission of Legionella is accomplished by way of aerosol inhalation or by micro-aspiration of water contaminated with the organism. Cooling towers, ultrasonic mist machines such as those used by grocery stores, respiratory equipment, and whirlpool baths have been commonly cited as vectors for disease transmission. Water distribution systems in nursing homes, workplaces, and private residences have each been implicated as primary sources of Legionellosis. Indeed, potable water sources have been associated with numerous reports of Legionella infection. The species L. pneumophila is capable of infecting and replicating in various protozoa found in soil and water, and may have increased virulence if replication occurs within amoeba. Due to L. pneumophila’s virulence, Legionella pneumonia is recognized as manifesting a more severe pneumonia than other bacteria commonly associated with CAP.

The group of atypical CAP represents systemic infectious diseases that can primarily or secondarily infect the lungs. Atypical CAP differs from CAP in the way the specific bacteria infect host cells. Atypical bacteria are facultative intracellular organisms most susceptible to tetracyclines, macrolides, or quinolones. Indeed, Legionella species are capable of exponential multiplication within human monocytes and alveolar macrophages. An intact cellular immune response is thus necessary to inhibit intracellular replication, with use of activated macrophage and monocyte cell-mediated immunity. Patients with immune-suppression have neutrophil ingestion of the organisms after complement and antibody have targeted the organism, but often are unable to effectively kill the bacteria. Typical pneumonias more commonly are comprised of organisms that invade interstitial spaces between cells and trigger neutrophil activation with cytokine release, thereby activating a generalized and immediate immune response.

Risk Factors and Disease Manifestations
Underlying disease is a major risk factor for acquisition of this disease. The risk factors most commonly implicated are cigarette smoking, chronic lung disease, and immunosuppression. Severely immunocompromised patients are said to fare worse in terms of disease severity, which may include lung abscess and bacteremia. They are also at risk for extra-pulmonary infections including sinusitis, pancreatitis, peritonitis, pyelonephritis, and most commonly, cardiac manifestations such as myocarditis.
pericarditis, postcardiotomy syndrome, and endocarditis (Table 1). Nasogastric tubes have been implicated as sources of nosocomial legionellosis as well. Also, patients who have recently undergone head and neck surgery, and therefore are susceptible to aspiration, have been noted as an at-risk population. Common clinical features of community-acquired pneumonias include: cough, fever, pleuritic chest pain, sputum production, and dyspnea. Scant sputum production is more typical of atypical community-acquired pneumonias, whereas typical pneumonias contracted within the community are more commonly characterized by mucopurulent sputum production.

Differential Diagnosis
- Chlamydia pneumonia
- Mycoplasma pneumonia
- Fungal pneumonia
- Viral pneumonia
- Q Fever
- Psittacosis

Owing to its potential degree of severity and its resistance to beta-lactam antibiotic therapy, Legionella represents the most important nonzoonotic CAP pathogen to differentiate from CAP pathogens. With observation of commonalities amongst patients infected with Legionella, it is possible to make presumptive diagnoses based on clinical presentation. Therefore, it is important to keep in mind the following differentiating features frequently seen with Legionella infection when narrowing a differential diagnosis:

a. relative bradycardia in the context of a febrile illness
   1. limits diagnosis to Legionella, Q fever, and psittacosis
b. unexplained mental confusion, including cerebellar ataxia
c. loose, watery stools

Clinical Diagnosis
Pneumonia is the predominant clinical syndrome. The disease may represent a broad spectrum of illnesses though, ranging from mild cough to respiratory failure. Typically seen early in the disease course are non-specific symptoms and signs such as fever, malaise, myalgias, headache, and anorexia. Cough tends to be only slightly productive, and temperature commonly exceeds 104°F. Diarrhea may be seen in approximately 25% of cases, with complaints of watery rather than bloody stools; loose, watery diarrhea was reported in approximately 6% of other types of community-acquired pneumonias. Other common characteristic findings are relative bradycardia, which is most common among the elderly or those with advanced disease states and hyponatremia (serum sodium levels less than 130 mg/dL). Additionally, in patients demonstrating an increased cold agglutinin titer, which is commonly checked for suspected mycosplasma infections, the diagnosis of Legionella pneumonia is essentially ruled out. Due to the variance in severity of disease, as well as specialized lab tests required to confirm the diagnosis, Legionellosis is often underdiagnosed.

The most important test for Legionnaire’s disease is the isolation of the organism by culture on buffered charcoal yeast extract. Obtaining adequate sputum for culture can often be problematic in these patients however. When Legionnaire’s is considered or suspected, a urine antigen test, Legionella culture, and a direct fluorescent antibody (DFA) staining from sputum or tissues should be considered. Indirect immunofluorescence assay (IFA) and/or enzyme-linked immunosorbent assay (ELISA) are also possible, but are not as useful in clinical decision making, as increased titers over four to eight weeks are required for confirmatory diagnoses (a fourfold rise in the titer of serum IgG antibody to \textit{L. pneumophila} with final titer of at least 1/128 is commonly considered positive). The urine antigen test is an enzyme immunoassay with sensitivity of approximately 70%, and nearly 100% sensitivity; this test however applies to \textit{L. pneumophila} serotype 1, which represents only 80-90% of Legionella infections. In contrast, the DFA test (sensitivity 33-68%, specificity 99-100%) can be performed in a manner of a few hours. ELISA tests are generally preferred over IFA tests nowadays, due to reportedly improved sensitivities (80% and 70%, respectively). Unfortunately this type of serum testing also lacks sensitivity for detecting serotypes other than serotype 1, as with the urine tests.

Treatment
Quinolones or doxycycline remain first-line therapy. Delay in initiation of treatment significantly increases mortality.
Treatment duration is two weeks with quinolones, or two to four weeks with other antibiotics. Another treatment option is macrolides, however there is variability between drug efficacy in this class for eradicating Legionella. For instance, erythromycin has been associated with therapy failures. Other macrolides, such as azithromycin are said to have better in vitro activity and improved pulmonary tissue penetration. Overall, quinolones have improved in vitro activity and intracellular penetration compared to macrolides. In patients who are severely ill, rifampin is recommended as an adjunct in combination therapy with a macrolide or quinolone, as it has high levels of activity against Legionella. Imipenem, trimethoprim-sulfamethoxazole, and clindamycin have all been proven efficacious for the treatment of Legionella pneumonia.

Treatment initiation exist, and in nosocomial or large outbreaks. Decreasing mortality trends have been noted recently due to increased awareness and consideration of the disease as a possible infectious etiology.

Prognosis

Patients with Legionnaire’s Disease usually experience symptomatic improvement within three to five days if treated early with an effective antibiotic. With early treatment and appropriate drug choice, the mortality rate for immunocompromised patients approaches that of immuno-competent patients. However, mortality can vary widely and is noted to be as high as 80% in cases, particularly in patients with underlying disease where lack of prompt recognition and treatment initiation exist, and in nosocomial or large outbreaks. Decreasing mortality trends have been noted recently due to increased awareness and consideration of the disease as a possible infectious etiology.

References

**ACQUIRED HEMOPHILIA A: A CASE REPORT**

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**Case Report**

A 61-year-old African American male, with a past medical history of asthma and benign prostatic hypertrophy, presented from an outside hospital with complaints of hematuria and hematemesis. He had initially noted increased bruising two months prior to admission. He also had symptoms suggestive of a non-traumatic thigh hemATOMA the month prior. He developed hematuria one month prior to admission and underwent an outpatient cystoscopy one week prior to admission which was non-diagnostic. Cystoscopy was repeated on the day of admission localizing the hemorrhage to his right kidney with a biopsy specimen suggesting a low-grade papillary neoplasm. The patient subsequently developed hematemesis. Emergent esophageogastrroduodenoscopy (EGD) at the outside hospital revealed a Mallory-Weiss tear. Epinephrine was injected with initial hemostasis. EGD was repeated after transfer due to recurrent hematemesis and clips were placed to control the hemorrhage. The patient experienced continued hematuria requiring repeat cystoscopy with laser ablation, as well as biopsy of the right ureter and right mid-pole infundibulum. However, multiple repeated biopsies failed to confirm the presence of malignancy.

On admission, he was afebrile, with a heart rate of 94 bpm, blood pressure of 142/88mm Hg, and oxygen saturation of 100% on room air. His physical exam was within normal limits. His initial hemoglobin was 7.6 g/dL, white blood cell count of 9,700 cells per cubic millimeter (cmm), and platelet count 138,000 cells per cubic millimeter. Coagulation studies revealed an elevated activated partial thromboplastin time (aPTT) of 76.5 seconds. An aPTT mixing study was performed with the aPTT correcting to 34.9 seconds (normal 23.6-35 seconds). Incubation was not performed. Additional laboratory evaluation demonstrated factor VIII <0.01 U/ml (normal 0.52-1.43 U/ml) and a factor VIII antibody was detected with a measured titer of 33.3 Bethesda Units (BU). Von Willebrand antigen and activity levels were in the normal ranges.

Given the undetectable Factor VIII level, lack of prior history of a bleeding diathesis, and the presence of an inhibitor with a high titer level, a diagnosis of Acquired Hemophilia A (AHA) was made.

The initial management strategy was to control the acute bleeding and eradicate the inhibitor. Hemostasis was initially obtained with recombinant Factor VIIa (rFVIIa) at 90mcg/kg every 3-4 hours episodically for major bleeding for 6-12 hours and prior to planned invasive procedures. However due to a decrease in clinical response during the admission, it was switched to activated Prothrombin Complex Concentrate (aPCC), specifically factor eight inhibitor bypass activity (FEIBA).

Immunosuppression was initiated with 60 mg of prednisone daily. He continued to experience severe hematuria requiring continuous bladder irrigation and multiple cystoscopies for clot evacuation and laser fulguration. Five days after initiation of prednisone, the patient failed to show significant clinical improvement, which warranted replacement with another type of immunosuppressive therapy. Pulsed high-dose dexamethasone 40 mg (Dex) and Rituximab were administered for a period of four days. However, the patient had a grade 4 reaction to the Rituximab consistent with anaphylaxis requiring cessation of the treatment. He then received intravenous immunoglobulin (IVIG) for two days without any clinical response.

Given his inadequate response to standard and high dose steroids and IVIG, and a factor VIII level of 2% with an inhibitor titer of 40 BU, oral cyclosporine was initiated on hospital day 22 and titrated to maintain a therapeutic goal of 200-400ng/ml. His hematuria gradually improved, and he required no further transfusions.

Over the course of his 36-day hospitalization he received a total of 22 units of pRBC, 9 units of FFP, 34 doses of rFVIIa, and 6 doses of FEIBA. He was discharged on a therapeutic dose of oral cyclosporine with a Factor VIII level of 4% and an inhibitor titer of 57.1 BU at the time of discharge (Graph 1).

He was evaluated weekly following discharge during which he did not have any major hemorrhage. His cyclosporine dose was titrated based on trough levels. He continued pulsed, high-dose dexamethasone for 4 consecutive days every 28 days. His Factor VIII level demonstrated gradual improvement during this period and inhibitor levels gradually decreased. Following the fourth cycle of high-dose dexamethasone, his Factor VIII level rose to 29% and his inhibitor level became undetectable. Dexamethasone was discontinued following the fourth cycle after obtaining an undetectable inhibitor level. Cyclosporine weaning was initiated following two consecutive factor levels greater than 80%.

**Discussion**

Acquired Hemophilia A (AHA) is a rare condition in which autoantibodies, usually of the IgG class, are produced against Factor VIII. This results in low plasma Factor VIII levels. Its incidence ranges from 0.2-4 cases/million/year according to various reports. However, given the complexity of diagnosis, the condition may be under diagnosed. The incidence increases with age with a peak incidence in the 7th and 8th decade of life. There is a small peak in the 3rd decade likely corresponding to postpartum inhibitors. The mortality rate is high, ranging from 8%-22%. This is related to severe hemorrhage that can occur in 85%-90% of the patients. Approximately half of the cases are associated with underlying conditions including pregnancy, autoimmune disorders, malignancy, medications, dermatologic conditions, inflammatory bowel disease, and
infections such as hepatitis B and C. The other half occur without evidence of a coexisting disorder (idiopathic). 3,6,7,8,9,10

This condition commonly presents with mucosal bleeding (including epistaxis, gastrointestinal, and genitourinary), ecchymosis, and soft tissue hemorrhage including retroperitoneal bleeding. In contrast to congenital Hemophilia A, hemarthrosis is rare.3,4

The diagnosis is confirmed by detection of a prolonged aPTT which does not correct by 1:1 mixing with normal plasma (aPTT mixing study). Occasionally, there is immediate correction but after incubation for 2 hours at 37°C there is reversal of the correction. Factor VIII levels are markedly reduced, and anti-FVIII antibodies are detectable.

The primary goals of treatment for AHA are to control acute bleeding and to suppress the autoantibody. Antibody eradication often requires treatment of the instigating condition when present. AHA can represent a transfusion emergency requiring intensive transfusion support.13 In patients with high titer inhibitors (>5 BU), bypassing agents, such as FEIBA and rVIIa, are the mainstay of therapy for acute hemorrhage.21 The recommended dose of FEIBA, ranges between 50–100 U/kg administered every 6–12 hours, not to exceed a single dose of 100 U/kg or a daily dose of 200 U/kg.3,14,15,16 In one study, FEIBA controlled hemorrhage in 86% of patients.14 The recommended dose of rVIIa ranges from 90 to 120 mcg/kg every 2–3 hours.17-21 A pooled analysis of data of 139 patients from different sources reported an efficacy rate of 88%.17 Venous thromboembolic disease (VTE) is an adverse event associated with both of these agents.

Factor VIII in large doses should be considered in patients known to have low-titer inhibitors (<5 BU). Porcine Factor VIII from pooled plasma, while not currently available in the US, has been used historically to increase plasma factor VIII levels, and it takes advantage of the minimal antigenic cross reactivity with human Factor VIII inhibitors.22,23,24 A recombinant porcine factor VIII, B-domain deleted (OBI-1) has recently been tested in a clinical trial in the US (50).

A number of immunosuppressive therapies have been used to control inhibitors. However, current treatment is based on small, uncontrolled, single-center cohorts and meta-analysis. Corticosteroids and cytotoxic drugs, used either alone or in combination, have been regarded as the mainstay of therapy. An alternate modality of inhibitor suppression is IVIG; however, this has generally been less effective.11,25,26,27 Removal of the inhibitor via an immunoadsorption process has been
attempted. It requires central venous access, specialized equipment and training, and close monitoring.

Oral steroids used alone at 1 mg/kg prednisone equivalent per day for 3–6 weeks can cause remission in one third to one half of patients with acquired hemophilia. Cyclophosphamide has been used as initial therapy and in refractory patients with high-titer inhibitors (>5 BU) leading to higher remission rates of up to two-thirds versus steroids alone. However, a 2-year national surveillance report of acquired hemophilia A by the UK Haemophilia Centre Doctors’ Organization concluded that there was no difference in inhibitor eradication or mortality between patients treated with steroids alone or with a combination of steroids and cytotoxic agents.

Several reports have demonstrated the effectiveness of Rituximab in acquired hemophilia A. The general high level of tolerance of this drug has led to initial use of this treatment. However, there is currently no data to establish its superiority over other treatments. The dose typically given is 375 mg/m² infused weekly for 4 weeks and administered concomitantly with other immunosuppressive drugs.

Cyclosporine (CsA) has also been used for inhibitor suppression. Use of CsA requires monitoring drug levels to ensure efficacy and prevent toxicity. However, its use is limited due to availability of other strategies such as cytotoxic drugs and Rituximab.

We describe a case of AHA with high titer antibody that experienced clinical deterioration on initial monotherapy with prednisone. The patient was unable to tolerate Rituximab due to anaphylaxis and was also refractory to IVIG.

We report a novel strategy of combining Cyclosporine with pulsed, high dose dexamethasone at a dose of 40mg daily for four consecutive days every 28 days. Pulsed dose dexamethasone is an acceptable modality of immunosuppression and has been used for the treatment of idiopathic thrombocytopenic purpura (ITP), another immune-mediated hematological disorder.

In general it is tolerated well, without producing the long term effects of steroid toxicity. No randomized trials exist comparing the efficacy and tolerability of pulse dose dexamethasone with longer duration steroids. However, we have experienced good results in our institution for the treatment of ITP, and this has become our preferred first line therapeutic modality. The patient tolerated this regimen extremely well and went into complete remission with undetectable antibody titers after the fourth cycle of pulse dexamethasone. He is currently in remission and is being weaned from cyclosporine.

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MANAGEMENT OF AN UNRESPONSIVE PATIENT WITH SEVERE ACIDOSIS

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Case Report
Congestive heart failure (CHF) is a chronic medical condition whose incidence is rising. The prevalence of CHF is approximately 1% to 3% in Western countries. Despite innovations in medical therapy, CHF is associated with high morbidity and mortality rates.

CHF patients commonly experience muscle weakness and fatigue as two major symptoms. An altered intracellular handling of ionized calcium has been suggested to play a vital role in impaired myocardial contraction. In isolated myocytes from patients with end stage heart failure, systolic ionized calcium levels were markedly decreased, while diastolic levels were elevated as compared to healthy controls. In addition, digitalis and beta-blocker medical therapy is frequently used in CHF patients and is known to increase myocardial ionized calcium levels.

The patient’s past medical history was notable for fibromyalgia and migraine headaches, and her past surgical history included a tonsillectomy. Her past psychiatric history was significant for depression and a prior suicide attempt, involving wrist slitting. The patient had no known drug allergies and her medications included valium, topamax, oxycontin, percocet and lunesta as needed. She did not take any over the counter medications or herbal supplements. The patient consumed alcohol occasionally and smoked cigarettes, but did not use any illicit drugs. Her family history was unremarkable.

Upon admission, the patient’s vital signs were notable for a temperature of 102°F and a heart rate of 140 beats per minute. Physical exam revealed dry mucous membranes and tachycardia. On neurologic exam, the patient was found to be unresponsive to all stimuli, including sternal rub. Neurologic exam was remarkable for a left pupil that was sluggishly reactive to light, a right pupil that was midposition and fixed, and the absence of a gag reflex and corneal reflexes. Routine laboratories were notable for a white blood cell count of 31B/L, hemoglobin 17.6g/dL, serum sodium 150mmol/L, serum chloride 118mmol/L, bicarbonate 5mmol/L, creatinine 1.6mg/dL, and an anion gap of 31mmol/dL. Also of note, an arterial blood gas performed at the time of presentation showed a pH of 6.76, PCO2 32mmHg, PO2 345mmHg, bicarbonate 4mmol/L, and an oxygen saturation of 99% on 100% FIO2. A CAT scan of the head at the time of admission showed diffuse cerebral edema with no infarct identified.

Hospital Course
This critically ill patient with a severe metabolic acidosis was admitted to the intensive care unit. She was aggressively hydrated and started on a bicarbonate infusion for treatment of her acidosis. She was also given a dose of mannitol to reduce the risk of cerebral herniation in light of her diffuse cerebral edema. Additionally, she was started empirically on broad spectrum antibiotics. As there was a concern for a possible suicide attempt via an overdose, a urine drug screen, an acetaminophen level, a salicylate level, a serum ethanol level, and serum and urine osmolalities were obtained. These laboratories were remarkable for benzodiazapines in the patient’s urine and a serum osmolality of 394mosmol/kg, resulting in an osmolar gap of 89.1mosmol/kg.

At this point, the differential diagnosis included ethylene glycol, isopropyl alcohol, or methanol toxicity and laboratories for these toxins were sent. Poison control was contacted and the patient was started on fomepizole infusion at 15mg/kg. The patient’s clinical condition continued to deteriorate. Her acidosis and acute renal failure worsened, necessitating the initiation of continuous venovenous hemodialysis. The patient remained unresponsive, and neurology consultation deemed that her prognosis was extremely poor.

On the second day of hospitalization, the patient’s metabolic disturbances continued to worsen, and she developed lactic acidosis with rhabdomyolysis. Her ethylene glycol level came back elevated at 39mg/dL. Since all other avenues of treatment had been exhausted and patient’s clinical status was continuing to decline, Thomas Jefferson University Hospital’s hypothermia protocol was initiated.

After 24 hours, patient was rewarmed and her electrolyte disturbances and acidosis began to resolve. The patient, however, remained unresponsive. On the forth day of hospitalization, the patient’s neurologic status began to improve, as she was able to open her eyes and move her extremities. At this point, she was noted to have right sided weakness so a CAT scan of her head was repeated, which showed a new left occipital lobe infarction and slightly decreased cerebral edema.

On the sixth day of hospitalization, the patient began following commands and was extubated. At this point, her mental status was completely back to baseline and she had no neurologic deficits. Her renal function remained poor and she was continued on hemodialysis. The patient was transferred to inpatient psychiatry on day 10 of her hospitalization. While on the inpatient psychiatry floor, her renal function improved and dialysis was discontinued. She was discharged home from inpatient psychiatry after 12 days, with no residual neurological symptoms.

Discussion
Although not a significant cause of mortality in the US, ethylene glycol consumption is responsible for dozens of fatal intoxications annually. It is a major constituent of antifreeze, de-icing solutions, windshield wiper fluid, solvents, cleaners, and fuels. Typically consumption is due to suicide attempt but can also be secondary to ethanol substitution or accidental consumption. Significant toxicity can be seen with consumption of small amounts, and toxic levels of 1g/kg are considered lethal.
Ethylene glycol is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase. The parent molecule itself is nontoxic, but is noted to cause CNS depression. Its metabolites, primarily glycolate, glyoxylic acid, and oxalate, are responsible for the toxic effects of ethylene glycol. Upon consumption, ethylene glycol is rapidly absorbed by the stomach and small intestine, achieving peak concentrations within one to two hours. The half-life of ethylene glycol ranges from 3 to 9 hours or longer if alcohol dehydrogenase is inhibited.1

Typically, the progression of symptoms from ethylene glycol consumption includes initial CNS symptoms, followed by cardiopulmonary manifestations, and ultimately renal involvement. The presentation can be largely variable depending on the amount ingested, the degree of metabolism, and the presence of ethanol co-ingestion. A wide spectrum of systemic effects can occur. In addition, in the preterminal stage of the illness, cerebral herniation and multi-system organ failure are often present.1,2

Blood work typically reveals a profoundly elevated anion gap metabolic acidosis with a lactate level insufficient to account for the degree of acidosis. Also, the patient can have an elevated plasma osmolar gap. However, no single laboratory study, with the exception of an elevated serum ethylene glycol level, is definitively diagnostic for ethylene glycol poisoning. A serum osmolar gap is present in a variety of intoxications including ethanol, isopropyl alcohol, and methanol toxicity.1,3

A high clinical suspicion for intoxication and early treatment are essential for the successful management of a patient with ethylene glycol ingestion. The core components of managing ethylene glycol toxicity include maintenance of cardiopulmonary function as well as the use of the alcohol dehydrogenase antagonist fomepizole, sodium bicarbonate infusion, hemodialysis, and consultation with medical toxicology and poison control.1

Generally, the use of intravenous sodium bicarbonate is recommended for metabolic acidosis with a pH less than 7.3. Infusions have been shown to increase excretion of active metabolites, as well as decrease end organ damage. Fomepizole is an antidote for methanol and ethylene glycol poisoning that acts as a competitive antagonist of alcohol dehydrogenase. It has a binding affinity of greater than 8,000 times ethanol and has efficacy that may obviate the need for hemodialysis. Hemodialysis rapidly removes toxic metabolites and is mostly indicated for use in patients with acute renal failure, as renal function may take days to months to recover.4 The hypothermia protocol utilized in our patient has no evidence-based support for treatment of ethylene glycol associated cerebral edema. Its established use has been in patients who are status post cardiac arrest to preserve neurological function in the setting of cerebral hypoperfusion. Bernard et al. conducted a study of 77 subjects randomized to normothermic and hypothermic treatment after ventricular fibrillation arrest and resuscitation with a significant improved survival in the group receiving hypothermic cooling.5 Similar findings were noted in the Hypothermia After Cardiac Arrest Study Group as well.6 A study using animal models elucidated mechanisms by which hypothermia may be neuroprotective including: decreased excitotoxic neurotransmitters, diminished oxidative stress, suppressed cerebral edema preserving blood brain barrier, decreased post-ischemic inflammation, normalized acid-base status in brain, and restoration of protein synthesis.7

At Thomas Jefferson University Hospital, the hypothermia protocol was adopted for use with patients status post cardiac arrest. However, given this patient’s neurological presentation, the protocol was instituted for neuroprotective purposes. In addition, intoxication due to ethylene glycol was the cause of her neurological dysfunction and also a contraindication to the use of hypothermic cooling per the institution’s protocol. However, in our patient’s case there were several mitigating circumstances: the threat of herniation, inability to use mannitol due to her elevated serum osmolality, and her young age that warranted the use of hypothermic cooling.

References
Case Report
Patient is a 30 year old male, with no significant past medical history, who was attending an outdoor party in a wooded area of New Jersey two weeks prior to this hospital admission. Three days following the party, patient noted several papules on his lateral left calf with surrounding erythema. The following day he went to the emergency department and was diagnosed with bacterial cellulitis (Figure 1).

Patient was discharged home from the emergency department with a 14 day course of Bactrim DS. However two days following his emergency room visit the rash had progressed despite adherence to the antibiotics prescribed. At that time, patient returned to the emergency department (Figure 2).

The patient was presumed to have either a refractory cellulitis secondary to skin flora or infection with Borrelia burgdorferi given his clinical history. Patient was started on broad spectrum antibiotics and doxycycline. The following day, rash was revaluated (Figure 3) and he was diagnosed with erythema migrans.

Patient’s condition improved quickly and he was discharged home on a 28 day course of doxycycline.

Discussion
Erythema migrans occurs in approximately 80 percent of patients and generally manifests within one month following the tick bite. Although the lesions of erythema migrans are typically described as a “bull’s eye” and central clearing is considered classic, it often requires considerable expansion of the lesion and, in some instances, is not present early on in the illness. Thus in the first days erythema migrans lesions may be uniformly red.

In light of this information, it is important to consider a wide differential, especially in the early stages of the disease. In addition to Lyme disease, other tick borne illness producing rash such as Rocky Mountain spotted fever, ehrlichiosis, and tularemia should be considered.

Despite the availability of an effective vaccine, measles (rubeola) can present as a blanching erythematous maculopapular rash beginning in the head and neck area and spreading down to the trunk and extremities. The rash of infectious mononucleosis is usually over the trunk but can involve the extremities, including the hands and feet. Acute retroviral syndrome occurring 2-4 weeks after primary HIV infection can manifest as a transient, maculopapular, nonpruritic rash that is usually truncal or facial in location. Approximately 20 percent of cases of erythema infectiosum occur in adults and can manifest with a rash described as first macular and then lacy and reticulated, spreading initially from the limbs to the trunk and buttocks. Additionally, mycoplasma infection may be accompanied by
skin findings ranging from a mild erythematous maculopapular or vesicular rash to Stevens-Johnson syndrome.

Treatment options for Lyme disease differ depending on the clinical scenario. For erythema migrans, amoxicillin is as effective as doxycycline and is preferred for children and pregnant or lactating women. Oral antibiotic treatment for 14-21 days shortens the duration of the rash and generally prevents development of late sequelae. Cefuroxime is also effective, but significantly more expensive. For patients with facial nerve palsy alone, oral doxycycline or amoxicillin may be effective. Patients with other neurologic involvement, such as meningitis, cranial nerve palsies, radiculopathy or cognitive deficits, should be treated with IV ceftriaxone or cefotaxime for 14-28 days.

In patients with minor cardiac conduction disease associated with Lyme disease treatment with oral doxycycline or amoxicillin should be sufficient; however, for those patients with more severe cardiac involvement, intravenous ceftriaxone or cefotaxime is recommended.

Oral therapy with doxycycline or amoxicillin for 28 days is usually effective for treatment of Lyme arthritis. Patients who have not responded to oral treatment may respond to a second course of oral therapy or to intravenous therapy with ceftriaxone or cefotaxime.

References
A Case of Acute Spontaneous Tumor Lysis Syndrome and New Diagnosis of Burkitt’s Lymphoma

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Introduction
Tumor lysis syndrome is a well-described phenomenon characterized by elevated serum levels of calcium, uric acid, potassium, phosphate, and lactate dehydrogenase due to lysis of tumor cells and release of intracellular contents. Acute kidney injury may occur as the result of precipitation of intrarenal calcium phosphate salts related to the rapid destruction of a large number of tumor cells. Tumor lysis syndrome most often occurs during induction chemotherapy for aggressive leukemia or lymphoma, particularly those with large tumor burden. While tumor lysis syndrome is more commonly seen in patients receiving chemotherapy, it can occur spontaneously and has been described in aggressive malignancies, such as AML, Burkitt’s lymphoma in children and adults, and in solid malignancies, such as breast cancer. This case describes a patient who presented with a neck mass and spontaneous tumor lysis syndrome.

Case Presentation
A 76-year-old male with a past medical history of hypertension, hyperlipidemia, and coronary artery disease presented with epistaxis and a neck mass that was first noted four weeks prior to presentation. In addition, the patient noticed gingival bleeding when brushing his teeth, malaise, decreased appetite, and night sweats, all of which developed during the previous week. His exam was significant for an ulcer with scab on his left buccal mucosa, a 6-cm left neck mass that was firm and non-tender, and several areas of ecchymosis on his arms bilaterally. There was no axillary or inguinal lymphadenopathy. The remainder of the exam was unremarkable.

A neck ultrasound prior to admission showed multiple left cervical cystic and solid masses consistent with necrotic lymph nodes. The patient also had an enlarged right cervical lymph node. He was admitted with a diagnosis of left neck mass suspicious for malignancy and acute kidney injury.

On admission, laboratory data showed white blood cell count of 5,300/μL, a platelet count of 3,000/μL, hemoglobin 12.5 g/dL, and a mean corpuscular volume of 94 fL. The white cell count differential included 23% neutrophils, 10% bands, 28% lymphocytes, 13% atypical lymphocytes, 2% monocytes, 1% metamyelocytes, 5% myelocytes, 2% promyelocytes, 16% blasts, and 3.4/100 WBC nucleated red cells. Other significant laboratory data included potassium of 4.5 mmol/L, blood urea nitrogen (BUN) of 46 mg/dL, creatinine of 1.6 mg/dL, total bilirubin of 2.1 mg/dL, direct bilirubin of 0.7 mg/dL, uric acid of 17.4 mg/dL, and lactate dehydrogenase (LDH) of 4795 IU/L.

The patient’s elevated LDH, uric acid, and creatinine raised suspicion of tumor lysis syndrome, so IV fluid hydration and allopurinol were initiated. A bone marrow biopsy was performed for diagnosis of suspected lymphoma. The patient’s creatinine, LDH, and uric acid levels continued to rise, and treatment with rasburicase was initiated given the concern for renal failure. In less than 12 hours, the patient’s creatinine increased from 2.6 mg/dL to 3.5 mg/dL and potassium increased from 5.2 mmol/L to 6.1 mmol/L. The patient suffered cardiac arrest before dialysis could be initiated. Although he was initially resuscitated, care was withdrawn the same day per the patient’s and family’s wishes.

The final bone marrow biopsy results, including flow cytometry and FISH analysis, revealed solid monotonous sheets of large atypical lymphoid cells with clear cytoplasmic vacuoles, which accounted for the vast majority of nucleated bone marrow cells. The cells demonstrated a monoclonal B-cell proliferation with translocations at 8;22 involving the C-myc gene, consistent with the diagnosis of Burkitt’s lymphoma. These results were obtained several days after the patient had expired.

Discussion
Tumor lysis syndrome is a familiar entity to physicians caring for patients receiving chemotherapy for treatment of leukemias and lymphomas. This syndrome is most commonly encountered upon initiation of chemotherapy in a patient for the first time, but it can occur in any patient with extensive tumor burden, including patients with solid malignancies. Patients may exhibit hypercalcemia, hyperkalemia, hyperphosphatemia, hyperuricemia and acute renal failure. Often prophylactic intravenous fluid hydration and administration of allopurinol or rasburicase are initiated prior to giving chemotherapy to reduce the risk of developing renal failure and fatal arrhythmias secondary to hyperkalemia. In addition, frequent monitoring of serum potassium levels allows for treatment of hyperkalemia, should it develop.

In the case presented above, tumor lysis syndrome was not an anticipated event since chemotherapy was not being given at the time of its development. Moreover, the patient had not been diagnosed with a malignancy at the time of development of the syndrome. Although it has been described before in the literature, this uncommon presentation of spontaneous tumor lysis syndrome could be easily missed. Knowing that spontaneous tumor lysis syndrome can occur, it seems reasonable to obtain serum lactate dehydrogenase and serum uric acid levels in patients suspected of having a new diagnosis of a hematologic malignancy even before the formal diagnosis is made. It is important to initiate standard treatment of IV fluid hydration and allopurinol or rasburicase as early as possible when tumor lysis syndrome is suspected.
References


"Notre Dame"

photograph by Cecilia Kelly, MD
A Case of Babesiosis Complicated by Hepatic and Renal Failure

Steven Krawitz MS IV, Nilay Kavathia MD, Pratik Choksy MBBS

Case Report
A 67-year-old male with a past medical history of chronic kidney insufficiency, splenectomy, and recurrent babesiosis infection was transferred to with jaundice and abdominal pain.

The patient initially presented to an outside hospital (OSH) with generalized weakness, chills, and gastrointestinal symptoms and was found to have Babesia on peripheral blood smears. The patient received seven days of azithromycin and atovaquone, followed by three days of clindamycin and quinine. The patient was discharged home with improved symptoms and a negative peripheral blood smear. Less than 24 hours later he returned to the OSH with worsening myalgias and abdominal pain. Physical exam was significant for jaundice and hepatomegaly. Laboratory data revealed anemia, elevated creatinine, bilirubin of 30 mg/dL, and 1% parasitemia. At this point the patient was transferred for further management.

Patient’s past medical history was significant for chronic renal insufficiency, congestive heart failure, type 2 diabetes mellitus, coronary artery disease, and hypertension. Previous surgical procedures included splenectomy after a motor vehicle accident, below the knee amputation (BKA) of the right leg, and cholecystectomy. Patient denied alcohol or substance abuse, and quit smoking tobacco approximately 10 years ago. He is a retired carpenter and denied any recent history of travel. Medications on admission included digoxin, clopidogrel, isosorbide mononitrate, carvedilol, sucralfate, esomeprazole, metoclopramide, amlodipine, octreotide, and insulin lispro.

On examination, patient looked fatigued, but in no acute distress. He was afebrile and had stable vital signs. Physical exam was significant for scleral icterus, ventral hernia and diffuse blanching, maculopapular rash on patient’s hands and soles. Patient was admitted and started on treatment with clindamycin and quinine. The patient’s blood smear showed Babesia species with a 1.7% parasitemia (figure 1). During the hospital stay, patient had an acute mental status change with asterixis. Laboratory data obtained at that time revealed elevated INR, bilirubin, and ammonia levels. Given the clinical findings, patient was started on lactulose for possible hepatic encephalopathy. Hepatitis serology was found to be negative. Dialysis was initiated in the setting of acute renal failure. Patient’s clinical status continued to worsen, so red blood cell exchange transfusion was initiated in an attempt to reduce the parasite load and help clear the infection. Despite the exchange transfusion and continued antibiotic treatment, the patient continued to have hemolysis, paracitemia, renal failure, and hepatic failure. At that point hospice discussion was initiated and patient was eventually transferred to hospice home care.

Discussion
Babesiosis is a tick born protozoan infection of red blood cells from the genus Babesia. The first human case was reported in 1957. The four Babesia species that most commonly infect humans in decreasing order of incidence are B. microti, B. duncanii, B. divergens, and B. venatorum. Babesiosis is a zoonotic infection requiring both an animal reservoir (usually mice) and a vector, which in humans is the Ixodid tick. The protozoan is transmitted through the saliva of a tick when it bites. Other possible modes of infection include perinatal transmission and blood transfusion.

The endemic areas for babesiosis show significant overlap with Lyme disease and ehrlichiosis. The disease is most commonly seen in the northeast of the United States, and the most common cause of babesiosis in America is the B. microti species. While the majority of the early cases were seen in coastal areas near Massachusetts, babesiosis is now diagnosed with regularity in Rhode Island, Connecticut, and even New York and New Jersey. Many cases have now been reported in other states stretching as far west as California and even Europe has confirmed cases of B. microti babesiosis.

The severity of babesiosis infection depends on the strain of parasite as well as host factors such as immune system status or asplenia. Clinically, patients infected with B.Microti typically fall into one of three categories of disease expression: asymptomatic, flu-like, and severe infection. Given the relatively high seroprevalence, many infected individuals are asymptomatic and unaware they carry the parasite. One study estimates the prevalence of asymptomatic infection at about one third of infected individuals. However, most infected individuals fall into the second category, mild to moderate flu-like illness. Similar to Lyme disease, up to two thirds of these symptomatic patients cannot recall getting bit by a tick, making diagnosis potentially difficult. Patients typically present with malaise and fatigue and develop intermittent fevers with one of the following in order of prevalence: chills, sweats, headaches, anorexia, cough, nausea. Patients with severe disease more often present with malaise, arthralgia, myalgia, and shortness of breath often combined with thrombocytopenia and abnormal liver function. Severe infection carries with it the potential of numerous serious complications including DIC, congestive heart failure, acute respiratory failure, liver and renal failure, and splenic rupture.

Diagnosis of babesiosis infection is typically made by microscopic examination and identification of the typical appearance of organisms on Geimsa stained thin red blood cell smears. Polymerase chain reaction (PCR) amplification, although more expensive, is more sensitive than microscopic identification and can be completed within one day. For diagnostic
confirmation or when both microscopy and PCR are negative, serologic diagnosis can also be made. The standard treatments for babesiosis are the antibiotic regimens of clindmycin and quinine, or atovaquone and azithromycin, both administered for 7 to 10 days. Infections with a high parasitemia load or those that are persistent or relapsing might benefit from red blood cell transfusion to lower the parasite level in the blood. However, even with appropriate treatment, babesiosis can be fatal in certain patient populations.

Although most cases of babesiosis in the United States are mild to moderate or even asymptomatic, some cases are severe and may be fatal. It is important to be wary of the potential devastation the disease can have as well as who is more likely to manifest severe disease. The risk factors for severe disease include age older than 50, asplenia, coinfection with HIV or Borrelia burgdorferi, and an immunocompromised state. The case above demonstrates severe and resistant infection in the setting of multiple risk factors, namely increased age and asplenia. Though the patient was on appropriate antibiotic treatment and received multiple red blood cell transfusions, he still suffered from complications of the disease and was unable to clear the infection.

This case demonstrates that babesiosis is a potentially severe and fatal disease. It is important to recall the risk factors for disease severity, especially in certain at-risk populations. In treating such populations, potential end of life issues should be considered, as mortality and complications from the disease are significant.

References

A 19 Year-Old Man With Chest Pain
Sam Barasch, MS IV, Sugeet Jagpal, MD

Case Report
A 19-year-old man with no past medical history presented to the ER with a sore throat, cough, and pleuritic chest pain. The patient had been well until 1 month before admission, when he developed a sore throat and felt ill. He presented to the emergency department twice for these symptoms. On the first visit, the patient had a positive rapid strep test. He was diagnosed with strep throat and treated with penicillin IM. However, his sore throat persisted. Five days before admission, the patient developed a non-productive cough. One day prior to admission he developed severe right sided chest pain that was throbbing, pleuritic, and radiated to his right shoulder. The pain, which was initially relieved by sitting forward and with Ibuprofen, continued to worsen, prompting the patient’s mother to bring him back to be re-evaluated.

Upon presentation, the patient denied shortness of breath, fevers, or chills. He had no personal history of prenatal or childhood disease, and denied family history of early heart disease, lung disease, cancer or bleeding disorders. He denied tobacco, alcohol, or illicit drug use. He reported being heterosexual with 4-5 lifetime sexual partners, and one new partner in the prior two months.

On examination, the patient was a well nourished, well developed, young African American man in moderate distress. The blood pressure was 117/57, heart rate 66, respiratory rate 16, oxygen saturation 98% on 2 L nasal cannula and temperature 37.5ºC. The physical exam was remarkable only for slight pharyngeal erythema and enlarged, non-purulent tonsils. His heart was without murmurs, rubs, or gallops. His lungs were clear to auscultation bilaterally. Initial labwork was normal, without any signs of malignancy. A rheumatologic workup, including an anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were negative. A hypercoagulable work up was sent prior to initiation of anti-coagulation therapy. Protein C, protein S, factor V leiden, antithrombin III, and anticardiolipin antibodies were normal. Eventually, after the patient had been discharged, his lupus anti-coagulant levels returned as abnormally elevated. The patient was diagnosed with primary antiphospholipid syndrome by his primary care doctor and was informed he would require lifelong anti-coagulation.

Discussion
Primary antiphospholipid syndrome is an auto-immune disease typically discovered when a patient has vascular thromboses or pregnancy complications in the presence of elevated anticardiolipin antibodies or lupus anti-coagulant antibodies. Primary antiphospholipid syndrome can be diagnosed in the absence of broader auto-reactive antibody production, i.e. lupus. Detection of the auto-immune antibodies must be found on two separate occasions more than six weeks apart.

Of the laboratory criteria, anticardiolipin antibodies are more sensitive while the lupus anti-coagulant antibodies are more specific. Lupus anti-coagulant antibodies were originally found in lupus patients who had a prolonged activated partial thromboplastin time (aPTT). While patients with the lupus anti-coagulant had prolonged in vitro coagulation studies, in vivo they were hyper-coaguable. Thus, these patients had high PTT or INR on blood work, in combination with a paradoxical tendency to clot in their body. This paradox is due to the fact that, in vitro, the lupus anti-coagulant antibody binds to critical phospholipids and prevents them from activating factor X and prothrombin. In vivo, however, the antiphospholipid antibody binds to a multitude of targets that result in a hyper-coaguable state.

The lupus anti-coagulant antibody has many significant targets within the body. The most clinically important in vivo target is β2-glycoprotien. Many patients have circulating lupus anti-coagulant antibodies that target phospholipids only, and do not have clinically significant thrombosis. However, when the antibodies target both phospholipids and β2-glycoprotien I, the patients become much more likely to have a thrombus that causes symptoms. Antiphospholipid antibodies also promote coagulation by enhancing activation and aggregation of platelets, activation and expression of adhesion molecules on endothelium, and activation of the coagulation cascade.

Infection can be an inciting factor for a thrombotic event in a patient with a circulating, but clinically silent, antiphospholipid antibody. Many different pathogens are cited, including HIV, HCV, VZV, H influenza, Streptococcus species, and Staphylococcus aureus. Common systems infected prior to

Given the finding of the patient’s pulmonary embolism, our top three differential diagnoses were a primary underlying hypercoagulable state, an infection predisposing the patient to a hypercoagulable state, or an underlying malignancy. The patient was admitted to the hospital, blood work was drawn, and he was started on Warfarin with an Enoxaparin bridge. During his work up, the patient was found to have elevated antistreptolysin O titers, consistent with a prior streptococcus infection. Blood cultures were negative. In addition, HIV, HSV, gonorrhrea, chlamydia, group A strep, and H1N1 PCR were all negative. CT of the abdomen and pelvis and testicular ultrasound were

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Staphylococcus aureus. Common systems infected prior to
thrombosis include skin, pulmonary, urinary, and upper respiratory tract. Some investigators propose a "two hit" hypothesis in which patients with underlying antiphospholipid antibodies receive a second hit when a pathogenic epitope is a molecular mimic of $\beta_2$-glycoprotein I or when an inflammatory cascade is activated by toll-like receptors on phagocytes of the innate immune system. It is possible this happened to our patient: his previously silent circulating antibodies were activated by an upper respiratory streptococcus infection, causing an inflammatory cascade that resulted in a thrombotic event.

Treatment for patients with primary antiphospholipid syndrome centers on anticoagulation therapy. An INR of 2-3 (maintained by oral warfarin) has been shown to reduce the probability of recurrent thrombosis. In catastrophic cases where life threatening thromboses affect multiple organs and cause microvascular disease, treatment includes high dose steroids, intravenous immunoglobulin, cyclophosphamide, or plasmapharesis. Treatment in a hemodynamically compromised patient with pulmonary embolism can also include embolectomy. For prevention of late term pregnancy loss related to primary anti-phospholipid syndrome, low dose aspirin and subcutaneous prophylactic heparin have been shown to prevent complications. For patients refractory to anti-coagulation, long term immunomodulating agents should be added.

Our patient did not have catastrophic antiphospholipid syndrome, and is currently doing well on oral anticoagulation.

**Take home points:**
1) Primary antiphospholipid syndrome is vascular thromboses or pregnancy complications and anticardiolipin antibodies or lupus anticoagulant antibodies.
2) Anticardiolipin antibodies are more sensitive while lupus anticoagulant is more specific for diagnosing antiphospholipid syndrome.
3) Infection can prompt a circulating but clinically silent antiphospholipid antibody to cause a thrombotic event. Exact mechanism of this is unknown.

**References**

"Tomb"
Photograph by Cecilia Kelly, MD
A 67 Year-Old Man with Fatigue

Sam Barasch, MS IV, Ajay Wagh, MD

Case Report

A 67 year-old male with a past medical history of hypertension and insulin-dependent type II diabetes complicated by neuropathy, retinopathy, and chronic kidney disease presented to the hospital with a complaint of fatigue. The patient noted generalized weakness that had begun the morning of admission after two days of malaise and subjective fever. This weakness prevented him from being able to rise from a sitting position, resulting in a fall off the couch. He denied injury from this fall along with shortness of breath or chest pain, however, he did admit to two episodes of vomiting the day prior to admission.

The patient was taking the following medications: furosemide, aspirin, isosorbide mononitrate, lipitor, levothyroxine, candesartan, metoprolol, clopidogrel, doxazosin, calcitriol and Insulin 70/30. Medical history included, hyperlipidemia, hypothyroidism, benign prostatic hypertrophy, stable angina, and peripheral vascular disease along with the conditions listed above. Past surgical history included 2 stents in the LAD coronary artery, vitrectomy, and transurethral resection of the prostate (TURP). Additionally, the patient noted that he lived alone after having retired from teaching and denied any drugs, smoking or alcohol.

On physical exam, the patient was febrile at 102.2°F, heart rate was 99, respiratory rate was 17, and blood pressure was elevated at 183/56 mmHg. Generally, the patient was dehydrated and appeared to be somnolent but responsive to questions. Neurological exam was remarkable for generalized bilateral upper and lower extremity weakness and asterixis with no focal neurological deficits. His cranial nerves were intact. Skin exam was significant for a warm, erythematous, blanching, non-pruritic rash on the left anterior tibial surface, as well as an eschar on the 2nd toe of the left foot. The rest of physical exam was within normal limits.

An arterial blood gas was performed due to his overall lethargic state and demonstrated a pH of 7.34, PCO2 34, PO2 66 and oxygen saturation of 91% on room air. His electrolytes were Na 134, K 5.3, Cl 106, HCO3 19, significant for a non-anion gap metabolic acidosis with a compensatory respiratory alkalosis. Glucose was elevated at 412mg/dl. Additional laboratory values revealed a BUN of 79 and creatinine of 3.1 (previous baseline of 2.3). Urine studies showed protein >300 mg/dl, urine pH of 5.5, urine glucose 500, and rare hyaline casts. Urine electrolytes results included Na 49, K 30.2, CI 54, and Cr of 98.7. Lactate was within normal limits.

The patient was treated acutely for dehydration and hyperglycemia with intravenous fluids and insulin. He was started on broad spectrum antibiotics for suspected cellulitis and osteomyelitis of the 2nd left toe. The combined results of the urine anion gap of + 25.2, the serum anion gap of 9, and hyperkalemia led us to a preliminary diagnosis of renal tubular acidosis type IV. Finally, the renin level returned low at 1.4 ng/mL/hr (normal 1.9-3.7) indicating a low renin – low aldosterone as an underlying cause of the metabolic acidosis.

Discussion

Type 4 Renal Tubular Acidosis is characterized by a low renin - low aldosterone state and non anion-gap metabolic acidosis. Low aldosterone levels impair the normal functioning of the Na-K-2Cl cotransporter in the distal nephron. This deficiency results in decreased reabsorption of Na+ in the distal nephron and decreased excretion of K+ and H+. Thus, RTA IV is characterized by salt wasting, hyperkalemia and acidosis.

RTA IV is caused by a decrease in ammonia recycling in medullary segments of the nephron and the subsequent increased gradient for alpha-intercalated cells of the collecting duct to pump protons against. In order to understand how ammonia recycling is affected in this condition we will examine the nephron from proximal to distal and discuss how hyperkalemia and acidosis derange normal physiology.

There are two mechanisms which are believed to be involved with the dysfunction of ammonia recycling. In the proximal convoluted tubule the presence of hyperkalemia creates an extracellular acidosis and intracellular alkalosis. In the loop of henle, there is competition between NH4+ and K+ for transport in the thick ascending loop by the Na+/K+/2Cl- transporter.

In the proximal convoluted tubule, hyperkalemia leads to diffusion of K+ across all cell membranes. In order to maintain electrical neutrality, H+ diffuses out of the cell into the extracellular space. This leads to an extracellular acidosis and an intracellular alkalosis. The intracellular alkalosis inhibits the de-amination of glutamine and the subsequent exchange of NH4+ with Na+ in the renal proximal collective tubule (PCT). The deficit of ammonium produced in the PCT makes less ammonium available in the ammonia recycling system of the renal medulla.1

In the loop of henle, hyperkalemia is believed to contribute to the acidosis by limiting the amount of ammonia/ammonium reabsorbed. Renal medullary ammonia recycling is reduced through hyperkalemia affecting the Na-K-2Cl cotransporter in the thick ascending limb. This cotransporter can take one ion of K+ or NH4+ across the luminal membrane of the thick ascending limb along with a Na ion and two Cl- ions. NH4+ and K+ directly compete for reabsorption. Under physiological conditions, NH4+ ions are transported intracellularly, lose their H+, and NH3 diffuses freely into the medullary interstitium of the kidney while return to the tubule is prevented by a membrane that is impermeable to NH3. In the absence of pathology, the high ammonia concentration in the renal medulla allows diffusion of NH3 down its concentration gradient into
the medullary collecting duct or the proximal tubule. Once in the medullary collecting duct, NH\(_3\) can accept a donated H\(^+\) ion, becomes ammonium, thereby facilitating the excretion of an acid load.

Under conditions of RTA IV, there is a lesser amount of ammonium available for renal medullary recycling, as less is generated in the proximal convoluted tubule, and this mechanism for excreting acid is further hampered by the high potassium in the tubule competing for and displacing ammonium from the loop cotransporter.\(^2\)

Therefore, both mechanisms of RTA type 4 work together to inhibit the excretion of NH\(_3\) into the collecting duct of the kidney and subsequently inhibit the excretion of NH\(_4^+\) and an acid load.

Under normal conditions, both mechanisms of hampering renal medullary ammonia recycling can be repaired by aldosterone, which promotes the re-absorption of Na and the wasting of K. However, the hallmark of RTA IV is a low renin/low aldosterone state. In this situation, it is not possible for normal physiological mechanisms to break the hyperkalemic acidosis of RTA IV.

**Treatment of RTA IV**

Treatment of RTA type IV focuses on correction of hyperkalemia, optimizing renal function, and addressing the physiological root of the disorder.

Correction of hyperkalemia begins with withholding medications that can cause or exacerbate hyperkalemia. Potassium-sparing diuretics, ACE-Inhibitors and ARB medications are common causes. This is especially important because renal insufficiency in combination with ACEI/ARB medications can have synergistic hyperkalemic effects.\(^3\)

Additionally, if the patient suffers from renal insufficiency he must be treated to optimize renal function. This includes omission of medications that aggravate interstitial nephritis such as NSAIDS, cyclosporine, or tacrolimus.\(^4\) Also, adjusting for pre-renal insufficiency by treating volume status and maximizing renal perfusion is critical in the process of increasing potassium excretion. Improving renal function will increase potassium excretion. For long term management of RTA IV, in cases of renal insufficiency, dietary sources of potassium must be limited.

Adrenal insufficiency is suspected in a low renin-low aldosterone state. It is more common in cases of autoimmune disease and HIV infection.\(^4\) If clinical suspicion is high for adrenal insufficiency, mineralcorticoids should be given. Fludrocortisone is an effective exogenous mineralocorticoid replacement.\(^5\) However, mineralocorticoid replacement is contraindicated in hypertensive or edematous patients. Instead, in these patients, hyperkalemia can be managed with a loop or a thiazide diuretic.

**References**


"Growth"

Photograph by Cecilia Kelly, MD
A 54 Year-Old Male with Cholangiocarcinoma and Biliary Sepsis
Leela Nayak, MD, Bhalaghuru Chokkalingam Mani, MD

Case Report
A 54 year-old male with a past medical history of cholangiocarcinoma and portal vein thrombosis was admitted to an outside hospital with right-sided abdominal pain, leukocytosis and hyperbilirubinemia. Prior to admission, he received 3 cycles of gemcitabine however his tumor had increased in size leading to development of obstructive jaundice. At the hospital, his pain was attributed to hepatomegaly and biliary obstruction secondary to tumor size. He was started on Zosyn for presumed diagnosis of pneumonia and leukocytosis. He was then transferred to Thomas Jefferson Hospital for a second opinion regarding his malignancy.

Upon transfer, patient noted right upper quadrant abdominal pain that he described as constant and dull. He also reported fatigue and weight loss over last few months. He denied nausea, vomiting, diarrhea or any change in his bowel movements.

On arrival, his vital signs were stable. Physical exam was significant for jaundice, distended abdomen and right upper quadrant tenderness. He also had significant peripheral edema up to his groin.

Laboratory studies revealed white blood count (WBC) of 24,500/μL, hemoglobin of 8.5 g/dL, and platelets of 416,000/μL. His sodium was 128 mmol/L and creatinine was 0.6 g/dL. His total bilirubin was 21.2 mg/dL and alkaline phosphatase was 320 IU/L. His INR was slightly elevated at 1.31.

The patient underwent endoscopic retrograde pancreatography (ERP). He was found to have an occlusive common hepatic duct stricture secondary to a tumor. A plastic stent was successfully deployed. Seven days after the initial ERP, patient became febrile, tachycardic and complained of worsening right upper quadrant pain. Repeat ERP revealed purulent debris in the stent and a stricture of the left hepatic duct. Two metal stents were successfully placed leading to decreased in bilirubin. Within 24 hours, the patient’s blood cultures speciated Stenotrophomonas maltophilia. He was started on intravenous trimethoprim-sulfamethoxazole (TMP-SMX). Once patient’s bacterimia cleared, he was discharged home with hospice services.

Discussion
In the last twenty years, Stenotrophomonas maltophilia has been increasingly found as an important cause of infection in hospitalized patients. This hydrophilic organism has been known by multiple names. It was originally called Bacterium bookeri when first isolated in 1943 and considered to be a member of the genus Pseudomonas. It was then classified as part of the Xanthomonas genus in 1983 until finally reclassified as Stenotrophomonas in 1993. Although not considered to be a highly virulent organism, S. maltophilia can cause serious infections in both immunosuppressed and immunocompetent patients. It is most commonly found in aquatic or humid environments including drinking water supplies, soil and on plants. In health care facilities the organism has been isolated from medical devices, vacuum blood collection tubes, disinfectant and sterile water.

Most infections do occur in severely immunocompromised patients particularly those with cancer and prolonged neutropenia. Risk factors for infection with S. maltophilia include extended hospitalization in critical care units, prolonged mechanical ventilation, presence of tracheostomy, indwelling devices such as intravascular catheters and endotracheal tubes, and exposure to broad-spectrum antibiotics. Most S. maltophilia bacteremias are related to infected in-dwelling catheters. These infections are usually easily treated with removal of the infected catheter and antibiotic therapy. In patients with non-catheter related S. maltophilia, bacteremia treatment failure rates and infection associated mortality are high.

In patients with cancer, risk factors associated with poor outcome include prolonged neutropenia, bacteremic pneumonia, shock syndrome, thrombocytopenia and inappropriate initial antibiotic choice.

The respiratory tract is the most common site of S. maltophilia infection however it has been found to be the cause of skin infections, endocarditis, urinary tract infections and hepatobiliary infections. There have been five reports in the literature of biliary sepsis secondary to S. maltophilia. All of these cases occurred in patients with hepatobiliary malignancy complicated by biliary tract obstruction. Each of these patients had undergone biliary tract instrumentation prior to developing S. maltophilia bacteremia. The organism was recovered from blood in three cases and from bile in the remaining two cases. All of the patients were treated with antibiotics, four out of five patients described made a full recovery, the fifth patient died. The four patients who survived underwent interventional procedures in addition to receiving antibiotics.

Choosing appropriate antibiotic therapy for S. maltophilia infections can be difficult and initiation of inappropriate antimicrobial therapy has been linked to poor outcome. Although trimethoprim-sulfamethoxazole (TMP-SMX) has the strongest in vitro activity against S. maltophilia, increasing resistance rates have been reported in the literature. Despite these reports, TMP-SMX is still considered the drug of choice against this organism. It has even been suggested that patients who have serious S. maltophilia infections and are allergic to sulfa drugs should undergo desensitization in order to be treated appropriately. Other classes of antibiotics such as aminoglycosides and quinolones are not as effective against S. maltophilia.

S. maltophilia, although not considered an aggressive pathogen, remains an important cause of morbidity and mortality among immunosuppressed patients. Patients with cancer particularly those with prolonged neutropenia continue to be at risk of...
infection with this organism. When *S. maltophilia* infection is suspected it is important to obtain sensitivity and susceptibility data and to institute treatment with TMP-SMX when possible. This organism commonly causes respiratory and catheter-related infections, however there are rare reports of urinary and hepatobiliary infections in the literature. When a patient with hepatobiliary malignancy and biliary tract obstruction presents with cholangitis or biliary sepsis infection, *S. maltophilia* should be considered in the differential of possible pathogens.3

References

“Ben Franklin Bridge”
Photograph by Cecilia Kelly, MD
Histiocytic Sarcoma: A case of a 52-year-old female with two synchronous primary malignancies at presentation

Ryan D. Gentzler, MD, Daron A. Kahn, MD

Case Report

A 52-year-old female with a past medical history of chronic obstructive pulmonary disease, coronary artery disease, and an 80-pack-year smoking history presented to the emergency room with complaints of right upper extremity weakness and imbalance while walking for the previous two days. She stated that the onset was abrupt and progressively worsening to the point where she could no longer lift her right upper extremity against gravity. She maintained the ability to move her hand and grasp, but admitted to decreased strength and decreased dexterity of her right hand. She denied changes in vision. She also denied having bowel or bladder incontinence. She has no known allergies and her only medications included occasional benzodiazepines for anxiety and acetaminophen/oxycodeine for low back pain. Her family history was notable only for lung cancer, which was the cause of death of her mother.

On admission, the patient’s vital signs were stable. She was afebrile, alert, and oriented to person, place, and time. Her physical exam was notable for profoundly reduced strength rated at 1/5 in her proximal right upper extremity. Her distal forearm and hand were reduced at 3/5 intensity. Her sensation in her right upper extremity was intact and symmetrical. All reflexes in her upper and lower extremities were 1+.

A CT scan of her head revealed a large enhancing mass in the left parietal region. The patient was given levetiracetam 500 mg twice daily for seizure prophylaxis and dexamethasone 4 mg every 6 hours to reduce inflammation and edema surrounding the brain mass. A CT scan of the chest, abdomen, and pelvis was obtained for further workup and staging prior to surgery. This study revealed cavitating lung masses in the anterior left upper lobe and posterior right lobe, likely representing synchronous primary lung malignancies.

An MRI of the brain (Figures 1–2) on the same date revealed a 1.6 x 1.5 x 1.7 cm mass centered on the left corona radiata with extensive surrounding vasogenic edema. T1 weighted Brain MRI at the time of admission demonstrates a 1.6 x 1.5 x 1.7 cm solid enhancing mass centered on the left corona radiata with extensive surrounding vasogenic edema.

Given the fact that the read on the MRI was inconsistent with metastatic disease from a possible lung origin and was more consistent with a primary CNS lymphoma, we felt it was...
necessary to proceed with a biopsy of the brain lesion before initiating treatment for lung cancer. During the course of the hospital stay, the patient was fortunate to have improved function of her right arm and her gait returned to normal. She was discharged with a steroid taper.

The final brain biopsy (Figures 3–4) results were obtained after discharge and confirmed the diagnosis of a second separate malignant process involving the brain. Evaluation of the biopsy in consultation with the pathology department at the NIH identified dense collections of histiocytes present within reactive brain tissue. Many of the histiocytes were atypical in appearance and stained CD68 and CD163 positive, which is consistent with a diagnosis of histiocytic sarcoma.

The patient initially responded well to steroids and regained most of the function of her upper and lower extremity and was discharged from the hospital after the initial workup. However, she was readmitted in less than one week with progressively worsening weakness and gait abnormalities and was found to have a slightly larger mass on imaging studies (Figure 5). Because of her severe neurological impairment, she was discharged to inpatient rehabilitation. Due to her functional status, she was not a candidate for chemotherapy, and she expired from severe hemoptysis that was likely secondary to erosion of her lung cancer through a pulmonary artery.

**Discussion**
The case presented above is noteworthy not only for the unusual presentation of synchronous primary neoplasms, but also for the diagnosis of a rare form of non-Hodgkin's lymphoma, histiocytic sarcoma (HS), which we believe to be a primary CNS histiocytic sarcoma. Histiocytic sarcoma is a rare malignancy that makes up less than 1% of all diagnosed non-Hodgkin's lymphoma and has mostly been reported only in small series of case reports. It is a malignancy of hematopoietic cells resembling histiocytes but can be confused with similar looking T- and B-cell neoplasms. An extensive array of antibodies must be evaluated to differentiate HS from Langerhans Cell Sarcoma, diffuse large B-cell lymphoma, peripheral T-cell

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**Figure 3.** Light microscopy of brain lesion biopsy shows dense collection of histiocytes, many of which are atypical in appearance. (10x magnification, H and E stain)

**Figure 4.** Atypical histiocyte seen at high power. (100x magnification, H and E stain)

**Figure 5.** Axial view of T1 weighted MRI of the brain 24 days after admission demonstrates a progressively enlarging mass (measuring 2.0cm x 1.6cm x 1.9cm) and worsening surrounding edema. This tumor progression is consistent with an aggressive nature of histiocytic sarcoma.
lymphoma, acute lymphocytic lymphoma (ALL), metastatic undifferentiated carcinoma, and melanoma. Unlike other lymphomas, HS usually presents with extranodal involvement. About one-third of cases present within lymph nodes, and two-thirds are extranodal at presentation. Of the extranodal cases, about half present with skin lesions, and the other half with various sites of involvement including the intestinal tract, and rarely the central nervous system (CNS). HS is usually an aggressive malignancy that presents with constitutional symptoms such as fever and weight loss and symptoms related to organ involvement such as pancytopenia, bowel obstruction, rash, and subcutaneous nodules. When diagnosed, HS is most often at an advanced clinical stage with high mortality and little response to chemotherapy. Patients with primary CNS histiocytic sarcoma described in case reports have expired within 3 to 8 months of diagnosis from various complications.

Our patient presented with only extranodal involvement of the CNS, suffered from severe neurological impairment and survived for one month after her diagnosis was made. Although she likely died from complications of lung cancer, her functional status was progressively worsening due to the increasing size of the histiocytic sarcoma in her brain.

Due to the rarity of the disease and lack of studies to validate diagnostic criteria, HS is difficult to diagnose. Several markers used to help diagnose HS are histiocyte-associated antigens, such as CD68, lysozyme, CD11c, and CD14. Diagnosis also requires a lack of expression of other known cell lineages such as B-cells, T-cells, myeloid cells, follicular dendritic cells, and CD30. More recently, CD163 has been identified as an important factor for the diagnosis of HS. CD163 is a hemoglobin scavenger receptor and its expression is limited to neoplasms of monocytic/histiocytic derivation. It is more specific than other markers such as CD68. Cao et al. published in 2007 a case of primary CNS HS and confirmed the importance of distinguishing CD68 and CD163 positive tumors as HS versus other malignancies. Before CD163 was identified, HS was more difficult to diagnose and perhaps overdiagnosed. There are several case reports identifying histiocytic sarcoma as a primary CNS tumor, but these reports came before identification of CD163 as an important factor for diagnosis. The patient presented in the case above had a primary CNS malignancy that stained positive for both histiocyte-associated antigen CD68 and histiocyte-specific CD163 receptor.

Cao et al. also commented that, considering their findings of mild cytologic atypia and a profound inflammatory component, their initial impression was one of a chronic inflammatory process. Prominent inflammatory infiltrates have been described in all five of the previously reported published cases in the literature of primary CNS HS. A chronic inflammatory process and was on our differential diagnosis in the beginning as well. Interestingly, due to the rarity of the final diagnosis, which required numerous histochemical stains and second opinions from pathology departments at other institutions, the final diagnosis of histiocytic sarcoma was not obtained for several weeks following the biopsy. During this time, other possible etiologies for the brain lesion, including infectious diseases, were ruled out and eventually eliminated.

There radiographic appearance of CNS lesions is the key to their differentiation. Features typical of metastatic disease include multiple lesions, spherical shape, well demarcated borders, and their location at the gray matter-white matter junction. The lesion in this case, although well-circumscribed, was felt to be uncharacteristic of metastatic disease due to the depth of location and lack of multiple CNS lesions. Ultimately, it was this radiographic appearance that lead us to pursue further pathologic diagnosis.

References
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Anomalous Origin of Right Coronary Artery
Neerav G. Sheth MD, Siva K. Kumar, MD

Introduction
Anomalous coronary arteries are rare but potentially life threatening abnormalities of the coronary circulation. Many of the variations can be benign in nature; however, some may lead to myocardial ischemia and/or sudden cardiac arrest. The most common anomalies described in the medical literature involve branches of the left coronary artery, with the left circumflex artery originating from the right sinus of Valsalva being the most prevalent. Patients may present at any age with symptoms ranging from syncope to sudden cardiac death. Here we present a case of a patient with anomalous right coronary artery circulation (RCA) who presented with atypical chest pain.

Case Report
A 38-year-old African American male with a past medical history of hypertension, COPD, and cocaine abuse presented with a three day history of atypical chest pain. Initial ECG showed Normal Sinus Rhythm, non-specific ST changes with premature ventricular contraction and a positive urine drug screen for cocaine metabolites (Figure 1). He underwent a Cardiac CTA from emergency room which revealed an anomalous origin of the RCA approximately 8mm above the sinotubular junction above the left coronary sinus of Valsalva. Furthermore, the proximal portion of the vessel traversed between the aorta and right ventricular outflow tracts (Figure 2). Given the patient’s anomalous RCA course, cardiothoracic surgery was consulted for surgical repair of the anomalous vessel. The rationale for surgical repair is based on a significantly increased risk for sudden cardiac arrest and myocardial infarction. His particular anatomy places him at an extremely high risk during exercise secondary to dilatation of the pulmonary artery and aorta resulting in compression of the proximal portion of the anomalous vessel thereby inducing ischemia and ventricular arrhythmia leading to sudden death. The patient was taken to the operating room for a one-vessel saphenous vein aortocoronary bypass to the RCA at the level of the posterior descending artery (PDA).

Discussion
Splanchnic mesoderm gives rise to all component of a normal heart. The mesoderm differentiates into the cardiogenic area that occurs during week 3 of embryogenesis. The cardiogenic area subsequently forms a pair of endocardial tubes which fuse to form the primitive heart tube. Normal coronary arteries arise from appropriate differentiation of pleuripotent cells into their...
respective anatomic and functional components. Anomalies of the coronary circulation result from processes that disrupt the normal differentiation and specialization of the primitive heart tube. In particular, abnormal involution, position of endothelial buds, or septation of the truncus arteriosus may give rise to anomalous origin of coronary arteries.

In general, anomalous coronary arteries can be described as those able to cause interruptions in coronary blood flow or significant or major anomalies, and those that do not, also known as nonsignificant or minor anomalies. Significant anomalies are exceedingly rare, but are responsible for 0.25% - 0.9% of congenital malformations.

With respect to our case, anomalous origin of the right coronary artery from the left coronary sinus of Valsalva occurs with an incidence of 0.05% to 0.1% in the general population. While anomalous coronary arteries occur with low frequency, there is a high risk of sudden death due to myocardial ischemia and resultant arrhythmia associated with them. Various mechanisms have been postulated to cause the aforementioned ischemia including: Origin in an acute angle and folding or occlusion caused by the angulation at the point of coronary artery emergence, coronary spasm resulting from its torsion movement, mechanical compression of the anomalous artery between the pulmonary and aortic trunks during physical exertion, and an intramural origin of the coronary artery from within the aortic tunica media. The majority of these complications may be exacerbated during or immediately after exercise, as exercise leads to compression of coronary arteries as well as increasing the preexisting angulation of the proximal portion of the anomalous vessel.

Clinical presentation of these patients ranges from asymptomatic for non-significant anomalies to syncope, chest pain, myocardial infarction and sudden cardiac death in significant anomalies. Diagnosis of anomalous coronary arteries may be suggested by echocardiography and a high index of suspicion. Depending on the course of the anomalous vessel, a nuclear stress test may reveal regional hypoperfusion abnormalities in the myocardium supplied by the vessel. In the current era, there is also a role for Cardiac CTA (CCTA) and Cardiac MRA (CMRA) as non-invasive diagnostic modalities prior to or in lieu of coronary angiography. A few small studies have shown CMRA to show a high degree of correlation to cardiac catheterization and have a sensitivity of 88% and a specificity of 100% as compared with traditional coronary angiography. Similarly, multi-detector row CCTA has also been shown to accurately depict anomalous origin of coronary arteries in those with equivocal findings at cardiac catheterization or echocardiography.

Treatment of significant anomalies should be guided by the nature of the anomalous vessel. The vessel may need surgical reconstruction, decompression, reimplantation in the correct sinus, or bypass with ligation of the native vessel to eliminate competitive flow in the graft. Particularly, if a vessel courses between the aorta and pulmonary trunks, has a narrow ostium, or arises from the pulmonary vasculature, it is highly susceptible to repeated episodes of myocardial ischemia. These patients would benefit from surgical intervention. Those with asymptomatic or non-significant anomalous coronary arteries may be observed and managed clinically.

Our patient did extremely well following a single vessel aorto-coronary bypass grafting to the RCA at the level of the PDA. He had complete resolution of his presenting chest pain upon completion of the bypass. He was medically optimized prior to discharge and had no further symptoms at follow up.

References

The “Great Imitator” Presents with Abnormal Liver Enzymes
Ikumi Suzuki, MS IV, Nicholas Orfanidis, MD, Stephanie Moleski, MD, Leo C Katz, MD, David Kastenberg, MD

Case Report
A 28 year-old male was referred to the gastroenterology clinic for evaluation of abnormal liver enzymes. Three months prior to presentation he was evaluated at a local emergency department for vomiting and upper abdominal pain. He described pain as epigastric and worse after eating. He denied fever, chills or changes in his urine. At that time, the patient was not jaundiced but reported having a rash. Laboratory testing was remarkable for elevated liver enzymes (Table 1). The patient was advised to follow up with his primary care physician. Though his symptoms resolved without medical therapy, liver enzymes obtained a few weeks later by his primary physician demonstrated progressive elevation and he was referred to the gastroenterology (GI) clinic for further evaluation.

At the time of presentation to the GI clinic, the patient reported a mild sore throat. He denied any recent sick contacts. The past medical history was significant for a Staphylococcus aureus (MRSA) infection 6 months prior for which he was successfully treated with antibiotics. Around the same time, he reports being HIV negative. Since the course of antibiotics, he had not taken any medications, herbal supplements, vitamins, or other over the counter medications, but drank green tea 2-3 times a week.

On physical examination, the patient was a well-developed, well-nourished African American male who appeared comfortable. Vital signs revealed a blood pressure of 137/89 and pulse of 67. There was no scleral icterus, the mouth and oral pharynx appeared normal, and there was no palpable lymphadenopathy. Cardiovascular and pulmonary exams were normal. The abdomen was soft with normal bowel sounds, non-tender, non-distended, and without hepatosplenomegaly, masses, or dullness at the flanks. Both the rectal and genital exams were normal. Skin examination revealed no rashes, jaundice, or stigmata of liver disease.

Liver enzymes were repeated and demonstrated a progressive rise in alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). (Table 1) Additional laboratory studies revealed a complete blood count within normal limits, total bilirubin 1.4 mg/dL (0.2-1.2 mg/dL), direct bilirubin 0.5 mg/dL (0.0-0.4 mg/dL), PT 13.3 seconds (normal 11.1-15.5 seconds) with INR 1.0 (normal 0.80-1.21), and PTT 56 seconds (normal 19- 39 seconds). The initial work-up for abnormal liver enzymes revealed the following: hepatitis A IgG/IgM antibody, hepatitis B PCR, hepatitis C PCR, CMV quantitative PCR, antinuclear antibody (ANA), antimitochondrial antibody (AMA), anti-liver kidney microsomal (anti-LKM) antibody were all within normal limits, and ceruloplasmin was 109 mg/dL (normal 22 - 58 mg/dL). An ultrasound of the liver and biliary tree was unremarkable.

A liver biopsy was entertained, but before proceeding an additional test was ordered based on the history of rash and pattern of liver enzyme elevation – a rapid plasma reagin (RPR). The RPR was reactive with a titer of 1:256. A confirmatory fluorescent treponemal antibody absorbed (FTA-ABS) was reactive and the patient was diagnosed with secondary syphilis with hepatic involvement. Upon diagnosis, the patient reported being informed of negative test results for both syphilis and HIV approximately 6 months prior to this presentation. He was treated with 2.4 million units of benzathine penicillin G intramuscularly. Given the new diagnosis of a sexually transmitted disease, repeat HIV testing was also recommended and was negative. As presented in Table 1, the liver enzymes improved rapidly following treatment.

Discussion
Syphilis is a complex disease caused by the spirochete Treponema pallidum. More prevalent in the pre-antibiotic era, this infectious disease remains a global health issue today. The disease was the leading cause of neurologic and cardiovascular disease among the middle-aged population at the turn of the 20th century. Many notable figures have been suspected of having syphilis including Ivan the Terrible, Napoleon Bonaparte and Ludwig van Beethoven. In modern times, the number of cases of

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<td>-------------------------------</td>
</tr>
<tr>
<td>Alkaline Phosphatase (29-92 IU/L)</td>
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<tr>
<td>AST (7-42 IU/L)</td>
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<td>ALT (1-45 IU/L)</td>
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Arrow indicates start of treatment
primary and secondary syphilis in the United States decreased during the 1990s and reached its nadir in 2000 since reporting began in 1941. However, recently the reported number of cases of early syphilis (primary and secondary) in the United States has begun to rise, as demonstrated by an increase from 5,979 reported cases in 2000 to 11,181 in 2007. This infection appears to particularly afflict men who have sex with men (MSM), with this group accounting for 65% of the cases as of 2007.

Untreated, this disease can span decades and cause a wide array of manifestations affecting multiple organ systems, which accounts for it being referred to as the “great imitator.” It can present acutely, or chronically with a more indolent course. Syphilis is typically acquired by contact with a skin or mucosal lesion, often sexually, but may also be acquired congenitally. The natural history of syphilis has been well described and progresses through distinct phases. Primary syphilis is characterized by a chancroid, a painless indurated lesion occurring at the primary site of inoculation. The time from inoculation to presentation of chancroid is inversely proportional to inoculating dose, but typically this incubation period ranges from 10 to 90 days.

About 25 percent of individuals with untreated primary infection will develop secondary syphilis, usually occurring 2 to 8 weeks after appearance of the chancroid. Secondary (disseminated) syphilis most commonly involves the skin as a maculopapular rash involving palms and soles; however, the disease can involve almost any organ in the body. Mucocutaneous, renal, neurologic, gastrointestinal, hepatic and pulmonary manifestations have all been reported. Constitutional symptoms such as fever, headache, malaise, anorexia, sore throat, myalgias, and weight loss may be present. As the manifestations of secondary syphilis subside, the disease enters a latent period. Latent syphilis is characterized by positive serologies with no clinical signs of infection. Relapse of secondary syphilis can occur as late as 4 years after initial contact, but 75 percent of relapses occur within the first year. Cellular immunity is thought to play a role in the pathogenesis. About one third of untreated patients with latent syphilis develop tertiary syphilis in as early as one year, or as late as 25 to 30 years, after initial infection. Tertiary syphilis presents with symptomatic involvement of the central nervous system (CNS), cardiovascular system, or the skin and subcutaneous tissues. CNS findings can include meningitis, general paresis, tabes dorsalis (disease of the posterior columns of spinal cord) and meningovascular disease. Cardiovascular disease mainly involves the aortic root, which can lead to aortic insufficiency. Gummatus syphilis can manifest as ulceration on the skin or a mass lesion involving the viscera.

Secondary syphilis, the diagnosis in the patient we have described, is an uncommon and often overlooked cause of hepatitis. Unfamiliarity with the wide-ranging clinical presentations of secondary syphilis may delay or prevent diagnosis, unfortunate given the availability of highly effective therapy. Approximately 10% of patients with secondary syphilis may have liver enzyme abnormalities, but clinically apparent hepatitis is rare. The exact mechanism of disease is unknown but it has been proposed that direct portal venous inoculation and immune complex-mediated processes may be involved. As in this case, the pattern of liver enzymes found in syphilitic hepatitis often has a cholestatic pattern with a disproportionate elevation of alkaline phosphatase and a less prominent elevation of aminotransferases. One study of HIV-positive patients with syphilitic hepatitis showed alkaline phosphatase levels ranging from 234 to 1870 IU/L at time of diagnosis. Hyperbilirubinemia is not commonly seen.

Liver biopsy, generally unnecessary if the diagnosis is entertained and appropriate serologic testing obtained, demonstrates nonspecific findings including periportal lymphocytic infiltration with focal necrosis around central veins, portal areas, and lobules. Treponemal or granulomatous changes are seen in nearly half of cases.

*T. pallidum*, the organism responsible for syphilis, cannot be cultured in a laboratory. The quickest and the most direct method of diagnosing primary and secondary syphilis is by direct visualization of exudate from the primary lesion using darkfield microscopy. This requires specialized equipment and experienced technicians to recognize the spirochetes. The use of this method is limited to clinics dedicated to diagnosing and treating sexually transmitted diseases. An alternative method of direct spirochete visualization is the use of direct fluorescent antibody testing (DFA-TP). DFA-TP utilizes fluorescein microscopy to examine specimens incubated with fluorescein-labeled anti-*T. pallidum* globulin. This method also requires specialized equipment and trained personnel which is not widely available, and therefore most patients suspected of having syphilis are diagnosed using an indirect method - serologic testing.

There are two types of serologic tests. The first type is the nontreponemal test, which detects antibodies against cardiolipin-cholesterol-lecithin antigens. Examples are the Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR). Positive results are reported as an antibody titer, and these tests are relatively inexpensive and easy to perform. The second type of serologic testing is specific treponemal tests, which detect antibodies against the treponemes and/or its cellular components. Examples of these tests are fluorescent treponemal antibody absorption (FTA-ABS) test, microhemagglutination test (MHA-TP) and *Treponema pallidum* particle agglutination assay (TPPA). These are qualitative tests reported as either reactive or non-reactive. Nontreponemal tests are 78% to 86% sensitive in primary syphilis and close to 100% sensitive in secondary syphilis. Both nontreponemal and treponemal-specific tests can be falsely positive for many reasons including acute febrile illnesses and immunizations. These test abnormalities typically disappear within 6 months. Chronic illnesses are also implicated as causes of false positive testing including autoimmune disorders like...
systemic lupus erythematosus, intravenous drug use, chronic liver disease and HIV infection. False negative results can also occur, and this may be seen in as many as 20-30% of patients presenting with a chancre of primary syphilis. Direct visualization techniques, i.e., darkfield microscopy and DFA-TP, are the only definitive methods of diagnosing early syphilis. Current recommendations state that use of only one serologic test is not adequate for making a diagnosis. For screening purposes in those who are asymptomatic, a VDRL test should be done and those with positive results should get confirmation using a treponemal test. Nontreponemal antibody titer is an indicator of disease activity and thus can be used to monitor disease progress. A four-fold change in titer is considered clinically significant. Contrary to this, a person with reactive treponeme-specific tests will have lifelong reactivity even if they are not symptomatic and therefore such testing is not appropriate for monitoring disease. Any person with positive treponemal tests should have a nontreponemal test with titer to assess the status of disease.

The recommended treatment regimen for adults with primary, secondary and early latent syphilis is benzathine penicillin G 2.4 million units IM in a single dose. Late latent syphilis or latent syphilis of unknown duration requires three doses of 2.4 million units IM each at one-week intervals. As seen in our patient, following treatment the liver enzymes rapidly improve and this response to treatment offers further confirmation of the diagnosis. All patients should be reevaluated 6 and 12 months after treatment. A four-fold reduction in titer of the nontreponemal antibody test (e.g., from 1:16 to 1:4) is considered evidence of an appropriate response. The two nontreponemal tests (VDRL and RPR) cannot be compared directly, so serial monitoring should be performed with the same test. Those without symptomatic improvement or a sustained four-fold reduction in nontreponemal titers should be retreated.

Early detection is imperative in a disease like syphilis where definitive treatment is available and devastating permanent consequences are possible if left untreated. Although a case of fulminant hepatic failure requiring liver transplant secondary to syphilitic hepatitis has been reported, patients should not have any sequelae of chronic liver disease if appropriate treatment is given. Because of the varied presentation of secondary syphilis, the diagnosis of syphilitic hepatitis should be entertained in anyone presenting with vague constitutional symptoms and acute liver dysfunction with a cholestatic pattern when obstruction, primary disorders such as primary biliary cirrhosis and sclerosing cholangitis, and environmental exposure have been excluded. Clinicians need to have a heightened index of suspicion for this disease in patients at higher risk for syphilis including those with HIV infection and MSM in order to eliminate the need for unnecessary and invasive testing and offer patients rapid resolution of their disease.

References
A 61-year-old morbidly obese woman first presented to a community hospital with complaints of feeling “unwell” for 2 weeks. Her family reported that she had been having increasing fatigue, diarrhea, nausea, and vomiting for that period, as well as “dusky” fingers and toes. Prior to this time, she had noticed a runny nose, cough, and “bluish” toes for about 3 weeks. On presentation, she was hypotensive with a systolic blood pressure in the 50’s mmHg and tachycardic to 115 beats per minute (bpm), but afebrile. Her creatinine was found to be 12 mg/dL from an unknown baseline. Treatment was initiated in the Emergency Department with fluids and antibiotics, and she was admitted to the Medical Intensive Care Unit for management of septic shock. The patient was also found to have a urinary tract infection, with negative blood cultures. Stool was checked for Clostridium difficile infection, which was also negative. After 7 days of treatment for septic shock in the ICU including 2 days of hemodialysis, she was transferred to our tertiary center for further management.

The patient’s past medical history included morbid obesity and obstructive sleep apnea, but no prior surgeries. Family history was remarkable for coronary artery disease in her father. She had no history of tobacco, ethanol or illicit substance use. She was not on any outpatient medications. Inpatient medications at the time of transfer included intravenous hydrocortisone, esomeprazole, regular insulin sliding scale and intravenous antibiotics. At the time of transfer, she was not requiring vasopressor medication support.

Physical examination showed an obese woman who was sedated and intubated, in no acute distress. She had a temperature of 95.9°F, a heart rate of 108 bpm, a blood pressure of 118/55mmHg, a respiratory rate of 24 breaths per minute, and an oxygen saturation of 94%. She had a BMI of 42.3. Notable physical findings were as follows: coarse breath sounds at bilateral lung bases, diminished bowel sounds, bilateral upper and lower extremity edema with cyanotic digits on all extremities and appearance of necrosis on several toes. She had a peripherally inserted central catheter (PICC) in the right upper extremity.

Studies on admission included the following: total white blood cell count of 16,600 with a left shift, hemoglobin of 9.9 g/dL and platelets 114,000. Chemistries were as follows: sodium 143 mmol/L, potassium 3.7 mmol/L, chloride 108 mmol/L, bicarbonate 25 mmol/L, blood urea nitrogen of 17 mg/dL and creatinine of 4.0 mg/dL. A chest x-ray showed multifocal consolidation with underlying bilateral pulmonary edema.

On the first day of admission the PICC line removed, and an internal jugular venous catheter and a femoral artery catheter were inserted. These were connected to a PICCO® (Pulsion Medical Systems, Munich, Germany) monitor for measurement of hemodynamic parameters as well as serial calculation of Extravascular Lung Water Index (ELWI) via transpulmonary thermodilution technique. ELWI was from that point onward calculated serially, and used to direct the amount of intravenous fluid resuscitation and the use of vasopressors. With hemodialysis initiated, the ELWI was also used to determine the amount of fluid volume to be removed at each session. Clinical and X-ray resolution of the pulmonary edema were in turn monitored and correlated with the calculated ELWI. Ventilator settings were adjusted as needed to optimize oxygenation and ventilation depending on perceived extravascular lung water content. Other primary and surrogate hemodynamic parameters recorded included cardiac index (CI), stroke volume index (SVI), stroke volume variation (SVV), mean arterial pressure (MAP), systemic vascular resistance index (SVRI), cardiac flow index (CFI), and global end diastolic volume index (GEDI).

**Discussion**

Fluid resuscitation in an ICU setting is a complicated affair because traditional cardiac monitoring does not always accurately predict fluid responsiveness. Specifically, a fluid challenge does not necessarily correlate with an increase in cardiac output (CO), and furthermore may not accurately reflect the development of pulmonary edema. For this reason, the measurement of extravascular lung water (EVLW) was developed. The PICCO system, developed by Pulsion Medical Systems from Munich, Germany, works by single thermal indicator transpulmonary dilution.

The main advantage of this system is that it requires only placement of a central venous and an arterial catheter, avoiding a pulmonary artery catheter and its associated risks. The central venous catheter and arterial catheter are connected to a pressure transducer and to the PICCO system. In difficult situations for catheter placement, such as in patients with a contraindication to the Trendelenburg position which makes placing a subclavian or internal jugular venous catheter tricky, the PICCO can still be used. This is unlike traditional Swan-Ganz catheterers. One study has shown that the EVLW and CO parameters correlated even with a femoral venous catheter, demonstrating the efficacy of the PICCO to guide fluid status in patients that have central access issues.

After calibration, ice-cold saline (5°C) is injected in three 10mL aliquots. The femoral arterial catheter measures the change in temperature through its thermistor tip. The subsequent pulse contour analysis calculates the area under the curve, the mean transit time (MTt), and the down-slope time (DSt). The mean transit time is the amount of time for half of the saline bolus to pass by the thermistor, while the down-slope time is the duration of the exponential decrease of the dilution curve. Using these measurements, the CO, global end diastolic volume (GEDV), and intra-thoracic blood volume (ITBV) are calculated.
Table 1. Serial sample readings of the parameters prior to and after 3 liters of fluid were removed via hemodialysis

<table>
<thead>
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<th>Date</th>
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<tbody>
<tr>
<td>Time</td>
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<tr>
<td><strong>CARDIAC OUTPUT</strong></td>
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<tr>
<td>CI (3-5 l/min/m2)</td>
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<td>2.52</td>
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<tr>
<td>Frequency</td>
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<tr>
<td>HR (1/min)</td>
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<td>67</td>
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<tr>
<td>Rhythm</td>
<td>SR</td>
<td>SR</td>
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<tr>
<td>Stroke Volume</td>
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<tr>
<td>SVI (40-60 ml/m2)</td>
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<td>37</td>
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<tr>
<td>Preload</td>
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<tr>
<td>GEDI (680-800 ml/m2)</td>
<td>760</td>
<td>602</td>
</tr>
<tr>
<td>SVV (&lt;10%)</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Afterload</td>
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</tr>
<tr>
<td>MAP (mmHg)</td>
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</tr>
<tr>
<td>SVRI (1970-2390 dyn's cm^-5%m2)</td>
<td>3455</td>
<td>2986</td>
</tr>
<tr>
<td>Contractility</td>
<td></td>
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<tr>
<td>CFI (4.5-6.5 1/min)</td>
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<td>6</td>
</tr>
<tr>
<td><strong>LUNG FUNCTION</strong></td>
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<tr>
<td>ELWI (3-7 ml/kg)</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td><strong>THERAPEUTIC INTERVENTION</strong></td>
<td></td>
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<tr>
<td>3L removed via HD</td>
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to estimate preload, and EVLW is calculated to indicate degree of pulmonary edema. These hemodynamic values are indexed to body surface area (BSA) by the DuBois formula with body weight in kilograms and height in centimeters squared. The area under the curve correlates with the CO. Multiplication of the CO and the DSt gives the pulmonary thermal volume (PTV), which is the largest individual volume in the series of indicator dilution mixing chambers. Intra-thoracic thermal volume (ITTV) is the volume of blood in which the ice-cold water is dissolved and is calculated by multiplying CO and MTt, which represents the total volume of the cardiac atria and ventricles and part of the systemic vascular blood volume or the right and left atrial end diastolic volumes (RAEDV and LAEDV), the right and left ventricular diastolic volumes (RVEDV and LVEDV), and the pulmonary thermal volume. Subtraction of PTV from ITTV represents the GEDV or the total diastolic blood volume of the heart. Previously, Sakka et al. determined the correlation of ITTV and GEDV to be 1.25 x GEDV – 28.4(ml). EVLW can be calculated via this equation by subtracting ITTV from IBTV. Normal values of EVLW are 5-7ml/kg, with values above 10ml/kg correlating with mild pulmonary edema, and up to 30ml/kg representing severe pulmonary edema.

The principle of measuring EVLW rests in the fact that large increases in EVLW predate the onset of alveolar edema and symptoms of flooding. One study found that the transpulmonary thermodilution method is actually more accurate in detecting small rather than large changes in EVLW, which allows for earlier detection of pulmonary edema. This is explained by the fact that when large amounts of liquid are introduced, and the lung is already edematous, the ice cold water may not have spread throughout the appropriate volumes assumed in the above formulas allowing some introduced fluid to be undetected. Previous comments about the clinical use of extravascular lung water have questioned the use of PICCO given that the significance of detecting small increases in EVLW is unknown. We propose that utilization of PICCO in measuring EVLW in the patient described above allowed us to clinically decide, in conjunction with ventilatory status, arterial blood gases, and chest x-rays, the appropriate time to attempt extubation.

This patient had developed renal failure prior to arriving at our institution, and as such had negligible urine output while on dialysis allowing for near complete control of volume removal. We intervened on her fluid status directly by removing numerous liters of fluid per dialysis session. After inserting the PICCO system, our patient’s EVLW was calculated to be 12ml/kg, correlating with some pulmonary edema, and remained at this level until 2 liters were removed through hemodialysis. Immediately following this intervention, the EVLW decreased to 10ml/kg. Subsequent resuscitation efforts increased this value again to 12ml/kg. Our solution was to remove 3 liters of fluid on two subsequent days, decreasing the EVLW to 7ml/kg, or within normal range. The patient’s chest x-ray and ventilatory status correlated with the improved values, and she was then successfully extubated.

Conclusion
Algorithmic decisions involving diagnosis and treatment of acute lung injuries are aided by the use of the PICCO system in measuring EVLW and may allow for the quantification of injury. Though several studies have not shown a correlation between chest x-rays and EVLW values, we suggest that the volume changes within the lung may be enough to cause clinical difference even if the radiography is not significantly different, however formal prospective studies are necessary to analyze this relationship.

References
A 50 Year-Old Homeless Man With Symptomatic Palpitations
Neerav G. Sheth MD, Daniel R. Frisch, MD

Case Report
The patient is a 50-year-old man with Hepatitis C, HIV, and pneumonia who recently became homeless and presented with 3 days of worsening palpitations and shortness of breath. Initially the palpitations were sporadic; however, they had become more frequent over the three days prior to admission. He had a corresponding increase in shortness of breath along with significant decreases in his exercise tolerance. He presented to the Emergency Department (ED) when he could no longer perform his usual activities of daily living. In the ED, patient was found to have a narrow complex tachycardia with a rate of 234 beats per minute (bpm) (Figure 1).

His past history is significant for HIV diagnosed in 1979 with a recent CD4 Count of 16. The patient was not on HAART medication due to noncompliance resulting from financial issues. He also has a history of Hepatitis C secondary to remote intravenous drug abuse. He had pneumonia approximately three weeks prior to admission, which was incompletely treated with antibiotics. The patient also noted a 30-pack year history of tobacco use.

In the ED, the patient was given large volumes of normal saline followed by 3 sequential doses of adenosine, all of which failed to terminate his tachycardia. He was then started on an esmolol infusion with resultant hypotension to a systolic blood pressure (SBP) of 80mmHg. The esmolol infusion was subsequently stopped and patient received diltiazem. Following the diltiazem infusion, the patient still had no decrease in his rapid heart rate. A cardiology consultation was requested and procainamide was recommended for chemical cardioversion; however, the patient’s blood pressure had deteriorated to SBP of 70mmHg with a heart rate of 240 bpm and the patient was urgently electrically cardioverted. Sinus rhythm was restored at a rate of 110 bpm and the SBP improved to 130 mmHg. He was then referred to the Electrophysiology (EP) service in order to evaluate for a more durable and definitive management of his supraventricular tachycardia (SVT). An EP study was performed and revealed an atrioventricular accessory pathway on the left lateral mitral annulus that was responsible for his SVT. The accessory pathway was successfully ablated as evidenced by intracardiac electrograms and by a lack of initiation of supraventricular tachycardia following isoproterenol administration after ablation (Figure 2).

Discussion
Supraventricular tachycardia (SVT) is an accelerated rhythm occurring with a prevalence of 2.25 / 1000 in the general population with an incidence of 35/100,000 person-years.1 The three most common mechanisms of SVT are atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and atrial tachycardia (AT). A common feature of all three mechanisms is a narrow QRS complex (usually identical to the QRS seen in sinus rhythm), which distinguishes these tachycardias from ventricular...
tachycardia. Of the three types, AVNRT is the most common, followed by AVRT. Women more often present with AVNRT, while men, particularly younger men, are more likely to present with AVRT. AT is more likely to present in patients with advanced age and/or structural heart disease. While a surface electrocardiogram can often diagnose which of the three mechanisms is present, an EP study is the gold standard for diagnosis.

A spectrum of strategies exists for the initial management of SVT. These include invasive EP studies (i.e. catheter ablation), noninvasive medical management, and even watchful waiting. Typically medications (beta blockers, calcium channel blockers) are used to control the heart rate in SVT. In rare circumstances, anti-arrhythmic medications such as digoxin and procainamide can be used as well. However, in all instances of proven SVT, an EP study with catheter ablation should be considered as a first-line treatment (ACC/AHA/ESC Guidelines Class I, Level of Evidence B recommendation). This is true even for a patient’s initial presentation of SVT.

In this case, the patient’s initial presentation of SVT was highly symptomatic and required urgent care for stabilization and an expedited EP study with catheter ablation for definitive treatment. Though it may seem aggressive, this was likely the best option for this patient. He had been previously non-compliant with prescribed medications and had an inability to follow up regularly with physicians, likely due to socioeconomic hardship. The dilemma posed here is how aggressively to treat this patient’s first documented episode of SVT. Despite the fact that EP studies are invasive and expensive procedures, frequently an EP study may be more clinically beneficial as well as cost effective. A single treatment that provides durable benefit is appealing and is likely to decrease a patient’s burden of disease and health care utilization for this issue. While ethically we are obligated as physicians to do what is in the best interest of the patient without regard to socioeconomic status, we are not immune from the economic reality of the price tag associated with our treatments. The initial investment of a relatively aggressive procedure in this case accomplished the goal of resolving this patient’s symptoms and addressing the challenge of medical compliance.

**References**

A Woman With Syncope and Severe, Progressive Headaches
Jennifer Koterwas MS IV, Hind Rahmouni MD, Joanna Kipnes MD

Case Report
A 61 year-old female who was status post-gastrectomy and chemotherapy for gastric cancer presented to the emergency department with complaints of two syncopal episodes and ongoing headaches for the last month. Her syncopal episodes occurred on the day of admission and five days prior and were preceded by shaking, dizziness, and a feeling of being in a “different dimension.” The losses of consciousness lasted for several minutes and were accompanied by shaking, but were not associated with any urinary or bowel incontinence or tongue biting. The patient denied any fevers or new medications, and felt that the episodes were not associated with a specific activity or time of day. The patient also complained of new onset headaches that had progressed in frequency over the last month from being present for only a few minutes a day to being present for the entire day. The headaches were described as a “brain freeze,” with 10 out of 10 pain that was not relieved by acetaminophen with codeine, ibuprofen, or morphine. The headaches were non-radiating and diffusely located throughout the head. The headaches were exacerbated by movement, and associated with an increase in nausea and vomiting. The patient did not have any lacrimation or rhinorrhea, and she denied any past history of migraines, head trauma, or neck pain. Review of systems was negative except for a progressive increase in blurry vision with occasional white spots in her vision over the last three weeks. One week prior to admission she had an outpatient brain MRI (Figure 1a) done, and two days ago a head CT both of which showed no evidence of metastatic disease, hemorrhage, infarct, or mass lesion.

Past medical history was significant for gastric adenocarcinoma (linitus plastica) status-post gastrectomy 3 months ago and neoadjuvant chemotherapy with the last dose 3 weeks ago. The patient was on her fifth week of radiation therapy out of six weeks. Her current medications included as needed acetaminophen with codeine, ibuprofen, prochlorperazine, and lorazepam.

On presentation the patient was afebrile with a temperature of 96.4°F, and had a respiratory rate of 18 breaths/minute. She had orthostatic heart rate changes as demonstrated by an increase in her heart rate from 87 bpm while supine to 101 bpm while standing. Her supine blood pressure was 160/100 and her standing blood pressure was 177/107. She was fully oriented to person, place, and time. The patient had no nuchal rigidity, nystagmus, or focal neurologic signs. Her cranial nerves, motor, sensory, and cerebellar functions were all intact. Reflexes were 2+ bilaterally in the upper and lower extremities and gait was normal.

The patient was admitted for a workup of syncope associated with severe, progressive headaches. Intracranial bleeding or a brain tumor was lower on the differential given the recent normal head CT and brain MRI. A cardiac etiology was also unlikely based on the negative history of cardiac disease and a normal physical exam, EKG, and echocardiogram. Dehydration was suspected based on the patient’s orthostatic heart rate changes and poor dietary intake. Cerebral vasospasm was thought to be high on the differential for the most likely cause of her headaches also because of unconcerning imaging and unusual presentation.

Seizures appeared to be the most likely cause of her loss of consciousness so an EEG was performed. The EEG revealed focal slow waves greater on the left mid-temporal region than the right and frontal intermittent rhythmic delta activity. Fluid resuscitation was initiated and neurology was consulted to help with diagnosis and treatment. Following the neurologist’s recommendation, an MRA of the brain was ordered which revealed no evidence of cerebral artery stenosis or aneurysms.

As there was no improvement in the patient’s symptoms, a lumbar puncture was performed on hospital day three which revealed a non-specific pattern of an elevated opening pressure of 24 mm H₂O, elevated cerebral spinal fluid (CSF) protein of 114mg/dL, and a normal glucose of 43 mg/dL. On hospital day six the patient became acutely confused, lethargic, and no longer oriented to time. Absence seizures were witnessed by the nurses. Her delirium continued to progress with agitation and...

Figure 1a. Initial MRI of the brain showing no evidence of metastatic disease, hemorrhage, infarct, or mass lesion.
new onset hallucinations and delusions. She also developed an unstable gait, and a new right cranial nerve six palsy. Due to her rapidly declining condition, dexamethasone was started.

Ophthalmology was consulted to examine the patient’s visual changes and to evaluate for papilledema due to her elevated opening pressure on the lumbar puncture. On exam, a choroidal lesion was detected that was suspicious for metastasis. The same day, CSF cytology results came back from the initial lumbar puncture revealing atypical cells highly suspicious for cancer of an unknown primary. The results of the lumbar puncture cytology and the suspected metastatic choroidal lesion prompted a repeat MRI and lumbar puncture. The results from the repeat MRI revealed increased FLAIR and enhancement in the subarachnoid space (Figure 1b). The repeat lumbar puncture revealed an elevated opening pressure of 36 mm H₂O, elevated fluid protein of 93 mg/dL, and a low glucose level of 37 mg/dL, findings which were more consistent with metastatic cancer. The repeat CSF cytology revealed malignant cells consistent with metastatic adenocarcinoma (Figure 2). Both results supported the diagnosis of leptomeningeal carcinomatosis (LC) secondary to linitis plastica adenocarcinoma. The patient was started on corticosteroids.

On the ninth day of her hospital course and the third day of steroids, the patient’s mental status markedly improved to being fully oriented to person, time, and place with only mild confusion. Her headache also improved and was now present transiently following her steroid treatments. She was able to understand her diagnosis and treatment options, and elected to begin a 5-day course of whole brain radiation followed by intrathecal chemotherapy. Her mental status returned to baseline and she was discharged home on hospital day 41.

**Discussion**

Linitis plastica is a poorly differentiated gastric adenocarcinoma that infiltrates the gastric wall and is commonly associated with peritoneal and lymph node metastases. Histologically, linitis plastica is characterized by signet ring cells along with a marked fibroblastic stroma reaction. Interestingly, LC arises in only 3% to 8% of all solid cancers and most frequently in patients with leukemia, breast cancer, lymphoma, melanoma, and lung cancer.¹³ The incidence of LC due to gastric cancer is 0.06%, although the diagnosis may be on the rise due to an increased survival time in gastric cancer patients.²⁴ Advanced gastric cancer patients classified as Borrmann type III and IV which includes linitis plastica, have higher rates of developing LC when compared to those with early disease. The majority of patients are diagnosed during the treatment of primary gastric cancer as seen in our patient.¹²

Extra-abdominal metastasis occurs in less than 13% of gastric cancer patients with the majority of cases spreading hematogenously to the lung or bone. Although still debated, it is believed that the Batson’s venous plexus which consists of longitudinally oriented, valveless paraspinal veins may be the primary route for...
tumor cells to reach the subarachnoid space. Another theory postulates that the gastric cancer spreads by direct extension along peripheral nerves to the subarachnoid space. Once the cancer reaches the leptomeninges and subarachnoid space it has access to all regions of the central nervous system, leading to a variety of nonspecific signs and symptoms. LC’s clinical presentations are variable, ranging from isolated to multiple central nervous system, spinal, and cranial nerve symptoms and signs. Some common clinical symptoms and signs include headaches, nausea, vomiting, altered mental status, seizures, cranial nerve palsy, visual changes, limb weaknesses, and speech difficulties. LC is difficult to diagnose not only because of the variety of presentations, but also because many of the symptoms resemble common chemotherapeutic induced side-effects, for example nausea, vomiting, sensory loss, hearing loss, vertigo, and nystagmus. 

Unfortunately there is no single laboratory test or imaging study that is capable of detecting all cases of LC. Diagnosis for LC rests on CSF cytology. The sensitivity of a single lumbar puncture in the detection of atypical cells diagnostic for LC is 54%, but higher sensitivities can be obtained through repeated tests. The sensitivity of LC increases to 75% after two lumbar punctures, and up to 85% after three lumbar punctures. Other CSF results suggestive of LC include: increased opening CSF pressure, increased CSF cellularity, elevated protein CSF content, and decreased CSF glucose concentration. The patient described in this case study had an increased CSF pressure, increased protein, and a decreased glucose consistent with the eventual diagnosis of LC.

The imaging study of choice for leptomeningeal carcinomatosis is an MRI of the brain, which characteristically shows focal areas of linear meningeal enhancement in a nodular pattern. The MRI sensitivity for detecting LC however ranges only from 66% to 77%. Given the low sensitivity of both CSF cytology and MRI when used alone, it has been reported that up to 18% of patients with LC are likely missed. The patient described in this case fell into this category because her diagnosis was missed initially based on her first MRI. Contrast enhanced CT scans are also commonly used to evaluate patients but it should be noted that at most the sensitivity is only 44%.

Unfortunately, the prognosis of LC secondary to gastric cancer is poor with a mean survival of four to six weeks for those who do not receive treatment and a mean survival of two to six months for those who receive treatment. Some factors that favor survival are a good performance status, a response to intrathecal chemotherapy, a low CSF lactate dehydrogenase concentration, and minimal neurological symptoms. The dismal prognosis of LC in the setting of gastric cancer stresses the importance of early diagnosis because early palliative treatment may help to improve quality of life. A high clinical suspicion is necessary to diagnose LC secondary to gastric cancer due to its nonspecific symptoms, low sensitivity tests, and rare association with gastric cancer. Therefore, even when imaging studies are not supportive as in the above case, the diagnosis of LC should not be ruled out and repeat studies such as a lumbar puncture should be considered. Although only a few cases of intraocular metastasis of gastric adenocarcinoma have been reported, a thorough ophthalmologic exam should also be considered especially in patients with new-onset visual changes as it may reveal metastasis (as in this case) and help to expedite the diagnosis.

References
A Case Report of a Patient With Liver, Psoas Muscle and Porta Hepatis Abscesses

Eugene Kofi Essandoh, MD

Case Report

A 26-year-old African American male with a history of HIV and CD4 count of 507 on HAART was sent to the Emergency Department after a biopsy of a psoas muscle collection demonstrated pustular drainage. The patient reported that approximately three weeks prior to presentation he was found to have elevated liver function tests on routine labs at his primary care office. Subsequently, the patient was sent for an abdominal ultrasound and CAT scan which showed a confluence of lymph node surrounding the porta hepatis as well as a psoas muscle collection. In review of systems, he reported chronic left-sided weakness and occasional muscle tightness in both legs. He denied weakness on the right side, as well as, fevers, chills, cough or shortness of breath. The physical exams was unremarkable except for 4/5 weakness in the left lower extremity. Radiographic imaging (Figure 1) revealed fluid collection in the psoas muscle and abscesses in the liver and spleen.

The patient was admitted to the hospital and started on vancomycin. His abscess was drained but the culture did not reveal any organisms. In order to obtain a fluid sample, surgery performed an exploratory laparoscopy of the fluid collection. The direct smear showed acid fast bacilli and the PPD demonstrated induration. Based on these findings, patient was diagnosed with tuberculosis and started on appropriate therapy.

Discussion

Extrapulmonary tuberculosis (EPTB) refers to tuberculosis infections of organs other than the lung. Affected patients usually have a positive tuberculin skin test and a normal chest x-ray. Tuberculosis can affect almost all organs. Common sites of infection include the lymph nodes, liver, spleen, psoas muscle, adrenal gland, kidney and osteoarticular areas. A resurgence of tuberculosis in USA occurred in the early 1980’s which coincided with the emergence of HIV/AIDS. Though the incidence of the disease is in decline in the US, the global prevalence of the disease is estimated at 32%. The pattern of the disease has changed over the years. Reports demonstrate an increased incidence of disseminated and extrapulmonary TB associated with HIV/AIDS as well as other immunosuppressed disease-states.1

The diagnosis of extrapulmonary TB especially without concomitant pulmonary TB can be elusive. It requires a high index of suspicion based on the patient’s history and risk factors. Clinical clues that should increase suspicion for EPTB are ascites with lymphocyte predominance and negative bacterial cultures; chronic lymphadenopathy; HIV infection; unexplained pericardial effusion or calcification; CSF lymphocytes with elevated protein and low glucose; and exudative pleural effusion with numerous lymphocytes and negative bacteria. A negative acid-fast smear does not exclude the diagnosis. Extra diagnostic tests such as a biopsy or PCR may be necessary in the diagnosis of certain types of EPTB.2

Musculoskeletal involvement accounts for approximately 35% of cases of EPTB. It mostly affects the spine (Pott’s disease) and sometimes articular joints. Paraspinal and psoas muscles abscesses can develop through local extension from a spinal abscess or as a primary site. This group of patients may present with symptoms of lower extremity weakness and localizing back pain. A bone, synovial or muscle biopsy for AFB smear and culture is necessary to make definite diagnosis. Patients with hepatic tuberculosis presents with abnormal liver function test. Clinically, they may have symptoms such as right upper quadrant tenderness, nausea and vomiting. The physical exam may reveal hepatomegaly.

The adrenal glands are rarely affected and even when they are, it rarely results in severe adrenal insufficiency. Less than 3% of TB of the adrenal glands resulted in decreased function of the

Figure 1. A: Psoas muscle with fluid collection
B: Spleen and liver with abscesses
adrenal gland. Tuberculosis rarely affects the myocardium but when it affects the heart, it usually results in pericarditis. Seeding of TB in the brain can produce meningitis and tuberculomas. In a study involving TB patients, about 1 out of 5 was found to have TB meningitis or tuberculomas.

In terms of the lymphatic system, TB most commonly affects the cervical nodes. However, axillary, inguinal, mediastinal and mesenteric nodes can be affected as well. Lymph nodes in symptomatic patients are firm, nontender and discrete but gradually evolve into fluctuant nodes. Diagnosis is made by excision biopsy with AFB staining or culture. FNA has a low yield in immunocompetent patients. One can also perform PCR on a lymph node aspirate.

Reference
A Case Report of a Pheochromocytoma Presenting With Neurological Manifestations

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Case Report
A 51 year-old Caucasian female with a past medical history of hypertension, coronary artery disease and cerebrovascular accident presented to the emergency room with acute onset dysarthria and right-sided hemiparesis. The patient reported that she noticed these symptoms when she woke that morning, but had resolved by the time she reached the emergency room, an hour later. She denied experiencing palpitations, headache, chest pain or shortness of breath.

On review of systems, it was revealed she had intermittent nausea and vomiting for a year with increasing frequency over the past two days. She denied blood or bile in the emesis. She also admitted to a 50-pound weight loss over the past year. Both esophagogastroduodenoscopy and colonoscopy were normal within the past year.

Her medical history was significant for coronary artery disease complicated by two myocardial infarctions the previous year. She had also suffered from two past cerebrovascular accidents – the second of which was complicated by hemorrhage and seizure. Despite several anti-hypertensive medications, the patient’s blood pressure remained uncontrolled.

On admission, the patient was afebrile, had an elevated blood pressure of 167/108, pulse of 95 beats/minute, respiratory rate of 18 breathes/minute, and pulse oximetry of 97% on room air. Generally, the patient appeared comfortable. Cardiovascular exam was benign and pulmonary exam revealed decreased breath sounds bilaterally. Abdominal exam was also benign with no masses appreciated. Neurological exam was significant for slight dysarthria, right homonymous hemianopsia, and right-sided facial droop. Upper and lower extremity strength testing was significant for weakness at 4/5 strength on the left side. Comparatively, the patient’s strength was 5/5 in the upper and lower extremities on the right side. Additionally, she was hyper-reflexive on the right side compared to the left. Sensation was intact throughout. These neurological deficits were consistent with her baseline deficits from past strokes.

CT of the head was significant for an old left middle cerebral artery stroke, but there was no evidence of an acute process. A CT of the abdomen was performed in the emergency room, which revealed an incidental finding of a 6.7 x 5.4 cm right sided adrenal mass (Figure 1).

The laboratory work-up revealed elevated catecholamines: plasma norepinephrine of 41.6, plasma metanephrine of 27.2, fractionated urine norepinephrine of 9390 and fractionated urine metanephrine of 8231.

Diagnoses of transient ischemic attack and pheochromocytoma were made. Her blood pressure medications were changed to the alpha-blocker, phenoxybenzamine. A beta-blocker was later added for additional blood pressure control. The mass was surgically removed four weeks later.

Discussion
A pheochromocytoma is a tumor that results in excess secretion of the catecholamines epinephrine and norepinephrine. It arises from chromaffin cells of the medulla of the adrenal gland, but it can also be located in extra-adrenal, retroperitoneal, pelvic or thoracic sites. Diagnosis relies on measurement of plasma levels of free metanephrines. This test has a high sensitivity (99%) and specificity (89%)1. Between episodes of catecholamine release, catecholamine levels may be normal, which is why the recommended test measures metabolites, rather than the catecholamines themselves. The sensitivity and specificity of other tests such as urinary catecholamines are high, but still less sensitive and less specific than measuring plasma free metanephrines1.

Although pheochromocytomas are rare, autopsy studies suggest a higher prevalence. The National Cancer Registry in Sweden has reported that pheochromocytomas are discovered in two patients per million people each year2. Interestingly, in autopsy studies, the prevalence of adrenal masses may be as high as 8%, and of these, 4.2% are diagnosed as pheochromocytomas1.

Due to its variable clinical presentation, pheochromocytomas have been called “the masquerader”. Retrospective studies show that of people with pheochromocytomas at time of autopsy, 61% had a history of hypertension and 91% had a history of “typical” symptoms, generally considered to be headaches, palpitations and sweating, but atypical symptoms have also been described. These atypical symptoms include: abdominal pain, nausea, vomiting, and dyspnea. Causes of death in people diagnosed with pheochromocytoma incidentally at time of autopsy include: myocardial infarction, cerebrovascular accident, arrhythmias, shock, renal failure and dissecting aortic aneurysm2. The catecholamines released by pheochromocytomas can lead to heart failure, pulmonary edema, arrhythmias, and intracranial hemorrhage. A pheochromocytoma presenting with cerebrovascular injury is rare and the incidence is unknown.

There are two proposed mechanisms for neurological injury resulting from a pheochromocytoma: hypertension and vasospasm. During excess catecholamine release, high blood pressure may overwhelm cerebrovascular autoregulation leading to hypertensive encephalopathy. The second proposed mechanism suggests that catecholamine excess or sympathomimetics cause spasm of the cerebral arteries. These vascular spasms can cause infarction or transient impairment of circulation34.

Management of cerebrovascular injury involves inhibiting the effects of the released catecholamines, epinephrine and norepinephrine. When these hormones are released, epinephrine
acts on alpha and beta adrenergic receptors while norepinephrine acts on the same receptors, except β2 adrenergic receptors. The cumulative effect is potent peripheral vasoconstriction by alpha receptor agonism and increased heart rate by β1 agonism. Thus, management of hypertension due to a secondary cause like pheochromocytoma is very specific. Pre-operative medical management includes initial alpha antagonism followed by beta antagonism. Of importance, an alpha blocker such as Phenoxybenzamine is recommended approximately 2 days before starting beta-blockade agents. The rationale is that beta-blockade alone would result in blocking of beta receptors that cause peripheral vasodilation, leaving alpha mediated peripheral vasoconstriction unopposed. Additionally, Metyrosine, a competitive inhibitor of the enzyme needed for catecholamine synthesis, has been proposed for pheochromocytoma management but is rarely clinically utilized at this time.

Definitive treatment of a pheochromocytoma is surgical removal, which is curative in up to 90% of cases. Prior to surgery, the patient’s clinical status is optimized with blood pressure control and volume repletion to avoid the consequences of the stress response from anesthesia and the surgery itself, which could involve a massive release of catecholamines.

References
Idiopathic Ventricular Tachycardia Associated With AV Reciprocating Tachycardia

Charles-Lwanga K. Bennin, MD, Avinash Chandra, MD

Case Report
A forty-six year old female patient with a medical history of asthma and seasonal allergies presented with a two day history of shortness of breath, associated with palpitations. She denied chest pain or diaphoresis. Patient reported past history of similar complains that usually lasted less than two minutes and were relieved with aspirin. The longest episode of palpitations lasted approximately twenty minutes.

Her social history was significant for tobacco and alcohol abuse, but negative for substance abuse. Her family history was significant for cardiovascular disease.

Pertinent findings on physical examination were significant for elevated blood pressure at 156 mmHg/112 mmHg and tachycardia at 112 beats per minute. Her electrocardiogram (EKG) showed tachycardia at a rate of 150 beats per minute with a long RP interval concerning for atypical AV reciprocating tachycardia (AVRT). The EKG also revealed right bundle branch block with a left axis deviation (Figure 1) and non-sustained ventricular tachycardia (Figure 2) indicating a diagnosis of idiopathic ventricular tachycardia. A urine drug screen was positive for cocaine.

Discussion
Idiopathic fascicular ventricular tachycardia has been reported in literature by Cohen in 1972 and Zipes in 1979. These electrophysiologic findings are unique in that the QRS complexes are narrow, especially when compared to the typical wide QRS complex ventricular tachycardia and a right bundle branch morphology. The fascicle activated on re-entry determines the axis - left axis deviation (left posterior fascicle) and right axis deviation (left anterior fascicle). Some case have been reported of familial presentations of idiopathic ventricular tachycardia.

Eighty percent (80%) of idiopathic ventricular tachycardia originates from the ventricular out flow tracts or the coronary cusp. The origin of these arrhythmias has been attributed to the posterior inferior left ventricle in a region of the left posterior fascicle. This region probably has a high degree of reentrant or triggered automicity. The adjacent posterior left bundle branch may or may not be involved in the anterograde limb of the reentrant circuit.

Idiopathic ventricular tachycardia, having a morphology of left bundle branch block and right axis deviation, is believed to originate in the right ventricular outflow tract, but may arise from the right ventricular outflow tract in about 18% of cases. According to Francis et al. idiopathic fascicular ventricular tachycardia has been limited to three subtypes in order of prevalence; left posterior fascicular ventricular tachycardia with a right bundle branch block morphology and superior axis configuration; left anterior fascicular ventricular tachycardia with right bundle branch block and right-axis

Figure 1. EKG on admission showing right bundle branch block with a left axis deviation.
deviation configuration; and the rare presentation of upper septal fascicular ventricular tachycardia with a narrow QRS and normal axis configuration.6

Nogami also classified idiopathic ventricular tachycardia into adenosine sensitive, propranolol sensitive and verapamil-sensitive fascicular ventricular tachycardia.9 It appears that fascicular ventricular tachycardia are sensitive to phenylalkylamine class L-Type calcium channel blockers such as verapamil as have been well described by Belhassen.10,11 Calcium channel blockers also suppress conduction through atrio-ventricular (AV) node, and are effective on both AV reciprocating tachycardia (AVRT) and AV nodal reentrant tachycardia (AVNRT).

Atrial pacing as well as supraventricular tachycardia has been shown to induce ventricular tachycardia due to either reentry or triggered automaticity. It is not uncommon to find co-existing tachyarrhythmia and a few cases have been reported of ventricular tachycardia initiated by atrial arrhythmias including AV reciprocating tachycardia also known as AV reentrant tachycardia (AVRT).5

Literature search using PubMed with the following keywords "Idiopathic ventricular tachycardia, AV reentrant tachycardia, AV reciprocating tachycardia, AVRT" produced 2 articles. One case series reported seven patients without structural heart disease in which AVNRT spontaneously triggered VT in three cases.12 Another case report illustrated a patient with Wolff-Parkinson-White (WPW) syndrome. Ventricular tachycardia originating from the right ventricular outflow tract was induced during isoprenaline infusion. This also led to atioventricular reentrant tachycardia (AVRT). This case report was significant in that the ventricular tachycardia was possibly driven by catecholamine stimulation13.

In our case report we present a patient with possible cocaine induced idiopathic ventricular tachycardia and AV reentrant tachycardia. Cocaine works on by increasing release of norepinephrine and dopamine and blocking reabsorption of norepinephrine, dopamine and serotonin. Cocaine also blocks sodium channels, thereby interfering with the propagation of action potentials. The release of catecholamines that occur in cocaine intake may exacerbate changes in the action potential threshold and hence stimulate automaticity. Management of idiopathic ventricular tachycardia includes radiofrequency ablation and intravenous verapamil.

Reference


A 30 Year-Old Man Infectious Endocarditis and Cerebrovascular Accident
Neerav G. Sheth, MD, Joseph DeSimone, MD

Case Report
A 30 year old male with a remote history of intravenous drug abuse (IVDA) and Hepatitis C was admitted in July 2008 with changes in mental status and a new right sided paresis. According to the family, the patient was in his usual state of health until approximately 2-3 weeks prior to admission when he developed headaches, generalized malaise, and fever to 101 degrees Fahrenheit after swimming in a lake. He was seen in an outside hospital emergency department, diagnosed with otitis media and subsequently discharged on prednisone and ciprofloxacin. The morning of admission, the patient was found naked, nonverbal, confused and was subsequently taken again to an outside hospital emergency department where he was found to have right sided weakness, diagnosed with a new cerebrovascular accident (CVA) and transferred to TJUH for further management.

On admission, the patient was found to have persistent right sided hemiparesis, a new loud systolic murmur best heard at the left lower sternal border and petechiae on his calves. Initial labs revealed a leukocytosis with left shift. His CT scan showed an acute left MCA territory infarction (Figure 1). A follow up MRI revealed additional punctuate foci of restricted diffusion in the right parietal and left occipital lobe (Figure 2), suggestive of embolic source of the patient’s CVA. The patient had a transthoracic echocardiogram which showed a myxomatous appearing mitral valve with an echodensity near the base of the posterior mitral valve with vegetations (Figure 3). A transesophageal echocardiogram revealed a mobile 0.5 cm x 0.5 cm echodensity attached to the posterior mitral valve leaflet as well as a second 0.9 cm x 0.5 cm echodensity attached to the anterior mitral valve leaflet (Figure 4). Of note, the patient’s TEE bubble study revealed patent foramen ovale (PFO), which is postulated to have contributed to the presence left sided infectious endocarditis in a patient with IVDA.

Given the patient’s history of IVDA, he was started on vancomycin for Staphylococcus aureus via a peripherally inserted central catheter. A few days later, the organism was found to be sensitive to methicillin and antibiotics were adjusted appropriately.

Discussion
Infectious endocarditis (IE) has been described in the medical literature for over 100 years. Prior to antibiotics, the condition was uniformly fatal, with a majority of cases diagnosed at autopsy. It wasn’t until the development of echocardiography that there was a significant reduction in the morbidity and mortality of IE.

![Figure 1. CT scan showing Hypoattenuation in Left Frontal and Temporal lobes compatible with Acute Left MCA Territory Infarct.](image1)

![Figure 2. MRI showing acute infarct involving left frontal and parietal lobes in left MCA distribution with punctate foci of diffusion restriction consistent with embolic phenomena.](image2)
Presently, there are 10-15,000 new cases of IE diagnosed in the United States each year with estimated national incidences ranging from 1.4 to 6.2 per 100,000. Moreover, epidemiology reports from the early 1990’s, report incidences as high as 11 per 100,000 in the Philadelphia area. In particular, IE has become more a disease of the elderly as over half of all new cases occur in those over the age of 60.

This older demographic, in addition to previously noted conditions of intravenous drug abuse, structural heart disease, and recurrent bacteremia may have additional risk factors that predispose them to develop IE. These include patients on hemodialysis, with indwelling catheters, severe native and/or artificial valve disease, diabetes, intravenous drug abuse, and HIV infection. These additional factors, coupled with a significant decline in rheumatic heart disease as a risk factor in younger patients has resulted in an increase in the median age of IE patients over the past 40 years.

Independent of age or risk factors, the most common offending organisms remain the same, with Staphylococcus aureus and Streptococcus spp. (including viridians, bovis, and enterococcus) being the most common. They have been associated with both native and diseased valve endocarditis. Gram negative bacteria including Haemophilus species (Haemophilus parainfluenzae, Haemophilus aphrophilus, and Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella species (HACEK organisms) have also been described as causes of infectious endocarditis, particularly in non-IVDA patients. These organisms have an increased affinity for adherence to native valve tissue. However, they are much less common in comparison to S. aureus and Streptococcus spp and are responsible for only 5-10% of non-IVDU native valve IE cases.

Those patients that develop IE, with or without prophylaxis, may present with a wide variety of clinical features. Some may present with classic signs and symptoms of low grade fevers, a new murmur, petechiae, Roth spots, Janeway lesions, and Osler’s nodes. The last three findings are highly specific and pathognomonic for IE, but have a low rate of occurrence. Often, some of the features may not be visible at the time of presentation. Occasionally, some patients, including the one presented, will present with symptoms of embolic phenomena.

The diagnosis of IE primarily includes clinical and echocardiographic criteria, divided into major and minor criteria (Table 1). Recently, the Duke Criteria were modified to include the echocardiographic criteria, as well as to distinguish between definite, probable, and rejected categories (Table 2).

Treatment of IE is directed towards the causative organism as well as the degree of valvular dysfunction. Staphylococcal and Streptococcal species are usually responsive to intravenous vancomycin, penicillins or third generation cephalosporins. If


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<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blood cultures positive for typical organisms</td>
<td>1. Predisposing heart lesions</td>
</tr>
<tr>
<td>2. positive cultures 12 hours apart</td>
<td>2. IVDA</td>
</tr>
<tr>
<td>3. 3 of 3 positive from different sites</td>
<td>3. Fever</td>
</tr>
<tr>
<td>4. Majority of &gt; 3 cultures positive</td>
<td>4. Vascular lesions:</td>
</tr>
<tr>
<td>5. Echocardiogram positive for IE</td>
<td>5. Janeway lesions, emboli, septic infarcts, hemorrhages</td>
</tr>
<tr>
<td>6. Immunologic phenomena</td>
<td>6. Glomerulonephritis, Osler’s nodes, Roth spots, Rheumatoid Factor</td>
</tr>
<tr>
<td>7. Microbiologic evidence not meeting major criteria</td>
<td></td>
</tr>
</tbody>
</table>
there is significant valvular dysfunction, cardiothoracic surgery consultation is warranted for valve repair and/or replacement. Since there is a significant morbidity and mortality associated with IE, focus has shifted towards prevention in those patients at increased risk. However, as previously mentioned, the group of patients “at risk” can encompass a wide array of individuals. As a result of this broadening category of “at risk” patients, it was necessary to identify those at high enough risk to warrant prophylaxis with antibiotics. Recently, the American College of Cardiology and the American Heart Association in conjunction with the Infectious Disease Society of America have reviewed the data on prevention of IE and have subsequently revised the guidelines regarding antibiotic prophylaxis (Table 3). These guidelines reflect significant changes from previously published ones and are based on the evidence for, or lack thereof, the efficacy of prophylaxis in patients identified as high risk for IE.

Amoxicillin is the antibiotic of choice for the majority of patients requiring prophylaxis and is given in a dose of 2 grams orally approximately 30 to 60 minutes prior to the procedure. Patients with a documented allergy to penicillins may be given any of the following 30 to 60 minutes prior to the procedure: 2 grams of cephalexin, 500 milligrams of either azithromycin or clarithromycin, or 600 milligrams of clindamycin.

In conclusion, IE is a real but preventable entity once the high risk patients have been identified. A review of recent data has greatly narrowed the number of patients considered “high risk” and has simultaneously limited the instances in which antibiotic prophylaxis is necessary. However, narrowing the spectrum of patients in which prophylaxis does not preclude the necessity of a pre-emptive approach in preventing infectious endocarditis and its sequelae.

References

Table 3. Updated ACC/AHA/ID Society recommendations for prophylaxis against IE

<table>
<thead>
<tr>
<th>Rule</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Although IE is a serious condition, the efficacy of antimicrobial prophylaxis is uncertain in all but a few select instances. Therefore, there are no longer any Class I recommendations for IE prophylaxis in patients with valvular heart disease.</td>
</tr>
<tr>
<td>2.</td>
<td>Antibiotic prophylaxis during dental procedures would prevent only a small proportion of cases of IE, even if it were 100% effective.</td>
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<tr>
<td>3.</td>
<td>IE prophylaxis during dental procedures is appropriate only in patients with underlying cardiac conditions associated with the highest risk for adverse outcomes. These conditions include:</td>
</tr>
<tr>
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<td>a. prosthetic valves or material</td>
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<td></td>
<td>b. Prior IE</td>
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<tr>
<td></td>
<td>c. Unrepaired cyanotic congenital heart disease (CHD) including shunts and conduits</td>
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<tr>
<td></td>
<td>d. Complete CHD repair within previous 6 months</td>
</tr>
<tr>
<td></td>
<td>e. Complete CHD repair with residual defects</td>
</tr>
<tr>
<td></td>
<td>f. Valve regurgitation secondary to structural abnormalities in cardiac transplant recipients</td>
</tr>
<tr>
<td>4.</td>
<td>In such high-risk patients, prophylaxis is appropriate for all dental procedures involving manipulation of gingival tissue or the periapical region of teeth, or perforation of oral mucosa (Class IIa).</td>
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<tr>
<td>5.</td>
<td>Increased lifetime risk for IE alone is not an indication for antibiotic prophylaxis</td>
</tr>
<tr>
<td>6.</td>
<td>Antibiotic IE prophylaxis is no longer indicated in patients with aortic stenosis, mitral stenosis, or symptomatic or asymptomatic mitral valve prolapse.</td>
</tr>
<tr>
<td>7.</td>
<td>Antibiotic IE prophylaxis is no longer indicated in adolescents and young adults with native heart valve disease.</td>
</tr>
<tr>
<td>8.</td>
<td>Genitourinary and gastrointestinal tract procedures (transesophageal echocardiography, esophagastroduodenoscopy, colonoscopy, etc.) do not warrant IE prophylaxis unless active infection is present.</td>
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65-Year-Old Man with Weight Loss, Anorexia, and Distal Extremity Numbness
Leigh Van Vranken, MS III, William Kim, MS III, Darren N. Seril, MD, Toshimasa Okabe, MD

Case Report

A 65-year-old Caucasian male with no significant past medical history presented to the emergency department with an unintentional 44-pound weight loss over a four-month period. The weight loss was preceded by fatigue and anorexia, which had been increasing for approximately eight months. In addition, he noted numbness and tingling of his hands and feet that began over the same time period. The patient was initially treated for depression with sertraline by his primary care physician. However, his symptoms persisted without significant improvement. An initial workup at outside hospital one month prior to presentation included an abdominal CT scan, which revealed a mass in the pancreatic head suggestive of a pseudocyst. He was also treated for Lyme disease with a course of doxycycline based on a rash finding on his left thigh. Lyme serologies were negative. He denied fever, chills, night sweats, changes in bowel habits or stool character, dysphagia, odynophagia, abdominal pain, cough, or shortness of breath. He also denied focal weakness, changes in speech, or changes in vision. He has no known drug allergies. Medications included sertraline for depression, zolpidem and diphenhydramine for sleep. He denied tobacco or illicit drug use. He drinks alcohol occasionally. Family history was noncontributory, with no history of malignancy, neurodegenerative or endocrine disorders.

On examination, patient was afebrile with normal vital signs. The patient appeared cachectic. Body-mass index (BMI) was 18.2 (normal range 18.5 to 24.9). Bilateral temporal muscle wasting was noted. Examination of the oral cavity revealed poor dental hygiene, black discoloration of the tongue, and dry mucous membranes. The abdomen was soft, non-tender, non-distended, with normal active bowel sounds. There was no hepatosplenomegaly. Skin was dry and showed decreased turgor. Neurological exam revealed altered sensation in upper and lower distal extremities, most marked on the feet and shins. Muscle strength was normal with the exception of mildly decreased thumb abductor and adductor muscle strength bilaterally. The knee-jerk and Achilles reflexes were present but diminished bilaterally. The remainder of the exam was unremarkable.

Hospital Course

The initial differential diagnosis for the patient’s unintentional weight loss included an occult malignancy, chronic infection or inflammation, malabsorption, and depression. Given the prior finding of a pancreatic cyst, endoscopic ultrasound with fine needle aspiration (FNA) was performed, which confirmed the presence of a benign pseudocyst. Esophagogastroduodenoscopy (EGD) and colonoscopy were performed to assess for malabsorption and gastrointestinal cancer. Both studies were unrevealing for diagnosis. Further evaluation for an occult malignancy included CT scans of the mandibular, neck, thorax, and abdomen. There was no evidence of solid tumor or lymphadenopathy from these imaging studies. CEA was 9.6 ng/mL (normal range: 0.0-5.0 ng/mL) and CA 19-9 was less than 1.0 ng/mL (normal range: 0.0-36.0 U/mL). Prostate-specific antigen (PSA) was normal. The patient was seen in consultation by psychiatry and it was determined that the patient did not meet criteria for clinical depression or dementia. He was subsequently tapered off of sertraline.

Further evaluation of the complaint of distal extremity numbness and tingling included screens for diabetes, vitamin deficiency, and occult malignancy. Vitamin B12 level was within normal limits. There were no signs of chronic inflammation or multi-organ involvement suggestive of systemic vasculitis. Paraneoplastic syndrome was also considered in the differential. Nerve conduction studies (NCS) and electromyography (EMG) showed impaired nerve conduction, axonal degeneration, and demyelination of both motor and sensory nerves. These findings were suggestive of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

The patient’s white blood cell (WBC) count was normal to mildly elevated throughout the hospital course. However, lymphocytosis (differential: neutrophil 39.2%, lymphocyte 53.8%, monocyte 4.3%) was noted on admission and persisted. Further evaluation of the peripheral blood smear (PBS) showed large granular lymphocytosis (LGLs) (Figure 1), possibly attributable to reactive phenomenon but a neoplastic process could not be ruled out.1 Flow cytometry showed a large (37% of all non-erythroid cells) cluster of CD45 positive cells.2 Electronic gating analysis revealed expansion of a natural killer (NK) cell

Figure 1. Peripheral blood smear showing large granular lymphocytes (LGL).
population lacking CD8 expression and expressing Kappa light chain, or a molecule immunoreactive with anti-Kappa light chain antibody (Table 1). Kappa light chain is typically expressed by B lymphocytes. The expression of this molecule in a NK cell population was suggestive of clonal expansion.

To investigate the possibility of leukemia, a bone-marrow biopsy was performed, revealing normal marrow architecture with LGLs similar to those observed on PBS. Polymerase chain reaction (PCR) analysis of the T-cell receptor (TCR) gene in peripheral blood samples showed a high frequency single mutation in the TCR-gamma gene, suggestive of clonality.

The patient continued to have a lack of appetite during his hospital stay, as well as inadequate oral intake to meet his nutritional needs. He was administered peripheral parenteral nutrition (PPN) throughout his stay, until a percutaneous endoscopic gastrostomy (PEG) tube was placed. His hospital course was otherwise uneventful and he was discharged to home with PEG tube feeds to supplement his oral nutrition, and arrangements to follow-up with hematology for further management of a hematologic malignancy.

Based on the results of his biopsy, the final diagnosis was natural killer cell large granular lymphocyte leukemia with possible paraneoplastic peripheral neuropathy.

**Discussion**

Differential diagnosis for unintentional weight loss with lack of appetite is broad. In the elderly, common causes of weight loss include malignancy, depression, and gastrointestinal diseases. Chronic pulmonary disease and congestive heart failure can cause involuntary weight loss by producing anorexia and increasing resting energy expenditure. In addition, medications such as antibiotics, non-steroidal anti-inflammatory drugs, and serotonin reuptake inhibitors, as well as socioeconomic hardships, can cause profound weight loss. The extensive workup in the present case suggested hematological malignancy as the cause of weight loss.

The causes of peripheral neuropathy are also numerous. Common causes include systemic diseases (i.e., diabetes mellitus, vasculitis), chronic liver disease, nutritional deficiency, infections, neoplasms, medications, and toxins. In our case, the results of NCS and EMG studies were suggestive of CIDP. CIDP is a chronically progressive or relapsing sensorimotor disorder with infiltration by lymphocytes and macrophages into peripheral nerve tissue. This is the chronic equivalent of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) found in the Guillain-Barré syndrome (GBS). However, unlike GBS, CIDP is usually idiopathic and lacks a strong association with an antecedent bacterial or viral infection. CIDP may also be part of a paraneoplastic syndrome associated with solid or hematologic malignancy. In our case, negative Anti MAG, normal TSH, and cortisol levels and normal protein electrophoresis excluded many of the alternative diagnoses. The occurrence of a peripheral neuropathy in the setting of a hematologic malignancy offers a plausible etiology for the patient’s neurologic symptoms (i.e., a paraneoplastic syndrome).

NK-cell leukemia is a disease within a spectrum of disorders ranging from the indolent “chronic NK-cell lymphocytosis” to the quickly fatal “aggressive NK-cell leukemia (ANKL)”. The diagnosis of NK-cell leukemia can be difficult to establish because of the lack of readily available clonal markers. Although a subset of NK cells have been shown to express a rearrangement of TCR-gamma, this marker is not reliably present. The natural history of NK-cell development is incompletely understood. It is currently believed to originate from a common lymphoid progenitor in the bone marrow, but it is also reported that immature thymocytes retain NK-cell potential with an unknown contribution to the steady state pool of NK-cells. In our case, the expansion of a NK-cell population with a lack of normal CD8 expression raised the question of clonality. The NK-cell population also expressed a unique surface marker for non-B lymphocytes. The marker was either the Kappa light chain or a molecule containing an epitope that cross-reacts with polyclonal antibodies to Kappa light chain. This finding was helpful in

<table>
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<tr>
<th>Marker</th>
<th>Cell type normally expressing this marker</th>
<th>% cells expressing marker</th>
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<tbody>
<tr>
<td>CD52</td>
<td>Mature lymphocyte</td>
<td>99%</td>
</tr>
<tr>
<td>CD2</td>
<td>T cell or NK cell</td>
<td>97%</td>
</tr>
<tr>
<td>CD19</td>
<td>B cell</td>
<td>2%</td>
</tr>
<tr>
<td>CD20</td>
<td>B cell</td>
<td>3%</td>
</tr>
<tr>
<td>CD3</td>
<td>T cells</td>
<td>12%</td>
</tr>
<tr>
<td>CD4</td>
<td>Helper &amp; regulatory T cell, macrophage &amp; monocyte</td>
<td>9%</td>
</tr>
<tr>
<td>CD8</td>
<td>Cytotoxic T cell &amp; 30-50% of NK cell</td>
<td>3%</td>
</tr>
<tr>
<td>CD56</td>
<td>NK cell</td>
<td>79%</td>
</tr>
<tr>
<td>Kappa light chain</td>
<td>B cell</td>
<td>77%</td>
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establishing clonality of the NK-cell population, given the lack of reliable NK-cell-specific markers as noted above.

The clinical presentation of NK-cell leukemia typically includes “B” symptoms (fever, night sweats, weight loss). In addition, other common findings included anemia, thrombocytopenia, hepatosplenomegaly, and gastrointestinal involvement.8 The complaints of appetite loss and unintentional weight loss described here represent an indolent and atypical presentation of NK-cell leukemia. To date there is no effective treatment for NK-cell leukemia. Although there is a case series reporting successful allogeneic hematopoietic cell transplantation9, the role of this modality in the treatment of NK-cell leukemia is yet to be determined. Most patients with this disorder have a severe and refractory clinical course.

References
Isolated Spontaneous Renal Artery Dissection
Carrie Ng, MS III, Melissa Gitman, MD

Case Report
A previously healthy 37-year-old man presented to an outside hospital with an acute onset of sharp left lower quadrant pain that radiated into his groin while mowing the lawn. The pain was continuous, lasting until the patient presented to the emergency room of his local community hospital. He denied any trauma or sudden changes in position. The patient identified no aggravating or alleviating factors for the pain. The pain was associated with nausea and one episode of bilious, non-bloody emesis. He also noted urinary hesitancy but denied hematuria.

The patient’s past medical history was significant for hyperlipidemia, controlled with gemfibrozil, and a 13-pack year smoking history. The patient presented to a local emergency department and underwent a CT scan of his abdomen that demonstrated an anterior left renal infarct due to a suspected thrombosis of anterior division of the left renal artery.

On transfer to the VA Hospital for further management, he was afebrile and normotensive. Physical examination was significant for an abdomen that was tender to palpation in the left lower quadrant and left costovertebral tenderness. Laboratory studies were notable for an elevated white blood cell count of 11,500 per mm³ and a decreased platelet count of 97,000 per cubic millimeter. His creatinine and blood urea nitrogen were within normal limits and were 1.0 mg/dl and 20 mg/dl respectively.

During his hospital course, his blood pressure ranged between 128-140/81-84, his Cr remained stable, and he had one episode of low-grade fever of 100.1°F. A magnetic resonance angiogram (MRA) was performed on day 2 of hospitalization (Figure 1).

Discussion
Introduction
The differential diagnosis for renal infarct includes embolic disease, thrombosis of the renal artery, renal artery dissection, and

Figure 1. MRA demonstrating renal infarct.
injury to the renal artery. Injury to the renal artery is responsibly for more than 75% of renal artery dissections and is generally due to extension of an aortic dissection, a trauma to the abdomen or an iatrogenic injury. The MRA the patient underwent on day two of his hospitalization confirmed the presence of a renal infarct but showed no focal aneurysm, dissection or stricture. Several diagnoses were entertained for possible etiologies of the renal infarct. The initial diagnosis of thrombosis was ruled out by the absence of clot on review of both the initial CT scan at the outside hospital as well as the MRA. The MRA failed to identify any abnormalities in the vasculature and serological studies did not demonstrate evidence of Polyarteritis Nodosa (PAN) thus this was felt to be unlikely to be the cause. An echocardiogram failed to demonstrate valvular vegetation and given the absence of other signs of embolic disease this diagnosis was ruled out.

The diagnosis in this patient was finally reached by exclusion. Although the MRA did not demonstrate a dissection it was felt that, SRAD was the most plausible cause of his renal infarct given the patient’s history and clinical presentation as evidenced by the discussion below.

Isolated SRAD is a rare event, with less than 200 reported cases in literature, and a quarter of those being autopsy findings. The actual incidence is higher than reported because many dissections are either silent or resolve spontaneously. As clinically apparent SRAD is uncommon, there is minimal data available concerning the optimal management strategy for this condition.

**Clinical Features**

The etiology of SRAD is often unknown. A few factors have been identified as risk factors for SRAD including atherosclerosis, fibromuscular dysplasia, connective tissue diseases and other conditions that might affect the integrity of the renal artery. The condition is more common among males, smokers and generally occurs between the ages of thirty to fifty. Most patients do not have other underlying co-morbid conditions. The most common clinical presentation is the acute onset of severe abdominal or flank pain. Another common finding is the presence of low-grade fever as seen in our patient. Much of literature on SRAD describes its clinical presentation as having severe hypertension and renal insufficiency. On the contrary, Ramamoorthy et al. and Misrai et al. suggest that most patients actually present like ours did with normal blood pressure and renal function with symptoms of kidney infarction.

**Work-up**

Diagnostic work-up should include checking a complete blood count for the presence of leukocytosis, basic metabolic panel to check renal function, liver function enzymes to rule out other causes of abdominal pain and a urinalysis for the presence of red blood cells. The diagnosis is not usually made until it is detected on radiologic imaging, because the history, physical, and laboratory findings results are usually non-specific. CT of the abdomen with contrast is generally the first imaging study ordered, usually undertaken for suspected nephrolithiasis. While MRA may be useful in making the diagnosis, angiography is the goal standard and remains the modality of choice as it can potentially be diagnostic and interventional.

**Treatment**

Once a SRAD is diagnosed, there are several options for treatment including medical, surgical, and interventional radiology depending on the renal function and lesion stability. Spontaneous resolution as seen in our case has been documented and observation or medical management of hypertension may be sufficient. Anticoagulation has also been suggested for medical management although it has not been demonstrated that this confers any long term benefit. Surgical treatments such as vascular reconstruction, and endovascular procedures such as stenting or coil embolization, have also described in literature. Surgical interventions have been identified as beneficial in cases where the patient does not have significant renal ischemia but continues to suffer uncontrollable hypertension. Vascular reconstruction has been described as having good long-term results, but post-operatively many patients still require anti-hypertensives and the procedure has a high morbidity rate including acute thrombosis of the renal artery and late anastomotic restenosis. Revascularization with stenting is indicated when there is a severely stenotic vessel that provides blood flow to an ischemic part of the kidney. If patient has an isolated involvement of an accessory renal artery, then percutaneous embolization is another option. Finally, nephrectomy is considered when the kidney is already severely damaged from the infarction or if revascularization would be not be an option.

**Conclusion**

The available literature suggest that SRAD is a relatively benign condition and surgical treatment are considered when patient has failed medical management. However, long-term follow-up of blood pressure and renal function are important since this condition is generally poorly understood. The patient in this case was managed conservatively with analgesics and anti-emetics and was discharged home without any sequelae of his renal infarct.

**References**

Coronary Heart Disease and Fish Oil
Talya Spivack, MD

Introduction
The benefits of fish consumption on cardiovascular disease has been suggested since the early 1980s in studies that demonstrated Greenland Eskimo’s low rates of death from coronary heart disease.1 This was followed by another observational study that demonstrated the same findings in Japan.2 The proposed linkage between these two groups of people is their propensity to consume fish. Since then many studies have examined the relationship between fish consumption and coronary heart disease (CHD) mortality rates. Current thinking suggests that the primary benefit of consuming fish is secondary to the omega-3 fatty acids found in fish oil.16,17

Omega-3 Fatty Acid Sources and Action
Omega-3 fatty acids are long-chain polyunsaturated fatty acids (18-22 carbon atoms in chain length) with the first of double bonds beginning with the third carbon atom. Plants and marine fish are the two main dietary sources of omega-3 fatty acids found in nature. For the purposes of this article, we will mainly discuss the role of marine omega-3 fatty acids. These are generally found in oily fish such as mackerel, lake trout, herring, sardines, albacore tuna and salmon. There are two types of marine omega-3 fatty acids: eicosapentaenoic acid (EPA) & docosahexanoic acid (DHA). In the human body, these are broken down by the enzymes cyclo-oxygenase and then lipooxygenase to create eicosanoids.

The exact mechanism of action of omega-3 fatty acids on CHD remains unknown. However, several ideas have been postulated. Omega-3 fatty acids have been shown to decrease serum triglyceride concentrations in a dose dependent relationship by 25-30%.10 Omega-3 fatty acids have also been linked to decreased platelet aggregation11,12, as well as the ability to stabilize the myocardium against ventricular arrhythmia in animal studies.13,14,15,6

The Evidence
One of the first significant prospective trials done demonstrating the correlation between consumption of omega-3 fatty acids and coronary heart disease was done in the Netherlands over a 20 year period. Information about the fish consumption of 852 middle-aged men without coronary heart disease was collected by a careful dietary history obtained from the participants and their wives. During 20 years of follow-up 78 men died from coronary heart disease. An inverse dose-response relation was observed between fish consumption in 1960 and death from coronary heart disease during 20 years of follow-up. Mortality from coronary heart disease was more than 50% lower among those who consumed at least 30 grams of fish per day than among those who did not eat fish. It was concluded that the consumption of as little as one or two fish dishes per week may be of preventive value in relation to coronary heart disease.3

The Netherlands study was shortly followed by the Diet and Reinfarction Trial (DART) of 1989. This was a randomized control trial with factorial design performed with the intent to examine the effect of dietary intervention in secondary prevention of MI. The major endpoints of the study were total mortality and ischemic heart disease events (IHD events and nonfatal MI). Men enrolled in the trial were weighed, measured, and randomly assigned to receive or not receive dietary advice on three factors. The first factor was total fat intake. The men in this arm were designated to reduce fat intake to 30% of total energy and to increase the polyunsaturated/saturated fat ratio as much as possible. The next arm was the fish arm. Men were told to consume at least two weekly portions (200-400 g) of fatty fish (mackerel, herring, kipper, pilchard, sardine, salmon, and trout). Men who could not tolerate fish were given the option of taking three fish oil capsules per day, providing a total of 900 mg EPA and DHA. The next arm of the study examined fiber intake. These men were instructed to increase their intake of cereal fiber to 18 g daily. Weight reduction advice and smoking advice were given as seen fit to all arms of the study. The results were surprising. The fish oil arm was shown to have the most CHD benefit demonstrated by an overall reduction of cardiovascular disease mortality by 29%. Surprisingly, the overall dietary fat group did demonstrate a significant decrease in the number of MIs suffered but did not show any overall benefit in mortality.4

The next large randomized control study to demonstrate a similar benefit was The Indian Experiment of Infarct Survival published in 1997. This randomized placebo controlled trial aimed to test the effect of fish oil and mustard oil supplementation versus placebo on complications and cardiac events in patients with prior suspected acute myocardial infarction during a follow-up period of 1 year after symptoms were first experienced. Participants were randomized to fish oil (6 capsules per day, providing approximately 2 g of omega-3 fatty acids), mustard seed oil (a source of a-linolenic acid, 2.9 g/d provided in 20 mL of oil), and placebo (aluminum hydroxide, 100 mg). After one year, total cardiac events were 25% and 28% in the fish oil and mustard oil groups, respectively, versus 35% in the placebo group.5,6

The success of the DART trial and the Indian Experiment of Infarct Survival trial spawned the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI) trial in 1999. This trial was a secondary prevention clinical trial designed to assess the effects of omega-3 polyunsaturated fatty acid and vitamin E supplementation on mortality and recurrent events in patients with recent MI. The study randomized 11,324
patients who had survived a myocardial infarction within the last 3 months to four arms: omega-3 fatty acid group received one capsule per day of a highly concentrated product containing about 850 mg of EPA and DHA, the vitamin-E group received 300 mg/d of synthetic α-tocopherol, the combined treatment group received both, and the control group received neither. The GISSI trial was the first demonstration that a pharmacutical preparation of omega-3 fatty acids in addition to and other accepted interventions has a favorable effect on clinical endpoints in post-MI patients. Another unexpected finding was that those taking the omega-3 fatty acids experienced a 20% reduction in overall mortality and a 45% decrease in risk for sudden cardiac death.8

One of the confounders of the above randomized control trials was that the trials had only included men. As a result, a retrospective analysis relating coronary artery disease and fish oil was performed on the cohort of female patients used for the Nurse’s Health Study. The end point for this study was incidence of CHD including CHD deaths and nonfatal MI. Women were divided into 5 categories based on frequency of fish consumption: <1 serving per month, 1-3 servings per month, 1 serving per week, 2-4 servings per week, and 5 servings per week. This trial showed a stepwise decrease in all arms related to more fish consumption in total coronary heart disease cases, fatal coronary heart disease events, and nonfatal MI.9 Although this study is convincing, it is also limited by the inability to control for the fact that people who consume more fish products may have an inherently healthier lifestyle.

Conclusions
The physician must weigh the risks and benefits of prescribing fish oil to their patients. It is important to realize the antiplatelet effects and theoretical ramifications in using omega-3 fatty acids therapeutically in patients with bleeding tendencies. In addition, pregnant and nursing woman must be cautioned against consuming certain fish such as shark, swordfish, golden bass, and king mackerel that have a higher proportion of mercury. Studies suggest that prenatal mercury exposure can be detrimental to neurological development in children.15,19

In 2002, the American Heart Association (AHA) published guidelines advocating the use of omega-3 fatty acids in patients with and without documented CHD. In patients without CHD they recommended eating a variety of (preferably oily) fish at least twice a week. In patients with CHD they recommended consuming approximately 1 gram of EPA and DHA daily, preferably from oily fish. In addition they suggested that in this patient population fish oil capsules could be considered in consultation with physicians. In the patients needing triglyceride lowering the AHA recommended 2-4 grams of EPA and DHA daily provided as capsules under a physicians care.6

Omega 3 fatty acids have been shown in epidemiological studies and randomized control studies to decrease the incidence of coronary heart disease both in patients with existing coronary heart disease and prospectively. Although more studies are needed to examine the exact mechanism of action of omega-3 fatty acids, studies do show a substantial benefit related to the increase of intake of fish oil, both in capsule form and through dietary sources. In conclusion, evidence suggests recommending omega-3 fatty acids to patients at risk for and who have suffered from cardiovascular heart disease.

References
JEFF CHEF 2009 WINNING RECIPES

ENTRÉE

SANJAY MAMA’S LAMB CURRY

INGREDIENTS

- 3-4 lbs leg of lamb cut into 1.5 inch cubes, fat trimmed off as much as possible (usually need to start with 7 lb bone-in leg of lamb and have butcher cut it for you, can save some of the bone to cook in the curry)
- Several tbsp peanut oil
- 2 cups whole canned tomatoes
- 8 garlic cloves
- 2/3 cup plain yogurt
- 3 1/2 cup chopped Spanish onion
- 16 cardamom pods
- 16 cloves
- 4 tsp turmeric
- 2 tsp red chili powder
- 4 tsp kosher salt
- 1 1/2 tsp cumin
- + fresh cilantro
- 6 cups hot water

PREPARATION

1. Preheat oven to 325 degrees F
2. In a blender/food processor blend tomatoes, garlic, ginger, yogurt until smooth. Set aside.
3. Heat 1-2 tbsp oil in very large pot and brown lamb cubes on all sides but do not cook through. Remove from pot and set aside.
4. In same pot, caramelize onions in 1-2 tbsp oil for about 20 min. Add cumin, chili powder, turmeric, salt, cardamom, and cloves. Cook for about 1 min.
5. Add puree (see above) to onions and spices and cook for about 5-7 min covered but occasionally letting steam out.
6. Add meat and 6 cups of hot water. Mix and bring to boil. Once boiling, place in oven (at 325°) for 2 hours. The pot should be covered with foil first, then the lid placed on top. Take out to stir every 30 min. Removed from oven after 2 hours. Stir.
7. Turn oven off and place back in oven for 15 minutes. Remove from oven.
8. Place in bowls, garnish with fresh cilantro. Serve with basmati rice and plain yogurt (if too spicy).

Yum!

SANJAY MAMA’S LAMB CURRY

LINDSAY BISCHOFF, MD

DESSERT

BANANA WHITE CHOCOLATE COFFEE CAKE

INGREDIENTS

- 3 3/4 cups all-purpose flour
- 1 1/4 tsp baking soda
- 1 tsp salt
- 2 sticks unsalted butter, melted
- 1 cup granulated sugar
- ½ cup firmly packed brown sugar
- 2 large eggs
- 3 tbsp dark rum
- 1 tsp vanilla extract
- 4 large ripe bananas, mashed
- 1 cup shredded coconut
- 1 cup (6 ounces) white chocolate chips or chunks

GLAZE

- ½ cup (3 ounces) white chocolate chips or chunks
- ½ cup unsalted butter
- 1 Tbsp whipping cream

PREPARATION

1. Preheat the oven to 350 degrees F. Butter and flour a 10 inch bundt pan.
2. Sift together the flour, baking soda and salt and set aside.
3. With an electric mixer, mix together the butter, sugar and brown sugar until blended. Over low speed, add the eggs, one at a time and beat until blended. Add the rum and vanilla and continue to beat, over medium speed for 5 minutes. Add the bananas and beat until blended. Over low speed, slowly add the flour mixture until just blended. If you overmix once the flour is added the batter will become tough.
4. With a wooden spoon, fold in the coconut and white chocolate. Pour into the prepared pan, smoothing the top with a spatula. Bake for 50 minutes, or until a toothpick inserted in the middle comes out clean. Cool in the pan for 15 minutes before removing to a serving plate.
5. To make the glaze: In the microwave melt together the chocolate chips, butter and cream. Whisk until blended and drizzle over the cake.

Bon Appétit!
Cover Art

Painting: “Bamboo and Citrus”, (left) acrylic on canvas
Artist: Cecilia Kelly, MD

Front Cover: Editors of Jefferson Forum 2010 (from left to right):
Bhalaghuru Chokkalingam Mani, MD, Andrew Lerner, MD,
Whitney Jackson, MD, Anastasia Shnitser, MD,
Laura Setlur, MD and Ankitkumar K. Patel, MD

Back Cover: Sameh Refat Gaballa, MD

Not pictured: Tina Shah, MD and Andrew Foy, MD