The Jefferson Medicine Forum
Every day our House Staff strive to deliver the most advanced and compassionate healthcare possible. Our clinical perspectives are constantly being challenged, prompting new avenues of inquiry and information to further our insight into the state of the human condition.

Hence, we are proud to present to you this 9th edition of the Jefferson Medicine Forum. This unique manuscript showcases only a glimpse of the fascinating cases encountered by our residents. Clinical mastery is exemplified by the ability to teach subject matter. Let it be recognized that each contributor to this journal has devoted a significant amount of time to do exactly that—to teach and advance our knowledge.

Our Residents are talented in Medicine as they are in the arts and literature. May their personalities shine in this issue of The Forum. Enjoy.

Senior Editors: Neilanjan Nandi, MD
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Editorial Staff: Ankitkumar Patel, MD
Anastasia Shnitser, MD
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JeffGraphics

A Growing Impact of Scholarly Work

To Friends of the Department of Medicine:

Each year, the House Staff further the impact of the Department of Internal Medicine through participation in research studies that are presented in their entirety or abstract form at society meetings throughout the country. This body of scholarly work reflects the breadth of interests of our residents and their energy and commitment to generating new knowledge to enhance the practice of medicine.

While I hope you enjoy this year’s issue of the Jefferson Forum, I also hope you’ll come to recognize the even more extensive body of work that is submitted to national subspecialty society meetings, competitions, and peer reviewed journals. A partial list of esteemed journals in which resident work has been featured includes:

- American Journal of Gastroenterology
- American Journal of Hospice and Palliative Care
- Cardiology in Review
- Circulation
- Clinical Gastroenterology and Hepatology
- Current Opinion in Drug Discovery and Development
- Digestive Disease Science
- Heart Rhythm
- Intensive Care Medicine
- Journal of Cardiovascular Electrophysiology
- Joint Bone and Spine

Our Jefferson Forum represents a small element of our scholarly work, but is important all the same as it is wholly designed and edited by House Staff themselves. This effort is notable because it parallels ongoing clinical and educational assignments and call responsibilities of each and every House Officer. Making time for scholarly pursuits is part of how we define ourselves and our approach to patient care.

With congratulations to each resident who has submitted scholarly work to the Forum or another publication.

Gregory C. Kane MD, FACP, FCCP
Professor of Medicine
Residency Program Director
Vice-Chairman for Education
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From the Editors
# Table of Contents

## Review Articles

**The Controversy Over Cocaine Use and Beta-Blockade Continues to Brew**
Ankitkumar K. Patel, MD, MPH ................................................................. 4

**Palmarplantar Keratoderma**
Melissa Gitman, MD, CM ........................................................................ 6

**Syncope**
Melissa Gitman, MD, CM ................................................................... 8

**Clopidogrel-Associated Thrombotic Thrombocytopenic Purpura: A Case Report and Brief Review**
Benjamin C. Creelan, MD ....................................................................... 11

## Case Reports

**Man With Spontaneous Intracranial Hemorrhage on Therapeutic Enoxaparin, Clopidogrel, and Aspirin**
Mihir K. Patel, MD, Sumeet K. Chhabra, MD, Michael Pfeiffer, MD ................................................................. 14

**Giant Negative T Waves**
Siva K. Kumar, MD, Rajesh M. Kabadi, MD, Paul J. Mather, MD ................................................................. 18

**Anomalous Origin of the Right Coronary Artery Diagnosed by Cardiac Computed Tomography**
Siva K. Kumar, MD, Faisal Shaik, MD, Paul J. Mather, MD ................................................................. 21

**A 42-year-old Male With Blurry Vision**
William H Chong, MD, Dorothy Chang, MD ................................................................. 22

**Silent Assassin: Coronary Artery Disease in a Type II Diabetic**
Srinath Vemuri, MS IV, Neerav Sheth, MD ................................................................. 24

**Left Atrial Myxoma**
Siva K. Kumar, MD, Rajesh M. Kabadi, MD, Paul J. Mather, MD ................................................................. 26

**A 41-year-old Woman With Rheumatic Mitral Stenosis, Atrial Fibrillation, and Right-sided Heart Failure**
Stephen Koczirka, MS-III ......................................................................... 27

**A Case Report of Idiopathic Giant Cell Myocarditis**
Bao Bui, MD, Sumeet Chhabra, MD, Siva K. Kumar, MD ................................................................. 29

**Man With Flu-like Symptoms**
Sandarsh Kancherla, MD, Ankitkumar Patel, MD, MPH ................................................................. 31

**A 22-year-old Woman With Systemic Lupus Erythematosus Develops Cardiac Tamponade**
Brooks Kuhn, MS-III, Arthi Reddy, MD, Sorin Lazar, MD ................................................................. 33

**Hemochromatosis**
Benjamin Creelan, MD .......................................................................... 35

**A 70-year-old Male With Abdominal Pain**
William H Chong, MD .......................................................................... 36

**Trust Your Gut**
Roger Coron, MD, Jennifer Hurd, MD, Steven Ludwin, MD, Patricia Kozuch, MD ................................................................. 38
Chest Pain as a Presenting Symptom for Gastric Phytobezoar
   Ankitkumar K. Patel, MD, MPH, Sandarsh Kancherla, MD, Darren Seril, MD

Foreign Body in the Small Intestine
   Benjamin Creelan, MD

Acuphagia
   Saurabh Bansal, MD

Vocal Cord Dysfunction in Asthmatics
   Yvonne L. McCarey, MD

Immunocomprised Heart Transplant Patient With Cryptosporidial Diarrhea
   Michael Dominic Lee, MSIII, Rajesh Kabadi, MD, Siva K. Kumar, MD

Infliximab-Induced Interstitial Lung Disease in a Patient With Psoriatic Arthritis
   Lan Quang, MD, Anthony Scarpaci, MD

A Man With Abdominal Pain and Acute Renal Failure
   Faisal Shatkh MD, Marina Serper, MD

Spiderbite
   Ayana Cannon, MD

Man with Malaria in Delaware
   Benjamin Ngo, MD

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Beams and Lights
Artwork courtesy of Lan Quang, MD
Cocaine Abuse Epidemiology

Cocaine is the second most commonly used illicit drug and the most frequent cause of drug-related deaths in the United States.1 Approximately 24 million people in the United States have used cocaine at least once, and five million abuse cocaine on a regular basis.2 Its use is associated with acute and chronic complications affecting many organ systems, the most common being the cardiovascular system.3

Cocaine Pharmacology

Cocaine acts as a powerful sympathomimetic agent. Cocaine has two main mechanisms of action. Its first mechanism involves the inhibition of cellular sodium ion transport through blockade of fast sodium ion channels, resulting in membrane stabilization and a local anesthetic effect. In the myocardium, this effect is similar to that produced by class 1 antiarrhythmic agents.1 The second mechanism is a marked increase in catecholamine levels at the synapse by blockage of presynaptic reuptake of epinephrine, norepinephrine, and dopamine. The result is elevated levels of these neurotransmitters at the postsynaptic receptors.8

Stimulation of α-adrenergic receptors leads to coronary vasoconstriction.9 Cocaine not only causes spasm of the large coronary arteries but is toxic to cardiac muscle. Excessive β-adrenergic stimulation from cocaine causes calcium overload, which directly leads to cardiac myocyte toxicity.7 Stimulation of β-adrenergic receptors has positive chronotropic and inotropic effects on the myocardium and thus increases myocardial oxygen demand. Due to increased norepinephrine activity on α- and β-adrenergic receptors, cocaine produces a dose-dependent increase in heart rate and blood pressure, which usually remains within physiological levels in recreational use. In human volunteers, intranasal cocaine produces a significant increase in blood pressure, heart rate, coronary vascular resistance, and myocardial oxygen consumption compared to intranasal saline administration.9

Lastly, cocaine can precipitate coronary thrombosis.10 It increases platelet aggregation through elevated levels of thromboxane A₂ and epinephrine.11

Cocaine and Chest Pain

Chest pain is the most common symptom reported by cocaine users.12 Data suggests that most patients with chest pain are not questioned about cocaine use and if they are, the answer is often not documented.13 Fifty-seven percent of cocaine users complaining of chest pain are admitted to the hospital.14

Acute coronary events and myocardial infarction can occur within minutes to days after cocaine administration.15 Cocaine-induced myocardial infarction is difficult to diagnose since the most common ECG finding is early repolarization and left ventricular hypertrophy.16 The anterior wall is involved in 77% of cases of cocaine-induced myocardial infarction.17 A small case study found users of cocaine have a transient 24-fold increase in risk of myocardial infarction in the first hour after use which decreases rapidly thereafter.18

Management of Cocaine-induced Chest Pain

Patients who have myocardial ischemia secondary to cocaine use are medically treated differently from patients who have myocardial ischemia unrelated to cocaine. Current recommendations for the treatment of cocaine-induced myocardial ischemia include use of benzodiazepines, cautious use of thrombolytics, and avoidance of β-blockers.19

Controversy over β-blocker usage

During myocardial infarctions, β-blockers prevent the excessive catecholamine stimulation that leads to myocardial necrosis or stunning.20 The benefit of β-blockers in myocardial infarction is the prevention of reinfarction and ventricular fibrillation.21 In 1976, Rappolt et al recommended the use of intravenous propranolol in the management of cocaine intoxication based on their observations of over 50 cases of successful treatment.22 As a result of these findings, propranolol became the preferred treatment for cocaine-induced hypertension until 1985 when Ramoska and Sacchetti suggested that propranolol should be used with caution due to its potential for causing paradoxical hypertension via "unopposed alpha stimulation."23 By blocking the β-adrenergic receptors, available neurotransmitters predominantly bind α-adrenergic receptors on smooth muscle and cause vasoconstriction of blood vessels, thereby elevating blood pressure.

However, a recent retrospective study of 363 consecutive telemetry and ICU patients who were admitted to a municipal hospital for chest pain and had positive urine toxicology results for cocaine demonstrated a decrease, rather than an increase, in the risk of death and myocardial infarction with β-blocker administration. The incidence of myocardial infarction in the group of patients treated with β-blockers was significantly lower than the group without therapy (6.1% vs. 26%; 95% CI: 10.3-30%).24 In a corresponding editorial, Freeman and Feldman question the premise that cocaine chest pain is due to coronary artery spasm.25 Firstly, cardiac catheterization in initial studies of patients with cocaine-induced chest pain was conducted in a delayed fashion, so that spontaneous thrombolysis could not be excluded.26 Secondly, reversible coronary perfusion defects, consistent with coronary vasospasm, are rarely demonstrated in acute myocardial perfusion imaging.27

In a small clinical study, labetalol was shown to reverse the cocaine-induced rise in mean arterial pressure, but does not alleviate cocaine-induced coronary vasoconstriction.28 However,
to date no clinical trials have been conducted on the initial management of cocaine-associated ischemia or infarction. Specifically, a study to assess the risk-to-benefit ratio of β-blocker usage in patients who complain of chest pain and test positive for cocaine would provide much needed clarification.

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Case Presentation
A 44 year old African American female with a history of seizure disorder and cirrhosis secondary to alcohol abuse was brought to the emergency department (ED) after a witnessed generalized tonic-clonic seizure on the street. While the patient was in the ED, she was observed to have 500cc of bright red hematemesis and promptly transferred to the intensive care unit with successful stabilization of an upper GI bleed. It was not until transfer back to the telemetry that she was noted to have a shiny, scaly lesions on her hands and feet bilaterally (Figures 1 and 2).

Discussion
When evaluating a patient with PPK, the first step is to perform a detailed history and physical, including a complete skin exam. Patel et al proposed an algorithm to evaluate patients thought to have acquired PPK of unknown etiology (Figure 3).²

Palmoplantar keratodermas (PPK) is comprised of a heterogeneous group of conditions that are characterized by hyperkeratosis of the palms and soles.² These conditions can be classified in several different fashions. First of all, a distinction between the hereditary and acquired forms must be determined. Furthermore the hereditary forms can be further subdivided depending on the extent of involvement of the epidermis (focal, diffuse or punctuate), the location of the lesions, the mode of inheritance, the age of onset and the presence of co-morbid conditions. Moreover, with advancements in molecular genetics, these conditions can also be classified by the type of gene dysfunction that occurs, including mutations in the genes responsible for synthesis of structural proteins, cornified envelope, cohesion, connexins and trans-membrane signal transducers.² While PPK may be found in the absence of other conditions, it is often found as part of a disease complex, such as skin findings associated with deafness, corneal dystrophy, cardiac structural abnormalities, gingival hyperplasia and esophageal malignancy. In the hereditary form, a genetics consult should be obtained in order to further evaluate the specific type of PPK present.²

Similarly the acquired form of the condition can be further subdivided into categories based on their etiology. Patel et al proposed the acquired PPK’s be subdivided as follows:
Keratoderma climactericum, drug related, malnutrition associated, chemically induced, systemic disease related, malignancy associated, dermatoses related, infectious etiology and idiopathic. Keratoderma climactericum is typically found in menopausal women, frequently with co-existent obesity or hypertension. The condition begins with involvement of the plantar aspect of the feet, where the patient develops erythema, hyperkeratosis and fissuring, leading to difficulty ambulating. Palmar involvement occurs later in the disease course. Chemical associated PPK has been described with a history of exposure to arsenic and chloracnegens. Symptoms generally resolve a few months after removal of the exposure, however, in some cases, symptoms have persisted for several years. Severe malnutrition in concentration camp inmates has also been reported to be associated with acquired PPK. A deficiency in both protein and vitamins led to the condition which improved with vitamin replacement. Multiple medications, including glucan, lithium, venlafaxine, verapamil, quinacrine and certain chemotherapy agents, have all had case reports in the literature associating their use with PPK. Generally, the diagnosis is made in retrospect with resolution of the symptoms upon discontinuation of the offending agent. Several dermatologic conditions, including psoriasis, lichen planus and eczema have all been reported to cause a reactive form of PPK. Certain infections, including HIV, syphilis, scabies and TB have all been reported to cause hyperkeratosis. PPK is also considered to be a paraneoplastic marker for malignancies of the esophagus, lung, breast, blood, bladder, and GI tract.

Tripe palm is a specific finding which refers to form of palmar keratoderma with a velvet-like texture and exaggeration of the lines of the palm and fingers. Greater than 90% of patients with this finding have an underlying malignancy. Of course, idiopathic acquired PPK is a diagnosis of exclusion after all other etiologies have been eliminated.

Treatment of PPK usually involves treatment of the underlying etiology. If no causative process is identified then a conservative approach is undertaken using topical therapies to lessen the dermatologic symptoms.

References
SYNCOPE
Melissa Gitman, MD, CM

Case Presentation
A 45 year old white female rising from her seat to give a lecture at the Philadelphia Convention Center suddenly collapsed and lost consciousness. An automated external defibrillator device, on hand at the conference, demonstrated her rhythm to be in ventricular fibrillation. She was subsequently defibrillated and intubated in the field yet was unresponsive on arrival. Her husband related that his wife’s past medical history was significant for hypothyroidism and a questionable diagnosis of lupus. Her medications included levothyroxine and Pycnogenal, a popular herbal supplement. She had no known drug allergies. The patient had no known tobacco, alcohol, or illicit drug abuse and works as an employee of federal government.

Hemodynamic vitals were stable. Cardiac exam revealed a regularly regular rhythm with normal heart sounds, and no jugular venous distention. Lungs were clear to auscultation and the abdomen was completely benign. The patient was warm with good distal pulses bilaterally and withdrew to pain and noxious stimuli though a complete neurologic exam was difficult to obtain at the time of admission.

Laboratories were significant for a potassium of 2.7 mEq/mL. The remaining electrolytes were normal. Her complete blood count, urine drug screen, and cardiac enzymes were within normal limits. Head CT demonstrated no intracranial abnormalities. An echocardiogram demonstrated normal left and right ventricular systolic size and function, though a small pericardial effusion was noted. Her initial EKG demonstrated a prolonged QT interval with a corrected QT value (QTc) of 510 ms.

Discussion
The differential diagnosis of syncope in the younger adult differs slightly from that of the more classic presentation of syncope in the older adult (Table 1). 1 However, in both age groups one must consider both cardiac and non-cardiac causes. Arrhythmias and structural abnormalities figure prominently, though in these patients greater consideration must be given to congenital anomalies. In this particular case, the differential is narrower still, as the patient suffered sudden cardiac death (SCD). The differential of this condition includes: Congenital and Acquired Long QT syndrome, Wolff-Parkinson-White syndrome, idiopathic ventricular fibrillation, and coronary artery spasm. 1 In light of the patient’s EKG findings, the diagnosis of prolonged QT syndrome was given and what follows is a discussion of this condition.

Long QT syndromes (LQTS)
Prolonged QT syndrome is defined as QTc > 440 ms in men or >460 ms in women. 2 This is based upon the QT interval as measured in lead II. The Bazett correction formula (QTc = QT x RR1/2) is frequently used to calculate the corrected QT interval. In acquired LQTS, an increase of greater than 25% from baseline is considered to be significant. 2 The condition is thought to be caused by lengthening of the repolarization phase of the ventricular action potential. It is a disease of ion channels due to mutation of genes encoding for transmembrane Na+ and K+ ion channel proteins. LQTS is hypothesized to be due to either a slowing of inward depolarizing Na+ currents or slowing of outward repolarizing K+ currents. 2

Two forms of the condition have been described, congenital LQTS and an acquired form. Congenital LQTS is an inherited disease which presents with sudden cardiac death in patients with structurally normal hearts. 3 It is an autosomal recessive condition and mutations in 7 genes have been identified accounting for ~60% of families affected. The precise incidence of LQTS is unknown, although it is estimated to be 1 in 7,000 to 10,000 in the US. 2 It is more prevalent in Utah and Finland. LQTS is thought to cause 3,000-4,000 sudden deaths in children and young adults in the USA. 3 Untreated, it is a lethal condition with a 10 year mortality rate being between 50-70%. 3

Risk factors for acquired QT prolongation
Several factors related to medication use lead to QT prolongation. This includes: the use of medications that prolong the QT interval (Table 2), concurrent use of medications that prolong the QT interval; the use of medications that slow drug metabolism due to inhibition of hepatic cytochrome P450 enzymatic system; impaired hepatic or renal function; dose and or concentration dependent response; the rate of medication infusion; and certain recreational drugs such as cocaine, amphetamines, and methadone. 4 It is believed that low potassium levels, low magnesium levels and other electrolyte disorders can causes acquired form of the condition. 4

Cardiac risk factors for QT prolongations include structural heart disease and recent conversion from atrial fibrillation. While bradyarrhythmias can lead to QT prolongation this is usually related to taking antiarrhythmic medications and therefore is not necessarily an independent risk factor. Neurologic risk factors include stroke and subarachnoid hemorrhage. HIV infection can lead to QT prolongation due to a number of factors such as myocarditis, subclinical cardiomyopathy, and autonomic neuropathy. Eating disorders can also lead to electrolyte disorders leading to conduction disturbances. Connective tissue disorders with anti-RO/SSA antibodies are additional risk factors for QT prolongation. Finally, the condition is more common in females compared to males, an association thought to be an estrogen mediated effect. 4

There is some controversy as to whether acquired LQTS is, in fact, its own distinct entity. Some schools of thought maintain that there is only a congenital form of LQTS that remains undetected until it is unmasked by one of the above mentioned factors. Of note, in patients with drug induced LQTS almost
all have blockade of the 1kr current which is mediated by the 
K+ channel encoded by the HERG gene. The same channel is 
involved in LQT2, raising the question of whether these patients 
have a genetic predisposition to developing the condition.1 
Additionally, one study of 817 family members of patients with 
documented congenital LQTS by genetic testing yielded an 
average penetrance of 60%.4

Work-Up
As with any other condition, the first step in diagnosis is a 
thorough history. Approximately 60% of patients with familial 
LQT are symptomatic.3 Palpitations are an uncommon finding 
because torsades usually are too fast to support any circulation. 
Rather patients might give a personal history of syncope or 
seizure-like activity especially with activity or severe stress. Each 
of the congenital forms possess their respective triggers. For 
example in LQT1, cardiac events are frequently associated with 
vigorous physical activity especially with diving and swimming. 
In LQT2 the patients are sensitive to sudden arousal such as 
sudden loud noises. On the other hand, LQT3 patients frequently 
experience events during rest or sleep. Asymptomatic patients 
come to medical attention after an affected family member or a 
prolonged QT, is identified on an ECG obtained for some other 
reason.2 Data from the International Registry demonstrated 
that by age 40, cardiac events (syncope, SCD, or cardiac arrest) 
ocurred in 17% of family members overall, and in 6% of 
those with a prolonged QT interval.3 First-degree relatives had a 
higher incidence of cardiac events by age 40 than second-degree 
relatives (26% vs 10%). Additionally, a detailed family history 
should be obtained to determine if there are any relatives with a 
history of sudden death in infancy or young adulthood during 
nocturnal, startle, or athletic activity, near-drowning, or any 
family history of SIDS. In general, the physical exam does not 
provide any specific findings. 

Of course, an EKG must be obtained in all patients suspected of having the 
condition to assess the QT interval. However, data from the International 
Registry for LQTS showed that 5% of 1345 family members presented 
with cardiac arrest had a normal QTc. In fact, only 70% of gene carriers 
have a prolonged QTc.3 Some additional ECG findings in this condition 
include notched T waves noted during the phase of exercise 
testing suggestive of LQTS and T-wave alternans noted during physical 
or emotional stress. Ten typical ST-T patterns have been described in 
LQTS. The QT dispersion in a 12-lead ECG (QT, max-QT, min) should 
also be noted.2 An EKG obtained during an acute event demonstrates 
either Torsades des Pointes or ventricular fibrillation with a short-long-
short sequence being the hallmark of LQTS. Repeat EKG testing is 
necessary in patients with a high clinical suspicion as normal QTc 
and normal T wave morphology do not exclude the disease. It can be helpful 
to obtain an ECG from immediate family members for comparison. 

Additional testing modalities have been examined for diagnostic 
purposes. Exercise stress testing can be used to detect the 
condition in patients with borderline length QT intervals, as 
an ECG obtained post-exertion may show QT prolongation. 
However, pharmacologic provocation studies have not been 
well studied. Holter monitoring can also be utilized to detect 
intermittent QT prolongation, bradyarrhythmia, T wave 
alternans, and notched T-waves. EP testing though, is not 
diagnostic of the condition. Finally, genetic screening may be 
useful in families with known genotype, however it is mainly 
used for research purposes.

Complications
The main concern in this patient population is the development 
of Torsades de Pointes and ventricular fibrillation. Sudden death 
is the only event in 30-40% of patients. Untreated symptomatic 
patients with LQTS have a greater than 20% mortality rate in the 
first year after an initial syncopal episode.3

Management
In the short term, immediate cardioversion to terminate 
arrhythmias is frequently required. This is usually followed 
by withdrawal of offending agents if present and correction of 
electrolyte abnormalities. Magnesium is effective in suppression 
of short term recurrences of torsades irrespective of baseline 
magnesium levels. A single bolus of 2 g of magnesium should 
give over 2-3 minutes followed by an intravenous infusion 
of 2-4mg/min. A second 2 g bolus should be administered 
either 15 minutes later or immediately if torsades recur while 
the magnesium is being infused.6 Potassium is used as an 
adjunct to intravenous magnesium. In pts with LQT2 some 
evidence to suggest maintaining high normal levels (4.5-5.0) 
of potassium may be beneficial.6 However there is no evidence 
of any effect on preventing or reversing torsades. Temporary 
transvenous cardiac pacing to a rate of 100 beats per minute 
can be used in patients who fail magnesium therapy. This 
has been demonstrated to be beneficial regardless of baseline 
heart rate. Isoproterenol can also be used as it controls short 
term recurrence of torsades by increasing heart rate. An initial 
dose of 2 mcg/kg/min is given and then titrated to heart rate 
of 100 bpm. Note, isoproterenol cannot be used in pts with 
congenital LQT because of adrenergic stimulating effects.5

In terms of long term management, it is clearly agreed upon 
that all symptomatic patients should be treated. Conversely, it 
is unclear as to whether other groups of asymptomatic patients 
should be treated. Prophylactic treatment is recommended in 
all intermediate and high risk patients. In patients with LQT1 
this means male and female patients with QTc >500ms. In 
LQT2 this includes male patients with a QTc of > 500ms and 
all females. All patients with LQT3 should be treated prophyl-
lactically. Asymptomatic patients who should be treated include 
all patients with congenital deafness, neonates and infants, 
affected siblings of children who have died suddenly, patients 
with documented T-wave alternans and patients with very long 
QT (>600ms).
Beta-blockers are the first line therapy in symptomatic patients. Approximately 75% of cardiac events are precipitated by adrenergic stimuli. As a result beta blockers reduce mortality from 71% to 6%, however syncope and other events recur in approx 25% of treated patients.\(^5\) Maximal beta blockade should be implemented to a target of <130 bpm at maximal heart rate. There have been no studies comparing different agents but agents with longer half-life are preferable secondary to non-compliance. Commonly used agents include propanolol at a dose of 2-3 mg/kg and nadolol dosed at 1 mg/kg.\(^2\) Pacemakers are used as an adjuvant to beta blockers in patients with bradycardia or AV node blockade.

Left cardiac sympathetic denervation has been attempted in patients who failed beta blocker therapy. The largest study to date looked at 123 patients and demonstrated a decrease in the number of cardiac events from 99% to 45%, with a 5 year survival rate of 94%.\(^7\) AICD devices are first line therapy for any patient surviving a sudden cardiac arrest. They are also commonly used in patients who fail all other therapies. However AICD devices, especially if they misfire, can produce emotional distress triggering arrhythmias and shocks, therefore one should continue adjuvant therapy with beta blockers. Finally the long term efficacy of ablation remains unknown.

Current therapies under investigation include: Na\(^+\) channel blockers such as mexiletine, flecainide, lidocaine, pentisomide, and phenytoin; K\(^+\) channel activators such as nicorandil, pinacidil, and cromakalim; alpha-adrenergic receptor blockers; calcium channel blockers; atropine; and protein kinase inhibitors.

Monitoring of these patients includes a baseline EKG with follow-up EKG’s on treatment with QT prolonging medication. Also, patient education is paramount. Patients need to be instructed to report any symptoms including palpitations, pre-syncope or syncope. Patients and physicians must be cautious with any new medications. Patients should also report clinical changes and side effects that may signal hypokalemia such as gastroenteritis. It is important for these patients to avoid activities that can act as trigger events. Finally, screening of family members is necessary to pick up subclinical cases.

### Table 1. Differential Diagnosis of Syncope in a Younger Adult

<table>
<thead>
<tr>
<th>Cardiac syncope</th>
<th>Noncardiac syncope</th>
</tr>
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<tbody>
<tr>
<td>Arrhythmia</td>
<td>Vasovagal response to pain</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>Situational syncope (Micturition, defecation, tussive, and carotid sinus syncope)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>Autonomic dysfunction</td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td></td>
</tr>
<tr>
<td>Supraventricular tachyarrhythmias</td>
<td></td>
</tr>
<tr>
<td>Bradycarrhythmias</td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td></td>
</tr>
<tr>
<td>High-grade atrioventricular blocks</td>
<td></td>
</tr>
<tr>
<td>Pacemaker malfunction</td>
<td></td>
</tr>
<tr>
<td>Low flow states</td>
<td>Neurovascular causes</td>
</tr>
<tr>
<td>Advanced cardiomyopathy</td>
<td>Volume depletion – dehydration, hemorrhage</td>
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<tr>
<td>Congestive heart failure</td>
<td>Addison’s disease</td>
</tr>
<tr>
<td>Valvular insufficiency</td>
<td></td>
</tr>
<tr>
<td>Cardiac outflow obstruction</td>
<td>Psychiatric disease incl cardiac manifestations of anorexia nervosa</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Hypertrophic obstructive cardiomyopathy</td>
<td></td>
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<tr>
<td>Mitral stenosis</td>
<td></td>
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<tr>
<td>Pulmonary stenosis</td>
<td></td>
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<tr>
<td>Pulmonary embolus</td>
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<tr>
<td>Left atrial myxoma</td>
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<tr>
<td>Pericardial tamponade</td>
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<tr>
<td>Acute MI</td>
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<tr>
<td>Aortic dissection</td>
<td></td>
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<tr>
<td>Primary pulmonary hypertension</td>
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</tbody>
</table>

### Table 2. Drugs That Prolong the QTc Interval

<table>
<thead>
<tr>
<th>CNS</th>
<th>ziprasadone, thioridazine, risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>clarithromycin, ketoconazole, fluconazole, moxifloxacin</td>
</tr>
<tr>
<td>Neoplastic Agents</td>
<td>arsenic, tamoxifen</td>
</tr>
<tr>
<td>Anti-rejection</td>
<td>tacrolimus</td>
</tr>
<tr>
<td>Class I and III Antiarrhythmic Agents</td>
<td>quinidine, sotalol, amiodarone, dofetilide</td>
</tr>
</tbody>
</table>

For complete list: www.qtdrugs.org, www.torsades.org

Beta-blockers are the first line therapy in symptomatic patients. Approximately 75% of cardiac events are precipitated by adrenergic stimuli. As a result beta blockers reduce mortality from 71% to 6%, however syncope and other events recur in

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Introduction
In 1991, Page and colleagues published a report of four cases of thrombotic thrombocytopenic purpura (TTP) attributed to treatment with the platelet ADP receptor antagonist, ticlodipine.\textsuperscript{1} Since then, ticlodipine has been established as an immune-mediated cause of TTP with an incidence of approximately 0.0 - 0.06%.\textsuperscript{2, 3} Due to its unfavorable side-effect profile, the use of ticlodipine has been mostly discontinued in the United States and replaced by clopidogrel. Both agents are thienopyridine-derivatives which differ only by a carboxymethyl moiety. In spite of their structural resemblance, no case of TTP was reported in phase III trials of clopidogrel with 19,185 patients.\textsuperscript{4} However, reports of clopidogrel-associated TTP have emerged since the FDA approved the drug in 1998, including a seminal publication of eleven cases.\textsuperscript{5} Five of these cases passed an independently conducted causality assessment.\textsuperscript{6} Despite the identification of additional clopidogrel-associated cases by pharmacologic surveillance,\textsuperscript{7} skepticism remains regarding whether clopidogrel actually causes TTP.\textsuperscript{8} Here we report a case of clopidogrel-associated TTP and briefly review proposed mechanisms of drug-induced TTP.

Case Report
A 55-year-old Caucasian female presented with fever, jaundice, hematuria and painful neuropathy. Three years earlier, the patient was diagnosed with colorectal cancer which was successfully treated with resection. The patient also suffered from severe peripheral vascular disease secondary to diabetes mellitus, for which she had received an axillofemoral and aortofemoral bypass grafts several years prior. Ten years earlier, she also received a total abdominal hysterectomy with bilateral salpingo-oopherectomy for an ovarian cyst. Her medications at admission included coumadin 3 mg qday, premarin 0.  mg qday, hydroxychloroquine 200 mg qday, glucosamine, lisinopril 20 mg qday, hydrochlorothiazide 12.5 mg qday, cilostazol 100 mg bid, and clopidogrel 75 mg qday. Clopidogrel had been added to her regimen within the past three months, ostensibly as adjunctive therapy for lower extremity claudication. She was an ex-smoker. She had no history of human immunodeficiency virus (HIV) or quinine exposure.

Physical exam was significant for fever (38.0°C), mild jaundice and petechiae of hands and abdomen. Laboratory testing revealed abnormal hemoglobin (5.6 g/dL), platelets (8.0 × 10\(^8\)/\(l\)), lactate dehydrogenase (2847 IU/L), indirect bilirubin (3.0 mg/dL), serum creatinine (1.6 mg/dL), and haptoglobin (< 0.6 µmol/L). Urinalysis revealed 66 red cells per high power field. Severe schistocytosis was noted on peripheral smear (Figure 1). Direct antiglobulin testing was negative and fibrinogen levels were normal (483 mg/ dL). Serum carcinoembryonic antigen to detect recurrence of colorectal cancer was negative, and computed tomography (CT) scan of the abdomen did not show local recurrence or metastases. Blood cultures did not grow organisms. Transthoracic echocardiography showed normal cardiac function.

Although TTP was considered in her differential diagnosis, her clinicians first attributed her microangiopathic hemolytic anemia to suspected urinary tract infection. However, her status did not improve after several days with antibiotics and with consultation from hematology, the diagnosis of TTP was made at hospital day six. Serum von-willebrand factor (vWF) protease (ADAM-TS13) samples drawn during her hospital stay returned with an activity of < 5% (normal > 67%) by fluorescence resonance energy transfer (FRET) assay, and > 8.0 inhibitory units by mixing (normal < 0.4), consistent with immune-mediated TTP. The patient received a total of 8 units of packed red blood cells during her stay, and therapeutic plasma exchange was performed at hospital day #7 with 12 units of fresh frozen plasma (FFP). Twelve hours later, the
patient decompensated with acute shortness of breath and hypotension, and was subsequently intubated and admitted to the intensive care unit. Shortly after transfer, she entered into pulseless electrical activity (PEA) and cardiac life support failed to resuscitate her. Her family declined autopsy. No evidence of fluid overload was seen. Based upon review of the events, it is plausible that the patient died from a massive pulmonary embolism likely secondary to her hypercoagulable state.

**Discussion**

With the addition of this case, there are now 38 identified instances of clopidogrel-associated thrombotic microangiopathy in the literature. The time course of drug initiation is consistent with prior case series in which patients presented with TTP within two to three weeks after beginning a thienopyridine-derivative.

Although our patient was also receiving a synthetic derivative of quinine, no association has been made between hydroxychloroquine and TTP. In fact, thrombocytopenia alone is not reported as an adverse effect of hydroxychloroquine therapy. It is conceivable that the added hydroxychloroquine group may alter the epitope of quinine that induces drug-dependent antibodies. Indeed, exquisite specificity has been demonstrated in other causes of antibody-mediated drug-induced thrombocytopenia, such as sulfamethoxazole and abciximab. Drug-induced auto-antibodies to ADAMTS13 may exhibit similar specificity, likely accounting for the remarkably fewer cases of TTP documented with clopidogrel compared to ticlopidine.

Plasma exchange treats TTP via two plausible mechanisms: infusion and removal. Infusion of fresh donor plasma supplies the patient’s circulation with the missing ADAMTS13 protease, thereby breaking down dangerous excesses of von-Willebrand factor multimers. Exchange of recipient plasma removes platelet aggregates, vWF multimers, and inhibitory autoantibodies to ADAMTS13. Plasma exchange may also filter culprit drug metabolites which may have induced TTP, such as thienopyridine derivatives. Not surprisingly, it has been observed that receipt of plasma exchange within three days of onset of clopidogrel-associated TTP results in 100% survival, vs. 27% if therapy is initiated afterwards. In our case, the fatality of our patient may be attributable to delayed diagnosis and consequent initiation of plasma exchange at hospital day seven.

The finding of a vWF multimer protease inhibitor in this case is consistent with prior reports of ticlopidine and clopidogrel-associated TTP. Immunoglobulins to ADAMTS13 have been found in other etiologies of TTP in which immune dysregulation is suspected, such as human immunodeficiency virus (HIV) and solid organ transplantation. Inhibitory auto-antibodies to vWF protease are almost always an IgG class, although IgA class are occasionally identified in the same sera. The presence of an ADAMTS13-activity inhibitor by mixing does not necessarily mean that an associated immunoglobulin will even be detected; nor does the presence of ADAMTS13 antibodies guarantee that a mixing test result will be positive. The latter situation is rather easily explained by observing that protease-associated antibodies need not necessarily inhibit the activity of the protease. The former situation is more problematic, but fortunately appears to be rare. In a rigorous cohort study of 35 TTP patients, Ferrari et al. found that an immunoglobulin was present in 91% of patients. Two of these patients had no detectable IgG/IgM/IgA

![Figure 3. Endothelial cells secrete vWF multimers into the circulation. The protease ADAMTS13 cleaves these multimers at the A2 domain (A). Platelets adhere to these multimers in the bloodstream (B) via the platelet glycoprotein Ib (GpIb). These multimers can also bind platelets to the endothelial surface (C). Deficiency or inhibition of ADAMTS13 causes vWF multimers to accumulate. Multimer accumulation results in increased platelet adherence and clot activation. This is the hypothesized mechanism of TTP. (diagram from Sadler)](image-url)
References
Man With Spontaneous Intracranial Hemorrhage on Therapeutic Enoxaparin, Clopidogrel, and Aspirin
Mihir K. Patel, MD, Sumeet K. Chhabra, MD, Michael Pfeiffer, MD

Case Presentation
A 65 year-old Caucasian male originally presented to an outside hospital complaining of worsening paroxysmal nocturnal dyspnea, orthopnea, and recent exertional chest pain associated with dyspnea. The patient’s past medical history was significant for coronary artery disease status post coronary bypass, severe aortic stenosis status post bioprosthetic aortic valve repair, congestive heart failure, atrial fibrillation on anticoagulation, dual-chamber pacemaker placement, history of a transient ischemic attack, and type 2 diabetes mellitus. At the outside hospital, coronary angiography revealed occlusion of native vessels and previous grafts. He was considered a poor surgical candidate. He was transferred to Thomas Jefferson University Hospital (TJUH) for a second opinion regarding percutaneous versus surgical intervention.

The patient’s initial hospital course was complicated by persistent volume overload treated with aggressive intravenous (IV) diuresis and atrial fibrillation refractory to medical therapy. Electrophysiology service recommended transesophageal echocardiogram (TEE) and electrocardioversion; TEE revealed no left atrial clot, and the procedure was successful in restoring sinus rhythm. Throughout his hospitalization, the patient was maintained on weight-adjusted therapeutic low molecular weight heparin (LMWH, enoxaparin), clopidogrel, and aspirin. Other medications included amiodarone, atorvastatin, digoxin, esomeprazole, ezetimibe, isosorbide mononitrate, metoprolol succinate (XL), spironolactone, levothyroxine, niacin, repaglinide, sertraline, and insulin.

Approximately two weeks after transfer to TJUH and two days after cardioversion, the housestaff was called overnight for an acute change in mental status and blurry vision. Upon evaluation, patient was unable to respond to questions appropriately. He complained of “not feeling well” and reported new bilateral blurry vision. The patient and nursing staff denied any recent trauma or fall. He was afebrile, normotensive (10/70) with normal sinus rhythm (6  bpm), saturating well (98%) in no respiratory distress (18 resps/min) with finger-stick blood glucose of 93 mg/dL. Exam revealed the patient was oriented only to person; Glasgow Coma Scale (GCS) on initial evaluation was 14. Complete neurologic exam was non-focal: pupils were equal in size and reactive to light and accommodation; visual fields were intact bilaterally; cranial nerves II-XII were intact and symmetrical; muscle strength was full in his upper and lower extremities bilaterally; and his distal upper and lower extremity sensation was intact and symmetric.

Stat head CT (Figure 1) revealed a large intraparenchymal hemorrhage in the left parietal and temporal lobes, involving the left lateral ventricle, third ventricle, and partial filling of right lateral and fourth ventricles. A 7 mm left-to-right midline shift with local mass effect is also observed.

Neurosurgery evaluated the patient and arranged transfer to the Neurological ICU for emergent right frontal ventriculostomy. Per consultation with hematology, the patient received enoxaparin-adjusted IV protamine sulfate to attempt reversal of therapeutic enoxaparin. The patient’s clopidogrel and aspirin were also discontinued. The patient remained normotensive throughout these events; however, his mental status and level of consciousness continued to deteriorate rapidly. Despite additional IV protamine sulfate, fresh frozen plasma, and factor IX, the hematoma continued to expand as demonstrated by repeat head CT (Figure 2) performed 10 hours after the initial diagnosis. Further surgical options were discussed with the
patient’s wife. Considering the low likelihood of significant functional recovery and her knowledge of the patient’s wishes, surgical options were declined. He was subsequently placed on a morphine infusion for comfort and expired the next evening.

Discussion

According to the American Stroke Association, intracerebral hemorrhages (ICH) affected an estimated 67,000 individuals in 2002, and only 20% of those individuals were expected to be functionally independent six months after the event. The 30-day mortality of an ICH is reported to be 35 to 52%, with the majority of deaths occurring within the first 2 days. Rapid recognition is critical due to the potential for quick deterioration of patients with this condition. The classic presentation is the sudden onset of a focal neurological deficit that worsens over minutes to hours. Other symptoms and signs include headache, vomiting, and decreased level of consciousness. There is usually a smooth progression of the neurological deficit over time. This progression is uncommon in ischemic strokes and subarachnoid hemorrhages. Nevertheless, clinical features alone are not sufficient to differentiate between ischemic and hemorrhagic strokes, and therefore, imaging is crucial. CT and MRI appear to be equal in detecting an ICH, as well as determining size, location, and extent of hematoma enlargement. Generally, CT is superior in detecting ventricular extension, while MRI is superior in detecting structural lesions, amount of surrounding edema, and herniation. Because of the urgency associated with a concern for ICH combined with the availability and duration of MRI scans, CT is more commonly obtained.

Other aspects of the initial evaluation include obtaining vital signs, laboratory studies, an EKG, and a chest x-ray. In a study conducted by the Spanish Neurological Society, a temperature greater than 37.5 °C, an elevated serum neutrophil count, and an elevated fibrinogen level were all associated with early neurological deterioration.

Patients diagnosed with an ICH need ICU level care along with neurosurgical evaluation or transfer to a facility with neurosurgical capabilities. The major aspects of medical management for ICH involve controlling blood pressure, decreasing intracranial pressure, and treating associated conditions, such as hyperthermia, concomitant infections, or hyperglycemia. Any anticoagulation should be immediately discontinued or reversed if possible. Treating fevers with antipyretics is valuable because lower body temperature lessens tissue damage by redistributing oxygen and decreases glucose consumption to permit relative tolerance to oxygen deprivation.

The data for treating hyperglycemia has been extrapolated from the data on ischemic strokes. Hyperglycemia in the first 24 hours (>140 mg/dL) after an ICH is associated with worse outcomes, and current guidelines recommend the use of insulin for blood glucose levels over 140 to 185. Ongoing research should provide more specific information and clarify these guidelines.

Treatment of elevated intracranial pressures should start with simple measures such as elevating the head of the bed to thirty degrees and keeping the head in midline position. If more aggressive measures are needed, options include IV mannitol to achieve plasma osmolality of 300 to 310 mosmol/kg, barbiturate coma, or hyperventilation to a P\textsubscript{a}CO\textsubscript{2} of 25 to 30 mm Hg. These patients also need concomitant measuring of intracranial pressure and blood pressure. Steroids should not be used as they increase complication rates, particularly infection, and have not been shown to improve outcomes. Many clinicians also use antiepileptic agents for seizure prophylaxis. A study in Italy aimed at characterizing ICH-related seizure revealed that use of antiepileptic agents soon after ICH onset could reduce the risk of early seizures. However, this benefit has yet to be substantiated by prospective clinical studies.

There are no clear guidelines on how to manage elevated blood pressure in ICH. On one hand, lowering the blood pressure potentially slows hematoma expansion. On the other hand, lowering blood pressure can also induce cerebral ischemia in the edematous portions surrounding the hemorrhage. Current...
Recent studies are clarifying the risk of ICH and ICH-related mortality associated with anticoagulation. Due to its predictable and reproducible anticoagulant effects, LMWH has become increasingly preferred over unfractionated heparin (UFH) for anticoagulation in the inpatient setting. LMWH and UFH have similar rates of major bleeding, yet studies comparing LMWH to UFH in patients with ST-elevation myocardial infarction who have also received thrombolytics have shown an increased risk of ICH in patients receiving LMWH over those receiving UFH. Predictors of anticoagulant-related ICH included coronary artery disease, atrial fibrillation, history of ischemic stroke, and history of pulmonary embolus or deep vein thrombosis. Patients with anticoagulant-related ICH also had a higher mortality rates than other ICH patients. The difference in mortality rates within the first 24 hours post event in one retrospective review was 33.2% in anticoagulant-related ICH versus 16.3% in patients with ICH not on anticoagulation. Anti-platelet therapy is also associated with worse clinical outcomes and is an independent predictor for acute hematoma enlargement, rapid death, and need for emergent hematoma evacuation.

There is no proven method for reversing the effects of LMWH. Unfractionated heparin and LMWH exert their effects by binding to and catalyzing antithrombin III, which inhibits certain coagulation factors, particularly factor IIa and factor Xa. LMWH has a reduced ability to inhibit factor IIa compared to UFH, but has a similar effect on factor Xa. Intravenous protamine in animal studies and in vitro studies significantly neutralizes the factor IIa activity of LMWH, but only neutralizes 60% of its anti-factor Xa activity. Moreover, studies demonstrating or refuting protamine’s beneficial effect on LMWH-related bleeding in humans are lacking. Nevertheless, in a patient who received LMWH within an 8 hour time window, the recommended approach is to administer 1 mg of IV protamine for every 100 anti-factor Xa units of LMWH. One milligram of enoxaparin is equal to 100 anti-factor Xa units. Therefore, a patient who received 80 mg of subcutaneous enoxaparin within 8 hours should be given 80 mg of IV protamine. A second dose of 0.5 mg of IV protamine per 100 anti-factor Xa units may be given if bleeding continues. If LMWH was administered more than 8 hours ago, a lower initial dose of protamine is recommended. For UFH, 1 mg of IV protamine will neutralize 100 units of UFH.

**Conclusion**

In summary, we have presented a case of severe intracerebral hemorrhage in a patient receiving therapeutic enoxaparin and antiplatelet agents. Initial suspicion for acute intracranial hemorrhage was low based on non-localizing neurological exam and lack of head trauma, but remained within the immediate differential given the patient’s history and current medications. The patient exhibited signs of slow global neurologic deterioration, but his exam remained non-focal throughout his hospital course. In this instance, radiographic evaluation was pursued promptly. Although the intent was to rule out, rather than confirm, suspected intracranial pathology, radiographic imaging remained an integral part of the complete patient evaluation.

Our experience suggests that while ICH classically presents with focal deficits, the absence of focal deficits does not exclude the diagnosis. It should remain high on any physician’s differential while caring for a patient with an acute mental status change, particularly in a patient on therapeutic anticoagulation or antiplatelet medications. In managing patients with an ICH, prompt neurosurgical evaluation is required. Additional immediate attention should focus on controlling hypertension, elevated intracranial pressure, hyperthermia, and hyperglycemia; reversing anticoagulants if needed; and monitoring the patient in an intensive care unit.

**References**


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**Table 1. Suggested Recommended Guidelines for Treating Elevated Blood Pressure in Spontaneous ICH**

1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.

2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg.

3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure (e.g., MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically reexamine the patient every 15 minutes.

SBP indicates systolic blood pressure; MAP, mean arterial pressure


Case Presentation
A 62 year old Caucasian man with a past medical history significant for (long standing and controlled) HTN, lymphoma (diagnosed 2 yrs ago and currently in remission), and diffuse esophageal spasm presented to an outside hospital with expressive aphasia and right sided weakness. He was treated with tissue plasminogen activator (t-PA) for left MCA embolic stroke with excellent clinical response with very minimal residual expressive aphasia. Further work up and evaluation there revealed a large left ventricular apical mass consistent with thrombus and he was subsequently transferred to our facility for further evaluation and management of this apical mass.

Hospital Course
On presentation, the initial physical exam was significant only for an expressive aphasia. The presenting EKG, however (see Figure 1), showed diffusely negative T waves in all leads, especially in the left precordial leads.

The patient was asymptomatic and was initially started on anticoagulation with heparin to bridge him to a therapeutic INR on coumadin, given the report of thrombus. As part of a workup here to further delineate and look at this area of thrombus a transthoracic echocardiogram (see figure) was obtained. This was read as showing an apical mass which was reportedly 3.1 x 1.6 cm in size. Despite the echocardiogram findings, there was still doubt as to whether or not this was truly a case of apical thrombus, especially since these are fairly rare. This clinical thinking combined with the EKG findings, lead us to sequentially perform a nuclear stress test to evaluate for the possibility of a silent MI as a cause of this. This study was subsequently negative for any sign of ischemia. Finally, for definitive diagnosis, a cardiac MRI was performed to further evaluate the anatomy of the heart (see Figure 3). This showed marked focal left ventricular apical thickening of 9 mm likely corresponding to the abnormality seen on echocardiogram. This region of thickening demonstrates signal intensity similar to myocardium on all sequences and therefore is consistent with focal [focal] apical hypertrophy.

Final Diagnosis
Left Ventricular Atypical Apical Hypertrophic Cardiomyopathy (HCM)

Discussion
Apical HCM is an uncommon morphologic variant of HCM, and accounts for probably less than 10% of all cases. First discovered in Japanese males in 1976, it is most commonly seen in seen in Asia and has been reported in 41% of patients in China and 25% of patients in Japan.
Typical presenting features consist of an audible and palpable fourth heart sound which reflects impaired ventricular relaxation. ECG features include “Giant” T wave negativity in the left sided precordial leads, as was the case with our patient. Furthermore, imaging shows a “spade-like” configuration of the left ventricular cavity at end diastole. Some patients may also present with symptoms suspicious for ischemia such as chest pain and dyspnea on exertion. This combined with the above ECG findings will often lead to an immediate work up to rule out infarction.

There are multiple imaging techniques that can be used to detect apical HCM, with the first line being non-contrast echocardiography. The diagnostic accuracy of this modality is limited, however, by the fact that the apex can often be difficult to properly image. In many patients, the image seen may mimic akinesia or apical thrombus with poor acoustic windows, as was the case in our patient. In such cases, where the clinical suspicion is strong, measures such as cardiac MRI or echo with contrast may be more confirmatory. One study showed that in 100 affected patients, traditional echo made the correct diagnosis in 91% of patients, and the remaining nine were diagnosed using MRI. A study by Pons-Llabdo, et al showed that MRI allowed better overall assessment of the degree and extent of LVH than echo did. In this same study it was stated that MRI was able to properly visualize the apex in all patients, while echo was successful in only 61%. Next to MRI, another useful modality is contrast echocardiography which may have better success than non-contrast with apical imaging. A case report presented by Acarturk et al demonstrated the value of contrast echo in diagnosing this condition. A final confirmatory sign which is often seen on diagnostic catheterization is that of the “spade like” configuration mentioned above. In most cases this is an incidental finding as the primary purpose of cardiac catheterization in this scenario is to evaluate for the possibility of concurrent coronary artery disease given the symptoms of chest pain and dyspnea on exertion that these patients will often present with. Patients with this form of HCM will often present at a young age and will be hospitalized due to symptoms and EKG criteria suspicious for coronary artery disease, so proper diagnosis can be of major importance. With a wall thickness of 9 mm, our patient would be classified as having a mild form of this condition.

While the overall course of this condition is benign (especially in Asian countries), approximately 1/3 of affected patients will experience serious cardiovascular events such as myocardial infarction or arrhythmia. In the asymptomatic patient with no significant ischemia or arrhythmia, no specific therapy has been outlined but counseling is certainly still recommended as a precaution. Compared to patients with normal variant HCM, there is a much lesser incidence of sudden cardiac death. The
The mainstay of therapy is symptomatic monitoring, with patients being asked to inform their physician immediately in the event of syncope or presyncopal symptoms. Interestingly enough, there has been at least one published case of this condition being associated with a multi-organ syndrome which also includes atrial septal defect, hypothyroidism and renal failure. It is unknown, at this time, whether or not this demonstrates any sort of defined syndrome.

References

Anomalous Origin of the Right Coronary Artery Diagnosed by Cardiac Computed Tomography
Siva K. Kumar, MD, Faisal Shaikh, MD, Paul J. Mather, MD

Case Presentation
A 34 year old female with no significant past medical history presented with intermittent left shoulder and chest pain. The pain was burning in nature over her left chest and radiated to her left arm. There were no alleviating or exacerbating factors. Initial electrocardiogram showed sinus bradycardia. Cardiac computed tomography angiography revealed anomalous origin of the right coronary artery, which arises from the left sinus of Valsalva (Figure 1) and then travels towards the right side between the pulmonary outflow tract and the aortic root, where it shows mild narrowing of about 50%, (Figure 2) for a length of approximately 1 cm. The woman performed 9 mets during her exercise stress nuclear test which demonstrated electrocardiographic evidence of ischemia with normal myocardial perfusion.

Discussion
Cardiac ischemia in this setting is presumed to be caused by compression of the anomalous right coronary artery (RCA) as it courses between the PA and the aorta during exercise. Coronary artery anomalies are noted on approximately 1.3% of all cardiac catheterizations. 1 Anomalous origin of the RCA from the left sinus of Valsalva has been reported in approximately 0.03–0.09% of patients undergoing coronary angiography. Although previously considered to be a rare, but benign anomaly, more recently it has been associated with myocardial ischemia, infarction and sudden death in up to 30% of patients. 1,2 Patients may be at risk for premature atherosclerosis. In the setting of an obstructive lesion, these vessels are amenable to successful percutaneous coronary intervention and stent placement. 8 The patient has been asymptomatic for the past year while being treated with beta blockers.

References
A 42-year-old Male With Blurry Vision
William H Chong, MD, Dorothy Chang, MD

Introduction
Hypertension affects approximately 25% of the population of the United States. Complications from hypertension include ischemic heart disease and stroke, and rates increase progressively as blood pressure increases. In some cases, the elevation of blood pressure can be significant and be life threatening. Situations where there is severe elevation of blood pressure and evidence of target organ dysfunction are termed hypertensive emergency. In this report, an unusual cause of hypertensive emergency is presented.

Case Report
A 42-year-old male with no significant past medical history presented to the emergency department after being seen at the optometrist for a complaint of blurry vision and was found to have markedly elevated blood pressure. He reported wavy vision from his left eye as well as decreased peripheral vision and decreased color vision. He noted episodes of left-sided headaches over the last month, but has otherwise felt well. He reported no chronic medications, and no substance abuse. Family history was significant for a brother with diabetes. Review of systems was negative aside from the above-mentioned visual changes. He reported no chest pain, no shortness of breath, no abdominal complaints, and no urinary complaints. Physical exam was significant for severe hypertension with blood pressure of 245/115. Otherwise his exam was unremarkable. A report from the optometry clinic noted that he had retinal changes consistent with hypertensive emergency (Figure 1a, 1b).

The gentleman was admitted to the intensive care unit for malignant hypertension. His admission labs were significant for a creatinine of 3.5 mg/dL. In addition to placing him on a labetalol infusion for blood pressure control, work-up of his renal failure revealed bilateral hydronephrosis and a massively distended bladder rising above the level of the umbilicus (Fig 2a, 2b). Upon placement of a Foley catheter and drainage of retained urine, his creatinine began to improve and his blood pressure became more manageable. Urologic evaluation revealed urethral stricture. Subsequent clinical inquiries revealed a distant history of urethral trauma as a child which had not been problematic previously. Work-up for other causes of his malignant hypertension were unrevealing. The cause of his hypertensive emergency was attributed to renal failure secondary to urethral stricture. He was placed on oral medications and instructed to perform clean intermittent catheterization to prevent future urinary retention and was discharged home. Outpatient discharge instructions included urology & nephrology follow-up with a scheduled lumbar spine MRI to evaluate for neurologic causes of urinary retention.

Discussion
Hypertensive emergencies are acute, life threatening, and usually associated with marked increases in blood pressure, generally above 180/120. Blood pressures elevated to this degree without evidence of acute and progressive dysfunction of target organs is termed hypertensive urgency. Most patients with hypertensive emergency have had previously uncontrolled or unknown chronic hypertension. However, the disorder can present in previously normotensive individuals. In addition to marked elevation in blood pressure, major clinical manifestations include retinal hemorrhages and exudates, papilledema, and also malignant nephrosclerosis.

Figure 1. 42 year old male presented to the optometry clinic with complaint of blurry vision and was found to have retinal findings consistent with malignant hypertension. (Images courtesy of Wilmington VAMC)
In assessing patients with severe hypertension to determine if hypertensive emergency is present, certain history and physical exam points should be emphasized. Medical history should include previous treatments, illicit drug use, cardiovascular manifestations, neurologic symptoms, and urinary habits. Eliciting information about other medical conditions, such as thyroid disease, Cushing’s syndrome, systemic lupus erythematosus, systemic sclerosis, abdominal pain, dyspnea, and most recent menstruation can be extremely helpful. Physical exam should also assess blood pressure measured in both arms to detect any significant difference. Additionally, assessment of peripheral pulses for absence or delay is of clinical utility. Fundoscopy, cardiac and lung auscultation, and assessment of mental status are also important. Target organ dysfunction can be further revealed by analysis of laboratory studies and the presence of any EKG abnormalities.

In treating hypertensive emergency, the main objective is to reverse end-organ damage, which is accomplished by reducing mean arterial pressure by up to 5%. In general, blood pressure should be reduced by ~10% in the first hour and another 15% gradually over the next two to three hours. This is best accomplished with a continuous infusion of a short acting, titratable, parenteral anti-hypertensive agent along with constant, intensive patient monitoring. Anti-hypertensive drugs of choice include sodium nitroprusside, nitroglycerin, nicardipine, fenoldopam, labetalol, esmolol, hydralazine, and phentolamine. Co-morbidities and the type of target organ dysfunction dictate which anti-hypertensive agent should be selected.

In summary, this is a case of a 42 year-old male initially presenting with blurry vision secondary to hypertensive emergency. It is presumed that the etiology of this hypertensive emergency episode was secondary to renal failure caused by a urethral stricture. Hypertensive emergency is defined by severe hypertension (usually above 180/120) and evidence of target organ dysfunction. In these situations, prompt blood pressure control by no more than 25% within the first several hours prevents further end organ dysfunction. Numerous titratable, anti-hypertensive agents exist and should be tailored to the patient’s clinical history to prevent acute relative hypotension and watershed infarct.

References
Case Presentation
A 53 year old white male with a past medical history significant for type II diabetes mellitus and orthotopic liver transplant (December 2006) secondary to hepatitis B cirrhosis presents as a direct admission to Thomas Jefferson University Hospital in September 2007 for an orthopedic preoperative risk evaluation. Patient has had a dull, worsening, non-radiating back pain of six months duration, beginning after his liver transplant for which he has been to several outpatient orthopedic physicians. Upon admission, the patient appeared well, but admitted to a consistent 8/10 back pain that he had been managing at home with narcotic medications. Of note, outpatient magnetic resonance imaging (MRI) showed diskitis at L4/L5. Spinal biopsy and cultures were performed to rule out cord compression, spinal injury and infection due to his previous surgery and were all negative. On review of systems, he denied any lower extremity tenderness, numbness, paresthesias or loss of bowel or bladder function. He has lost over 70 pounds since his liver transplant. The remainder of the patient’s past medical history was negative except for a history of cataracts due to his diabetes mellitus. He reports a strong family history of hypertension, coronary artery disease and both type I and type II diabetes mellitus.

On physical examination, the patient was afebrile with stable and normal vital signs. Cardiovascular exam demonstrated normal S1 and S2 heart sounds, no murmurs, rubs or gallops, no jugular venous distention, and no carotid bruits. His lungs were clear bilaterally without wheezes, rhonchi, or rales. His abdomen did have a clean, dry and intact Mercedes type scar indicative of his liver transplantation. The remainder of his physical examination was within normal limits. Admission labs (Complete Blood Count, Basic Metabolic Panel, Electrolytes, PT/PTT/INR, Liver Function Tests), chest X-ray, and EKG were all within normal limits.

The patient was admitted to the general medical floor to undergo risk assessment for the laminectomy procedure. As part his cardiac evaluation, the patient underwent a nuclear and exercise stress test that showed distal anterior and apical hypokinesis. Cardiac catheterization was deemed necessary for further evaluation. Cardiac catheterization demonstrated a 100% RCA stenosis with significant stenoses in the LAD (70%), LCx (50%), and OM1 (50%). In light of these findings, the patient’s orthopedic procedure was delayed until cardiac revascularization could be achieved.

Discussion
This case illustrates a typical example of significant coronary artery disease (CAD) in an asymptomatic diabetic patient. Type II diabetes mellitus is a major risk factor for the development of CAD. Moreover, it is considered a CAD equivalent. Similarly, CAD is the major cause of morbidity and mortality in people with type II diabetes. Atherosclerosis occurs earlier, has an accelerated course, and is more extensive in diabetics compared with the general population. There are probably several factors that contribute to this. Type II diabetes is associated with abnormalities in lipoprotein metabolism and an increased propensity for oxidative damage; the hyperglycemia of diabetics, in itself, may accelerate vascular damage; and diabetes is a hypercoagulable state attributable to enhanced coagulation and decreased fibrinolysis, as well as platelet hyperaggregability and endothelial dysfunction.

The Insulin Resistance Atherosclerosis Study (IRAS) reported finding considerably greater intima-media thickness in the common and internal carotid arteries among patients with established diabetes compared with non-diabetic subjects. Diabetic patients without previous myocardial infarctions (MI) and non-diabetic patients with a previous MI have been found to have equally high risk for MI. Diabetic patients also have a high mortality rate from a first MI. These observations suggest that diabetics without obvious CAD may still have extensive atherosclerosis that, if untreated, could lead to serious cardiovascular complications. Some have suggested that this provides a rationale for assessing and treating cardiovascular risk factors in diabetic patients with the same aggressive approaches recommended for non-diabetic patients with a prior MI.

Diabetes treatment protocols (diet, exercise, pharmacological agents, and insulin) concentrate on controlling glycemia which leads to CAD. However, glycemia is not as strongly associated with macrovascular disease as it is with microvascular disease. Macrovascular disease appears to result from dyslipidemia in the diabetic patient. The form of dyslipidemia most frequently observed in diabetics is characterized by increased triglyceride levels and decreased high density lipoprotein (HDL) cholesterol levels. Diabetics also tend to have a higher level of smaller, denser low density lipoprotein (LDL) subclass pattern B than non-diabetics due to increases in hepatic triglyceride lipase.

Several studies have provided evidence of the link between diabetic dyslipidemia and CAD. In diabetic patients who had CAD events during a 7-year follow-up period had higher levels of total triglycerides, LDL, triglycerides, and VLDL cholesterol, and lower levels of HDL and HDL, cholesterol than diabetic patients who did not have such events. Other studies have found that both high levels of apolipoprotein B (apoB) and small, dense LDL among patients with high apoB levels also predict coronary artery disease.

References

Photo courtesy of Vaibhav Mehendiratta, MD
Left Atrial Myxoma
Siva K. Kumar, MD, Rajesh M. Kabadi, MD, Paul J. Mather, MD

Case Presentation
A 65 year-old female with a past medical history of hypertension and diabetes presented to her cardiologist’s office with symptoms consistent with progressive heart failure over an eight month period. A transthoracic echocardiogram done in the office demonstrated a normal-appearing mitral valve and normal left ventricular systolic function. Additionally, it also revealed a large left atrial myxoma (pictured above). The mass obstructed flow through the mitral valve, resulting in a mean valvular gradient of 18 mm Hg, consistent with mitral stenosis-like physiology. As a result of these findings, the patient was admitted to our institution for further evaluation. A transesophageal echocardiogram was performed for further assessment and showed a 6.7 x 4.6 cm homogenous mass which appeared to be attached by a stalk to the interatrial septum at the fossa ovalis. The patient subsequently underwent excision of this myxoma along with a patch repair of the interatrial septum. Postoperatively she was stable and discharged home six days later with surgical and cardiac follow-up.

Discussion
Benign myxomas are the most common tumors arising in the left atrium. Typically they are pedunculated and gelatinous in consistency with size varying from 1 to 15 centimeters. Cardiovascular manifestations largely depend on the anatomic location of the tumor, with 80% being found in the left atrium. Like our patient, ~70% of patients with left atrial myxoma suffer symptoms of heart failure, as well as syncopal episodes. Nearly 30% suffer from embolic events.1

Once diagnosed, treatment involves prompt resection due to the risk of potential embolization and/or cardiovascular complications. Postoperative recovery is generally rapid.

References
1. Pinede L, Duhaut P, Loire R; Clinical presentation of left atrial cardiac myxoma: A series of 112 consecutive cases. Medicine (Baltimore) 80;159-172,2001.

Figure 1. Transesophageal echocardiogram demonstrating a large 6.7 x 4.6 cm left atrial myxoma obstructing flow through the mitral valve.
A 41-YEAR-OLD WOMAN WITH RHEUMATIC MITRAL STENOSIS, ATRIAL FIBRILLATION, AND RIGHT-SIDED HEART FAILURE

Stephen Koczirka, MS-III

Case Presentation

A 41-year-old Southeast Asian woman presented to the Emergency Department (ED) complaining of acute onset of nausea and abdominal pain as well as a two weeks of palpitations and two months of cough productive of white sputum. The patient also complained of fever, shortness of breath and dyspnea on exertion over the previous week. Patient history revealed a past medical history of asthma. The patient had no prior surgical or psychiatric history, had no known drug allergies, and consumed no chronic medications. The patient reported that she had immigrated to the United States from Laos in 1986. She denied any tobacco, alcohol or illicit substance abuse.

The patient was afebrile and demonstrated hemodynamic stability in face of her EKG demonstrating atrial fibrillation at a ventricular response rate of 80 bpm. Lung auscultation revealed bilateral crackles at the lower bases, but no rales or wheezing. Cardiac examination demonstrated an irregularly irregular pulse with a mid-diastolic rumbling murmur heard best at the apex without radiation. She demonstrated elevated jugular venous distention to ~12 cm H₂O and demonstrated 1+ pitting lower extremity edema.

Laboratory data was significant for a beta-natriuretic peptide (BNP) of 972 pg/mL. The patient had a microcytic anemia with a hemoglobin 12.6 mg/dL. Troponins were all within normal limits and the EKG did not reveal any ischemic changes. X-ray findings, later corroborated by chest CT, demonstrated bilateral pleural effusions, bilateral lower lobe infiltrates with mediastinal and hilar lymphadenopathy. The patient was admitted to the critical care unit for transesophageal echocardiogram (TEE) which demonstrated:

The left atrium is severely dilated. The right atrium is moderately dilated. There is moderate to severe tricuspid regurgitation. Right ventricular systolic pressure is elevated at >60 mmHg. Left ventricular systolic function is borderline reduced. Flattened septum is consistent with RV pressure/volume overload. The right ventricle is mildly dilated. The right ventricular systolic function is hypokinetic. There is severe mitral stenosis. The mean gradient was 11 mm Hg and the peak gradient was 20 mm Hg. The valve area is 1.1 cm².

The results of the TEE suggested that the most likely etiology for the patient’s valvular and clinical findings was that of rheumatic mitral stenosis. The patient’s age, immigration status, and relative lack of medical history also fit the prototypical model of a patient with complications of prior acute rheumatic fever. Possibly superimposed on this disease process is a bacterial pneumonia causing the bibasilar infiltrates or these radiologic findings which may simply have been an extension of the sequelae of the rheumatic heart disease.

Discussion

Rheumatic fever is a delayed consequence of pharyngeal infection with *group A streptococcus* (GAS). The disease manifestations can affect several areas of the body, namely the cardiovascular, musculoskeletal, neurological and dermatological systems. These are believed to be a result of a diffuse inflammatory process that results in an autoimmune attack on the body due to the phenomenon of molecular mimicry. The GAS cell wall contains M proteins that are antigenically similar to proteins found in the human body. When an immune response is mounted to the initial GAS infection, antibodies are formed against this M protein, which then circulate throughout the body and bind to normal protein epitopes in human tissue. The complexes formed then induce a T-cell mediated attack on normal tissues, causing the long term sequelae of the disease.

Diagnosis of acute rheumatic fever has remained relatively unchanged since it was first described in 1889 by William Cheadle in London. In 1965, the American Heart Association released the Jones guidelines, laying out a specific set of criteria to be used for diagnosis. In 1992, the Jones criteria were revisited and revised, and these guidelines are currently used in clinical practice:

**Table 1.** For diagnosis, two major criteria OR one major criterion with two minor criteria is needed, in addition to evidence of prior GAS infection

<table>
<thead>
<tr>
<th>5 major manifestations</th>
<th>4 minor manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis</td>
<td>Arthalgia</td>
</tr>
<tr>
<td>Migratory polyarthritis</td>
<td>Fever</td>
</tr>
<tr>
<td>Sydenham’s chorea</td>
<td>Elevated ESR or CRP</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>Prolonged PR interval</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
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**Evidence of preceding streptococcal infection:**

- Positive throat culture for GAS or positive rapid streptococcal antigen test

Rheumatic carditis is considered to be the most serious of the manifestation of GAS infection. It is very difficult to detect before the disease is severe enough to become symptomatic. The disease can manifest in any of the three layers of the myocardium, but most often affects the cardiac valves, especially the mitral valve (85% of affected patients). Small nodules known as Aschoff bodies initially form on the valve leaflets and slowly enlarge due to increased fibrin deposition. These deposits slowly decrease the functional ability of the valve leaflets causing mitral stenosis or mitral regurgitation, and functionally limit normal
blood flow. Chronically, this leads to left atrial enlargement (which can lead to atrial fibrillation), pulmonary hypertension, and eventually right-sided heart failure. Natural history studies suggest that the average amount of time from the onset of rheumatic fever to onset of mitral valve symptoms is 16.3 years. Further progression to severe mitral disability from the onset of symptoms is 9.2 ± 4.3 years.

Treatment of rheumatic carditis is dependent on the extent of the disease on presentation. If the cardiac damage is not extensive, prophylactic treatment includes aspirin for mild cases and steroids for more severe cases. In patients with severe mitral regurgitation or stenosis, surgery is indicated to improve blood flow through the cardiac system. It has been shown that percutaneous balloon valvuloplasty and mitral valve repair have shown similar initial results and efficacy at three years; therefore, percutaneous balloon valvuloplasty is the preferred surgical treatment due to better long term patency, lower cost, and decreased need for open thoracotomy.

Patient Course
The patient’s atrial fibrillation was rate controlled with a combination of beta-blockers and digoxin. She was bridged from intravenous heparin to oral warfarin for anticoagulation and her bibasilar pneumonia was treated with broad spectrum antibiotics. She was transferred to another institution for cardiothoracic evaluation of potential percutaneous balloon valvuloplasty of the mitral valve.

References
A Case Report of Idiopathic Giant Cell Myocarditis

Bao Bui, MD, Sumeet Chhabra, MD, Siva K. Kumar, MD

Case Report
A 32 year old African American male was admitted to an outside hospital in July 2007 with symptoms of severe heart failure that required implantation of a short-term left ventricular assist device (LVAD). He was subsequently transferred to our facility due to worsening left ventricular heart failure, episodes of Torsades de Pointes, and monomorphic ventricular tachycardia. His device was replaced with a longer-term LVAD and he was discharged home in October. Fortunately, he underwent successful orthotopic heart transplant in November 2007.

Surgical pathology of the explanted heart revealed widespread cardiomyocyte necrosis, marked polymorphous inflammation, and giant cell formation consistent with idiopathic giant cell myocarditis (figures). Follow-up post transplant endomyocardial biopsies did not reveal recurrence of giant cell myocarditis or acute rejection.

Discussion
Idiopathic Giant Cell Myocarditis (IGCM) is a rare and generally fatal entity that has been largely confined to scattered case reports and observational studies, most notably a multi-center registry created by Cooper et al in 1997. While IGCM has historically been a histological diagnosis at autopsy, the current gold standard method of diagnosis remains endomyocardial biopsy. This
disorder typically afflicts younger adults with mean age of forty-three. It is most commonly characterized by rapid and progressive congestive heart failure generally refractory to conventional heart failure treatments. Other common clinical presentations include ventricular arrhythmias, heart block, and less commonly as early symptoms of acute myocardial infarction.

While no uniform guidelines yet exist for the treatment of IGCM, animal models suggest involvement of CD4 T-lymphocytes with reported success with combined steroid and immunosuppressive therapy. Reported associations with autoimmune disorders are also consistent with this theory.

Patients in the IGCM registry that received immunosuppression lived longer than those that did not. Heart transplantation also appeared to be efficacious with 5-year survival data reported at 71% despite recurrence of disease in 20–42% of the newly transplanted hearts. Our case of IGCM illustrates the importance of surveillance biopsies and the growing evidence that transplantation and immunosuppression may be effective therapy for an otherwise rapidly fatal disease.

References
MAN WITH FLU-like SYMPTOMS
Sandarsh Kancherla, MD, Ankitkumar Patel, MD, MPH

Case Presentation
A 69 year-old male presents to the Emergency Department with complaints of malaise, myalgias, rhinorrhea, increased congestion, and occasional fevers for one week. The symptoms have gradually worsened over the past week, and Tylenol has minimally alleviated his symptoms. He denies exacerbating factors. He denies any trauma, shortness of breath, chest pain, or recent weight change. He has no sick contacts or recent travel history.

Past medical history is significant for coronary artery disease status post myocardial infarction and coronary artery bypass graft in 2000, hypertension, hyperlipidemia, and atrial fibrillation. Medications on admission include amiodarone, aspirin, atorvastatin, docusate, losartan, metoprolol succinate (XL), and warfarin. He does not smoke, drink alcohol, or use illicit drugs.

On admission, temperature was 99.7, blood pressure was 118/72, heart rate was 74, respiratory rate was 18, and oxygen saturation was 96% on room air. Physical examination was significant for dry mucosa and mild proximal muscle weakness. Initial labs on admission revealed an elevated creatinine of 1.9; CBC, UA, and LFTs were within normal limits. The patient was admitted with the diagnosis of upper respiratory tract infection with dehydration and started on intravenous fluids and supportive therapy for flu-like symptoms.

Approximately 3 days after admission, his rhinorrhea and congestion had resolved, but he complained of worsening myalgias. Physical exam at that time revealed worsening tenderness to palpation over his shoulder muscles and proximal lower extremities, as well as 4/5 muscle strength in his quadriceps and deltoids. He had difficulty standing from a seated position. Range of motion of all extremities was intact. At that time, it was revealed that his atorvastatin dose had been increased from 0 mg to 80 mg approximately 6 months ago as an outpatient. The CPK level drawn shortly thereafter was 5,317, supporting a diagnosis of statin-induced myositis, which is a form of drug-induced myopathy. Upon discontinuing his atorvastatin, his symptoms improved, and CPK trended down until it was within normal limits.

Discussion
Drug-induced myopathy is among the most common causes of muscle disease. Symptoms range from mild myalgias with or without mild weakness, to chronic myopathy characterized by severe weakness, to massive rhabdomyolysis with acute renal failure.1

Drug-induced myopathy results from direct myotoxicity from lipid-lowering drugs and other agents such as alcohol, cocaine, glucocorticoids, antimalarials, and colchicine.2 Statins are considered effective and generally safe, but experience in clinical practice suggests that muscle side effects are relatively common; some of the side effects are severe enough to warrant discontinuation of statin therapy.

The mechanism by which statins cause muscle toxicity is not well understood. They inhibit the conversion of HMG-CoA to mevalonic acid, which is an important early step in cholesterol synthesis. Statins can also decrease the synthesis of coenzyme Q10 (CoQ10), which plays an important role in muscle cell energy production.3 This pathway is thought to contribute to statin-induced muscle injury.

The onset of muscle symptoms is usually within weeks to months after the initiation of statin therapy. Typically, the presentation of statin-induced myopathy is very non-specific. It has a very insidious onset and includes progressive weakness, generalized pain, and fatigue. Myalgias and weakness generally resolve, and serum creatinine kinase levels return to normal within days to weeks upon discontinuation of statin therapy.

The muscle symptoms in patients taking statin therapy can range from mild symptoms to severe symptoms. The incidence of mild myalgias, defined as muscle ache or weakness without increases in CPK levels, in patients taking statins ranges from 2 to 11 percent.4,5 Symptoms generally resolve within 2 to 3 weeks after stopping a statin. Myositis, defined as a serum CPK elevation more than 10 times normal in association with muscle symptoms, occurs in less than 0.5% of patients.4,5 Rhabdomyolysis resulting from severe muscle destruction is rarely seen and occurs in less than 0.1% of patients.6 Rhabdomyolysis has primarily been seen when a statin is given concurrently with cyclosporine or gemfibrozil.7

The risk of muscle injury due to statins appears to vary among the different drug formulations. The risk of myopathy is lowest with pravastatin (less than 0.1%) and fluvastatin.8 These two medications are also less likely to cause drug interactions since they are not extensively metabolized by CYP3A4. Patients with acute or chronic renal failure, obstructive liver disease, and hypothyroidism have increased susceptibility to statin-associated myopathy.

The risk of myopathy is much greater in patients who are also taking drugs that inhibit CYP3A4, must notably cyclosporine, gemfibrozil, macrolide antibiotics, itraconazole, and HIV protease inhibitors. These drugs increase the serum concentration of the statins. Initial studies of lovastatin and simvastatin showed clinically significant myopathy in 13 to 30% of patients taking cyclosporine.4 Approximately 5% of patients taking atorvastatin or lovastatin in addition to gemfibrozil experience significant myopathy.4,9 In contrast, pravastatin and fluvastatin, which are not metabolized by CYP3A4, do not appear to increase the risk...
of myopathy when given with cyclosporine.\textsuperscript{10,11} This is a very important consideration when treating transplant patients.

Routine monitoring of CPK levels is not recommended, but it is useful to obtain a baseline serum CPK before initiation of statin therapy for reference. Patients should be alerted to the potential side effects of statins and report new onset of myalgias or weakness to their physician. CPK levels may be abnormal in conditions such as hypothyroidism, trauma, and high impact sports. In general, a CPK level more than 10 times the upper limit of normal, in the absence of other clinical risk factors, is generally felt to be due to a statin. It is an indication to discontinue the medication. If a patient experiences muscle myopathy on a statin, with the exception of rhabdomyolysis, the statin should be discontinued until symptoms resolve. It is reasonable to consider restarting pravastatin or fluvastatin with careful monitoring. In the case of rhabdomyolysis, the statin should be discontinued indefinitely. If muscle toxicity occurs while on pravastatin or fluvastatin, a trial of CoQ10 supplementation may be initiated, although there is only limited evidence for its benefit.\textsuperscript{12}

\section*{References}


\textit{Photo courtesy of Vaibhav Mehendiratta, MD}
A 22-YEAR-OLD WOMAN WITH SYSTEMIC LUPUS ERYTHEMATOSUS DEVELOPS CARDIAC TAMPONADE

Brooks Kuhn, MS-III, Arthi Reddy, MD, Sorin Lazar, MD

Introduction
Systemic lupus erythematosus (SLE) is a common cause of pericardial effusion and acute pericarditis, but very rarely it can cause cardiac tamponade.1 We describe the case of a young female with SLE who developed cardiac tamponade after finishing treatment for acute pericarditis with a small pericardial effusion.

Case Report
A 22-year-old college student at a local university with a history of SLE diagnosed in 2003 (ANA+, anti-dsDNA+, and anti-SS-A+) presented to an outside hospital complaining of shortness of breath, fever, and pleuritic chest pain. These symptoms began acutely in the presence of a week-old lupus flare characterized by a butterfly malar rash and arthralgias. A chest CT demonstrated a small pericardial effusion without evidence of tamponade. She was diagnosed with pericarditis and subsequently her outpatient dose of prednisone was increased from 15 mg/day to 60 mg/day. However, she showed little clinical or radiographic improvement on CT. She was then scheduled to receive pulse dose steroids (methylprednisolone) for 3 days.

The patient presented to our hospital on Day 3 after her initial presentation to the outside hospital with continuing complaints of shortness of breath, though without chest pain or fever. Her past medical history was significant for multiple hospitalizations for pleuritis and pericarditis, most recently seven months prior for pericarditis. That episode had resolved after a three day course of pulse steroids. Vitals demonstrated a temperature of 98.4°F, a pulse of 79 bpm, a respiratory rate of 20/min, and a blood pressure of 118/70. Physical exam illustrated a rash, symmetrically distributed across the malar aspects of her face. Her exam including cardiac auscultation was reportedly benign. An echocardiogram showed the persistence of a small pericardial effusion and mild left atrial enlargement. A chest x-ray revealed bilateral pulmonary edema with bibasilar atelectasis and cardiomegaly. EKG and laboratory tests were within normal limits except for an elevated ESR and CRP. The patient was promptly started on pulse steroids for 3 days.

Despite completing her course of steroids, repeat transthoracic echocardiography visualized persistence of a small pericardial effusion. A repeat chest CT to evaluate her pleural effusion imaged a 2.1 cm dense lesion in the right upper quadrant of her lung. PPD and an acid-fast bacilli (AFB) stain were negative. A bronchoalveolar lavage did not demonstrate any purulent secretions or notable AFB stains. Clinically, the patient had markedly improved, denying shortness of breath, chest pain, and cough. Nevertheless, empiric antibiotic therapy with vancomycin and piperacillin/tazobactam was initiated.

On the evening of Day 8, the patient began complaining of severe chest pain. On examination, she had visible jugular venous dilation to her mandible and pulsus paradoxus of approximately 10 mm Hg. She was tachycardic at 109 beats per minute, blood pressure was 92/60, and her respiratory rate was 25 resps/min. A stat echocardiogram revealed markedly increased pericardial fluid causing IVC collapse with mitral valve inflow respiratory variation. The right heart was not collapsed. EKG showed sinus tachycardia with T-wave flattening in V5, V6, and aVL. The patient was immediately taken to the cardiac catheterization lab for pericardiocentesis. A total of 680 cc of yellow, purulent fluid was drained with staining revealing gram positive cocci in clusters which eventually grew methicillin-sensitive Staphylococcus Aureus (MSSA) on culture. Vancomycin was continued and piperacillin/tazobactam was discontinued. Two days later the patient received a pericardial window to prevent further episodes of effusion and tamponade. Vancomycin was initially narrowed to nafcillin but after developing a bout of acute renal failure this was changed to cefazolin. Despite a complicated hospital stay, she was discharged home in good health.

Discussion
Cardiac tamponade is a known complication of SLE, albeit a very rare manifestation.1 More typical cardiac manifestations of SLE include pericarditis and pericardial effusion, as seen in our patient, along with myocarditis, endocarditis, and conduction abnormalities.2 Causes of pericardial effusions include idiopathic, viral, bacterial, uremic, traumatic, or neoplastic pathologies. In connective tissue disorders, effusions are most typically caused by inflammatory cell infiltrate and immune complex deposition within cardiac tissue, causing a serous or serosanguanous exudate similar to synovial fluid to encompass the heart.1 This pericarditis and effusion can be significant, but rarely causes pericardial tamponade.3 When it does, it tends to occur in males later in life.4

While rare, it is not necessarily surprising that the patient presented here developed cardiac tamponade early in life. There are numerous published case reports which detail SLE patients developing tamponade, even as their presenting symptom.5,6 This case is noteworthy due to the bacterial etiology of her pericardial effusion & tamponade. A similar case was presented by Knodell et al. in Chest 1974 which chronicled a female with known SLE who presented with fever, chills, and a significant pericardial effusion, but without positive blood cultures.7 It was only when thoracentesis revealed a Staphylococcal effusion that the source of her infection was found after steroid treatment on her 11th day of hospitalization. The patient described in our case differs in that she remained afebrile throughout the course and did not show any tell-tale signs of infection until her chest CT revealed the cavitary lesion in her lung. It is unusual for such a significant infection to remain relatively asymptomatic throughout its course. The origins of our own patient’s pericarditis remain
elusive. Obviously, her lengthy course of steroids contributed to her infection, but no source could be identified apart from the loculated lesion in her lung.

The clinical course of this patient is unique as well. Pericarditis with effusion is typically treated very successfully with high-dose steroids. This patient was on a full course of high-dose steroids, along with a three day course of pulse steroids. Though she initially improved clinically, she rapidly developed cardiac tamponade overnight. The dramatic exacerbation of her effusion could indicate the infection developed later in her course and caused the rapid progression of illness.

References
Hemochromatosis
Benjamin Creelan, MD

Case Presentation
This 50 year-old adult male suffered from iron overload due to repetitive blood transfusions for HbSS sickle cell anemia. Computed tomography (CT) scan of the abdomen revealed high attenuation and massive enlargement of the liver consistent with hemochromatosis. A normal liver and spleen is included for comparison (inset). Splenic calcification is also noted, a rare finding in sickle cell anemia.1,2

Discussion
Secondary hemochromatosis causes reticuloendothelial cell iron deposition. The disease has homogeneously increased liver attenuation on CT and decreased signal intensity with magnetic resonance imaging. Portal vein branches stand out as low-attenuation structures against the background of the hyperattenuating liver. Other deposition diseases such as amiodarone toxicity may create a similar appearance.3 In iron overload states, there is a direct correlation between liver intensity on CT imaging and serum ferritin.4

References
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Inset: Normal abdomen for comparison.
A 70-year-old Male With Abdominal Pain
William H Chong, MD

Introduction
Acute pancreatitis is an acute inflammatory process of the pancreas. It is usually associated with severe acute upper abdominal pain and elevated blood levels of pancreatic enzymes. Serum amylase and lipase are common tests obtained as biochemical markers for acute pancreatitis. Pancreatitis, however, is not the sole cause of elevated pancreatic enzymes. Non-pancreatic causes of hyperamylasemia include inflammation or trauma to the salivary glands, bowel perforation or infarction, renal failure, abdominal trauma, and macroamylasemia. An unusual cause of elevated pancreatic enzymes is reported in this case report.

Case Presentation
A 70 year old male was admitted to the hospital after being evaluated by his primary care physician for abdominal pain. He initially complained of abdominal pain and had labs and x-rays ordered from the office. After 2 days, he called for results and was admitted to the hospital for abnormal lab studies.

At admission, he described his pain as dull and achy, located primarily in the right upper quadrant. Initially the pain was rated a 7/10 in severity, but had improved to 2/10 by the time of admission. The only treatment he had used over this period was ibuprofen. His symptoms were worse with deep inspiration, and he noted no other symptoms such as nausea, vomiting, constipation, or diarrhea.

His past medical history was significant for benign prostatic hypertrophy, hyperlipidemia, coronary artery disease, reflux, and vitiligo. Past surgeries included appendectomy and hand surgery. He had no allergies and the only medication that he was taking was terazosin. Social history was negative for alcohol, tobacco, or drugs, and family history was non-contributory. Review of systems was otherwise unremarkable.

On physical exam he was in no acute distress and his vital signs were stable. Cardiovascular and pulmonary exam were unremarkable. Abdominal exam was significant for tenderness to palpation in the right upper quadrant over the rib cage, but a negative Murphy’s sign. Labs and studies obtained from his physician’s office were significant for a serum amylase level of 699 units/dl. Other labs including complete blood count, electrolytes, and lipase were all within normal limits. X-rays of his ribs and spine showed no evidence of fractures.

His physician admitted him with concern for pancreatitis. Further studies obtained while admitted to the hospital including abdominal ultrasound and CT scan showed no evidence of pancreatitis or gallstones. Serial amylase levels continued to be elevated throughout his hospitalization. His pain was attributed to chondritis from having moved furniture prior to initial presentation. An amylase-creatinine clearance ratio was calculated and found to be low at 0.2%, consistent with macroamylasemia, and his elevated amylase level was attributed to macroamylasemia.

Discussion
The typical presentation of acute pancreatitis includes an elevated serum amylase level and steady, severe upper abdominal pain radiating to the back. For patients with acute pancreatitis, hospitalization is almost always required. Management includes bowel rest, IV hydration, pain management, supportive care, and serial laboratory tests to monitor for improvement or worsening of the patient’s condition. However, not all elevations in amylase are related to pancreatitis.

In 1964, Wilding et al reported a condition found in three patients with persistently elevated serum amylase levels. These patients were found to have amylase-globulin complexes that were too large to be readily excreted by the kidney. In 1967, Berk et al reported a condition in the New England Journal of Medicine which he termed macroamylasemia. Aside from immunoglobulins, the amylase molecule can also bind to polysaccharides forming these enlarged complexes. The size of the complex prohibits renal excretion and results in persistently elevated levels of amylase. Several diseases have been described in association with macroamylasemia, including celiac disease, HIV infection, lymphoma, ulcerative colitis, rheumatoid arthritis, and monoclonal gammopathy. However, macroamylasemia does not have to be associated with these disease states and can occur in any condition in which abnormal immunoglobulins are present.

Diagnosis of macroamylasemia can be made by applying a simple diagnostic algorithm. The initial step is to evaluate for elevated serum lipase. If this is also elevated, acute pancreatitis should be strongly considered. The next step is to then measure urinary amylase. If it is elevated, acute pancreatitis should again be strongly considered. If neither of these is the case and renal function is abnormal, secondarily elevated amylase due to renal disease should be considered. Once these causes have been eliminated, isoamylase testing to exclude non-pancreatic sources of amylase can be performed. If the amylase is indeed pancreatic in origin, the amylase-creatinine clearance ratio can be calculated using the formula:

\[
\text{Urine Amylase} \times \frac{\text{Serum Creatinine}}{\text{Serum Amylase}} \times 100
\]

If this is found to be less than 1% macroamylasemia should be suspected. If desired, further analysis can be performed with electrophoresis, polyethylene glycol precipitation testing, and gel chromatography.

Acute pancreatitis needs to be suspected in any patient with abdominal pain and elevated pancreatic enzymes. These
symptoms, however, need not be related and other causes for elevated pancreatic enzymes should be considered. Non-pancreatic sources of enzymes and other causes for increased release of pancreatic enzymes should be considered. In addition, decreased clearance of enzymes can create elevated serum levels. Decreased clearance can be due to impaired renal function, or abnormal amylase-globulin complexes that can not be readily excreted. An example of the latter is presented here as a case of a patient with abdominal pain and elevated amylase.

References

Case Presentation
MG is a 56-year-old female with no significant past medical history who presented to TJUH in October 2007 with a two year history of abdominal pain and weight loss. At presentation, she described her pain as non-radiating, 7 out of 10, gnawing, burning and located in the epigastrium and left upper quadrant. The pain initially occurred approximately 15 minutes post-prandially and lasted 30 minutes. Over the two year period, the pain progressed to lasting for hours following meals. Dietary modifications and food consistency did not help the pain. The patient began avoiding oral intake, and her weight declined from 120 to 80 pounds. She denied nausea, vomiting, diarrhea, constipation, hematochezia, melena and change in stool frequency. Over the two years prior to admission the patient had an extensive workup with multiple gastroenterologists. Her initial workup included a colonoscopy, EGD, abdominal ultrasound and computerized tomography (CT) of the abdomen and pelvis. These were all reportedly normal and the patient was diagnosed with irritable bowel syndrome and treated symptomatically with a PPI. Due to lack of improvement, a second gastroenterologist repeated the EGD/colonoscopy and diagnosed her with peptic ulcer disease secondary to multiple gastric ulcers. She was treated with a PPI and carafate. A capsule study showed gastric and jejunal ulcers with cobblestone appearance of the small bowel which led to the diagnosis of Crohn’s disease. She was treated briefly with Pentasa. The patient sought care as an outpatient at TJUH Division of Gastroenterology. Mesenteric ischemia was initially high on the differential. An MRI of the abdomen revealed patent mesenteric vessels. Other workup included gastric emptying scan, push enteroscopy, endoscopic ultrasound (EUS), full-thickness biopsy in the operating room, fasting gastrin level, and an NSAID level. These studies were mostly inconclusive. Other studies including an octreotide scan, gastrin levels, and chromogranin A levels were either normal or inconclusive. Furthermore, it was discovered that the gastric pH was 4.4, arguing against a gastrin producing tumor as seen in Zollinger-Ellison Syndrome.

At the time of admission, her medications were pantoprazole 40 mg BID and ciprofloxacin 500 mg BID, both of which offered only mild relief. She has a 25 pack year smoking history, does not drink alcohol or use other drugs. Her family history is significant for a brother and father having coronary artery disease. On examination the patient appeared thin and pale. The abdomen was not tender to palpation, however, an abdominal bruit could be auscultated. Admission labs were within normal limits except for a WBC count of 1,000 without a left shift. The question of mesenteric ischemia was again entertained. An abdominal ultrasound with dopplers revealed a greater than 70% stenosis of the superior mesenteric artery (SMA). CT angiography (CTA) of the abdomen revealed occlusion of the celiac artery, near occlusion of the SMA, and stenosis of the inferior mesenteric artery (IMA). The magnetic resonance angiogram (MRA) done six months earlier was post-processed and finally revealed stenosis of the SMA. Vascular surgery was consulted and a decision was made to pursue traditional angiography and stenting by interventional radiology. Interventional radiology placed 2 overlapping stents in the SMA which subsequently demonstrated excellent filling of the SMA and branches. Since adequate collateral circulation was observed, the celiac artery was not treated. The post-procedure course was complicated by thrombosis of the left brachial artery prompting thrombectomy. Approximately two weeks after her procedure, the patient had no abdominal pain, is eating voraciously and had already gained 5 pounds.

Discussion
Chronic mesenteric ischemia (CMI) can be distinguished from acute mesenteric ischemia by the time course of the symptoms and etiology of the disease. Acute mesenteric ischemia can be caused by four mechanisms: SMA embolus or thrombosis, acute mesenteric venous thrombosis, and non-occlusive mesenteric ischemia. The focus of this article will be chronic mesenteric ischemia. Common risk factors include hyperlipidemia, diabetes, and smoking. Although there are many possible causes of CMI, most commonly it is secondary to atherosclerosis. The celiac artery (CA) and SMA are the most commonly affected, although the IMA can be involved. Due to the slow development of the stenosis, particularly when atherosclerosis is the etiology, patients may develop collateral circulation to the affected vessels. Often symptoms do not develop until two vessels have become occluded. Symptoms commonly include post-prandial pain beginning ~15-60 minutes after food ingestion and last ~1-4 hours, manifest by sitophobia, weight loss, nausea, and vomiting. Involvement of the CA distribution may also cause gastroparesis, gastric ulceration, and even gallbladder dyskinesia. While both physical exam and common laboratory tests are usually unremarkable, it is common for patients to have cachexia and stigmata of vascular disease including an abdominal bruit.

Traditional angiography has been the gold standard for diagnosis of CMI. Recently, however, duplex ultrasonography (US), CTA, and MRA are increasingly used to evaluate compromise of the mesenteric arteries. Duplex US is more accurate in identifying SMA stenosis (90%) in comparison to CA stenosis (80%). Areas of stenosis are identified by increases in peak systolic or velocity of blood flow (CA>200cm/s, SMA>275cm/s). Results may be affected by variations of body habitus, bowel gas, respiration, and anatomy. CTA and MRA are also reliable methods for the diagnosis of CMI. In the presence of a negative CTA study (particularly the multidetector-row CTA), it is unlikely for the patient to have CMI. MRA can identify greater than 90% of SMA lesions, 75-90% of CA lesions, and 25% of IMA lesions. Furthermore, some studies have reported 100% sensitivity of diagnosing...
CA and SMA stenosis when compared to the gold standard of invasive angiography.²

When two or more mesenteric vessels are occluded or significantly stenosed in the setting of post-prandial abdominal pain and weight loss, there are two therapeutic options. In the past, surgical revascularization used to be the only option available. This involved transaortic endarterectomy or antegrade vs. retrograde bypass surgery. One study showed a 93% success rate for endarterectomy with a high patency rate at 1 and 3 years. Unfortunately, many of the patients requiring revascularization are malnourished and at higher risk for perioperative complications. Complication rates range from 15-33% with mortality up to 17%.³

The other therapeutic option for CMI is percutaneous angioplasty (PCA) with or without stent placement. Unfortunately, it is difficult to compare this modality to surgery. A study involving 25 patients revealed that clinical benefit at 11 months was 91% and patency of the stents was 92%.³ Furthermore, the mean complication rate for endovascular therapy is 10% with a mortality rate up to 5%.³ Overall, it appears that endovascular repair may have less associated morbidity and mortality, however surgery offers the benefit of a lower re-stenosis rate.⁴

Finally, it should be emphasized that this case reiterates the importance of clinical history in diagnosis. This patient’s diagnosis was initially prolonged despite a fairly classic history, hence CMI was not entertained. However, a false negative MRA further delayed her diagnosis. Furthermore, the authors point out that this patient should never have been diagnosed with irritable bowel syndrome. The diagnosis of IBS can be made using the Rome criteria. Weight loss is a red flag and should have excluded this diagnosis.

While imaging and laboratory tests are generally very useful in assisting clinicians make diagnoses, these results should never supercede clinical acumen.

Key Points

Postprandial abdominal pain and weight loss are the typical symptoms seen in chronic mesenteric ischemia (CMI).

1. Usually, 2 of the 3 major mesenteric vessels must be occluded before the patient develops symptoms.
2. Diagnosis can be made by MRA, US with dopplers, or CTA.
3. Treatment options include vascular surgery and endovascular stenting.

References

Chest Pain as a Presenting Symptom for Gastric Phytobezoar

Ankitkumar K. Patel, MD, MPH, Sandarsh Kancherla, MD, Darren Seril, MD

Introduction
Chest pain is a common chief complaint of patient presentation to the emergency room. It also presents itself as one of the most challenging symptoms for clinicians to manage. The differential diagnosis for chest pain involves a multitude of organ systems. Failure to recognize potentially serious life-threatening causes such as acute ischemic heart disease, aortic dissection, tension pneumothorax, or pulmonary embolism can lead to serious morbidity and mortality. At the same time, overly conservative management of low-risk patients leads to unnecessary hospital admissions, studies and procedures. The following case illustrates the need to broaden the differential diagnosis for chest pain once life-threatening causes have been ruled out (Table 1).

Case Presentation
The patient is a 55 year old female with a past medical history of spinal fusion, chronic back pain, gastroesophageal reflux, and anxiety who was in her usual state of health prior to admission when she started having crushing chest pain that radiated to the left arm. The patient was resting when the pain first awoke her and was of 8/10 constant intensity. The pain was associated with diaphoresis and nausea. The patient took ranitidine at first onset, but this provided no relief. The patient came into the emergency room eight hours after onset of chest pain because she was feeling fatigued and lightheaded at work.

In the emergency room the patient’s pain went from 8/10 to 4/10 with the administration of sublingual nitroglycerin and omeprazole.

The patient’s past surgical history included hysterectomy, cholecystectomy, and breast reduction. The patient’s family history includes: mother with ovarian cancer, father with heart disease, and a brother with heart disease and 3 stents. The patient has a 40 pack year history of smoking cigarettes, occasional alcohol consumption, no illicit drug use and works as a cashier. The patient stated that due to the significant family history of heart disease and her significant smoking history, she had started eating a “heart healthy” diet consisting predominantly of fruits and vegetables. The patient had no known allergies. Medications on admission were omeprazole, celecoxib, naproxen, acetaminophen/hydrocodone, cyclobenzaprine, zolpidem, alprazolam, and varenicline.

On presentation, the patient was afebrile (97°F) with EKG demonstrating normal sinus rhythm (72 bpm), blood pressure 100/58, saturating 100% on room air with no respiratory distress noted (16 resp/min). The cardiopulmonary physical examination was within normal limits. Initial laboratory studies including a complete blood count and chemistry panel were within normal limits. A recent nuclear thallium stress test 2 months prior showed no ischemia and a LV ejection fraction of 60%.

The patient was admitted to the general medicine service. Serial troponins were negative. Hemoglobin A1C level was 5.5%. A fasting lipid panel had triglycerides of 351 mg/dl, HDL of 34 mg/dl and total cholesterol of 211 mg/dl. A chest x-ray showed no active pulmonary disease and a normal cardiac silhouette. The patient underwent a nuclear thallium gated stress test which showed no exercise induced reversible myocardial perfusion defects, increased lung uptake (most likely secondary to COPD or smoking history), no evidence of regional wall motion abnormality and a calculated left ventricular ejection fraction of 58%.

The patient’s pain was diminished but had not been obliterated. A cardiology consultation suggested the patient be ruled out for pulmonary embolism. Though the patient did not demonstrate normal signs and symptoms of a PE, a CTA was performed which showed no signs of aortic dissection or pulmonary emboli. After a negative cardiac workup, the patient underwent endoscopy to investigate whether her symptoms were secondary to gastrointestinal pathology. The endoscopy found a medium sized phytobezoar in the stomach compatible with gastroparesis and mild antral gastritis. A gastric biopsy was taken for investigation for H. pylori. The phytobezoar was not removed.

The patient was discharged with a diagnosis of gastroparesis secondary to gastric phytobezoar with subsequent initiation of metoclopramide therapy. In addition to her previous outpatient medications, we added ezetimibe and simvastatin for hypercholesterolemia. Six weeks later, the patient reported no further episodes of chest pain.

Discussion
Traditionally, bezoars were valued as cures for disease. The name derives from the Arabic word for “antidote.” Bezoars come in three varieties: phytobezoars, comprised of vegetable material; trichobezoars, formed from hair; and lactobezoars, composed of milk. Phytobezoars, the most common type of bezoar found in adults, are formed from the cellulose and lignin found in fibrous fruits and vegetables, most commonly oranges, figs, apples, persimmons, green beans, and brussel sprouts. Medications and supplements, such as coated aspirin, sucralfate, and vitamin C, are also known to form bezoars.

Most bezoars reside in the stomach but can be found anywhere in the gut. The formation of bezoars is typically associated with altered stomach physiology. Disturbances in gastric motility or gastric acid production, as well as poor mastication, are predisposing factors. Bezoars commonly arise in individuals following gastric surgeries (vagotomy, gastrectomy), and dementia or mental retardation (particularly in the case of trichobezoars).
Many bezoars are asymptomatic, so the reported cases underestimate the prevalence in the population. Bezoars were found in 0.4% of patients in two large endoscopic series. The main risk factors for bezoar formation are abnormal mastication, vegetarian diet, ingestion of persimmons, gastric operation, diabetic gastroparesis and hypothyroidism. The patient described above had started a vegetarian diet.

Most cases are asymptomatic and therefore go undetected. Presenting symptoms vary depending on the site of concretion formation. Bezoars are most commonly formed in the stomach, but may also arise in the esophagus, small bowel, and rectum. Reported findings include dysphagia, abdominal pain, nausea and vomiting, early satiety, bloating, anorexia, weight loss, halitosis, constipation, and gastrointestinal bleeding. Phytobezoar impaction has been known to cause gastric outlet obstruction, and distal migration of gastric bezoars can cause small bowel obstruction and associated symptoms. Bezoars are capable of serving as the nidus of common bile duct stone formation. Physical exam may reveal a palpable abdominal mass. Imaging studies, including plain radiographs, ultrasound, and barium studies, may be useful in the diagnosis of bezoars. On CT, bezoars appear as ovoid, “mottled-appearing” or “feces-like” (gas-containing) masses. Endoscopy can definitively identify a concretion, while at the same time providing therapeutic options.

Treatment options include medical management, endoscopy, and surgery. Surgical approaches, laparoscopy or laparotomy, are reserved for cases where medical and endoscopic modalities fail. Endoscopy provides a variety of tools for the removal of bezoars, including mechanical disruption with biopsy forceps, proteolytic enzymes such as papain and cellulase, gas expanders, and mucolytics (N-acetylcysteine). Coca-cola, administered via either endoscopic injection or lavage, has been reported effective in the management of bezoars. The sodium bicarbonate content and low pH of Coca-cola have been cited as possible mechanisms of action. Other carbonated beverages would likely be just as effective.

The presentation of chest pain, as in the present case, is not typical of symptomatic bezoar and is not reported elsewhere in the literature. Gastric phytobezoars often present with epigastric abdominal pain, and esophageal bezoars can cause dysphagia and associated coughing and vomiting. It is well established that gastrointestinal processes, most notably gastroesophageal reflux disease (GERD) and esophageal spasm, can mimic chest pain related to ischemic heart disease. Indeed, GERD is the most common alternative explanation for the complaint of chest pain (Table 1). Esophageal bezoars are known to form in the setting of altered esophageal pH and GERD and there are reports of gastric bezoars impacting in the esophagus following episodes of vomiting. However, as mentioned above, the usual manifestation of such an esophageal obstruction is dysphagia. It is certainly possible that the bezoar in the present case was an incidental finding and was unrelated to the patient’s chest pain.

On follow up 2 months later, the patient reported no more episodes of chest pain. The resolution of the chest pain symptoms with removal of the bezoar would be suggestive of an association, but would certainly not be conclusive. It is well known that chest pain due to esophageal spasm can be ameliorated by nitroglycerin, as in the present case. In addition, the patient has a history of GERD, which may provide another explanation for her symptoms. The relationship between gastric bezoars and gastroesophageal reflux has not been reported.

### Table 1. Differential Diagnosis of Patients Admitted to Hospital with Acute Chest Pain Ruled Out for Myocardial Infarction

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>42</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>31</td>
</tr>
<tr>
<td>Chest wall syndrome</td>
<td>28</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>4</td>
</tr>
<tr>
<td>Pleuritis/pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.5</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>1</td>
</tr>
</tbody>
</table>


### References

8. Brady PG, Richardson R. Gastric bezoar formation secondary to gastroparesis.
FOREIGN BODY IN THE SMALL INTESTINE
Benjamin Creelan, MD

Case Presentation
This adult was working on a ladder during a home restoration project. She placed the bit in her mouth while changing the screwdriver bit, then fell from the ladder and inadvertently swallowed the bit. In the emergency room, her review of systems and laboratories were unremarkable. Imaging revealed the bit to be within the duodenal lumen and after four days of serial x-rays, the bit was retrieved by snare colonoscopy at the ileocecal junction. The patient remained asymptomatic and had no complications.

Discussion
Although most ingested foreign bodies will pass through the gastrointestinal system unaided, 10-20% may require endoscopic intervention, and less than 1% will require surgery. Erosion, obstruction, and perforation are more likely to occur at regions with sharp angles or narrowing, particularly the upper esophageal sphincter and ileocecal junction. Endoscopic retrieval of foreign bodies should be employed for any object that has failed to pass through the esophagus after 24 hours due to the high risk of perforation. Fever, vomiting, or abdominal pain demands a prompt surgical consultation. If endoscopic retrieval is unsuccessful, laparoscopy may be employed. Snare or forceps endoscopy should be avoided in cases where rupture of the foreign body may be fatal, such as in concealed colonic narcotic packets, a practice called “body packing.”

References
A 29 year old male with a history of swallowing objects and recent abdominal surgery presented to the emergency department (ED) after “accidentally” swallowing a pen. A chest radiograph was performed that verified the presence of the pen. The gastroenterology service performed an emergent EGD to remove the pen. Six hours after the procedure the patient signed out against medical advice. The patient returned to the ED 10 days later with complaints of hematemesis that was unwitnessed by any medical staff. On laboratory evaluation his hemoglobin was the same as the previous admission. Psychiatry subsequently interviewed the patient and found he had gone to Hahnemann Hospital after swallowing a knife and was subsequently transferred to a Psychiatric facility after being medically cleared with no knife having been found or retrieved from the patient’s abdomen. After re-presenting to Jefferson he left against medical advice once again.
Case Presentation
A 44 year old female with a past medical history of type 2 diabetes, hypertension, congestive heart failure, coronary artery disease, 2 strokes, 2 myocardial infarctions, questionable history of pulmonary embolus twice, bipolar disorder, schizophrenia, and multiple asthma exacerbations presented to the Emergency Department (ED) with SOB and wheezing. Her symptoms began at home earlier that day and were not improved by bronchodilators. On arrival to the ED, she was lethargic in severe respiratory distress with laboring accessory muscle use. She had only an allergy to latex. Outpatient medications included albuterol inhaler, fluticasone/salmeterol inhaler, inhaled budesonide, furosemide, and warfarin for empiric treatment of an unidentified hypercoaguable disorder. She reported having a 15 pack year smoking history including marijuana and cocaine use up to several days prior to admission, but she denied any prior alcohol or intravenous (IV) drug abuse. Family history was non contributory. Her respiratory distress prohibited a thorough review of systems on admission, but the rest of her history was obtained through family at the time of arrival. They related that she had described some chest tightness earlier.

Vitals revealed the patient to be afebrile, tachypneic (26 resp/min) saturating 100% on room air with her other hemodynamic parameters within normal limits. Significant inspiratory and expiratory wheezing were auscultated on exam and despite treatment with magnesium sulfate, bronchodilators and IV steroids, her respiratory distress did not improve. She was emergently intubated for the 6th time in her life. Laboratory studies were significant for a normocytic anemia with a hemoglobin 8.5 mg/dL and a urine drug screen revealing the presence of cocaine. Otherwise, she had a normal metabolic panel, coagulation studies, d-dimer, normal troponins, and no EKG changes to support an ischemic event.

Hospital Course
The patient rapidly weaned off the ventilator and was extubated within 7 hours. Notably, her peak inspiratory pressures ranged from 23-26 mm Hg. Her steroids were rapidly tapered and scheduled nebulizer treatments were regularly delivered. She was discharged home without any further complication several days after admission.

Discussion
This patient carries a diagnosis of asthma with repeated intubations in our hospital’s Emergency Department resulting in multiple hospital stays per year. While it is not infrequent for a severe asthma attack to require intubation, certain features are usually present, including the observation of increased peak airway pressures once ventilated. In the case presented here, the patient’s peak airway pressures were normal, intubation rapidly relieved symptoms, and the patient recovered quickly. This scenario is consistent with Vocal Cord Dysfunction (VCD) sometimes referred to as Paradoxical Vocal Cord Motion Disorder (PVCMD), Laryngeal Dyskinesia (LD) or a host of other terms, which can occur alone or in conjunction with asthma. In an acute state this condition can closely resemble an asthma attack and may therefore go unrecognized for years leading to wasted healthcare dollars for unnecessary intubations not to mention the delayed delivery of appropriate treatment. Demographics include a 2:1 female to male predominance with 71% of cases being adults above age 18. The disorder does affect neonates, however, though this is believed likely secondary to gastroesophagela reflux disease (GERD).

During an attack, the vocal folds adduct during inspiration and/or expiration leading to dyspnea, wheezing, cough, chest pain and stridor. Once thought to be psychogenic, evidence is growing to support mechanisms of glottic hypersensitivity secondary to various stimuli including GERD, chemical irritants, upper respiratory infection, and exercise. Altered autonomic balance, stimulation of the sensory nerve endings in the upper or lower respiratory tract, hyperventilation and hypocalcemia are also thought to play a role. It is important to rule out neurologic causes of VCD including brainstem compression, stroke, myasthenia gravis, amyotrophic lateral sclerosis, and focal dystonias.

Clinical features distinguishing the disorder from asthma include irritant, exercise, and anxiety induced symptoms especially those refractory to usual asthma treatments. Lack of nocturnal awakenings and sputum may also be important clues. In addition, wheezing heard loudest over the larynx or larger airways, a normal alveolar-arterial gradient, and normal oxygen saturation, as in this patient, may help distinguish between the two. Recently, however, several cases of VCD have been observed in the setting of hypoxemia. Laryngoscopy remains the gold standard of diagnosis. During an attack of VCD, laryngoscopy will reveal adducted vocal cords. However, during an asthma attack, the vocal cords will not be adducted. Pulmonary function tests may be normal when asymptomatic but will show a flattening of the inspiratory and/or expiratory limb while affected. Unfortunately, methacholine challenge can induce VCD symptoms and cannot reliably be used to distinguish between asthma and vocal cord dysfunction.

The similarity of symptoms and the difficulty distinguishing between VCD and asthma poses a challenge for clinicians responding to a patient in severe respiratory distress as presented above. In the acute setting, does the clinician intubate the patient, despite the increased chance of ventilator associated pneumonia and likely prolonged hospital stay? Or does the clinician risk the possible consequences of not intubating a severe asthma attack? It is likely that most clinicians would stay the conservative route...
of intubating the patient rather than attempting to discern the two entities and risking disastrous consequences.

Once VCD is adequately diagnosed several treatments can be used, even during an acute setting. The anxiety created by the patient hearing their own wheezing can be minimized by reassurance and judicious use of benzodiazepines. Heliox is the non-commercial name for a unique mixture of helium and oxygen that reduces air density therefore reducing turbulence in the airway, and in turn reducing the work of breathing and possibly relieving symptoms. Similarly, using a mask with a one-way pressure valve increases resistance to inspiration which will reduce stridorous sounds and diminish the patient’s distress. Continuous positive airway pressure (CPAP) presumably improves symptoms by slowing expiratory flow and increasing lung volume resulting in a more open glottis. Inhaled anticholinergics, likely through a vagally mediated mechanism have been shown to prevent exercise induced symptoms in case reports only. Interestingly, botulinum toxin type A has also been reported as useful treatment to prevent attacks.²

The aforementioned techniques may be utilized in the treatment of patients strongly suspected to suffer from VCD with the objective of avoiding repeated intubation and the consequences of steroid over-use. Many patients will improve with proper treatment. Long term treatment aimed at preventing attacks involves regular follow up with ENT, Pulmonary, Psychiatry and importantly a speech therapist to optimize control of the laryngeal muscles and proper breathing techniques.

References

Corridors
Photo courtesy of Neilanjan Nandi, MD
IMMUNOCOMPRISED HEART TRANSPLANT PATIENT WITH CRYPTOSPORIDIAL DIARRHEA

Michael Dominic Lee, MSIII, Rajesh Kabadi, MD, Siva K. Kumar, MD

Case Presentation
A 22 year-old female with a past medical history of postpartum cardiomyopathy status post orthotopic heart transplant (OHT) was admitted for diarrhea of 12 days’ duration. The diarrhea was watery, non-bloody, and occurring at a rate of 10 episodes per day. She denied nausea, vomiting, fever, or chills, but reported abdominal cramps. On physical exam, she was afebrile, and vital signs were stable. The patient had a regular heart rate and rhythm. Lung sounds were clear to auscultation bilaterally. Her abdomen was soft, non-tender, without rigidity, guarding, or distention. There was no edema in the extremities.

Laboratory studies were all within normal limits. The patient’s CMV quantitative analysis, adenovirus culture, CMV culture, blood cultures, fecal culture and C. difficile EIA tests were negative. In addition, serum antigens for Rotavirus, Entameoba Histolytica, Giardia, and Cryptosporidium were negative. Finally, a flexible sigmoidoscopy was performed to define the etiology of her diarrhea and demonstrated erythematous mucosa in the sigmoid. Biopsies were taken in the sigmoid mucosa and the colon. Five days later, the biopsies in both the sigmoid mucosa and colon revealed the presence of scattered organisms suspicious for cryptosporidium.

Before the results of the biopsies were back, the decision was made to discontinue the patient’s mycophenolate mofetil (Cellcept®). Mycophenolate mofetil is normally part of the immunosuppressant regimen used to prevent rejection in organ transplantation. One of the common adverse effects of mycophenolate mofetil is diarrhea. Holding mycophenolate mofetil had the added benefit of lessening its suppressive effects on the patient’s immune system. After the discontinuation of the mycophenolate mofetil, the patient’s diarrhea finally began to abate to less than two episodes of semi-watery diarrhea per day. The patient was able to tolerate an oral diet and no longer had abdominal cramps. The patient was discharged a day later with instructions to discontinue mycophenolate mofetil.

Discussion
Cryptosporidium is an intracellular protozoan parasite that is recognized as a major cause of diarrhea in immunosuppressed hosts. This includes patients with HIV, organ transplantation, IgA deficiency, hypogammaglobulinemia, and on immunosuppressive therapy. In the United States and Europe, 8-30% of HIV patients excrete Cryptosporidium oocysts, and in developing countries, this figure climbs to 15-50%, making it one of the most common enteropathogens.1 The prevalence in HIV-negative, immunocompromised patients is unclear.

Diagnosis of Cryptosporidiosis can be tricky because there are no characteristic laboratory findings indicative of Cryptosporidium infection other than identification of the organisms. As a result, the diagnosis is primarily based on microscopic identification of the oocysts in stool or tissue. Other sites to look for the organisms include duodenal aspirates, bile secretions, biopsy specimens from affected gastrointestinal tissue, or respiratory secretions. Diagnosis is also complicated by the low sensitivity of ova and parasite tests in stool. In one report, examination of a single stool specimen identified only 30% of intestinal Cryptosporidial infections.2 Therefore, it is recommended to test three stool specimens before excluding the diagnosis of Cryptosporidiosis.

Finally, there is currently no reliable therapy for Cryptosporidiosis. Recovery from Cryptosporidiosis is based upon the immune status of the patient. Immunologically competent patients usually have a spontaneous recovery within a few weeks without requiring any specific therapy. For immunocompetent children, nitazoxanide is the drug of choice. For HIV-infected patients, the recommendation is to initiate HAART in order to restore immune system function. Restoration to a CD4 count > 100 cells/μL is associated with complete resolution of symptoms.3 There are currently no recommendations regarding how to treat HIV-negative, immunocompromised patients.

References

Figure 1. Arrows point to Cryptosporidial organisms located intracellularly within bowel tissue.
**Infliximab-Induced Interstitial Lung Disease in a Patient With Psoriatic Arthritis**

*Lan Quang, MD, Anthony Scarpaci, MD*

**Introduction**

Infliximab (Remicade, Centocor, Inc., Malvern, PA), a chimeric monoclonal antibody derived from both murine and human antibody sequences and directed against TNF-α, is one of the disease modifying anti-rheumatic drugs (DMARDs) used in the treatment of psoriatic arthritis and other autoimmune inflammatory conditions such as rheumatoid arthritis, ankylosing spondylitis, and Crohn’s disease. It is commonly used in combination with methotrexate for increased efficacy and reduction of the development of anti-infliximab antibodies. A concerning feature of infliximab therapy is its association with an increased risk of infection or reactivation of diseases that can cause pulmonary complications, most notably tuberculosis and fungal infections. Additionally, there are a number of patients who have developed non-infectious interstitial lung disease following treatment with infliximab. These events usually occur after the second to third infusions and can be preceded by a course of methotrexate. In the setting of prior methotrexate therapy, it is suggested that infliximab may potentiate the manifestations of pulmonary toxicity due to methotrexate, specifically methotrexate pneumonia. In the following case report, we cite an example of the development of interstitial lung disease after infliximab therapy in a patient with psoriatic arthritis.

**Case Presentation**

A 59-year-old female with a previous medical history of asthma and psoriatic arthritis with recent infliximab therapy presented to the Emergency Department (ED) with a chief complaint of progressive shortness of breath for two weeks. She experienced chest tightness and dyspnea with exertion. She denied wheezing and received minimal relief with nebulizers. She also stated the presence of subjective fevers and sweating that started two weeks ago. She denied leg swelling, weight gain, recent trips, or sick contacts. Upon examination, she had difficulty speaking due to shortness of breath and had rales on her left lung. No wheezing or jugular venous distention was noted. She required 2 liters of oxygen by nasal cannula to maintain her saturations at 96%. Cardiac examination was within normal limits. The rest of the patient’s exam was normal. Initial chest x-ray was read as prominence of interstitial lung markings.

Additional pertinent medical history includes: psoriatic arthritis diagnosed 7 months prior to admission for which she had received prior treatment. She had received intra-articular steroid injections into the hand joints. After that therapy did not relieve her symptoms she received two doses of weekly methotrexate. This therapy was discontinued due to patient intolerance. The patient began infliximab therapy three months later. She had received three infusions of infliximab on a biweekly schedule. The last infusion was administered two weeks prior to admission. Her medications at presentation included: metoprolol succinate (XL) 50 mg po qday, fenofibrate 145 mg po qday, omega-3-fatty acid 4g po qday, irbesartan 150 mg po qday, ezetimibe 10 mg po qday, rosuvastatin 20 mg po qday, diphenhydramine 50 mg po qhs, furosemide 20 mg po qMWF, fluticasone/salmeterol 250/50 mcg diskus day, alprazolam 1 mg po qhs PRN, oxycodone/acetaminophen 5/325 mg po PRN, and albuterol nebulizers PRN. The patient stated that she develops seizures from gabapentin.

The patient’s medical and surgical histories also included: HTN, hyperlipidemia, mitral valve prolapse, history of supraventricular tachycardia, anxiety, steroid-induced diabetes mellitus, steroid-induced psychosis, thyroid cysts, MRSA pneumonia, ocular surgery, ulnar nerve surgery, and breast lump removal. Her social history is significant for drinking 2-3 alcoholic beverages per week and no use of tobacco or recreational drugs. She is normally fully functional and lives alone. She works for a newspaper publisher.

Pertinent positives on review of systems included: chest tightness, shortness of breath, cough, hoarseness, and epistaxis. Pertinent negatives on review of systems included: no sputum production, wheezing, edema.

**Management**

The patient’s radiologic studies and pathology are consistent with drug-induced pulmonary toxicity. After extensive review of her medications, it was felt that the only drug that was temporally related to the patient’s symptoms was...
infliximab. After nebulizers, antibiotics, and diuresis failed to provide symptom relief, the patient was started on prednisone 50 mg orally daily. She was discharged 7 days after admission on a prednisone taper and maintained on two liters portable oxygen with mild improvement in her symptoms.

**Discussion**

Recent literature has implicated infliximab in the development of interstitial pneumonitis. Many of the cases are in patients with rheumatoid arthritis or Crohn’s Disease. Often, rheumatoid arthritis patients are concurrently receiving methotrexate therapy to maximize disease modification. Notably, the pulmonary toxicity can be quite severe. A prior case series reports four patients with interstitial pneumonia and one patient with bronchiolitis obliterans organizing pneumonia following infliximab therapy. The patients had rheumatoid arthritis and were not treated with methotrexate due to pre-existing lung disease. Each of the patients except the patient with bronchiolitis obliterans experienced rapidly declining hospital courses and eventually expired from respiratory failure despite steroids and ventilatory support.

The pathophysiology of infliximab induced pneumonitis is not known. One possible theory is that infliximab may potentiate the pulmonary toxicity of methotrexate. However, this does not account for patients who were not receiving methotrexate therapy. Animal models of bleomycin-induced lung toxicity have shown that blocking TNF-α worsens toxicity. Other research has shown that inhibition of TNF-α may increase proinflammatory cytokines. Additionally, when infliximab binds to TNF-α on CD-4+ T cells and macrophages, proteolytic enzymes are released which can lead to pulmonary damage.

This is the first reported case of interstitial pneumonitis due to infliximab in the psoriatic arthritis population. Our patient’s exposure to methotrexate was limited to only a short treatment of two doses, which was terminated secondary to intolerance. Thus, the lack of a prior therapeutic methotrexate regimen and the temporal relationship of the development of lung symptoms with the start of infliximab infusion suggest that infliximab alone may have induced interstitial lung disease.

As pulmonary complications associated with infliximab are further documented, it becomes important to screen patients for risk factors for pneumonitis prior to initiating therapy. Some of the identified risk factors specifically for methotrexate pneumonitis include preexisting lung disease, older age, diabetes, hypoalbuminemia, and previous use of DMARDs.

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**Figure 1. High Resolution Chest CT:** Cross-section demonstrating diffuse bilateral groundglass opacities and pulmonary edema.

**Figure 2. H&E stain of tissue sample from transbronchial lung biopsy.** The above slide demonstrates active pneumonitis with interstitial inflammation, edema, and fibrosis. Airspaces are lined by type II pneumocytes and contain macrophages, fibrin and organizing pneumonia.

**References**

A Man With Abdominal Pain and Acute Renal Failure
Faisal Shaikh MD, Marina Serper, MD

Case Presentation
A 33-year-old African American male with a past medical history significant for HIV on HAART therapy presented to the emergency department (ED) with acute onset of right upper quadrant abdominal pain and mild shortness of breath. The abdominal pain was not associated with any fevers, chills, nausea, vomiting or diarrhea. The patient denied any chest pain, palpitations, lightheadedness or syncopal episodes. He did report some dysphagia with solids more than liquids over the last 2 months as well as decreased oral intake. His review of systems was otherwise significant for weight loss which he was unable to quantify.

He denied any medication allergies. His medications on admission included trimethoprim/sulfmethaxazole, azithromycin, fluconazole, lopinavir/ritonavir, and emtricitabine/ tenofovir. His most recent CD4 count was 114 cells/mm³ and he had no other known past medical history.

On initial physical exam, the patient was found to be tachycardic at 115 bpm, hypotensive with a blood pressure of 80/40 mm Hg, and tachypneic exhibiting 32 respirations/minute. The head and neck exam were significant for oral thrush. Other than resting tachycardia, the cardiovascular exam was unremarkable. The pulmonary exam was notable for tachypnea, but the lungs were clear to auscultation and there was no observed accessory muscle use. The abdominal exam was significant for tenderness to palpation in the right upper quadrant without rebound or guarding. The patient was alert and oriented and had no focal neurological deficits.

Admission labs were notable for a white blood cell count of 19.3 cells/µL with 22% bands, creatinine 1.8 mg/dL (no baseline available), total bilirubin 1.8 mg/dL, direct bilirubin 1.2 mg/dL with an alkaline phosphatase of 1233 IU/L. AST and ALT were 90 U/L and 6 U/L, respectively. The patient was also noted to have a lactate of 86.7 mEq/L.

Hospital Course
The patient responded to 3L normal saline fluid resuscitation to 110/60 mm Hg. Broad spectrum antibiotics (vancomycin and piperacillin/tazobactam) were begun and the patient was admitted to a telemetry floor. Initial studies included an abdominal ultrasound which showed 2 hypoechoic masses in the left lobe of the liver without intra- or extrapheptic ductal dilatation noted. A non-contrast CT of the abdomen and pelvis demonstrated innumerable lymph nodes scattered diffusely throughout the mesentery and retroperitoneum measuring up to 1.5 cm, likely related to the history of HIV infection. A renal ultrasound showed normal sized kidneys, and no hydronephrosis. The nephrology service was consulted and the working diagnosis at the time was renal failure secondary to tenofovir.

The tenofovir was discontinued and his abdominal pain workup was continued.

The hospital course was notable for diarrhea, progressive lethargy, fever up to 104°F, worsening abdominal pain, continued rise in serum creatinine to 5.1 mg/dL, and decreased urine output to 200 cc’s over 24 hours. On hospital day 3, the patient was transferred to the intensive care unit after an arterial blood gas demonstrated a profound metabolic acidosis characterized by a pH 7.15. A repeat non-contrast CT of abdomen and pelvis now revealed diffuse, marked small bowel and large bowel wall thickening with two focal segments suggestive of small bowel intussusceptions without bowel obstruction.

The patient’s abnormal though non-specific intra-abdominal findings in the setting of worsening acidosis and elevated lactate levels prompted an exploratory laparotomy. Seven areas of easily reducible intussusceptions were discovered. In fact, innumerable mesenteric lymph nodes were found, believed to act as lead points for the pathogenesis of these intussusceptions. Fortunately, the bowel was still viable avoiding the need for resection.

Post-op, the patient continued to be oliguric with severe electrolyte imbalances (Urate 7.5, K+ 6.8 mEq/L, Ca++ 3.0 mEq/L, PO4 17.4 mEq/L, LDH 1154 mEq/L). Spontaneous tumor lysis syndrome was diagnosed and the patient was begun on emergent hemodialysis. Intra-operatively obtained mesenteric lymph nodes demonstrated atypical lymphoid cells with a high mitotic rate that focally demonstrate a “starry-sky” pattern consistent with a diagnosis of Burkitt lymphoma. Due to the patient’s poor functional & physiologic status, it was decided that he was a poor candidate for chemotherapy. The patient elected no other therapies and elected for hospice care.

Discussion
Burkitt lymphoma is a rare disorder comprising less than 1% of non Hodgkin B cell lymphomas. First described by Dr. Dennis Burkitt in Uganda in 1958, it is an aggressive lymphoma frequently presenting in extranodal sites, or as a leukemia, characterized by monomorphic medium sized cells with a basophilic cytoplasm and very high proliferation rate. It is classified by three major types: endemic, sporadic, and immunodeficient.1 2

The endemic form is most common in Africa and New Guinea, where is it the most common childhood neoplasm. The endemic form typically affects facial bones in children (mean age 4-7) and is associated with EBV more than 95% of the time. The sporadic form occurs most commonly in developed countries and a mean age of onset of 30. The sporadic form arises from lymphoid tissue in the gut and respiratory tract with most cases being extranodal and jaw involvement less than 30% of the time. The immunodeficient form is associated with HIV infection and
most commonly affects the lymph nodes and bone marrow. Paradoxically, these patients typically have a high CD4 count with few opportunistic infections.

The clinical presentation is varied and nonspecific, but frequently involves the abdomen (i.e. pain, ascites). Patients may also present with classic B symptoms of fevers, night sweats, and weight loss. The diagnosis is confirmed with lymph node biopsy, bone marrow biopsy, and lumbar puncture (the last two necessary for deciding on treatment options).

The biology of the disease involved chromosomal translocation and dysregulation of the c-myc gene, which controls cellular proliferation. Tumor cells express a high level of the ki67 protein indicating high levels of mitotic activity. On pathology, sheets of B cells are seen with frequent mitotic figures classically giving the tumor cells a “starry sky” appearance. It is important to differentiate between Burkitt and diffuse large B cell lymphoma (which can sometimes have a similar pathologic appearance) because the former is a more aggressive type of lymphoma requiring intrathecal chemotherapy. Recently, molecular gene signatures have been used to aid in this differentiation.

Typically, the Ann Arbor system is used in staging lymphomas; however, Burkitt lymphoma does not lend itself well to the staging system due to its extremely aggressive course. Due to the nature of the tumor, chemotherapy needs to be initiated as soon as possible, preferably within 48 hours of diagnosis. A standard regimen includes cyclophosphamide, vincristine, doxorubicin, and high dose methotrexate and intrathecal therapy with alternating ifosfamide, etoposide, and high dose cytarabine. In one study, this regimen showed a 92% two year event free survival in children and adults. The significant side effects experienced were neurotoxicity, bone marrow suppression, severe mucositis, and tumor lysis syndrome. Another study showed that rituximab, a CD20 monoclonal antibody, further increased two year event free survival (80-88%) when added to the standard regimen. Studies are now under way with other monoclonal antibodies and other biologic agents. There is no clear role for bone marrow transplantation in the treatment of the disease.

Once entertained, the diagnosis of Burkitt lymphoma should be promptly confirmed with prompt initiation of chemotherapy to combat the aggressive nature of this specific type of lymphoma. New monoclonal antibody agents currently offer new survival benefits not previously seen before.

References
SPIDERBITE
Ayana Cannon, MD

Introduction
In North America alone, there are more than 3,000 species of spiders. While most are harmless, several species including the Latrodectus (black widow), Atrax (funnel-web), and the Loxosceles (brown recluse) have been known to inflict varying degrees of injury to humans. While an overwhelming majority of spider bites may go unnoticed, others result in local skin reactions, necrotic cutaneous lesions, or a severe syndrome associated with hemolysis and death.

While proper identification of spider bites is paramount to the prevention of rare, life-threatening systemic reactions, their misdiagnosis can be equally hazardous. According to the literature, Loxosceles reclusa bites are more frequently being mistaken for community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) infections, due to the similarity of their classic lesion appearances. With the incidence of CA-MRSA infections increasing, it is vital for members of the healthcare community to effectively differentiate these lesions to prevent delays in proper care. Complications resulting from improper treatment of both CA-MRSA infections and spider bites may be devastating.

Case Report
A 1 year-old man presented to the emergency room with a one-week history of multiple, painful bumps on his left and right forearms, accompanied by fever and chills for two days. One day prior to the onset of his symptoms, the patient reported receiving a shipment of sheet metal from Chicago, Illinois at the construction company where he is employed in New Jersey. Upon opening the large cardboard boxes, he noticed large, dark brown, spiders scurrying amongst the parcel. Later that night, after returning home, the patient recalls redness and swelling bordering two bumps on his right arm and 1 bump on his left arm. The next morning he presented to an outside hospital emergency department (ED) after awakening to sharp pains in both of his arms. He was evaluated and discharged home with oral trimethoprim/sulfamethaxazole to treat possible MRSA cellulitis. The next day, he noticed 2 additional spiders associated with the materials shipped from Illinois, and captured one in a bottle. According to the patient, this spider appeared to be the same as those which he initially observed. The patient continued his antibiotics, but noticed increasing pain and swelling around the lesions on his arms with development of fever 100°F and chills. He again reported to the ED with arachnoid in tow. He had prior medical history of hyperlipidemia, no previous surgical history, reported occasional alcohol use, but denied tobacco and illicit drug use.

Vitals revealed a febrile temperature 101.5°F, mild hypertension 145/87 mm Hg, heart rate regular at 95 bpm, and normal oxygen saturation without respiratory distress. Physical exam demonstrated two indurated 2.5 x 1 cm erythematous nodules on his right medial forearm that were warm and tender to palpation. The left forearm revealed 1 similar appearing nodule with a 0.5 cm crusted central lesion. Serum laboratory tests revealed an elevated erythrocyte sedimentation rate 33 mm/hr and C-reactive protein 4.20 mg/dl. Complete blood count and metabolic panel were within normal limits.

Figure 1. The patient was diagnosed with spider bite, presumptively of the brown recluse type. He was discharged with a one week course of Dapsone 50 mg, to be taken once daily. Within 48 hours, wound cultures obtained from the patient upon presentation grew methicillin-resistant staphylococcus aureus. The patient was contacted and instructed to return to the outpatient clinic for incision, drainage, and subsequent antibiotic treatment.

Discussion
In recent years, it has been reported that CA-MRSA has become the most frequent cause of skin and soft tissue infections (SSTI’s) presenting to ED’s in the United States. One study, carried out at 11 geographically diverse institutions across the U.S. in August 2004 showed that 99% of SSTI MRSA isolates were characteristic of CA-MRSA. Studies published this year further suggest that the incidence of MRSA infections may be higher than previously believed with rates in 2005 approaching 32% across 9 distinct U.S. communities. Among these infections, researchers also found 15.7-22.2% of the isolates to be USA300 pulsed-field type, a characteristic historically associated with CA-MRSA strains. Infection with such a pathogen can lead to serious systemic complications such as bacteremia, septic shock, and serious metastatic infections including endocarditis,
pneumonia, osteomyelitis, and arthritis. Skin lesions due to MRSA classically present as a furunculosis with an area of inflammation around a darker purpuric center with overlying dermonecrosis that is raised from the surrounding skin. The differential diagnosis of such wounds includes Staphylococcal or Streptococcal infection, cutaneous anthrax, and Lyme disease, among others. Although CA-MRSA outbreaks have shown a predilection for certain groups in the past, including prisoners, men who have sex with men, IV drug users, military recruits, and athletes, current data support the notion that CA-MRSA strains are widespread among varying demographic populations and associated with most SSTI’s presenting to the ED.

In contrast, reports show that in cases of reported spider bites, up to 80% are eventually found to be from other insects, arthropods or arachnids. It is worthwhile to note that Moran et al report a relative risk of MRSA infection of 2.8 for reported spider bites. In 90% of reported spider bites, no identifiable arachnid is brought in to the physician, and patients rarely remember any sense of actually being bitten. In all, spider bites, particularly those of the *Loxosceles*, are exceedingly uncommon in the United States and rarely, if ever, occur outside of areas where this spider is endemic. Isolated, verified cases have also been reported in Arizona, California, the District of Columbia, Florida, North Carolina, New Jersey, Pennsylvania, Washington, and Wyoming, although reports far exceed verified specimens. It is possible that single *Loxosceles* specimens may find conveyance outside of their range by commercial transport, but almost all such examples, including those in Pennsylvania, have been single specimens that die without reproducing or biting a human. Furthermore, *Loxosceles* is not an aggressive arachnid and will only bite a human if threatened or pressed against the human’s skin by clothing, towels, or bedding. In the face of the paucity of verified cases, the restricted endemic region, and the ‘reclusive’ nature of *Loxosceles*, the “brown recluse bite” should be near the bottom of the differential for dermonecrotic wounds and in non-endemic regions possibly removed altogether.

References
Case Presentation

A 7-year-old African American male presented to the hospital complaining of high fevers over the past two weeks associated with severe posterior headache. He described having had a very poor appetite recently, but denied any cough, abdominal pain, diarrhea, or urinary symptoms. He did not recall sustaining any head trauma. He did relate, however, that he had recently returned from a three-month trip to Kenya ~1 month prior to this presentation. He had no past medical history and was not on any medications. He did not use IV drugs. Physical exam confirmed a fever of 102.1°F though normotensive 110/82 mm Hg and a resting heart rate 110 bpm. The complete physical exam including cardiopulmonary, abdominal, and neurological examination was normal. Laboratory analysis was unrevealing. A head CT performed prior to the lumbar puncture also failed to reveal any abnormalities. However, given the patient’s recent travel history, the team empirically began him on antimalarial treatment against *P. falciparum* (quinine sulfate 10 mg/kg every eight hours and doxycycline 100mg po bid) while awaiting confirmatory histologic diagnosis. The next day malaria was confirmed when the results of the thick and thin smear were positive for *plasmodium* with a viral level greater than 1%. During his hospitalization he was noted to have recurrent fevers occurring almost every other day. His clinical status remained stable without any alterations of his laboratory data. He was discharged to complete his course of oral medications.

Discussion

~300,000 to 500,000 new cases of malaria occur worldwide with 700,000 to 2.7 million deaths estimated worldwide. ~30,000 travelers from industrialized nations countries reportedly contract malaria. Infection occurs through the transmission of an infected *Anopheles* mosquito. Human malaria is caused by four species of *Plasmodia*: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Each of the four species causes clinical disease by resulting ultimately in hemolysis. *P. falciparum* has the ability to invade red blood cells of all ages and it is associated with the highest risk and rate of morbidity and mortality. Relapsing fevers remain the clinical hallmark of malaria. Anemia, thrombocytopenia, splenomegaly, hepatomegaly and jaundice can develop, and splenic rupture can occasionally occur as well. Altered consciousness, oliguria, hypoglycemia, and organ failure are characteristics of severe *P. falciparum* infection.

The diagnosis should be suspected in patients with recurrent fevers that travel to endemic areas. The gold standard of diagnosis is through examination of thick and thin smears with light microscopy. Parasite levels are measurable and levels can correlate with both type of species as well as portend overall morbidity. Microscopy is regularly employed to assess a patient’s response to treatment. Other diagnostic tests available include antigen detection, fluorescent microscopy, PCR and serologic markers analysis. Thick and thin blood smears should be examined at least every 12 hours to monitor the efficacy of therapy until the parasitemia is below 1%. Smears should also be obtained at 3, 7, and 28 days to rule out recurrence or incomplete clearance of parasitemia.

There are several medications available for the treatment of malaria including quinoline derivatives, antifolates, artemisinin derivatives, and antimicrobials. *P. ovale* and *P. malariae* are universally sensitive to chloroquine. Several strains of chloroquine-resistant *P. vivax* have been reported. The Centers for Disease Control (CDC) recommend treatment of chloroquine sensitive species of malaria with chloroquine followed by a course of primaquine. Resistant *P. vivax* can be treated with mefloquine or quinine sulfate plus doxycycline. Clinically, it is very important that one distinguish between *P. falciparum* and the other species of malaria, as *P. falciparum* is largely resistant to chloroquine and this discernment will ultimately affect the final drug cocktail prescribed. Failure to identify *P. falciparum* could otherwise result in inadequate and delayed treatment with the wrong medications. Fortunately, many treatment regimens exist for the treatment of *P. falciparum*. The most commonly recommend regimen is quinine sulfate with pyrimethamine-sulfadoxine or doxycycline.

When advising patients on foreign travel, physicians should be aware of resistance patterns of malaria based upon geographic locale. This will tailor the choice of malarial prophylaxis unique to the area. Prevention is paramount for travelers to endemic areas and many resources through the CDC exist to provide education to both clinicians and patients on anti-malarial drugs.

References

WHAT’S UNDOCUMENTED

There’s a calm stillness
To the sick at night—
The sound of quiet healing, I hope,
But inevitably, a few cannot be healed.

Some patients walk that journey slowly, with
Humble shoulders slouched, weathered eyes closed,
Faltering against heavy feet.

Others stand and then seem to fall,
Out of nowhere, out of nothing,
Suddenly without breath, or pulse, or chance.

It can seem futile, our work,
At those moments, or sometimes tragic.
We don’t know the person being saved as a person well—
Their stories, their triumphs, their beginning—
We see only their scars, their end.

We then write a story in medical prose
That has its own inevitable circle—
A downward tailspin of vital signs, recorded in jargon,
Meant to document the loss of a life.

Death and dying as a sterile procedure,
That we all know is contaminated
By private prayers and irrational hope,
Questions about mortality and afterlife,
Suppressed emotions and subjectivity.

We leave out details, of course, of the heaviness,
Or sometimes the supreme lightness
That is somehow left—
Pervasive, tense, uncertain—
Undocumented and unspoken, but captured within.

Tamara Solitro, MD

Dominican
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Ana Shnitser, MD
Distant Silhouette

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Bath House Door

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