FROM THE RESIDENCY PROGRAM DIRECTOR

A Community of Scholars
The ideal of a University is that we live and work together as a community of scholars dedicating ourselves to the advancement of Medicine. Our community is at its best when we share ideas, knowledge, perspective, and a passion for Medicine. As a routine, this can occur at Morning Report or Noon Conference, but also on rounds or hopefully at the bedside when dealing with a particularly challenging case.

This journal serves as an outlet for observations or studies of particular merit. Its publication is an important element of our scholarly focus in the Department. Indeed, nearly a score of contributors from all three classes of residents have participated; making this issue quite representative of our community. As a clinician and educator in the Department, I have been regularly challenged by the spirit of inquiry among our residents. This serves as a true reflection of the vitality of our community.

Rounding in the MRICU during early November, I was also struck by the incredible gift that we have been granted as physicians in our society. During the span of one week, our team which included Drs. Aleyas, Mehtotra, Callahan, Moon, Cheski, Nandi, and Levin faced a challenging array of scholarly questions. These included identifying the cause for interstitial pneumonitis in a pregnant woman, dealing with an active TB patient from New Orleans who was refusing care, and facilitating diagnosis for a patient with diffuse lymphadenopathy who was only willing to accept minimally invasive diagnostic and therapeutic interventions. This community of scholars in the ICU found answers rapidly, defended their differential diagnoses, and pushed the limits of medical knowledge to provide outstanding care. They did so with compassion and respect. Their work, together with the dedicated nurses and therapists of the MRICU defined a University as no words could express.

The editors of this journal have sought to capture the excitement and vitality of our work in the Department. They deserve our gratitude for doing this while managing the routine expectations of the residency. I thank them for contributing to our community of scholarship and elevating our work within this University.

Gregory C. Kane MD
Associate Professor of Medicine
Residency Program Director
Department of Medicine

FROM THE EDITORS

Welcome to the 7th Edition of the Jefferson Medicine Forum! In this edition we have highlighted some of the many interesting and diverse cases encountered by our Internal Medicine students, residents, and fellows. Every case is an opportunity to take what a small number of people have learned and share it with the rest of the Jefferson community. From the pedestrian Wolf-Parkinson-White syndrome to the esoteric Milk Alkali Syndrome, our residents see it all. Every contributing author represented in this edition has left a touch of their enthusiasm, curiosity, and analytical skills in each report. We extend our appreciation to all our colleagues who captured their experiences in images and prose for us to share.

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An 18-Year Old Man with Fever and Headache

Amy Baranoski, MD

An 18-year-old man was transferred from an outside hospital for evaluation of recent headache, fevers, and laboratory abnormalities. The patient had a past medical history significant for attention deficit hyperactivity disorder (ADHD) and had presented to an outside hospital with complaints of fatigue, fever, and headache. He described the headache as frontal, severe, and stabbing in nature without associated neck stiffness, photophobia, or phonophobia. He also reported fevers to 105°F. He was evaluated one day after the onset of symptoms at a local emergency room where a lumbar puncture was performed. By report of the patient and his mother, the lumbar puncture was negative and he was given a prescription for ketorolac for his headache. The patient went home and continued to have fevers and headache for which he was taking acetaminophen and ketorolac. Two days after his initial discharge from the emergency room he presented to another hospital complaining of sharp epigastric pain without radiation in addition to the headache and fevers. He denied nausea, vomiting, or melena. Laboratory data at that time revealed a creatinine of 4.6 and mildly elevated transaminases and the patient was transferred to this hospital for further evaluation and management.

The patient denied chest pain, cough, dyspnea, sore throat, or dysuria. He reported that he had noticed a “sweat rash” in his groin a few weeks prior to his symptoms that went away after persisting for several days. His past medical history was only significant for ADHD. He denied surgical history. Family history was significant for hypertension in both parents. He reported occasional alcohol use. He had recently graduated from high school and lived in a suburban neighborhood. He had been working as a groundskeeper at an outdoor chlorinated pool. He denied tick bites, recent travel, or sexual activity.

Prior to transfer to this hospital, he was given empiric antibiotic treatment with doxycycline and ceftriaxone and was placed on maintenance intravenous fluids, pantoprazole, and prophylactic dose subcutaneous heparin. His only out-patient medication prior to the onset of his symptoms was methylphenidate (Ritalin®).

The temperature was 97.4°F, the pulse rate was 71, the blood pressure was 105/59, the respiratory rate was 14 and the oxygen saturation was 98% on room air. On physical examination, the patient appeared well. His pupils were equal and reactive. His sclera were anicteric in contrast to a previous documented examination. He had no oral lesions. The heart and lung examination was unremarkable. The patient had normal bowel sounds and his abdomen was soft, mildly distended and non-tender to palpation with no appreciated organomegaly or masses. He had no costovertebral tenderness, lower extremity edema, or neck stiffness. Neurological exam revealed no focal deficits with intact cranial nerves.

The patient’s initial lumbar puncture results were a glucose of 69, protein of 29, no red blood cells, and one white blood cell. Urinalysis was positive for protein, blood, and bilirubin, with 10-25 WBC per high-powered field (HPF), 5 RBC per HPF, occasional WBC and granular casts. Arterial blood gas was 7.37/24/66/14/95% on 3 liters oxygen via nasal canula. Other laboratory data collected after his transfer to this institution were negative and included HIV, EBV antibody and PCR, CMV, HSV, toxoplasmosis antibodies, lyme antigen, and hepatitis serologies. Multiple sets of blood cultures were negative. Complement levels were normal. Leptospirosis antibody was pending during his hospitalization.

The patient’s electrocardiogram was normal except for diffuse T wave flattening. His chest x-ray showed no infiltrate or effusion. An echocardiogram was significant for mild mitral, tricuspid, and pulmonary valvular regurgitation with an ejection fraction of 50%. A right upper quadrant ultrasound showed that his spleen and liver were top normal in size, but was otherwise not remarkable. A CT scan of his abdomen was only significant for a distended stomach and multiple sub-centimeter lymph nodes.

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Doxycycline and ceftriaxone were continued during his hospitalization and he was given supportive treatment with intravenous fluids. His creatinine and liver function tests improved upon admission and returned to baseline values in several days. The patient was discharged home on doxycycline with the presumptive diagnosis of leptospirosis.

After discharge to home, the patient’s leptospirosis antibody level came back at 12,800 (Negative <50, borderline 50-100, positive >100). This patient was seen for follow up one month after discharge and was feeling well.

Discussion

Leptospirosis is an illness caused by the organism Leptospira interrogans. This is an aerobic spirochete with 18 or more coils per cell. This organism is usually found in tropical environments, but has a world-wide distribution. The highest incidence of illness is after large precipitation events. The organism is found in mammals; most commonly rodents, cattle, goats, horses, or dogs. Animals can become asymptomatic reservoirs with bacterial shedding in the urine. The organism can survive weeks to months in soil and water. The most common mode of transmission in humans is secondary to exposure to contaminated urine via mucus membranes, conjunctiva, or damaged skin. The leptospires then travel in the bloodstream and are carried to multiple organs, where there is endothelial cell disruption leading to vasculitis and ultimately, organ dysfunction.

The largest risk for exposure to leptospirosis is occupational and includes farmers, ranchers, sewer workers, and military personnel. There is also a risk through recreational exposure such as freshwater swimming and kayaking. In 1998, an outbreak occurred in Illinois among triathlon participants. People can also be infected through pets, rodent exposure, and living in contaminated rainwater catchment areas.

Leptospirosis can generally be divided into two groups. 90% of patients have a mild, self-limited illness. The severe form of leptospirosis is also known as Weil’s Disease. It is characterized by hepatic and renal failure. These patients can also have pulmonary hemorrhage, ARDS, and cardiac arrhythmias. EKG changes can vary from frequent premature ventricular contractions to atrial fibrillation or flutter, or even ventricular tachycardia. The mortality rate in Weil’s Disease ranges from 5-40%.

The illness is characterized by abrupt onset of fevers, headache, and myalgia in the majority of patients. There is usually an acute phase which is a one to three day period of constitutional symptoms. The immune phase then follows. There is a two to thirty day incubation period before onset of symptoms. Approximately 50% of patients have nausea, vomiting, and diarrhea. Less than a third of infected patients have develop a non-productive cough. Conjunctival suffusion is present in >80% of patient with leptospirosis and should cause a high suspicion for the disease if present. Less common symptoms include arthralgias, bone pain, sore throat, and abdominal pain. Muscle tenderness, especially in the calf and lumbar regions, may be present. Less than 10% of patients develop a pretibial maculo-papular rash. Other less specific signs such as lymphadenopathy, hepatomegaly, or splenomegaly may be present. Aseptic meningitis is usually not seen in acute illness but may occur in up to 80% of patients later in the course of illness. The aseptic meningitis is secondary to an immune reaction and not caused by the organism itself.

The laboratory data in leptospirosis is non-specific. The WBC count is generally less than 10,000 B/L. Patient may have mildly elevated transaminases, which are usually less than 200 U/L. Urinalysis reveals mild proteinuria and more than 5 WBC per HPF. Patient may have hematuria or hyaline casts. Cerebrospinal fluid is also non-specific with normal glucose, protein between 50-100 and cell counts less than 500. It is possible to grow leptospires in CSF, blood, or urine, especially if cultured during the first seven to ten days of infection. This is a fastidious organism which usually takes one to two weeks to grow, but can take up to three months in some cases. The organism requires Fletcher’s, Ellinghausen’s, or polysorbate 80 media in order to grow.

Darkfield microscopy will show spirochetes and can be used to make a presumptive diagnosis. PCR can also be used to diagnose leptospirosis. In addition, there are indirect methods of detection including microscopic agglutination test (MAT), which is a highly sensitive and specific test for leptospirosis antibodies. MAT also provides serotype specific information. There are also ELISA and indirect hemagglutinin assays available. These tests do not provide serotype information.

Mild disease can be treated with doxycycline 100 mg PO bid, ampicillin 500-750 mg PO every six hours, or amoxicillin 500 mg PO every six hours. Moderate to severe disease requires intravenous treatment with penicillin G 1.5 million units every 6 hours or ampicillin 0.5-1 gm every 6 hours.

Leptospirosis can be prevented by immunization of livestock and pets. High-risk workers should wear protective clothing including impermeable boots and gloves. Rodent control is also very important in preventing outbreaks, especially after heavy rains. The CDC recommends chemoprophylaxis for people at increased risk with doxycycline 200 mg weekly beginning 1-2 days before exposure.

References

7. www.cdc.org
PRESENCE OF CONCOMITANT ASYMPOMATIC AND SYMPTOMATIC EMBOLI RESULTING FROM ACUTE STAPHYLOCOCCUS AUREUS ENDOCARDITIS

Jason T. Bradley, MD, Nicole M. Orr, MD, and Siva Ramachandran, MD

A 25-year-old male intravenous heroin user with Hepatitis C presented with a syncopal episode and left sided weakness. Examination revealed sub-conjunctival hemorrhages and diffuse bilateral petechiae on his lower extremities. He had multiple irregular, erythematous, painless macules on his hands and feet, and linear, red, subungal lesions bilaterally. These findings were consistent with Janeway lesions and splinter hemorrhages, respectively. His vital signs were stable on admission. Cardiac auscultation revealed a grade 2/6 holosystolic apical murmur radiating to the axilla. A brain MRI revealed multiple areas of hyperdensity, particularly in the right parietal lobe (Figure 1). Blood tests revealed leukocytosis and six of six blood cultures yielded methicillin sensitive Staphylococcus Aureus. The patient was treated with intravenous nafcillin and gentamicin.

One week later the patient’s neurologic status improved. A transesophageal echocardiogram was performed and revealed both a vegetation on the posterior leaflet of an otherwise normal mitral valve and moderate mitral regurgitation. The following day, the patient developed diarrhea that was positive for both heme and Clostridium difficile toxin. Metronidazole was started and an abdominal CT scan was ordered (Figure 2). Although there was no corresponding clinical presentation, imaging revealed bilateral renal infarcts, a splenic infarct, and sigmoid thickening. The patient regained full neurologic functioning within two weeks of initial presentation and was discharged after a 6 week course of intravenous nafcillin. He is currently awaiting a mitral valve replacement.

In the setting of presumed septic emboli to both the skin and brain secondary to bacterial endocarditis, we were concerned that the hemiparetic stool was the result of embolization to the mesenteric arteries. Although the abdominal CT showed no evidence of bowel infarction and sigmoid thickening is non-specific, the renal and splenic infarcts were determined to be secondary to septic emboli. A previous case of bacterial endocarditis with simultaneous multiple organ involvement including the kidney, spleen, brain, skin, and intestines has not been documented. This case demonstrates that in the setting of diffuse symptomatic septic emboli, involvement of additional organ systems is likely but may be missed due to absence of clinical findings.

Concomitant symptomatic emboli to more than one organ system are rare according to the literature. It is interesting to note that petechiae occur in only 20-40%, Osler nodes in only 10-25% of patients, and Janeway lesions in less than 10% of patients with bacterial endocarditis. Splenic septic emboli in infective endocarditis are a common finding and incidental splenic infarcts were found in 38% of 29 asymptomatic patients in one study.

Majumdar et al. found that 18% of 354 patients with infective endocarditis had renal involvement and 45% of that subpopulation was found to have localized renal infarction, making it the most common renal lesion. The authors of that study acknowledge this renal subpopulation does not represent all patients with endocarditis but a prospective study to assess symptomatic and asymptomatic renal involvement has not yet been done.

The incidence of septic emboli to the brain has been well documented. Whether or not embolization is a result of vegetation size is currently disputed, but current data suggest that vegetations greater than one centimeter in length have increased risk for cerebral embolism. Brain embolization has been previously described in a case report and several studies, but not with concomitant lesions to other organ systems. Eighteen percent of patients with mitral valve endocarditis develop stroke and in over one-half of these cases, stroke was the initial presenting symptom. The authors concluded that all patients with endocarditis and neurologic symptoms should undergo neurologic imaging to determine the exact location of the lesions. Bakshi et al. even concluded that neuroimaging should be used to diagnose bacterial endocarditis in patients presenting with neurologic symptoms and nonspecific constitutional symptoms. In addition, that study cites that 50% of patients with neurologic sequelae of bacterial endocarditis do not have clinical evidence of additional peripheral emboli.

In conclusion, although the patient was admitted for symptomatic emboli to the skin and brain, non-symptomatic emboli to the kidney, spleen, and intestine were incidentally found. It is well known that infective endocarditis can infect the spleen, kidney, and brain, but normally such emboli are symptomatic and isolated. This case demonstrates that asymptomatic lesions may also be present in the face of already existing symptomatic emboli and careful investigation of critical organ systems should be done empirically.

The authors encountered this case during their time with the Department of Pulmonary and Critical Care at Hahnemann University Hospital, Philadelphia, PA.

References

Figure 1. MRI of the brain identifying multiple areas of septic emboli.

Figure 2. CT of the Abdomen identifying multiple embolic infarcts of the spleen (S) and bilateral kidneys (Rk, Lk).
A 32 YEAR OLD MAN WITH LOSS OF CONSCIOUSNESS
Dana Critchell, MD

A 32-year-old man with no past medical history presented to the emergency department after losing consciousness at the end of a half-marathon. The patient was in his usual state of good health until the last mile of the marathon when he began to feel unsteady on his feet and short of breath. At the end of the race, he collapsed and was found unresponsive by EMS. The patient had no memory of the subsequent events and could only recall waking up in the emergency department feeling “numb” and “confused” several hours later. The patient denied any palpitations, chest pain, nausea, blurry vision, dizziness, urinary incontinence, or headache before or after the event. Of note, he was running outside approximately 3 to 4 times a week prior to this episode.

The temperature was 99.1°F (37.3 ºC), the pulse rate was 154, and the blood pressure was 94/30.

On physical examination, the patient had regained consciousness, but remained confused and disoriented with a GCS score of 13. The patient was pale and diaphoretic, however he had moist mucous membranes and no evidence of skin tenting. His pupils were equal and reactive and the sclera were anicteric. The heart, lungs, abdomen, and extremity examination were unremarkable. He had no costovertebral tenderness, lower extremity edema, or neck stiffness. Neurological exam revealed no focal deficits with intact cranial nerves. Several hours later, the patient was noted to be alert and oriented to person, place, and time. In the interim, the patient had several episodes of watery vomit.

Laboratory results on admission were notable for a normal CBC with a platelet count of 225 B/L and a normal coagulation profile. The creatinine was 2.4 mg/dL, the myoglobin was 303 ng/mL, the CK was 157 IU, and the troponin was 0.15 ng/mL. Electrocardiogram on admission revealed sinus tachycardia with an isolated ST elevation in AVR and ST depressions in II and V4-V6. A repeat electrocardiogram showed resolution of these abnormalities. A chest x-ray and head CT scan showed no abnormalities. The patient was fluid resuscitated with normal saline at 200 cc/hr and admitted to the hospital with the diagnosis of heat exhaustion and rhabdomyolysis with acute renal failure.

During his hospital stay, the troponin peaked at 0.54 ng/mL and his creatinine dropped to 1.6 mg/dL with fluids resuscitation, and plans were made to discharge the patient the following morning. However, a CBC the following morning revealed marked thrombocytopenia with a platelet count of 64 B/L and the CK levels were now significantly elevated at 7105 IU. The patient remained in the hospital to monitor his platelet count, which rose to 97 B/L the following day. The patient was then discharged with instructions for a follow-up CBC with his primary care provider in the near future. Interestingly, another participant in the half-marathon presented with acute renal failure followed by thrombocytopenia to 80 B/L the day after presentation.

Discussion
Heat exhaustion represents only one part of a continuum of heat-related illnesses, ranging from heat stress to heat exhaustion to heat stroke. While heat stress is simply perceived discomfort in a hot environment, typically during physical exertion, heat exhaustion is a more severe form of heat stress secondary to water or salt depletion from excessive heat. Patients start becoming symptomatic at this point, with many experiencing dizziness, weakness, extreme thirst, headache or syncpe. More serious manifestations, such as delirium and seizures, are notably absent. Body temperatures can vary anywhere from 37 to 40°C. Once core body temperatures rise above approximately 40°C, patients begin to develop heat stroke, the most virulent form of the heat-related illnesses.

Heat stroke requires two findings for its diagnosis, namely a core body temperature greater than approximately 40 ºC and central nervous system dysfunction, whether it be convulsions, coma, delirium, or simple confusion. While heat stress and exhaustion are typically considered relatively benign conditions, heat stroke is a true medical emergency with mortality rates ranging from 20% to 70% depending on patient age. Its pathogenesis and potential lethality are thought to be due to a combination of the direct cytotoxic effects of heat, the physiological demands this heat places on the body, and the host’s inflammatory and coagulation response.

Two types of heat stroke are described, one being classic heat stroke and the other, exertional heat stroke. Classic heat stroke is typically seen in those at the extremes of age and also in those with underlying medical illnesses, including certain cardiovascular, neurological and psychiatric disorders. In addition, individuals on certain medications such as diuretics or anticholinergic agents are at an increased risk. Exertional heat stroke, on the other hand, often affects young, healthy individuals engaged in strenuous activity during times of high heat and humidity. Interestingly, testing on some of these patients reveals a susceptibility to malignant hyperthermia which may predispose them to the development of heat stroke.

Despite this patient’s modest temperature elevation and moderate physical stressor given his history of regular physical exercise, this patient appeared to suffer from many of the more serious sequelae classically seen only with heat stroke, including a change in mental status, myocardial stress, rhabdomyolysis, acute renal failure and thrombocytopenia. Neurologic dysfunction, whether secondary to metabolic derangements, edema, infarction, or hypernatremia, is, by definition, seen in all cases of heat stroke. While some patients have gross neurological disturbances such as coma or encephalopathy, other patients present with more subtle signs such as inappropriate behavior or impairment in judgment. Unfortunately, patients often do not recover fully from these neurological insults. One study found that 33% of patients who presented with heat stroke and survived during the 1995 Chicago...
heat wave suffered long-term moderate to severe functional neurological impairment.

Other potential complications of heat stroke involve virtually any organ system and can rapidly lead to multi-organ dysfunction and death even with proper supportive measures. Among these complications are acute respiratory distress syndrome, myocardial or hepatocellular injury, rhabdomyolysis, and acute renal failure. Also commonly seen in heat stroke are bleeding diatheses, most notably disseminated intravascular coagulation and isolated thrombocytopenia.

One proposed theory behind the phenomenon of DIC in heat stroke involves the splanchnic vasoconstriction and peripheral vasodilation that occurs as part of the body’s compensatory mechanisms after exposure to extreme heat. This vasoconstriction can lead to intestinal ischemia and oxidative stress, resulting in loss of the protective gastrointestinal barrier and leakage of endotoxins into the systemic circulation. In addition, heat shock itself induces an acute-phase response to help protect the body from tissue injury. Inflammatory and anti-inflammatory cytokines, most notably interleukin-1 and 6, TNF-alpha and interferon-alpha, are elevated in heat shock, which contributes to the thermoregulatory failure and circulatory shock not only directly but also via increased production of nitric oxide which further promotes intestinal permeability.

Researchers have found that thrombocytopenia can also develop in heat stroke in the absence of DIC. Furthermore, one case report detailed a patient very similar to our patient with heat exhaustion who presented with thrombocytopenia as well as leukopenia, both presumably secondary to thermolysis. Thus, the hemostatic changes in heat stroke are likely multifactorial in nature, a combination of DIC, thrombocytopenia independent of DIC, and failure of coagulation factor production secondary to hepatic injury.

Treatment of heat stroke focuses on mainly on rapid cooling and support of organ systems. Various cooling techniques can be employed since no specific method has been shown to be superior. Common methods include whole body immersion or the use of fans to aid in conductive heat losses with cold water or ice to the skin. Regardless, achieving a rectal temperature of 39.4°C or less within thirty minutes of presentation has been shown to improve survival. As of yet, there appears to be no role for medications such as dantrolene, and the use of anti-pyretics has not been evaluated thus far. Unfortunately, prompt cooling may not prevent the development of tissue injury, patients should continue to be observed even after stabilization and resolution of hyperthermia.

This case is unique in that despite his diagnosis of heat exhaustion, this patient developed several complications that typically occur with the more deadly form of heat-related illnesses, heat stroke. In addition, the dramatic fall in his platelet count highlights not only the potential virulence of heat stroke but also, its pathogenesis. In summary, due to a combination of heat toxicity itself and a breakdown of the gastrointestinal barrier with production of inflammatory cytokines, patients with heat stroke and even heat exhaustion are vulnerable to thrombocytopenia isolated from or in conjunction with DIC. As such, even after hyperthermia has resolved, one should remain vigilant of this potential complication, as well as many others, in all patients who present along the continuum of heat-related illnesses.

References
A 41 year-old African American female with a history of asthma, hypertension, and schizophrenia presented to the ER in February 2005 with shortness of breath, wheezing, and a “wet-sounding” but non-productive cough. She reported chills, subjective fever, rhinorrhea, and malaise for five days prior. Her only medication was albuterol, which she normally used twice weekly as needed. She was never intubated for asthma. On review of systems, she had progressive dyspnea on exertion of less than two blocks for the last year. She denied night sweats, weight loss, or sick contacts, HIV exposure, alcohol or drug abuse. She admitted to smoking 1 pack per day for more than 15 years.

On physical exam, her temperature was 97.0 F, pulse 96 beats per minute, respirations 22 breaths per minute, blood pressure 130/100 mmHg. She had an oxygen saturation of 77% on room air which improved to 93% on 4 liters oxygen. She was an obese female in moderate respiratory distress. Her oropharynx was clear. Her neck was supple without thyromegaly or lymphadenopathy. Jugular venous distension measured at 10 cm above the Angle of Louis. Heart exam revealed tachycardia without murmur, rub or gallop. Lungs had scattered rhonchi and wheezes bilaterally. Faint crackles were audible at the bases. She had trace symmetrical ankle edema.

Laboratory data on admission showed a WBC of 5900/L, (mostly neutrophils and 30% lymphocytes) hemoglobin 14.7 g/dL, platelets 142k/L. Chemistries were grossly normal except for a bicarbonate of 31 mmol/L. ABG on 4 L O2 showed pH 7.32, PCO2 of 31, PaO2 71. LDH level was elevated at 687. Her coagulation indices, liver function, cardiac enzymes, and urinalysis were within normal limits. Chest X-ray showed a right lower-lobe consolidation and diffuse infiltrates bilaterally. A chest CT further revealed hilar adenopathy and a small right pleural effusion while excluding pulmonary embolism (Figure 1). Blood cultures were sent, ceftriaxone and azithromycin were administered, and serial nebulizer treatments were given for her asthma.

The patient eventually became more hypoxic and was moved to the ICU where she was intubated. Pressor agents were required for hypotension, and her degree of hypoxia required an FiO2 of 100% with +15 of PEEP. On her subsequent chest radiographs, she developed diffuse alveolar infiltrates in multiple areas consistent with ARDS. Bronchoscopy and thoracentesis did not elicit any bacterial, fungal, or neoplastic etiology for her respiratory failure. Silver stain for PCP was negative. HIV serology was negative.

She remained intubated and on pressors for over 1 week. During this time, admission influenza titers came back elevated for both influenza A and B (Each was 1.6 with a reference range <0.20) Viral culture from BAL later grew influenza A.

Discussion
At first glance this case appeared to be one of bacterial pneumonia, sepsis and ARDS. The lobar consolidation on her X-ray was more consistent with bacterial pneumonia. Her septic hemodynamics also suggested a bacterial infection (although influenza mimicking septic shock has been reported in very young patients) Therefore, it is not clear if her critical illness was due solely to influenza. More likely, she suffered from influenza complicated by secondary bacterial pneumonia. Regardless, her case illustrates how quickly and severely a patient with underlying lung disease (which probably was more severe than she reported, given findings of cor pulmonale and compensated respiratory acidosis) can deteriorate when infected with influenza. Clinical awareness is paramount to timely diagnosis, prophylaxis, and effective treatment.

In the northern hemisphere, influenza epidemics occur yearly from December to April. Normally the illness is most severe in the elderly, very young, or those with chronic medical problems. Uncomplicated illness typically resolves within 1 week, but can progress to primary influenza viral pneumonia or secondary bacterial pneumonia in susceptible persons. The latter occurs as the virus denudes ciliated epithelium, allowing bacterial entry into the lower respiratory tract. Streptococcus pneumoniae, staphylococcus aureus, and Haemophilus influenza are the most common pathogens isolated in this setting.

As was demonstrated in this case, serologic influenza tests, while relatively sensitive and specific, do not generally yield data within a clinically relevant time period. A diagnostic test should produce a fourfold or greater rise in antibody titer between acute illness and the convalescent phase approximately 10 days later. Our patient did not have such a follow-up titer drawn, and diagnosis was based upon viral culture. Cultures could also be obtained by throat swabs, nasal washes, or expectorated sputum. It takes 48 to 72 hours for the cytopathic effects of virus to appear in tissue culture. Rapid diagnostic tests are also available. These include immunofluorescence (IF) assays, enzyme immunoassays (EIA), and polymerase chain reaction (PCR) and yield results as early as 15 minutes to 2 days.

In the United States, four medications are currently available for treatment: amantadine, oseltamivir, rimantadine, and zanamivir. Amantadine and rimantadine have activity against influenza type A, but not type B. Oseltamivir and zanamivir are neuraminidase inhibitors with activity against both influenza A and B. If given within 48 hours of the onset of symptoms, these medications can reduce symptoms, fever, and viral shedding by about 1 day. However, none of these medications is effective in preventing serious complications of influenza such as those seen in the case of this patient.

Current treatments for influenza can only benefit a select group of patients who present early with uncomplicated disease. Therefore, prophylactic immunization in appropriate patients remains the most effective means of controlling infection.

References
A POST-PARTUM WOMAN WITH DYSPNEA
Saaron Laighold, MD

A G1P1 40 year-old Caucasian female without significant past medical history presented to an outside hospital with worsening shortness of breath and hemoptysis. The patient was 10 days status post caesarian section for preeclampsia. Her course after delivery was complicated by a stay in the ICU for shortness of breath. She was discharged home 7 days post-delivery and then returned to the hospital 3 days later. The patient was intubated at the outside hospital for hypoxia (O2 sats of 50% on room air) and transferred to TJUH for further management.

The patient’s family history was significant for her father being deceased at age 40 from an MI and her mother being alive and well. The patient lives at home with her husband and her child who is healthy and well. She has no history of drug, alcohol, or cigarette smoking.

Prior to delivery her medications included multivitamin, folate, and ferrous sulfate. After delivery, the patient was discharged home on metoprolol extended release 25 mg, furosemide, and hydralazine. Upon transfer to TJUH she was on a dobutamine drip, propofol drip, nitroglycerin drip, and intravenous enalapril.

The patient was transferred to the TJUH CCU already intubated and sedated. Vitals signs were stable with temperature of 97.8F, pulse of 105, respiratory rate of 19 and blood pressure of 143/78. The physical exam was significant for jugular venous distension to 15cm, presence of a third heart sound (S3), soft systolic ejection murmur, bilateral coarse breath sounds, and 2+ lower extremity edema to her knees.

Laboratory values including CBC, chemistry panel, cardiac enzymes and electrolytes were normal at time of transfer. BNP was 158, protein was 4.7 g/L, and albumin 2.9 g/L. Urinalysis revealed 3+ blood and trace ketones while serum cortisol was 17.5 and TSH was 1.95 mIU/mL.

Studies at the outside hospital showed no pulmonary embolus on CT scan of the chest and no deep vein thrombosis by lower extremity dopplers. Echocardiogram revealed left ventricular ejection fraction of 25-30% and moderate to severe mitral regurgitation. Chest x-ray on arrival to TJUH was consistent with pulmonary edema as shown below (Figure 1).

Differential diagnosis included peripartum cardiomyopathy, accelerated hypertension, diastolic dysfunction, systemic infection, pulmonary embolism, preeclampsia, amniotic fluid embolus, or cardiomyopathy due to infection; ischemia; or toxicity. The time course, clinical presentation, and studies helped to narrow in on the etiology of her symptoms.

The patient presented 10 days post-partum with signs of left-sided congestive heart failure with a decreased ejection fraction on her echocardiogram. The fact that the patient presented in the post-partum period rather than earlier in her pregnancy would seem to eliminate an underlying cardiomyopathy. Her echocardiogram revealed systolic dysfunction making diastolic dysfunction unlikely to be the cause for this woman’s symptoms. She was ruled out for a pulmonary embolus and did not have any signs of systemic infections or indications of an underlying ischemia to account for the new onset cardiomyopathy.

Amniotic fluid embolism can cause hypoxia in the post-partum period. However, the onset of symptoms typically presents during labor and delivery or within the first 48 hours after delivery as opposed to symptoms of severe hypoxia 10 days after delivery, as was the case with this patient. Also, patients with amniotic fluid embolism will typically present with disseminated intravascular coagulation and symptoms similar patients with anaphylactic or septic shock.

Preeclampsia and accelerated hypertension were though to be implausible causes in this case because the patient did not present with severe hypertension at the time of her severe hypoxia. The patient’s symptoms of preeclampsia should have improved after delivery instead of causing her to become hypoxic 10 days post-delivery.

The patient’s presentation was thought to be consistent with peripartum cardiomyopathy. She was treated for congestive heart failure with intravenous furosemide and ACE inhibitor along with the dobutamine and nitrates. After several days of diuresis, a repeat echocardiogram revealed mild to moderate mitral regurgitation, moderate left atrium enlargement, and an ejection fraction of 40-45% with mild global LV dysfunction. The patient was extubated after several days and transferred to a telemetry floor. She continued to improve with medical treatment for her heart failure.

The patient was discharged home on an ACE inhibitor, beta-blocker and diuretics with the recommendation that she avoid future pregnancies.

The patient had several risk factors for the condition including older maternal age and the development of preeclampsia during her pregnancy. The improvement in symptoms and the improvement in LVEF with supportive therapy were consistent with a peripartum cardiomyopathy as opposed to other causes for her presentation.

Discussion
Peripartum cardiomyopathy (PPCM) was first described in the 1700s and first defined in 1937. It is a rare form of dilated cardiomyopathy of unknown etiology which affects women in late pregnancy or early post-partum. The true incidence of this condition is unknown but it is thought to be 1 per 3000 to 1 per 4000 live births or between 1000 and 1300 women each year in the US. For unknown reasons, the incidence of PPCM is higher in certain regions of the world. In one area of Haiti the incidence is estimated to be 1 in 300 pregnancies.
Peripartum cardiomyopathy is defined by cardiac failure within the last month of pregnancy or within 5 months postpartum. The condition is characterized by the absence of other causes of congestive heart failure and the lack of heart disease prior to the last month of pregnancy. Most patients with PPCM present with symptoms of congestive heart failure within the first 4 months post-partum (78%). 9% of patients present in the last month before delivery while 13% present more than 1 month antepartum or more than 4 months postpartum. The time course for peripartum cardiomyopathy contrasts with the time for presentation of congestive heart failure due to other etiologies. The 2nd trimester of pregnancy is the greatest hemodynamic burden of gravid state and most patients with underlying cardiac dysfunction tend to develop symptoms of heart failure at this time. Normal pregnancy causes increased blood volume, increased cardiac output and decreased afterload so that patients with underlying cardiac disease present earlier during pregnancy than patients with PPCM.

Patients are judged to have PPCM after they present in congestive heart failure within the last month of pregnancy or within the first 5 months postpartum. By echo criteria, women with PPCM have LVEF<45%, decreased fractional shortening<30%, and end/diastolic dimension>2.7 cm/m3. Symptoms for congestive heart failure in patients with peripartum cardiomyopathy are similar to heart failure symptoms for patients with other etiologies of CHF. Symptoms include dyspnea, orthopnea, PND, MR murmur. Physical exam signs include cardiomegaly, S3, JVD, peripepheral edema, arrhythmias, and pulmonary rales.

While the cause of peripartum cardiomyopathy remains unknown a number of risk factors are associated with the development of the condition. Risk factors include age greater than 30 years, multiparity, women of African descent, pregnancy with multiple fetuses, history of preeclampsia, eclampsia, postpartum HTN, cocaine abuse, nutritional deficiencies including Selenium, and long term oral tocolytic therapy with Beta-agonists such as terbutaline.

While the etiology of PPCM remains elusive, investigation of women with PPCM and associated risk factors has led to identification of several possible etiologies. Viral myocarditis is one suspected cause of PPCM. Studies have reported the incidence of myocarditis among PPCM patients to be from 9% to 78%. Some studies have estimated the incidence of myocarditis to be similar to controls with idiopathic dilated cardiomyopathy while other studies have estimated the incidence of myocarditis to be much higher among patients with PPCM. The variation among study results is thought to be due differences in the timing of myocardial biopsies and due to variations in the definition of myocarditis used by pathologists. Investigators have speculated that pregnancy may increase patient susceptibility to viral myocarditis leading to PPCM.

It has been postulated that PPCM may be caused by an autoimmune reaction. Supporting evidence for this theory includes the finding that high titers of autoantibodies against cardiac tissue proteins have been identified in women with PPCM. The suspected autoimmune mechanism is that fetal cells escape into the maternal circulation and take up residence in cardiac tissue triggering an autoimmune reaction against the myocardium. After delivery, it is theorized, the fetal cells in the myocardium are recognized as nonself when the autoimmune-suppresion of pregnancy subsides and the patient’s immune system attacks the cardiac myocytes causing cardiomyopathy.

Other theories for the etiology of PPCM include systemic inflammation, hormonal involvement and nutritional deficiencies. Inflammation is believed to be involved in the pathogenesis of PPCM as it does in other etiologies of CHF. TNF-alpha, IL-6, Fas/APO-1 are significantly elevated in patients with PPCM compared to controls. FAS: apoptosis-signaling receptor is significantly elevated in patients who died from PPCM as compared to controls. Relaxin is an ovarian hormone produced during pregnancy which is thought to play a role in PPCM. Relaxin has positive inotropic and chronotropic properties and abnormalities of this hormone are speculated to participate in the pathogenesis of PPCM. Nutritional deficiencies, especially selenium deficiency have been found among women with PPCM. In one area of Haiti where PPCM is exceptionally common pregnant women commonly suffer from nutritional deficiencies. Selenium deficiency may play a role in the pathogenesis of PPCM because it may make the heart more susceptible to injury from viruses, hypertension, or hypocalcemia.

Therapy for PPCM involves standard heart failure management including diuretics, inotropes, and blood pressure control. Management of PPCM in the antepartum period must account for possible teratogenicity of certain medications typically used for heart failure patients. ACE inhibitors are contraindicated in
pregnancy and so they should be avoided. Hydralazine and nitrates are safer to use for blood pressure therapy. Similarly, anticoagulation to prevent the risk of embolism formation should avoid coumadin in the antepartum period because of its possible teratogenicity. Both heparin and coumadin should be safe to use postpartum because neither are excreted into breast milk. If the diagnosis of PPCM is made in the antepartum period, delivery should be strongly considered because of the risk of continuing the pregnancy to both the fetus and the mother.

PPCM has a high incidence of serious morbidity and mortality with listed mortality rates between 18% and 56%. Complications from PPCM include arrhythmias, progressive heart failure necessitating BiV pacemaker and defibrillator implantation or heart transplant, and thromboembolism. Clot formation is an important complication with an incidence which has been reported to be as high as 50%. The high frequency of thromboembolism is due to the hypercoaguable state of late pregnancy, stasis and turbulent blood flow in dilated cardiomyopathy and the common practice of placing patients in late pregnancy on bed rest.

The outcome for women with PPCM is extremely varied with the serious consequences of the condition usually occurring in the months following the diagnosis. In some patients with PPCM, clinical and echocardiographic status improves quickly and returns to normal. Other patients deteriorate rapidly necessitating device implantation or transplantation. Still others, will respond to therapy and have persistent signs of cardiac dysfunction. US mortality ranges from 25% to 50% with close to 50% of deaths occurring in the first 3 months postpartum.

Women who do recover usually do so within 6 months of the diagnosis and a substantial number of affected women will have significant improvement within the first 6 months. In one study, 50% of patients with PPCM had resolution of cardiomegaly and LV dysfunction at 6 months after delivery without reported cardiac mortality. Patients with persistent cardiac abnormalities at 6 months after delivery had a mean survival of 4.7 years and an 85% mortality at 5 years.

Left ventricular size and severity of left ventricular dysfunction are related to worsening outcomes in the acute and subacute phase following the development of PPCM. Poor outcome is associated with worsening LV size and dysfunction, higher parity, being an older patient, and later onset of symptoms following the pregnancy.

Future pregnancies for women with PPCM carry substantial risk. Small studies have shown that women with PPCM have worse outcomes in future pregnancies compared to normal patients even if their left ventricular size and function has returned to normal. Studies have shown worse outcomes for mother and fetus in women with persistent LV dysfunction as compared to women with PPCM who have regained normal function. In one NEJM study, in women with PPCM who regained normal function 25% of future pregnancies were associated with cardiac dysfunction. In patients with persistent left ventricular dysfunction, 50% of subsequent pregnancies were associated with worsening cardiac dysfunction. Table 1 shows that women with PPCM had a high incidence of maternal complications during subsequent pregnancy with a higher incidence among those whose LV function had not recovered from the initial pregnancy.

Fetal health has also been found to be worse among women with PPCM in future pregnancies. In the NEJM study, of the women who had regained normal function 13% of women delivered prematurely. In women with continued left ventricular dysfunction, 50% of pregnancies ended in premature births and 25% of the patients required therapeutic abortions.

References


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34 YEAR OLD WOMAN WITH THROMBOCYTOPENIA AND WEAKNESS

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Patient is a 34 year old Liberian Female with past medical history significant for Systemic Lupus Erythematosus (SLE) that was recently admitted to the hospital for weakness and was diagnosed with encephalomyelitis due to SLE. At that time the patient was also noted to have low platelets felt secondary to Immune Thrombocytopenic Purpura (ITP). She has history of thrombocytopenia with her four pregnancies. During this past admission the patient was treated with hydroxychloroquine and high dose steroids for the CNS involvement of SLE but no platelet response was noted with administration of steroids. She was discharged to a rehabilitation facility, but returned to the hospital with a new episode of worsening weakness.

On admission the patient was again noted to be thrombocytopenic and anemic. She denied epistaxis, easy bruising, rash, fatigue, fevers, chills, shortness of breath, or symptoms related to upper respiratory infection. Her only complaint on presentation was weakness in the upper and lower extremities that worsened over the last week.

Medications she was taking included prednisone, hydroxychloroquine, alendronate, calcium carbonate and pantoprazole. She denied any drug allergies. Past medical history was significant for SLE complicated with encephalomyelitis and questionable history of ITP with exacerbations during pregnancy. Past psychiatric history included possible conversion disorder. No previous surgeries were noted. She denied any alcohol, tobacco, non-prescription medications, herbal substances or illegal substance use. Patient had previously worked with her husband in their restaurant, but was currently on disability. She is married with 4 children.

Physical exam revealed she was afebrile with a blood pressure 120/66 mmHg, heart rate 79 beats per minute, respirations 12 breaths per minute, and 98% oxygen saturation on room air. She was alert awake and oriented times three, pupils were equal, round and reactive to light and extraocular muscle movements were intact. Sclera was anicteric and no petechiae were noted on buccal mucosa. No lymphadenopathy in cervical, axillary or inguinal regions was appreciated. Lungs were clear and heart was regular without murmurs to auscultation. Abdominal exam was benign and there was no edema in the lower extremities. On neurological exam, cranial nerves and cerebellar exam were within normal limits. The patient had decreased strength in the upper and lower extremities bilaterally, graded as 4/5 and 1/5 respectively. Deep tendon reflexes were symmetrical and graded as 2/4 and plantar reflex was down-going. On examination of the skin no rash, petechiae or purpura were noted.

Her labs and studies were remarkable for hemoglobin of 10.8 g/dL, platelets 57000/microL, MCV 70fl, RDW 21.7%, reticulocyte 2.2%, LDH 188 IU/L, haptoglobin 115 mg/dL, total bilirubin 0.5 mg/dL, creatinine 0.5 mg/dL. INR 1.21, PT 15.8 sec, PTT 27 sec. Fibrinogen 480 mg/dL, D-Dimer 6.49 mg/mL. Peripheral smear showed decreased platelets without clumping and scarce schistocytes.

The patient’s blood smear was not consistent with TTP. ITP was felt to be the most likely cause of her thrombocytopenia and she underwent treatment initially with high dose steroids and subsequently with IVIG, both without significant response. Her bone marrow biopsy showed hyperplastic megakaryocytosis consistent with peripheral destruction. She also underwent treatment with rituximab for encephalomyelitis without platelet response. A CT Angiogram of chest was ordered during her hospitalization for an episode of shortness of breath. There was no evidence of pulmonary embolism but a large heterogeneous splenic mass was visualized (Figure 1). This mass upon further evaluation with MRI was hypervascular and the differential diagnosis included angiosarcoma and hemangiomia.

The patient underwent splenectomy and pathology revealed a large splenic hemangiomia with necrosis. Platelet counts steadily rose from the day of splenectomy and remained stable during the remainder of her hospitalization.

Discussion

This patient had thrombocytopenia from splenic sequestration due to a large hemangiomia. Hemangiomas are the most common primary tumor of the spleen with a prevalence of 0.03-0.14%. This is a congenital lesion arising from sinusoidal epithelium resulting from proliferation of vascular channels lined by a single layer of endothelial, most often resulting in a cavernous lesion.

Hemangiomas are variable in size ranging from a few millimeters to several centimeters. The majority of these tumors are less than 4 cm, but there are reports of lesions up to 17 cm in diameter. Hemangiomas may be single or multiple as in Klippel-Trenaunay-Weber Syndrome.

The majority of hemangiomas are asymptomatic and incidentally discovered. However, larger lesions may enlarge the spleen leading to fullness and left upper quadrant discomfort, spontaneous splenic rupture or Kasabach-Merritt phenomenon (thrombocytopenia and/or coagulopathy, now called disseminated intravascular coagulation or DIC, that results from platelet trapping within a vascular tumor). Thrombocytopenia results from shortened platelet survival caused by sequestration of platelets in the vascular malformation. Episodes of acute DIC have been reported in pregnant women with congenital hemangioma and in one woman during two successive pregnancies. The hormonal
A 50-year-old white male was admitted to the hospital with erythema and swelling of both lower extremities.

The patient had a medical history significant for liver transplant five years prior for end-stage liver disease secondary to alcoholic cirrhosis. Following transplant, he developed mitral valve insufficiency with heart failure and pulmonary hypertension. He had been in his usual state of health until approximately a week prior to admission when he noticed that his lower extremities had increased in girth. For several days, he noted that there had also been increased redness and pain over the affected area.

The patient denied other symptoms such as headache, photophobia, phonophobia, or weakness. He had no report of dyspnea or a new productive cough. There was no other significant past medical or surgical history. Prior to his initial diagnosis, his alcohol consumption was difficult to quantify, however, since several years prior to transplant, the patient had remained abstinent. He had not traveled outside of the United States. His immunosuppressive regimen consisted of prednisone 10mg and sirolimus 1mg once a day and knew of no allergies to medications.

The vital signs were significant only for a temperature of 100.8ºF; all other vital signs were normal.

On physical examination, the head, neck, heart, lungs, and abdomen were normal. Multiple, irregularly-shaped, deep ulcerations with surrounding erythema were seen on both lower extremities. There was no evidence of necrosis, however, there was significant edema of the lower extremities.

The patient was started on a regimen of broad-spectrum antibiotics consisting of intravenous vancomycin and piperacillin/tazobactam for the treatment of cellulitis in an immunocompromised host. Initially, there was no resolution of the cellulitis or ulceration. Blood cultures remained persistently negative. Magnetic resonance imaging of the lower extremities revealed cellulitis of the right lower extremity and myositis with fasciitis on the left.

Biopsy of the skin lesions revealed diffuse yeast forms with mucicarmine positive capsules consistent with cryptococcus infection. Cryptococcal antigen titer was markedly elevated at 1:251, consistent with cryptococcus infection. Evaluation of cerebrospinal fluid did not reveal meningeal involvement. The patient was started on amphotericin B with complete resolution of the lesions.

Cutaneous involvement is an uncommon manifestation of cryptococcal disease, but it may be the initial manifestation of systemic cryptococcosis in solid-organ transplant (SOT) recipients and other immunocompromised hosts. Only 36 cases have been described in the literature and majority of them are in renal transplant recipients. No cases of cellulitis with fasciitis and myositis without systemic involvement have been described for liver transplant patients. We describe a liver transplant recipient diagnosed with cellulites, fasciitis, and myositis as the only presenting manifestation of cryptococcal infection.

Cryptococcal infection must be included in the differential diagnosis of cellulitis in SOT recipients. Deep soft tissue involvement may occur concomitantly with primary cutaneous cryptococcosis. Because the clinical appearance of cutaneous cryptococcosis is non-specific, early diagnosis requires tissue acquisition for testing. Tissue samples should be stained with the fungal stain mucicarmine to reveal the characteristic organisms. Cryptococcal antigen test is a simple blood test that may aid in the diagnosis of cryptococcosis.
A 55 year old Caucasian female smoker, with past medical history significant for hypertension and peptic ulcer disease presented to the emergency department with a four day complaint of malaise, fever, and myalgias. She was seen by her primary care physician who started her on amoxicillin clavulanate for possible strep throat infection. Her family reported a productive cough with green sputum, pleuritic chest pain, nausea, vomiting and diarrhea for one week. They also felt she was getting more confused over the past several hours.

The patient was found to be confused, hypotensive, and hypoxic. Temp 98.1F, heart rate 107 beats per minute, respiratory rate 16 breaths per minute, blood pressure 73/51 mmHg, and oxygenating at 89% on room air. Physical exam revealed bilateral wheezing that was more prominent in the right lung field. She was tachycardic with no murmurs or rubs. The abdomen was soft and non-tender with no organomegaly and she had no evidence of a rash.

Labs on admission: WBC 2,600/mm3, Hemoglobin 13.3 g/dL, platelets 255,000/mm3, Na+ 134, K+ 4.5, HCO3- 19, BUN/Cr 49/2.8, AST 85, ALT 53. ABG: pH 7.2, PaCO2 49, PaO2 75, O2 Sat 92%

The differential diagnoses at the time of presentation included community acquired pneumonia with Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis being high on the list of pathogens along with the atypical organisms such as Legionella, Mycoplasma and Chlamydia. Other infectious pathogens such as anaerobes and fungi are also included. Non-infectious etiologies including pulmonary embolism, vasculitis, hypersensitivity pneumonitis and neoplastic lymphangitis spread were also considered.

The patient was admitted to the ICU with presumptive admission diagnosis of septic shock secondary to pneumonia and was intubated within 1 hour of admission due to hypoxic respiratory failure requiring FIO2 100% and 16+ PEEP to maintain PO2 of 70 mmHg. Stress dose steroids were started empirically, as well as empiric antibiotic coverage with azithromycin, pipericillin/tazobactam, and vancomycin. Recombinant human activated protein C was also administered 12 hours after admission. Two days later urine legionella antigen was found positive and antibiotics were switched to levofoxacin.

The patient required pressure support for ten days and was extubated on the fifteenth day of hospitalization.

**Epidemiology and clinical manifestations**

First identified in 1976 during an outbreak at the annual meeting of the American Legion in Philadelphia (where out of 221 people infected, 34 died), Legionella is a facultative intracellular aerobic gram negative rod producing beta-lactamase, hardly visible on Gram stain due to its diminutive size. There are two major presentations of Legionella infection, the first being Legionnaires’ Disease which is a community acquired pneumonia whose course can become very dramatic and the second being Pontiac fever which is a more benign and self limited disease manifested through headaches, low grade fevers, malaise and chills without respiratory complaints and no radiological x-ray findings. Pneumonia is the most common clinical manifestation and Legionella has been reported as the third or fourth most commonly identified pathogen in community acquired pneumonias. However, it did account for only 4.7% of the CAP cases in one large study. Its prevalence is highlighted by the fact that it is also mentioned as one of the most common pathogens identified in nosocomial pneumonia.

**Legionnaires’ Disease**

With an incubation period of two to ten days, this pathogen is considered transmitted through to the air conditioning and water cooling systems, rather than transmitted from person to person. Although first thought to manifest only as severe pneumonia (second only to S. pneumoniae in organisms identified in ICU admissions for pneumonia) accompanied by gastrointestinal symptoms and high fevers, current diagnostic testing proved that presentation of Legionella infection may vary widely and that symptoms may be nonspecific.

Among the clinical clues for diagnosis of Legionnaires’ disease are the gastrointestinal symptoms, especially diarrhea; neurological findings such as confusion, headache and lethargy; and fever > 390 C. Cough is usually mild and only slightly productive, hemoptysis is rarely encountered, and chest pain is infrequent. Physical exam is nonspecific with rales and subsequent signs of consolidation, fever as high as 40° C, bradycardia, lethargy, and stupor. Spumt gram stain shows WBC abundance but scant or no microorganisms. Hyponatremia (Na+ often less than 130)5,6, hepatic and renal dysfunction, hematuria, thrombocytopenia and failure to respond to classic beta lactam antibiotic treatment are often specifically seen in patients with Legionella. One should always maintain a higher index of suspicion for Legionella infection in patients considered at risk including smokers, those with chronic
pulls the nosocomial Legionnaire’s disease may be as high as 50%12. Treatment may also be seen on x-ray, although infrequently9. In the immunosuppressed host, densities may appear as round opacities at the lung base, often progressing into cavitary lesions. Of note, radiological changes usually lag behind the clinical course, with complete resolution of the infiltrates within 4 weeks to several months from the debut of the illness.

Although some clinical manifestations are distinctive for Legionella infection, none of them are pathognomonic or highly specific. Early detection with prompt and appropriate antibiotic treatment have been known to save lives10,11. Culturing for Legionella spp. is the single most important laboratory test, but is time consuming and requires adequate respiratory specimen and a special culture media. Other tests have proved to be more beneficial: urinary antigen testing is rapid, sensitive, specific, and not costly. However, it is only useful for the diagnosis of L. pneumophila type 1 infection (accounting for 90 percent of community-acquired Legionella infections in the United States). The combination of culture of an appropriate respiratory specimen and urinary antigen testing are optimal as a diagnostic approach. Serologic tests, although available, are generally far less useful for the diagnosis of an individual patient but very useful for large epidemiological studies. While PCR-based tests exist, to date they do not exceed the sensitivity of culturing the organism. Given the severity and the high incidence of Legionella infection it is reasonable to perform specific diagnostic tests for all patients requiring hospitalization for community-acquired pneumonia.

Treatment

The mortality of untreated or inadequately treated community-acquired Legionnaires’ disease is 16-30%, while the mortality for the nosocomial Legionnaire’s disease may be as high as 50%12. Timely use of the current diagnostic tests as well as prompt antibiotic treatment with active drugs have decreased mortality to less than 10%.

Although frequently used in the past, erythromycin has now been supplanted by newer macrolides as well as respiratory tract quinolones. Two studies13,14 showed the higher efficacy of levofloxacin compared to macrolides as well as fewer complications and shorter hospitalizations. Current recommendations are a 7-10 day course of azithromycin or 10-14 day course of levofloxacin, with a longer 21 day course for immunosuppressed patients and patients requiring ICU admission. Given the high incidence and the severity of this disease, current recommendation for community acquired pneumonia requiring hospitalization is azithromycin either as monotherapy or along with ß-lactame antibiotics15,16. Monotherapy with an active quinolone is also acceptable. For nosocomial pneumonia, a quinolone (ciprofloxacin or levofloxacin) is the empiric drug of choice since the nosocomial infections are frequently associated with gram negative bacilli. For endocarditis and other extrapulmonary infections, a combination therapy is recommended with levofloxacin or azithromycin plus rifampin. Despite a significant decrease in mortality with prompt and proper antibiotic treatment, patients often have residual symptoms 17 such as chronic fatigue syndrome (75%) and residual neurological deficits (63%).

Our case patient finished 21-day course treatment with levofloxacin for ARDS secondary to Legionnaires’ disease. Hospital course was complicated by development of quadriaparesis thought to be secondary to ICU neuropathy. Of note, Legionella Pneumophilla has also been linked independently with quadraparetic complications. The patient did achieve further improvement in her neurological status and was able to be transferred to a rehabilitation facility.

References

Case Reports

A 56-Year-Old Man with Vertigo and Hypercalcemia

Veronica Rivera and Andrew Rose, MD

A 56-year-old Man with a past medical history significant for lower back pain and GERD was admitted to the hospital for dizziness and laboratory abnormalities.

Five days prior to admission, the patient noted that he felt dizzy and unsure while walking. These symptoms persisted without change and he went to see his primary care doctor the day prior to admission. The patient was given meclizine for his dizziness and routine labs were drawn. He received a call from his doctor on the day of admission instructing him to be evaluated for an elevated serum calcium.

He described his primary complaint as if his surrounding were moving. He did not complain of lightheadedness or syncope and reported that his symptoms did not change with position. The symptoms did not change if he closed his eyes or when he sneezed, coughed, or strained. There was no associated nausea or vomiting.

His medical history was significant for severe GERD for which he took ten to fifteen over-the-counter calcium carbonate tablets daily with moderate symptom relief however had not had a medical evaluation for these symptoms. He also reported severe lower back pain that he attributed to his strenuous occupation which began approximately nine months prior to admission. At first, his back pain was alleviated by occasional ibuprofen use, however at present, the patient was taking six to eight 200 mg over-the-counter tablets of ibuprofen daily. He had not been evaluated medically for his back pain. He also reported unilateral glaucoma as a child and had required enucleation of his right eye. Recently, he had arthroscopic exploration of his left knee and was aware that he would eventually require knee replacement.

He reported that he knew of no allergies to medications and was only taking the over-the-counter medications as above. His family history was notable only for multiple members of his family with coronary artery disease at a young age. He knew of no family members with cancer or kidney disease. He occasionally drank alcohol at social functions and had never been a tobacco user. He works in maintenance and lives with his wife and daughter.

His review of systems was generally unremarkable. He reported that he had decreasing urinary stream and volume and increasing frequency during the past month. He reported no weight loss or constitutional symptoms.

The temperature was 97.3ºF, the pulse was 73 and regular, the blood pressure was 159/70 and he was breathing comfortable at 16 respirations per minute. His oxygen saturation was 94% on room air.

On physical examination, he was a pleasant and mildly obese man in no distress. He was normocephalic, his left pupil reacted briskly to light; he had a prosthesis in his right enucleated eye. There was no notable nystagmus. The heart, lung, abdominal, and extremity examinations were all unremarkable. His rectal examination revealed normal sphincter tone and an asymmetric nodule on the left lobe approximately 1 cm in diameter. His neurologic exam was non-focal and his cranial nerves were intact.

On admission, laboratory values of note were a serum calcium of 15.6 mg/dL and a creatinine of 3.2 mg/dL. The remainder of his chemistry and hematologic values were within normal limits. An initial troponin drawn in the emergency department was normal.

He was admitted with a diagnosis of hypercalcemia and for a thorough evaluation of an underlying oncologic or endocrine process. His initial treatment with 4 mg of zoledronic acid, 400 international units of salmon-calcitonin, as well as aggressive intravenous hydration. He was placed on 40 mg intravenous pantoprazole for relief of his reflux symptoms and he was provided with acetaminophen for his back pain. On hospital day 2, the serum calcium level was 8.3 mg/dL and his creatinine was 1.8 mg/dL.

A CT of his head was performed which was read to have no intracranial pathology. His initial lumbar x-ray was read as spondylothesis, likely compression fractures at L4 and L5. A follow-up MRI of lumbar spine showed multilevel disc bulging, protrusions, and facet arthropathy with moderate bilateral foraminal narrowing, however there was no evidence of compression fracture as previously suggested.

A CT of the chest and abdomen were performed and showed no acute pathology. The radiologist noted that severe gastroesophageal reflux was evident by contrast refluxing into the esophagus as well as faint nonobstructing calculi in the lower pole of the right kidney. A renal ultrasound revealed no hydronephrosis or renal calculifications, and there was clear cortical medullary differentiation.

The results of his serum parathyroid hormone, vitamin D level, and prostate specific antigen were all within normal limits. Urine electrolytes were evaluated and the calculated fractional excretion of sodium was 7.2%, suggestive of acute tubular necrosis. Of note, his total cholesterol was 291 mg/dL and his low density lipoprotein was 200 mg/dL.

The consulting urologist felt that his exam findings may be consistent with asymmetric benign prostatic hypertrophy and planned a transrectal biopsy as an outpatient. The consulting gastroenterologist performed esophagogastroduodenoscopy and the results were consistent with Barrett’s esophagus secondary to a hiatal hernia. The patient was continued on pantoprazole.

Without evidence of an oncologic process or elevated parathyroid hormone, the diagnosis of milk-alkali syndrome was made. High dose ibuprofen likely resulted in acute tubular necrosis and a decreased ability to excrete the high doses of calcium that the patient was ingesting. The hypercalcemia and acute renal failure resolved and the patient was discharged on pantoprazole, atorvastatin, and acetaminophen as needed for pain. He was instructed to stop taking calcium carbonate and non-steroidal anti-
inflammatory medications. Appointments with gastrointestinal, urologic, and cardiovascular specialists as well as for a stress test were made for the patient.

**Discussion**

There is an extensive list for the differential diagnosis of hypercalcemia. Hyperparathyroidism is the most common cause in ambulatory patients and malignancy is the most common cause in hospitalized patients. The differential of hypercalcemia can be divided into three major categories. Increased bone resorption can be caused by hyperparathyroidism, cancer, hyperthyroidism, and Paget’s disease. Increased calcium absorption can be caused by increased calcium uptake and hypervitaminosis D. Miscellaneous causes of hypercalcemia include drug toxicity and conditions such as pheochromocytoma.

The presentation of this patient with milk-alkali syndrome and underlying renal insufficiency has become rather rare since the introduction of modern ulcer therapy. It has, however, increased in frequency with more use of calcium carbonate for osteoporosis prophylaxis. Subsequently, this syndrome has experienced an increased prevalence in females, whereas before it was more common in men. Prior to 1990, the milk-alkali syndrome accounted for less that 2% of admissions related to hypercalcemia with a small reported rise during the 1990s. Since calcium has various roles in the body including cardiac and smooth muscle contraction, and in platelet aggregation and function, proper treatment and management of hypercalcemia is imperative.

In this patient, milk-alkali syndrome was suspected as the cause of hypercalcemia after ruling out other causes of hypercalcemia. In one case series, five patients who had milk-alkali syndrome patients were ingesting large quantities of calcium and absorbable alkali and presented with the triad of hypercalcemia, metabolic acidosis, and renal failure. In two of these patients, renal failure resulted in the need for dialysis. Kapnser, et al. reported on 297 heart and heart-lung transplant recipients who were being treated with calcium carbonate after cardiac transplantation. This treatment resulted in sixty-five patients who developed serious hypercalcemia after transplantation. Thirty-one of these patients experienced alkalosis and thirty-seven had renal impairment.

The use of calcium in patients with preexisting renal insufficiency is an important consideration. Four patients in a case report with mild, asymptomatic chronic renal failure took daily over-the-counter antacids and required hospital admission for hypercalcemia. It is also imperative to monitor calcium use in pregnant patients. Maternal prolonged hypercalcemia secondary to primary hyperparathyroidism can affect the fetal circulation and lead to suppression of fetal parathyroid function and lead to neonatal hypocalcemia and tetany or may result in spontaneous abortion and stillbirth. Therefore, monitoring calcium intake in pregnant patients is also very important.

In the setting of hypercalcemia, initial medical management includes intravenous fluids that promote the renal excretion of calcium. In the setting of hypervitaminosis D such as those in granulomatous disease, steroids are effective by inhibiting the effects of vitamin D. In the setting of hypercalcemia of malignancy, treatment of the underlying cancer promotes a return to normal calcium levels. Bisphosphonates may also be used as medical management and potentially may inhibit osteoclast activity for up to one month. Calcitonin directly inhibits osteoclastic bone resorption and promotes the renal excretion of calcium by decreasing tubular reabsorption.

The milk-alkali syndrome is increasing in prevalence and should be considered in any presentation of hypercalcemia. Patients prophylactically taking calcium supplements or using over-the-counter antacids should be carefully monitored given their increased risk for hypercalcemia.

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A 74 Year Old Woman with Left Shoulder Pain

Jane V. Mayrin, MD

A 74 year old woman presented to the emergency department complaining of two weeks of left shoulder pain. The pain was sharp, 8 out of 10 in intensity, located in the left shoulder, made worse with breathing, and associated with mild chest discomfort, diaphoresis, and neck pain. There was no radiation and the pain was not worsened with exertion. The patient has a history of Warthin tumor of the left parotid gland and had undergone laryngoscopy and polypectomy two weeks prior to presentation. Around this time she developed the shoulder pain along with overall weakness. At the time of presentation she reported the pain was only present with deep breathing. She denied any shortness of breath, headache, lightheadedness, dizziness, or cough.

In addition to the Warthin tumor, the patient has a history of colon cancer with resection 25 years ago. She has a 50 pack-year smoking history but denied alcohol or substance abuse. She was a retired nurse and lived at home with her husband. Her family history included a father who died in his eighties from a myocardial infarction and a mother who died in her eighties from cancer. She only took zolpidem 10mg at night as needed for sleep and reported no allergies to medications.

On physical exam she was afebrile at 97.8 F, heart rate 87 beats per minute, respiration rate 18 breaths per minute, blood pressure 117/79, and had an oxygen saturation of 98% on room air. Her pupils were equal round and reactive to light with normal extraocular movements. The left parotid gland was enlarged. The neck was supple without lymphadenopathy and a jugular venous distension of about 10 cm was noted. Her heart had a regular rate and rhythm with a II/IV systolic murmur heard best at the left sternal border with no radiation and no third heart sound. Auscultation of the lungs revealed fine crackles at bilateral bases without any wheezing. Her abdominal exam was unremarkable and she had 2+ pulses in the lower extremities bilaterally without any edema. The left upper extremity had full range of motion without any pinpoint tenderness or effusion.

Laboratory data included hemoglobin of 11.4 g/dL, WBC count of 8,300/mm3, platelets of 451,000/ mm3, BNP of 365 pg/mL, and a chemistry panel that was within normal limits. Her first set of T roponin I was 0.23 ng/mL, with the trend of 0.22, 0.20, 0.15 (Reference range <0.05 to 0.5). The EKG showed normal sinus rhythm at 85 bmp, with Q waves in leads II, III, and inverted T-wave in lead III. Chest x-ray showed bibasilar atelectasis with prominent right paratracheal stripe likely due to vascular congestion without any interstitial edema. Due to the nature of the patient’s pain, she had a chest CT performed while in the Emergency Department which showed no pulmonary embolus but was notable for a 3 cm left ventricular aneurysm of the posterolateral wall at the base of the heart along with a small amount of adjacent pericardial fluid and thickening (Figure 1).

The patient was admitted to the medicine service for further work up of her pain and to rule out myocardial infarction. Even though her cardiac enzymes were not in a negative range, she ruled out for myocardial infarction with three sets of enzymes within the normal reference range. The night following admission the patient developed rapid atrial fibrillation. Given her baseline hypotension, her rate was controlled with amiodarone, and she was fully anticoagulated with enoxaparin.

The following morning a persantine stress test demonstrated a large inferolateral perfusion defect with partial reversibility at the basal segments indicative of persantine-induced ischemia. The left ventricular ejection fraction was measured as 56%. She also had a transthoracic echocardiogram performed, which was notable for a region of the mid posterior wall with very marked thinning and aneurysmal dilatation. Her left ventricle internal dimensions and wall thickness was normal with overall moderate LV systolic dysfunction with inferior, posterior, and basal-mid lateral akinesis, mild mitral and tricuspid regurgitation and borderline pulmonary hypertension.

Given the findings of the above diagnostic studies, the patient was scheduled to have coronary catheterization the following morning. However, that night the patient was found unresponsive and asystole noted on the cardiac monitor. Despite resuscitative efforts during the PEA code, she never regained a pulse or a blood pressure and died that evening.

Autopsy revealed 500 cc of hemopericardium (Figure 2a and 2b), atherosclerotic cardiovascular disease with thrombotic occlusion of circumflex artery, 50% occlusion of LAD and RCA, and posterior wall recent myocardial infarction with aneurysmal dilatation.

Figure 1. CT chest showing 3cm left ventricular aneurysm of the posterolateral wall at the base of the heart.
Discussion
There are 3 major mechanical complications of acute myocardial infarction:
- Rupture of the LV free wall;
- Rupture of the interventricular septum;
- Development of mitral regurgitation.
This discussion will focus mostly on the rupture of LV free wall.

Incidence
Myocardial free wall rupture is the third most common cause of death after myocardial infarction and is 10 times more common than rupture of ventricular septum or papillary muscles. It is a relatively common finding in patients who died of acute myocardial infarction, with some large studies showing cardiac rupture in 14-26% of these patients. However, of all patients with acute myocardial infarction, the incidence of cardiac rupture is only 1-3%. If thrombolytics are used, death from rupture occurs earlier among these patients and often within 24 hours of drug administration. However, the use of thrombolytics does not increase the incidence of myocardial rupture.

Risk factors for myocardial rupture include the use of thrombolytics, lack of prior history of angina or myocardial infarction, ST-segment elevation or Q wave development on the initial ECG, peak CK-MB above 150 IU/L, anterior location of the infarction, age greater than 70, and female sex. These associations suggest that the absence of collateral blood flow, as suggested by the lack of previous ischemic symptoms, and the size of the infarct are important determinants of the likelihood of myocardial rupture.

Pathology
Myocardial rupture occurs within the first 5 days after acute myocardial infarction in about 50% of cases and within 2 weeks in more than 90% of cases. It more frequently involves the left ventricle compared to the right ventricle and rarely involves the atria. The infarct commonly affects the anterior and lateral walls of the left ventricle and the rupture typically occurs near the junction of the infarcted and normal myocardium.

Morphologic types of free wall rupture
1 - normal wall thickness with through and through rupture
2 - expansion of soft necrotic zone with wall rupture
3 - numerous small perforations in the area of myomalacia (multicanicular rupture)
4 - normal wall thickness with rupture of the outer layer of infarcted area
5 - large epicardial hematoma under pressure
6 - hemorrhagic infarction with grossly intact but abraded and leaking epicardial surface (bleeding infarct)

Evolution of rupture
Within the first week after the myocardial infarction, neutrophils populate the infarcted area between the necrotic myocytes and produce a zone of coagulative necrosis which is very soft and predisposed to rupture. A myocardial rupture usually occurs at the interface between necrotic and spared myocardium. Once rupture occurs, the pericardium rapidly fills with blood (hemopericardium) and as a result the right ventricle cannot fill and cardiac output rapidly declines.

Pathology of healing
As mentioned above, the initial phase of acute myocardial infarction is characterized by neutrophil infiltration and myocyte necrosis. The healing phase (after the first week), however, is typified by mononuclear cell and fibroblast infiltration and the absence of polymorphonuclear cells. Resorption of necrotic myocytes often precedes scar formation with accumulation of fibrillar collagen into an increasingly organized network. The complete healing process takes 5-6 weeks and results in a stable
scar absent of cellular infiltration. The thinned infarct region is stable and not very vulnerable to mechanical disruption.

**New insights into pathology of free wall rupture**

There is a suggestion that defective cardiac remodeling may predispose the heart for rupture. The matrix metalloproteinase (MMP) has been shown to play an important role in cardiac extracellular matrix (ECM) remodeling and cardiac rupture. Over-expression and activities of MMPs induced by TNF (from inflammatory response) at the site of myocardial infarction may increase the degradation of existing collagen in the early stage of infarction, thus contributing to cardiac rupture.

**Effects of reperfusion**

It has been shown that rupture is less common in patients with a patent infarct-related coronary artery. Rupture typically occurs in an area that has been infarcted without successful reperfusion. A number of studies has shown that thrombolytic therapy early after myocardial infarction improves survival and decreases risk of myocardial rupture. Late administration of thrombolytics (6-24hr after onset of symptoms) does not increase the risk of cardiac rupture, but appears to accelerate the time of onset of rupture events (within 24 hrs of treatment).

**Clinical presentation**

Myocardial rupture may present as sudden death in an undetected or silent myocardial infarction. Complete rupture of LV free wall leads to hemopericardium, cardiac tamponade, and subsequent death. Presence of rupture is first suggested by sudden acute right heart failure and shock, which then progresses rapidly to Pulseless-Electrical-Activity (PEA) codes. During the resuscitative efforts, emergent pericardiocentesis will confirm the diagnosis and transiently relieve the tamponade.

Incomplete rupture occurs when organized thrombus and the pericardium seal the ventricular perforation. This may progress to frank rupture with tamponade and death, formation of a false aneurysm walled off by pericardial tissue and communicating with the left ventricle through the perforation, or formation of left ventricular diverticulum. Incomplete rupture may present as recurrent chest pain, nausea, restlessness, abrupt and transient hypotension. It can also cause ECG features mimicking regional pericarditis.

**Management**

The survival of patients with free wall myocardial rupture largely depends on rapid recognition and administration of immediate therapy. Bedside echocardiogram and echocardiogram-guided pericardiocentesis should be obtained if the diagnosis of rupture is suspected. If the pericardial fluid includes blood, the patient should immediately proceed to surgery. Fluids, inotropic agents, pressors, and intra-aortic balloon pumps can be used for hemodynamic stabilization while the patient is being transported to the operating room.

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A 63-year-old male is admitted to the CCU for chest pain, shortness of breath, and an elevated troponin.

The patient is a 63-year-old male with a past medical history significant for hypertension and hypercholesterolemia who presented to the emergency room with a chief complaint of shortness of breath and chest pain. The chest pain began two days prior and was associated with nausea. The patient proceeded to have increasing shortness of breath over the subsequent two days which brought him to the emergency room for evaluation.

In the emergency room, the patient was noted to be in atrial fibrillation with rapid ventricular response and hypotension. He was cardioverted into sinus rhythm. The ECG showed sinus rhythm, RBBB and inferior myocardial infarction age indeterminable. The cardiac enzymes drawn in the emergency room showed a troponin of 30 ng/mL. The patient was transferred to the Coronary Care Unit. An echocardiogram performed in the Coronary Care Unit demonstrated a ventriculoseptal defect. The patient was emergently taken to the catheterization lab.

The right heart catheterization demonstrated a mean right atrial pressure of 18 mmHg, right ventricular pressure of 42/18 mmHg, pulmonary pressure of 40/24 mmHg, and a pulmonary capillary wedge pressure of 23 mmHg. The right atrial oxygen saturation was 31% and the right ventricular oxygen saturation was 81%.

The left ventriculogram demonstrated severe anterolateral hypokinesis and apical hypokinesis. There was evidence of dye extravasation just superior to the anterolateral segment with late filling of the pulmonary artery suggesting a left to right shunt. Coronary arteriography demonstrated a 100% proximal occlusion of the left anterior descending artery after the first diagonal. The left circumflex artery had diffuse disease in the marginal system. The remaining vessels were angiographically normal.

The patient was taken emergently to the operating room. Intraoperative transesophageal echocardiogram revealed a large ventricular septal defect in the apical portion of the septum located primarily anteriorly. The patient underwent coronary artery bypass grafting of the left internal mammary to the left anterior descending artery and the left radial artery to the first diagonal artery. The patient also received a bovine pericardial patch repair of the anterior apical VSD.

The remainder of his hospital stay was unremarkable and he was discharged, however soon after discharge the patient began to develop progressively worsening shortness of breath requiring readmission to the hospital.

Echocardiogram showed a large color flow turbulence moving across the septum consistent with a VSD. This was confirmed by cardiac MRI which showed a VSD between the left ventricle and

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**RUPTURE RECURRENCE AFTER SURGICAL REPAIR OF A POSTINFARCTION VENTRICULAR SEPTAL RUPTURE IN THE REPERFUSION ERA**

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right ventricular outflow tract with a Qp:Qs ratio of 1:2.5. This appeared secondary to a torn patch.

The patient underwent a repeat cardiac catheterization. The left anterior descending artery was 100% occluded (Figure 1). The Right coronary artery demonstrated eccentric lesions (Figure 2). The LIMA to LAD graft was patent (Figure 3). The Radial graft was 100% occluded proximally (Figure 4). The left ventriculogram demonstrated dye extravasation into the right ventricle consistent with a VSD (Figure 5) and akinesis of the anterolateral and septal segments.

The patient was taken to the operating room where inspection of the ventricular cavity revealed a 2 cm diameter hole in the anterior left ventricle extending into the right ventricular outflow tract. This area was closed using the patient’s own ventricular muscle with a sandwich technique employing felt.

The patient tolerated the operation and was discharged from the hospital after 2 weeks. Currently, the patient is doing well with no complaints of chest discomfort, shortness of breath, orthopnea.

**Discussion**

Ventricular septal rupture (VSR) is a potentially fatal mechanical complication of an acute myocardial infarction. Prior to the use of reperfusion therapy, ventricular septal ruptures complicated three percent of acute myocardial infarctions.1 With reperfusion therapy, this has decreased to 0.2%.2 Early surgical treatment remains the treatment of choice. The operation on weak and fragile myocardium may lead to postoperative recurrence of the ventricular septal rupture. We present the case of a 63-year-old male who developed a ventricular septal rupture after an acute anterior myocardial infarction treated with percutaneous coronary intervention. This VSR required surgical repair. His course was complicated by a recurrence of the VSR and redo-surgery.

Ventricular rupture complicating acute myocardial infarction leads to a high mortality. Reperfusion therapy demarcates a change in the incidence and demographics of septal rupture complicating acute myocardial infarctions. These differences have been demonstrated by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial.

Ventricular septal rupture is the result of a full thickness infarction of the interventricular septum. This is followed by necrosis that results in septal rupture. This necrosis can produce two types of pathologic ruptures, either a simple or complex rupture. The simple rupture represents a direct connection between the two ventricles. A complex rupture has a convoluted communication between the two ventricles. Complex morphology is more often associated with inferior wall myocardial infarctions, whereas simple morphology is seen after anterior wall myocardial infarctions.3
Right heart catheterization is the standard for diagnosing ventricular septal rupture. Sampling of the oxygen saturations demonstrate a step up between the right atrium and pulmonary artery. Transthoracic echocardiogram with color flow doppler can also be used to diagnose. Left ventriculography has also been used in diagnosing; however, the contrast load may be detrimental to the ventricular and renal function.

There exists a significant difference in outcomes and patient demographics in relation to the development of ventricular septal ruptures when comparing the pre and post-thrombolytic era. The GUSTO-I trial established the incidence of VSD after acute MI in patients treated with thrombolytic therapy and to identify the enrollment characteristics and angiographic patterns associated with its occurrence. Patients enrolled in the GUSTO-I trial presented to and emergency room within six hours of an STElevation myocardial infarction. Patients were randomized to streptokinase with either subcutaneous heparin, accelerated alteplase with intravenous heparin or the combination of alteplase and streptokinase with intravenous heparin. Patients who developed VSDs were identified by review of case reports.

Review of the GUSTO-I data demonstrated an incidence of 0.2% of patients who developed VSDs after acute myocardial infarctions. The median time from MI symptom onset was 1 day. This differs from the 3-5% and 3-5 days without thrombolysis. Risk factors for the development of VSDs in the post-thrombolytic era included: elderly, female and hypertensive, no history of smoking, anterior infarction, tachycardia and worse Killip classification on admission.

Patients who developed VSDs were found to have TIMI grade 0 or 1 flow, and 57% had total occlusion of the infarct artery. The left anterior descending artery was more often the infarct related artery. This is consistent with findings in patients not receiving reperfusion.

Despite the institution of thrombolytic therapy, the mortality from VSD remains high. From the GUSTO-I data there is no difference in mortality at 30 days as compared with 1 year. It can be surmised that if a patients survives the initial insult his prognosis is good.

Surgical treatment remains the standard of care for patients with VSDs. The mortality from medical management is 94%. Early surgical repair is technically demanding. Early surgery is associated with a 40% incidence of residual shunt. Two additional difficulties in the operation are identifying the margins of the infarct and suturing the patch. A pericardium sutured to the myocardium is used to decrease the amount of residual shunt. The pericardium also reduces the amount of stress on the sutures due to its compliance.

Despite the improved surgical methods, rupture reoccurrence remains a feared complication. Review of the literature demonstrates a reoccurrence of VSR between 5 and 25% of operated patients. Early thrombolysis is the main determinant of recurrence of the VSR. There is a higher incidence of VSR after thrombolysis. There are two possible reasons for this. The first may be that there is a viable appearance to the infarcted tissue after thrombolysis. This may cause an underestimation of the infarcted area and lead to a mismatch in reconstruction of the repair. The second may be the edema that is caused to the myocardium by reperfusion injury. Once the edema resolves there may be added stress on the sutures leading to rupture of the sutures.

Reperfusion therapy, in particular thrombolysis, has had an impact on the mechanical complication of acute myocardial infarction known as ventricular septal rupture. Thrombolysis has influenced the incidence, timing and patient demographics. Although the incidence has decreased the onset from symptoms of myocardial infarction is now 24 hours. The elderly, female and hypertensive are predisposed to this complication. Once treated surgically, there is a higher incidence of recurrence in those patients treated with thrombolysis. The effect of percutaneous coronary intervention on the outcome of ventricular septal rupture remains to be seen.

References:
A 53-YEAR-OLD WOMAN WITH WORSENING RASH AND DIARRHEA

Bryan Kavanaugh, MD

A 53-year-old white female was admitted to the Bone Marrow Transplant Unit with a worsening pruritic rash.

The patient had a history of IgG lambda multiple myeloma status post autologous stem cell transplant one year prior and more recently, matched sibling allogenic transplant. Since transplantation, she had a history of rash, which was diagnosed as graft-versus-host disease (GVHD) by skin biopsy. During that same hospitalization, she had a transjugular liver biopsy to rule out GVHD which was complicated by a large intrahepatic and subcapsular hematoma. A catheter to drain the hematoma was placed by interventional radiology, which was still in place. The patient was discharged following her allogenic transplant with successful engraftment of donor stem cells on bone marrow biopsy, without evidence of residual multiple myeloma. She was on GVHD therapy with tacrolimus, prednisone, and Cellcept. Recently, her rash had returned and was becoming increasingly pruritic over several weeks prior to admission.

The patient did not report headache, sore throat, chest or abdominal pain, dyspnea, diarrhea, or dysuria. She had no other significant past medical or surgical history. She reported occasional alcohol consumption and a remote, but limited smoking history. Her activities had been limited recently by her illness and she denied any travel. She had no knowledge of starting any new medication, lotions, detergents, or soaps in the recent past.

On this admission, the vital signs were normal and she appeared chronically ill. The head, neck, lungs, and heart were unremarkable. Her abdominal exam was significant for a mildly tender right upper quadrant without rebound or guarding. She had normoactive bowel sounds. She had a right upper quadrant drainage catheter with serosanguinous drainage. Her dermatologic exam was notable for a maculopapular rash on her back, abdomen and thighs noted, which was non-blanching. There were no vesicles or bullae.

Upon admission, skin biopsy revealed interface dermatitis consistent with GVHD and the patient was placed on intravenous steroids. In addition, patient had an Adenovirus PCR of 4,600 copies. On hospital day 7, the patient developed acute diarrhea. Stool sample was positive for white blood cells; stool culture and C. difficile were negative. She had a right upper quadrant drainage catheter with serosanguinous drainage. Her dermatologic exam was notable for a maculopapular rash on her back, abdomen and thighs noted, which was non-blanching. There were no vesicles or bullae.

Initially on steroids, her GVHD dermatitis resolved and she was treated with Cidofovir and IVIG for her adenovirus infection. Her diarrhea and adenovirus PCR titer both responded appropriately to treatment.

Discussion

Adenovirus is a common infectant causing mild and self-limited infections in immunocompetent individuals. In an immunocompromised population, such as bone marrow transplant recipients, it can have severe consequences. Patients who have undergone allogenic stem cell transplant are at highest risk for adenovirus disease. Other risk factors are age (children more often than adults), T-cell depleted grafts, presence of GVHD, and the use of mismatched and unrelated donors. It can manifest as pneumonia, hepatitis, hemorrhagic cystitis, interstitial nephritis, gastroenteritis/colitis, and encephalitis. In one-half of the patients with invasive adenoviral disease, the outcome is death. Adenovirus can be acquired via a primary infection (person to person), or via reactivation of latent infection/donor organ infection. Adenovirus colitis is not well studied, as most studies rely on detection of virus in stool in symptomatic patients without tissue confirmation. Often adenoviral infections of the bowel coexist with GVHD.

Adenovirus can be diagnosed by a number of means. Viral culture it the most sensitive and specific. Cultures from stool or urine may be positive for months after an acute infection in an immunocompromised patient. Viral antigens detected by enzyme-linked immunosorbent assay (ELISA) are not as sensitive as culture, but can give rapid diagnosis. PCR can be used to detect adenovirus in body fluids and tissues and is highly sensitive and specific. Histopathology can also be used to identify the characteristic intranuclear inclusions seen in adenovirus infection. These can be similar to CMV; however, adenovirus does not cause intracytoplasmic inclusions or multinucleated cells like CMV. Immunohistochemical stains can be used to identify to identify HSV, CMV, or adenovirus. Electron microscopy can identify the characteristicicosahedral virus seen in adenoviral infections present in the nuclei of infected cells.

Since this infection is associated with significant mortality in the post-transplant population, it is often treated. Antiviral agents are the mainstay of treatment, although limited evidence is available for efficacy. Ganciclovir, ribavirin, and vidarabine have shown some activity in vitro, and there are a number of case reports associating Ribavirin with a successful outcome. Cidofovir, a nucleotide analog effective against a number of viruses, has been shown to be active against adenovirus. No prospective, controlled studies have been performed to date. Intravenous Immunoglobulin (IVIG) theoretically contains neutralizing antibodies against adenovirus; it has been used in conjunction with antiviral therapy in a number of reports. Another strategy used is reduction in immune suppression as this allows clearance of virus in some patients.

References


Figure 1. Area of ulceration in sigmoid colon.

Figure 2. Punctate erythema of sigmoid colon.
The patient is a 40 year old African-American female with no significant past medical history who presented to the ED with a 2 week history of lower extremity edema and shortness of breath. She also noticed intermittent palpitations, dry cough, easy fatigue and a 30 pound weight loss. On examination, the patient’s temperature was 98.9F orally, pulse was 155-170 beats per minute, and blood pressure was 133/93 mmHg. EKG revealed long P-R tachycardia with heart rate of 170. Chest X-ray was done and showed large right pleural effusion with compressive atelectasis and small left pleural effusion. Transthoracic echocardiogram at the time of admission was consistent with severe global LV dysfunction with EF<20% and moderate pulmonary hypertension. CT Chest, which showed bilateral hilar adenopathy and subsequent biopsy was consistent with non-caseating granulomatous lesion. Her initial basic laboratory values, including TSH level, were normal except for BNP which was 569. She underwent left and right heart catheterization, which revealed normal coronary arteries and decreased cardiac index. During the hospital stay, telemetry monitors revealed rhythms consistent with various degrees of AV conduction abnormalities. She was started on steroids and intravenous milrinone for possible sarcoid cardiomyopathy and listed for heart transplant. Her symptoms were gradually improved and she was discharged home with steroids, beta blockers, diuretics, ace inhibitors and an implantable defibrillator. She is currently followed as an outpatient and doing extremely well without any cardiac symptoms.

Myocardial sarcoidosis may have restrictive as well as congestive features because cardiac infiltration by sarcoid granulomas results not only in increased stiffness of the ventricular wall but also in diminished systolic contractile function. Occasionally patients with extensive involvement of the left ventricular myocardium develop left ventricular aneurysms; it has been suggested that corticosteroid treatment may convert granulomas to scar tissue and contribute to the development of aneurysmal dilatation. First-degree heart block due to disease of AV Node or bundle of His, and various types of intraventricular conduction defects, are common among patients with cardiac sarcoidosis. Complete heart block is the most common finding in patients with clinically evident cardiac sarcoidosis, and occurs at a younger age in patients with sarcoidosis than in individuals with complete heart block due to other etiologies. Corticosteroids can be used to halt progression of disease, but it has little to no benefit once EF is <30%. Heart transplantation for sarcoidosis with advanced heart failure has been performed less commonly than lung transplantation. Survival has been similar to that of patients undergoing heart transplantation for other indications. Despite the possibility of recurrence of sarcoidosis in the graft or the appearance of progressive extracardiac disease, available evidence supports transplantation for cardiac sarcoidosis in patients with extensive cardiac involvement and advanced heart failure as long as there is minimal extracardiac involvement.

Credits: H&E stains prepared by Bernadette Wildermore MD
Figure 2. Higher power magnification reveals lack of necrotic material within the granuloma. Also seen is peri-granulomatous connective tissue (arrow) consistent with fibrosis which can sometimes be a marker of long-standing sarcoid.

**IMAGE IN MEDICINE**

*Amy Baranoski, MD*

Pictured here is the back of a man with leprosy who had been treated at Acworth Leprosy Hospital in Mumbai, India. Note the diffuse, macular, hypopigmented rash. Leprosy is a chronic disease caused by infection with Mycobacterium leprae. The disease can affect a variety of organs including peripheral nerves, skin, muscle, eye, bone, and testes. Leprosy is diagnosed clinically by the presence of at least one of the following: hypopigmented patches, loss of cutaneous sensation, thickened nerves, and acid-fast bacilli in nasal or skin smears.

The prevalence of leprosy has decreased worldwide due to multi-drug therapy and public health programs focused on education and detection of the illness. Multi-drug therapy consists of the bactericidal drugs: rifampin, dapsone, clofazimine, ethionamide and protionamide. Quinolones, minocycline, and clarithromycin are not part of the normal regimen, but can be combined with rifampin, primarily in single lesion leprosy.

In November 2005 Dr. Baranoski spent several weeks observing various clinics and hospitals in Mumbai, India where she captured the following image.
44 year old Hispanic male with no significant past medical history, recently discharged from prison, presented to the hospital with rash all over the body with itching. The rash started on the face, at the back of the ear and then spread to the trunk and legs. He denied fever, chills, cough, shortness of breath or sick contacts. Physical examination revealed a young, comfortable looking male with stable vital signs except for a temperature of 102 F. Skin examination was significant for maculo-papular rash (Figures 1 and 2) with vesicles and pustules, some of which were crusted, found diffusely over face, chest, abdomen, and extremities yet sparing the palms and soles. Oral cavity also showed mucosal lesions. The laboratory values included WBC count of 7,700/mm3 with 78% segmented neutrophils, Hgb of 15.4 g/dL, ESR of 13, creatinine of 0.8 mg/dL, albumin of 3.3 g/dL, aspartate transaminase of 73 IU/L, alanine transaminase of 70 IU/L, and lactate dehydrogenase of 924 IU/L. Arterial blood gas on room air showed a PaO2 of 70. Chest x-ray (Figure 3) showed diffuse bilateral alveolar infiltrates. Chest CT (Figure 4) was significant for wide spread interstitial pneumonia. Serology was positive for varicella zoster IgM antibodies. The patient was treated with intravenous acyclovir 800 mg every 8 hours for 7 days with excellent clinical improvement and without any adverse sequelae.

References
2. Emerson L Gasparetto Varicella pneumonia on immunocompetent adults: report of two cases, with emphasis on high resolution computed tomography findings
A 41-year-old Caucasian female with a history of hypertension presented with exertional chest pain. Her vital signs were stable on admission and physical examination was unremarkable. An Electrocardiogram (EKG) revealed inferior ST segment elevations consistent with acute myocardial infarction and cardiac enzymes were elevated. She was started on heparin, and underwent immediate cardiac catheterization. Cardiac catheterization revealed an occluded distal right posterior descending artery (RPDA), suggestive of intracoronary thrombus (Figure 1). However close inspection of the RPDA revealed subtle evidence of a dissection. Ventriculography showed preserved left ventricular function and mild hypokinesis of the distal inferior segment. The RPDA was non-intervenable and she was medically managed.

The hypercoagulable work up was negative. The patient remained stable for the next two days and was discharged home. Six days later, she returned to the emergency room with recurrent chest pain and at that time the EKG showed ST segment elevations in both the inferior and lateral leads. She was started on intravenous nitroglycerin and heparin and was taken to the cardiac catheterization lab. Angiography showed spontaneous dissection in the left circumflex artery (Figure 2) and another dissection in the posterior descending branch of right coronary artery (Figure 3). Both the circumflex and RPDA vessels were deemed too small for percutaneous intervention. There was no recent history of trauma, cocaine use, estrogen use or pregnancy. The patient was discharged home with medical management.
A 76 year-old African-American female with a history of hypertension, type II Diabetes Mellitus, hyperlipidemia, and gastroesophageal reflux presented to emergency room complaining of epigastric pain radiating to left substernum which started the night before presentation. The onset of her sharp pain was at rest, lasted for two hours, and was aggravated by eating and drinking. Her chest pain was followed by gagging and regurgitating of liquid contents. Her chest pain was non-exertional, and not associated with shortness of breath, diaphoresis, nausea, or vomiting. In the Emergency Department, her pain subsided with two sublingual nitroglycerins and 2 milligrams of intravenous morphine. On further questioning the patient stated that the pain had been intermittent for two months. She had seen her outpatient doctor one week prior to admission, who recommended ranitidine and an outpatient stress test.

Past cardiac history was significant for a Persantine stress test two years prior that showed normal myocardial perfusion. An echocardiogram done 3 months prior showed asymmetric septal hypertrophy, impaired relaxation of left ventricle, and a low-normal left ventricular systolic function with ejection fraction of 55-60%.

Physical exam on admission revealed an afebrile, elderly woman with stable vital signs who showed no signs of discomfort. She had normal heart sounds with no murmurs and no reproducible chest pain. Her lung, abdomen and extremity examinations were likewise unremarkable. At the time of admission, her blood work was remarkable for hemoglobin of 12 g/dL, creatinine of 1.3 mg/dL, amylase of 97 U/L, lipase of 20 U/L, myoglobin of 143 ng/mL, and troponin I of 0.50 ng/mL (reference range 0.05 - 0.50). A chest x-ray performed in Emergency Department showed no acute disease. The admission EKG is shown below (Figure 1).

The patient was taken to cardiac catheterization on the next day and was found to have a 99% occlusion of left main stem, 99% occlusion of LAD with active thrombus, and 50% occlusion of RCA. Patient was emergently taken for CABG, where she underwent grafting of the LAD, obtuse marginal, and PDA.

Discussion

In retrospect, the patient’s history was consistent with unstable angina, although she did manifest atypical symptomatology. Because of her past medical history including GERD and diabetic neuropathy, such comorbidities may have masked true cardiac chest pain. Unfortunately, our patient went on to develop anterior myocardial infarction.

The clinical history and EKG findings are consistent with Wellens syndrome (WS). The syndrome is also referred to as LAD coronary T-wave syndrome. Syndrome criteria include T-wave changes plus a history of anginal chest pain without serum marker abnormalities: no pathological Q waves, no ST segment elevation, and no loss of precordial (V1-V6) R waves. EKG abnormalities of WS appear in one of two ways. The more common variant presents with symmetric and deeply inverted T waves in the precordial leads, usually V2 and V3 (Figure 2). The less common variant presents with biphasic T waves in the precordial leads, again, usually in V2 and V3 (Figure 1). This case highlights the
fact that EKG abnormalities are present in patients even when they do not have the typical chest pain. Moreover, the EKG findings tend to disappear during bouts of angina with normalization of ST segment or T wave abnormalities.

WS was originally described in 1982 by Wellens in his paper with de Zwann and Bar. In this landmark study, 75% of all patients with WS EKG pattern went on to develop extensive anterior myocardial infarctions within a few days of hospitalization despite management of pain with medical management. In a follow up retrospective study where urgent PCI was performed on all 180 patients meeting WS criteria, 100% were found to have at least a 50% obstruction in their LAD artery.

It is essential that clinicians recognize that patients admitted to the hospital because of unstable angina who show the characteristic EKG findings described have a high likelihood of having a critical proximal LAD lesion. Such patients are at high risk for the development of an extensive anterior wall MI as was the case for the patient described. In this subgroup of patients, urgent coronary angiography and, when possible, coronary revascularization should be undertaken. Furthermore, exercise stress tests are contraindicated due to presence of extensive lesions and several case reports of death following treadmill stress testing.

**References**


A 19 YEAR OLD GIRL WITH LIGHTHEADEDNESS AND PALPITATIONS
Andrew Rose, MD

A 19 year old patient with a past medical history significant only for recurrent syncope presented to the emergency department after 90 minutes of palpitations, chest tightness, lightheadedness and shortness of breath. Electrocardiogram on admission is shown in Figure 1.

The patient was immediately treated with infusions of procainamide and amiodarone and the tachycardia broke to reveal a sinus rhythm. An electrocardiogram from several hours later is shown in Figure 2.

The patient underwent electrophysiologic study and a trans-septal ablation of a left lateral accessory pathway. The post-procedure electrocardiogram is shown in Figure 3. Interestingly, the delta waves on her initial electrocardiogram (Figure 2) are no longer present, an indication of the success of the procedure. She tolerated the procedure well and was discharged the following day.

In 1930, Louis Wolff, Sir John Parkinson, and Paul Dudley White published a review of 11 patients who suffered from bouts of tachycardia similar to this patient. To this day, their names are still well associated with the condition.

References

Figure 1. Wide complex tachycardia with a ventricular rate of approximately 250.
Figure 2. The rhythm is regular and initiated by the sinus node. There are slightly shortened PR intervals and the QRS has a slurred upstroke in leads V3-V5 (arrows).

Figure 3. Post ablation EKG. Note the disappearance of the delta waves present in Figure 2.
RISK OF ISCHEMIC STROKE ASSOCIATED WITH LOW-DOSE ORAL CONTRACEPTIVE USE: A META-ANALYSIS

Dae Hyun Kim, MD, MPH, Joachim Bleys, MD, MPH, Marlis Gonzalez-Fernandez, MD, Rebecca Gottesman, MD, and Michelle Hudspeth, MD

Abstract

Context: Oral contraceptive (OC) use has been shown to be associated with increased risk of ischemic stroke. However, most studies were conducted before low-dose OC became available.

Objective: To determine whether low-dose OC use is associated with increased risk of ischemic stroke

Data Sources: All relevant human-subject and English-language studies in MEDLINE, EMBASE, and Science Citation Index from January 1970 through February 2005

Study Selection and Data Extraction: All published studies of OC or estrogen with any type of stroke as an outcome were included. Studies were excluded if they included populations at high risk for ischemic stroke or did not include low-dose OC use, ischemic stroke, or a control group.

Data Synthesis: A meta-analysis of the nine included studies showed positive association between current low-dose OC use and ischemic stroke (Overall pooled odds ratio [OR], 2.1; 95% confidence interval [CI], 1.7 - 2.7). Compared to never users, current users had slightly higher risk (OR, 1.2; 95% CI, 0.4 - 3.2) and former users had significantly lower risk (OR, 0.6; 95% CI, 0.5 - 0.7). Current users of second and third generation OC had 2.4 times (95% CI, 2.0 - 3.0) and 2.0 times (95% CI, 1.3 - 3.0) increased risk of ischemic stroke, respectively, compared to former or never users. The independent effect of low-dose OC use on the risk of ischemic stroke was stronger among women less than 35 years, nonsmokers, and normotensive women.

Conclusion: Current use of low-dose OC compared to former or never use is associated with about two times increased risk of ischemic stroke. However, considering its health benefits and effectiveness of birth control and very low incidence of ischemic stroke in young women, use of low-dose OC is generally safe.

Methods

Study Selection

We conducted a literature search using MEDLINE, EMBASE, and Science Citation Index (January 1970 through February 2005). The following key words and subject terms were used: (intracerebral hemorrhage OR venous sinus thrombosis OR cerebral infarct OR cerebral ischemia OR cerebrovascular accident OR cerebrovascular disease OR stroke) AND (oral contraceptive OR birth control pill OR estrogen). The search was restricted to English and humans. The original search yielded 1183 citations from MEDLINE, 730 from Science Citation Index, and 132 from EMBASE (excluding duplicates from MEDLINE), for a total of 2045 citations.
A preliminary title review was done by five investigators and 377 potentially eligible articles were selected for abstract review. Each abstract was reviewed independently by two investigators, with the following exclusion criteria:

1. hormone replacement therapy,
2. inclusion of postmenopausal women without stratification,
3. subarachnoid or subdural hemorrhage as the only primary outcome,
4. estrogen dose exclusively more than 50 mg (first generation OCs) or dose not specified or progesterone-only contraceptives,
5. stroke not as a primary outcome,
6. women with coagulation disorders,
7. case series without controls, and
8. recurrent stroke.

With these exclusion criteria, we excluded 277 articles. Considering the time when high-dose OCs were withdrawn from the market and low-dose OCs became widely available, we further restricted our analysis to the articles published since 1985, which left 55 articles for full-text review. The 55 articles identified during the literature search were reviewed by an investigator (who initially had not reviewed the abstract of the article in question) who reassessed the article and discussed the reasons for inclusion or exclusion with the rest of the investigators. From the 55 articles, we excluded 6 studies because of the inclusion of postmenopausal women without stratification, 4 because of fatal stroke or hemorrhagic stroke as the only outcome, 5 because of duplicate publications using the same data, and 10 because of the lack of comparison group (case series only). Ten articles were excluded, because they were published as abstracts only, review articles, letters to editor, or editorials and did not contain enough information for the analysis. We also exclude 11 studies that were conducted before 1990 and did not specify estrogen dose. Finally, data from nine remaining studies were abstracted for our analysis (See Figure 1). There were no randomized controlled trials or cohort studies that satisfied our criteria.

**Data Abstraction**

Data were abstracted by the reviewers of each study and verified by the rest of the investigators. Any disagreements were resolved through full discussion. Information on study quality as well as data was collected. Years of study conducted, study region, type of control (hospital or population control), age distribution of participants, and numbers of case and control were abstracted. Outpatient control was considered as hospital control. Definition of current OC users varied among studies and we followed the definition used by individual studies. Non-current users were defined as both former and never users. Estrogen dose was defined as low-dose, either when an OC contained less than 50 mg of estrogen or when it belonged to second or third generation. The generation of OCs was determined by estrogen dose and types of progesterone. Although the definition of generation was not consistent among studies, estrogen dose in each generation was consistent among studies (50 mg or more for first generation, 30-40 mg for second generation, and 20-30 mg for third generation) and we followed the classification used by each study. Estrogen dose or generation of OCs was abstracted from each study when it was mentioned in the article. When it was not mentioned, it was estimated from the prevailing use pattern in the study area during the study period. Generally, the estrogen dose was assumed to be less than 50 mg if a study was conducted after 1990. When a study was conducted before 1990 and did not specify the estrogen dose or generation of OCs, it was excluded from our analysis. Information on exposure to OCs (current, past, or never use) was obtained. Information on definition of stroke and diagnostic methods, such as use of clinical or radiographic diagnosis or both, was gathered. We excluded hemorrhagic stroke, such as subarachnoid, intracranial, and intraparenchymal hemorrhage. Refusal rate was calculated separately for cases and controls as the percentage of eligible individuals who declined to participate in a study.

**Figure 1. Retrieval of Eligible Studies**
Risk estimates used in our meta-analysis were determined a priori. For the primary analysis, the odds ratio (OR) comparing current with non-current users after adjusting for potential confounders was chosen and pooled. Standard errors were calculated from adjusted odds ratios and their 95% confidence intervals (CIs). Information about potential confounders that were adjusted for in individual studies was also collected. When a study did not provide the adjusted odds ratio or its 95% CI comparing current with non-current users, we excluded the study from the analysis.

In subgroup analyses, we dichotomized age as 35 years or more vs. less than 35 years, smoking as current vs. non-current smokers, and hypertension as present vs. absent. Then we collected the data relevant to ischemic stroke from each stratified analysis.

Statistical Analysis

We combined the odds ratios (ORs) comparing current with non-current users from each study using both fixed-effects model and DerSimonian and Laird random-effects model. However, results from the random-effects model are presented in this report because significant heterogeneity was identified among studies. In the four studies that provided adjusted ORs for each generation of OCs, we combined the adjusted ORs for second and third generations using the random effects model. In a study that had stratification by presence or absence of migraine, overall adjusted OR was calculated in a similar fashion. A forest plot was created using adjusted ORs and 95% CIs from each study. One study that did not provide the adjusted OR of ischemic stroke comparing current with non-current users was not included when calculating overall OR, but included in other analyses. Heterogeneity among studies was calculated using chi-square test and studies were defined as heterogeneous when p-value was less than 0.05.

Preplanned subgroup analyses were performed according to exposure classification (current vs. never users and former vs. never users), progesterone type (second generation, third generation, and second vs. third generation), and presence or absence of other risk factors for ischemic stroke (≥ 35 years old vs. < 35 years old, smokers vs. non-smokers, and hypertensives vs. normotensives). To evaluate which study characteristics contributed to the heterogeneity, we examined the influence of study characteristics on overall OR by applying different inclusion criteria. In addition, the influence of each study was evaluated by eliminating each study at a time and calculating the resultant overall OR after the study was excluded. To examine the presence of publication bias, Egger’s test and Begg’s test were performed and a funnel plot was plotted. All statistical analyses were performed using STATA 8.2.

Table 1. Characteristics of Nine Eligible Case-Control Studies for Data Abstraction

<table>
<thead>
<tr>
<th>Source (Year)</th>
<th>Region</th>
<th>Years of Study</th>
<th>Control Type</th>
<th>Age (Years)</th>
<th>Case/Control#</th>
<th>Estrogen Dose (g)</th>
<th>Exposure Assessment</th>
<th>Stroke Type</th>
<th>Stroke Diagnosis</th>
<th>Case/Control Refusal Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidegaard et al. [1993]</td>
<td>Denmark</td>
<td>1985-1989</td>
<td>P</td>
<td>15 - 44</td>
<td>320 / 1197</td>
<td>≥50, 30-40, 20</td>
<td>Questionnaire</td>
<td>Ischemic</td>
<td>Clinical</td>
<td>2.2% / 0.1%</td>
</tr>
<tr>
<td>Lidegaard et al. [2002]</td>
<td>Denmark</td>
<td>1994-1998</td>
<td>P</td>
<td>15 - 44</td>
<td>609 / 3946</td>
<td>≥50, 30-40, 20</td>
<td>Questionnaire</td>
<td>Ischemic</td>
<td>Clinical</td>
<td>2.2% / 0.5%</td>
</tr>
</tbody>
</table>

Abbreviations: WHO, World Health Organization; P, population controls; H, hospital controls; NS, not specified; HTN, hypertension; DM, diabetes mellitus; BMI, body mass index; RHD, rheumatic heart disease; FH, family history; OC, oral contraceptive; UK GPRD, UK General Practice Research Database

* Nested case-control study using the UK General Practice Research Database
Results

Qualitative Analysis

The characteristics of nine case-control studies that satisfied our criteria were summarized (Table 1). Among the selected studies, six,6,8,14,15 were conducted in Europe, one in the US, one in Mexico, and one in Europe and developing countries in Asia, Africa, and Latin America. Three studies7,14 involved participants from more than one country. All the studies were conducted since 1985 and published since 1993. Five studies,6,8,14,15 used population control, three,6,14 used hospital control, and one used both. Age distribution of study subjects ranged from 11 to 49 years old. The number of cases varied from 130 in the study by Barinagarrementeria et al16 to 697 in the study by World Health Organization (WHO) collaborative.7 There was only one study7 in which estrogen dose in OCs was exclusively less than 50 μg. Six studies,6,8,14,15,16 reported both estrogen dose less than 50 μg and greater than 50 μg. Two studies,6,14 did not state estrogen dose explicitly. As for the study outcome, seven studies,6,8,14,15,16 reported ischemic stroke and two studies,6,14 reported both ischemic and hemorrhagic stroke.

Several methodological issues were examined. In most studies, exposure to OCs was measured by mailing questionnaires6,8 or personal interviews.7,9,14 One study,6 did not report how they obtained the information on OC exposure and one study8 used General Practice Research Database which is an automated national database collected for research purpose and contains medical and prescribing records for more than 8.5 million people throughout the UK. With regard to outcome ascertainment, four studies,6,8,15,16 used a combination of clinical and radiological diagnosis, whereas five studies,6,8,14,15 used only clinical diagnosis.

Cases and controls were matched for age in eight studies.6,7,14,16 Age was adjusted in three studies6,8 and socioeconomic status was adjusted in two studies.6,14 Smoking was adjusted in eight studies,6,7,14,15 and hypertension was adjusted in seven studies.6,7,8,14,15 Four studies,8,15 adjusted for diabetes. The study by Lidegaard et al6 controlled for hypertension and diabetes in their initial model, but excluded them from the final model because of lack of confounding influence by the variables. The study by Barinagarrementeria et al15 did not provide any information on potential confounders that they adjusted for (Figure 2).

All of the studies except for one study4 reported adjusted OR comparing current with non-current users. Adjusted OR comparing current with never users was provided in two studies14 and adjusted OR comparing ever vs. never users was provided in one study.7 There were three studies7,9 reporting OR by smoking, two studies6 reporting OR by age, four studies5,8 reporting OR by the generation of OCs, three studies7,14 reporting OR by history of hypertension, and one study6 reporting OR by history of migraine.

The definition of exposure to OCs was inconsistent among studies. Current OC use was defined as the use of OCs within 1 month up to 1 year.

Quantitative Analysis

The overall pooled OR for ischemic stroke comparing current with non-current users calculated by the random-effects model was 2.14 (95% CI, 1.69 - 2.72) (Figure 2). Significant heterogeneity was observed among studies (P = 0.02).

In the subgroup analysis by exposure classification, there was weak evidence that current users were associated with increased risk of ischemic stroke compared to never users (OR, 1.18; 95% CI, 0.44 - 3.16) (See Table 2). In contrast, former users were associated with decreased risk compared to never users (OR, 0.58; 95% CI, 0.48 - 0.71). By progesterone type, second generation was associated with 2.41 times increased risk of ischemic stroke (OR, 2.41; 95% CI, 1.96 - 2.96) and third generation was associated with 1.98 times increased risk (OR, 1.98; 95% CI, 1.29 - 3.03). Third generation OCs seemed to be associated with less increase in risk compared to second generation, but there was little difference between the two formulations in direct comparison. Test of heterogeneity was not significant among studies pooled for current vs. never users and for third generation OCs.

Current use of low-dose OCs was associated with 1.2 times increase in risk of ischemic stroke among women of 35 years or older (OR, 1.20; 95% CI, 0.19 - 7.56) and 1.48 times increase among women less than 35 years (OR, 1.48; 95% CI, 0.77 - 2.83). Non-smokers who currently use OCs (OR, 2.60; 95% CI, 1.49 - 4.54) seemed to have higher risk of ischemic stroke than smokers (OR, 2.09; 95% CI, 1.68 - 2.59). Similarly, increase in risk of ischemic stroke related to OC use was greater among normotensive women (OR, 2.55; 95% CI, 1.50 - 4.32) than among hypertensive women (OR, 0.71; 95% CI, 0.22 - 2.31).

The findings from the analysis examining the influence of study characteristics on overall pooled OR were presented (Table 3). When we included four studies that used radiographic imaging for the diagnosis of stroke, the pooled OR changed from 2.14 to 2.45. The combined OR was 2.81 when the studies with hospital control were all excluded, whereas it was 1.89 when the studies with population control were all excluded. Significant heterogeneity was observed only when the studies that did not report estrogen dose were excluded.

Sensitivity Analysis

The influence of each study on overall OR was examined (Figure 3). The study published in 2002 by Lidegaard et al6 had moderate influence on overall OR. Overall OR after omitting the study by Lidegaard et al6 was 2.42 (95% CI, 1.98 - 2.94). Omission of other studies made little difference.

Publication Bias

The possibility of publication bias was evaluated by using the Egger’s test (weighted regression) and Begg’s test (rank correlation method). P-value for bias in the Egger’s test was 0.62 and p-value in Begg’s test was 0.75. A funnel plot showed symmetry around the overall pooled OR, indicating the absence of publication bias (Figure 4).
### Table 2. Pooled Odds Ratios and 95% Confidence Intervals (CIs) of Ischemic Stroke from Stratified Meta-analyses*

<table>
<thead>
<tr>
<th>Data Stratifications</th>
<th>Number of Studies Pooled (References)†</th>
<th>Pooled Odds Ratio (95% CI)</th>
<th>Test for Heterogeneity, P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All studies</strong></td>
<td>9 [4, 5, 6, 7, 8, 9, 14, 15, 16]</td>
<td>2.14 (1.69 - 2.72)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Exposure classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current vs. Never users</td>
<td>2 [4, 9]</td>
<td>1.18 (0.44 - 3.16)</td>
<td>0.06</td>
</tr>
<tr>
<td>Former vs. Never users</td>
<td>2 [4, 9]</td>
<td>0.58 (0.48 - 0.71)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Progestosterone type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd generation</td>
<td>5 [5, 6, 7, 8]</td>
<td>2.41 (1.96 - 2.96)</td>
<td>0.33</td>
</tr>
<tr>
<td>3rd generation</td>
<td>5 [5, 6, 7, 8]</td>
<td>1.98 (1.29 - 3.03)</td>
<td>0.07</td>
</tr>
<tr>
<td>3rd vs. 2nd generation</td>
<td>2 [7, 8]</td>
<td>1.12 (0.76 - 1.64)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Independent effect of oral contraceptive use among</strong>:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 35 years old</td>
<td>2 [8, 9]</td>
<td>1.20 (0.19 - 7.56)</td>
<td>0.06</td>
</tr>
<tr>
<td>&lt; 35 years old</td>
<td>2 [8, 9]</td>
<td>1.48 (0.77 - 2.83)</td>
<td>0.71</td>
</tr>
<tr>
<td>Smokers</td>
<td>3 [7, 8, 9]</td>
<td>2.09 (1.68 - 2.59)</td>
<td>0.33</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>3 [7, 8, 9]</td>
<td>2.60 (1.49 - 4.54)</td>
<td>0.14</td>
</tr>
<tr>
<td>HTN present</td>
<td>2 [7, 8]</td>
<td>0.71 (0.22 - 2.31)</td>
<td>0.06</td>
</tr>
<tr>
<td>HTN absent</td>
<td>3 [7, 8, 9]</td>
<td>2.55 (1.50 - 4.32)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**Abbreviation:** HTN, hypertension

* Pooled odds ratios are comparing current vs. non-current oral contraceptive users, except for those under exposure classification.
† The study by WHO collaborative5 was counted as two separate studies (Europe and developing countries).
Discussion

In our meta-analysis, all the nine studies showed positive association between current low-dose OC use and ischemic stroke and six of them had statistically significant association. The overall pooled OR of ischemic stroke among current low-dose OC users, compared with non-current users, was 2.14 (95% CI, 1.69 - 2.72) (Figure 2). Therefore, our meta-analysis suggests that low-dose OC use is a risk factor for ischemic stroke.

Among the nine included studies, the study published in 1993 by Lidegaard et al was not included when calculating overall OR, because the authors did not report the standard error or 95% CI associated with the adjusted OR of 3.46 comparing current with non-current users. The study by WHO collaborative had two distinct components - Europe and developing countries including Asia, Africa, and Latin America - showing different results and it was considered as two different studies. The studies by Barinagarrementeria and Nightingale were included despite the lack of information on estrogen dose, because the dose was estimated to be less than 50 μg considering the region and years of study. During the literature search, we found three cohort studies, but they did not meet our criteria. One cohort study by Stampfer et al was conducted from 1976 through 1984 and did not have information on estrogen dose. Considering the time period when it was conducted, we suspected that it had included a significant proportion of high-dose OC users. The other two cohort studies that were conducted from 1980 through 1982 by Porter et al and from 1968 through 1994 by Mant et al reported only proportion of low-dose OC users without stratified results. High-dose OC users consisted of 59% in the study by Porter et al and over 32% in the study by Mant et al. We were unable to extract the data related to low-dose OC use from the three cohort studies. They were not included in the analysis, because including significant proportion of high-dose OC users will overestimate the risk of ischemic stroke.

Significant heterogeneity was observed when we combined all the studies to obtain the overall pooled OR (P = 0.02). It is because all the included studies are case-control studies of varying qualities and characteristics. They are particularly susceptible to confounding and bias, compared to cohort studies and randomized controlled trials. Each study recruited participants at variable risk by applying different inclusion and exclusion criteria and used different methods for assessing exposure and ascertaining outcome. Thus, we used the DerSimonian and Laird random-effects model to encompass non-random variation between study results and allow more conservative CI for the overall OR. Residual confounding always exists in a meta-analysis of observational studies. Some studies did not measure or control for important risk factors for ischemic stroke, such as age, smoking, hypertension, and diabetes (Figure 2). In addition, there are several potential sources for bias in case-control studies. Information on past exposure to OCs relies on participants’ recall and the extent of recall between cases and controls tends to be different, leading to biased results. The studies by Lidegaard et al and Kemmeren et al mailed questionnaires to participants, whereas the studies by Petitti et al, WHO collaborative, Heinemann et al, and Chang et al used personal interviews based on standardized questionnaires. The accuracy of information collected by these methods varies among studies and is a source of information bias. Only Nightingale et al used a reliable database that has medical and prescribing records collected for research purpose. Classification of exposure to OCs was also inconsistently between studies. Differential refusal to participate in the study between cases and controls may indicate the presence of selection bias.

We performed subgroup analyses to examine how the association between low-dose OC use and risk of ischemic stroke changes according to exposure classification, progesterone types, and women with different risk factors for ischemic stroke (Table 2). Compared to never users, current users seemed to have slightly higher risk (OR, 1.18; 95% CI, 0.44 - 3.16) and former users had significantly lower risk (OR, 0.58; 95% CI, 0.48 - 0.71). Decreased risk in former users was consistent between studies. Possible explanation is that never users may have multiple risk factors and are at higher risk for ischemic stroke than users. Women who stopped taking OCs may be more health-conscious and have a reduced risk due to healthier lifestyle. Past use does not seem to have a long term “hangover” effect. Different progesterone formulation in OCs was also associated with different risk of ischemic stroke. This may be due to the effect of different progesterone components, different risk profiles between users of second generation and users of third generation, or preference of prescribing physicians between studies in different countries. Thus, it is possible to underestimate or overestimate the risk of ischemic stroke associated with third generation OC use. The independent effect of low-dose OC use on the risk of ischemic stroke was stronger among women less than 35 years compared to women of 35 years or older, nonsmokers compared to smokers, and normotensive women compared to hypertensive women. These results are not consistent with recent meta-analyses by Gillum et al and Chan et al and some studies that suggested greater risk among OC users with additional risk factors for ischemic stroke. Because only small number of the selected studies reported stratified information on risk factors, the pooled estimates from our subgroup analyses are less precise, which may explain the inconsistency with previous reports.

To find out which study characteristics contributed to the heterogeneity, we examined the influence of certain study characteristics on the pooled OR (Table 3). When we only included the studies that used combination of clinical and radiological diagnosis, the overall OR was 2.45 (95% CI, 1.99 - 3.06) and test of heterogeneity was insignificant. Exclusion of two studies...
that did not report estrogen dose made very little change in the overall OR and heterogeneity. Studies with population control had much lower pooled OR than studies with hospital control, meaning that control subjects from hospital underreported or less frequently used OCs for some reasons. We also evaluated the influence of each study on the overall OR by eliminating each study at a time (Figure 3). Although the study by Lidegaard et al appeared to have moderate influence, there was not one particular study that has significant influence on the overall OR. 

A meta-analysis by Gillum et al on this topic reported in subgroup analyses that low-dose OC use is associated with about two times increased risk of ischemic stroke (Relative risk, 2.04; 95% CI, 1.51 - 2.76). Another recently published meta-analysis by Chan et al also reported 2.7 times increase in risk for thrombotic stroke associated with low-dose OC use (OR, 2.74; 95% CI, 2.24 - 3.35). However, Chan et al included the studies that did not have information on estrogen dose and their primary outcome was not confined to ischemic stroke. Our finding of 2.1 times increase (OR, 2.14; 95% CI, 1.69 - 2.72) is consistent with their findings.

This meta-analysis has several limitations. As mentioned above, a meta-analysis of observational studies has methodological limitations and susceptibility to bias and confounding, leading to imprecise estimate of true association. We limited our analysis to the studies in which the exposure and outcome were clearly stated as low-dose OC and ischemic stroke, respectively. Therefore, only nine studies were included. This small number substantially limited our subgroup analyses and yielded less precise 95% CIs. Due to the small number, we could not conduct a meta-regression to assess risk of ischemic stroke related to low-dose OC use controlling for several study-level covariates. In addition, we could not investigate the dose-response relationship between low-dose OC use and ischemic stroke, because most of studies did not report the duration of OC use. As a result, potential biases and confounders were not adequately addressed and reasons for heterogeneity between studies were not sufficiently examined.

Presently, more than 10 million women in the United States and more than 76 million worldwide use OCs. Our meta-analysis found that current use of low-dose OC increases the risk of ischemic stroke approximately by two times. However, when we consider its health benefits and effectiveness of birth control and very low baseline incidence of ischemic stroke in young women of less than 10 per 100,000, low-dose OC use in premenopausal women is generally acceptable and safe. Future research is warranted to identify high-risk groups for ischemic stroke associated with low-dose OC use and to investigate the dose-response relationship between the exposure and outcome.
Table 3. Influence of Study Characteristics on Overall Odds Ratios and 95% Confidence Intervals (CIs) of Ischemic Stroke*

<table>
<thead>
<tr>
<th>Data Stratifications</th>
<th>Number of Studies Pooled (References)†</th>
<th>Pooled Odds Ratio (95% CI)</th>
<th>Test for Heterogeneity P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>9 [5, 6, 7, 8, 14, 15, 16]</td>
<td>2.14 (1.69 - 2.72)</td>
<td>0.02</td>
</tr>
<tr>
<td>Studies that used radiologic imaging for diagnosis of stroke</td>
<td>4 [7, 8, 15, 16]</td>
<td>2.45 (1.99 - 3.06)</td>
<td>0.78</td>
</tr>
<tr>
<td>Studies that reported estrogen dose</td>
<td>7 [5, 6, 7, 8, 9, 14]</td>
<td>2.10 (1.59 - 2.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>Studies that used hospital control</td>
<td>5 [5, 7, 14, 16]</td>
<td>2.81 (1.83 - 4.30)</td>
<td>0.22</td>
</tr>
<tr>
<td>Studies that used population control</td>
<td>5 [6, 7, 8, 9, 15]</td>
<td>1.89 (1.52 - 2.35)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* Pooled odds ratios are comparing current vs. non-current oral contraceptive users, except for those under exposure classification.
† The study by WHO collaborative5 was counted as two separate studies (Europe and developing countries).

References
The Spectrum of Advanced Liver Disease in a Tertiary Care Institution

Kuntal M. Thaker, MD, Kuldip S. Banwait, MD, Maya Spodik, MD, Steven K. Herrine, MD and Victor Navarro, MD

Purpose
In population based studies, the rise of HCV infection has surpassed alcoholic liver disease (ALD) as the most common cause of chronic liver disease. However, it is unknown if HCV is becoming the dominant cause of advanced liver disease. The aim of this study was to determine the distribution of etiologies in a cohort of patients presenting with advanced liver disease.

Methods
A retrospective review of patients presenting with advanced liver disease defined as the presence of endoscopically identified esophageal or gastric varices for the period between January 1999 and December 2002. Etiologies of hepatic injury were identified from the clinical record and laboratory database. Patients were excluded if their disease could be attributed to more than one cause (i.e. alcohol and HCV) or had a non-hepatic cause of portal hypertension. Patients were grouped according to etiology: 1) HCV, 2) ALD, 3) hepatitis B (HBV), or 4) other (cryptogenic cirrhosis, non-alcoholic fatty liver disease, autoimmune hepatitis, portal vein thrombosis).

Results
A total of 411 patients were identified as having either esophageal and/or gastric varices. The mean age was 56.1 years (range 19-89). There were 275 males (66.9%) and 136 females (33.1%). The proportions of females in those with HCV and ALD were similar although women were predominant in non-viral, non-alcohol related disease group compared to other diagnoses (59.4% vs. 24.3%, p<0.0001). Etiology of liver disease differed in those older than 65 years of age compared to younger patients for all diagnostic categories (p<0.0001) with ALD being more prevalent than HCV in older patients (p=0.0120). Race was evenly distributed amongst groups. Hepatitis C represented the single most common etiology (42.1%) followed by alcohol (29.9%), other predominantly non-viral, non-alcohol diagnoses (20.0%), and hepatitis B (8.0%).

Conclusion
Etiology of liver disease drastically differs in those older than 65 years of age compared to younger patients. Higher prevalence of ALD rather than HCV in elderly population alludes to different risk behavior pattern between the two groups (i.e., intravenous drug use more common in younger patients). For patients younger than 65 years of age, HCV is the major cause of cirrhosis and burden of complications of cirrhosis attributable to HCV infection should be expected to rise as this population ages.
Stanley Hsu, MD is currently a Third Year Internal Medicine Resident with a hobby in sketches and paintings. “Fruit Mystique” is Dr. Hsu’s first publication debut.