The Medicine Forum
To the Friends of the Department of Medicine:

“The only thing that is constant is change.”

What a year we have had! From new time slots for morning report, patient surges in the hospital, moving the fellowship match to December and the addition of Dim Sum Fridays, things are in a constant state of flux. The hallmark of a Jefferson resident is the ability to evolve and adapt to the circumstances while continuing to think of further changes to benefit our patients, colleagues and ourselves. I cannot contain the pride I have in our residents and what they can achieve. With more changes on the way with the Next Accreditation System from the ACGME, launching the Milestones evaluations and potential changes in health care delivery as Obamacare gets fully implemented, it is more important than ever to have a spirit of innovation! It helps that we are led by the Fantastic Four—Christopher Henry, Tasha Kouvalatsos, Sanjay Linganna and Michael Tobin. Our chiefs are tireless advocates for education and are creative problem solvers and have achieved many things in their short tenure! I am so grateful for their efforts and have had an amazing time working with them!

You will also notice some changes to the Forum this year. In addition to the research abstracts, case reports, artwork and photography, you will notice some new additions—medical app review and patient safety projects are among the selected pieces included. The Editors, in the spirit of change and evolution, have identified these areas as being useful, informative and necessary to the way we will practice medicine now and in the future. Congratulations to the Editors and all the contributors for another amazing edition! And thank you to all our contributors—without you, the Forum would not exist!

Enjoy this edition of the Jefferson Forum!

Gretchen Diemer, MD, FACP
Assistant Professor of Medicine
Program Director Internal Medicine Residency
We are proud to publish the 14th issue of the Jefferson Medicine Forum. The editorial staff would like to acknowledge the support of Dr. Diemer in producing this year’s forum. We appreciate your guidance and support in bringing this issue to print.

Over the years, the Medicine Forum has provided a unique opportunity for our housestaff and medical students to not only share scholarly activities, but also to pursue their interests outside of the medical field. This year, we are proud to announce the addition of medical application reviews as well as an opinion piece on the use of opiates in primary care – a controversial topic that often leads to heated debates. We have also been fortunate enough to include interesting travel experiences, unique case reports, and exciting review articles, along with some breathtaking photography and original cartoon.

We would like to thank our internal medicine residents and colleagues, for without their endless enthusiasm and passion for medical knowledge, we could not have produced this wonderful issue. We hope you enjoy this year’s forum with all of its new glitz and glamor.

Regards,

Rina Shah, MD and Mitul Kanzaria, MD
Executive Editors
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“The Red Coat”
photograph by Ryan C. Cleary
Cerebrovascular Accident Caused by Embolic Atrial Myxoma
Eugene Han, MD, Andrew Garrett, MD

Background
Atrial myxomas, the most common type of cardiac tumors, can cause life-threatening complications. As most cardiac myxomas are surgically curable, early diagnosis is crucial. Cardiac tumors can present with cardiac and embolic manifestations, and should be considered in the differential diagnosis of patients presenting with such symptoms. In this case report, we describe a young, healthy patient who presented with stroke symptoms secondary to embolic atrial myxoma.

Case Presentation
A 45-year-old male with no past medical history presented with an acute onset of dysarthria, described as garbled speech. He also experienced weakness and heaviness of his right hand, which impaired his ability to brush his teeth and write. He denied left-handed or lower extremity weakness, head trauma, facial droop, dysphagia, migraines, diplopia/visual changes, confusion, or memory loss. He denied tobacco, alcohol, or drug use. Review of systems was otherwise negative, although the patient reported that whenever he participated in strenuous physical activity over the past few years, he would become nauseated.

Investigations
The patient initially presented to an outside hospital after his symptoms persisted for over 24 hours. Computed tomography (CT) of the head was negative for intracranial bleed and he was discharged. While his dysarthria improved, he continued to have weakness and went to another hospital for evaluation. Brain magnetic resonance imaging (MRI) at the second hospital showed two acute left basal ganglia infarcts. As part of the stroke workup, he had an echocardiogram, which revealed a 5 cm left atrial myxoma. He was transferred to Thomas Jefferson University Hospital (TJUH) for further management.

On presentation to the TJUH Cardiac Critical Care Unit (CCU), the patient’s vital signs were as follows: temperature 98.2°F, blood pressure 142/80 mm Hg, pulse 100 beats per minute, respiratory rate 19 breaths per minute. Cardiac examination was notable for a soft diastolic rumble heard best in the left upper parasternal area. Neurological examination revealed minor dysarthria. The remainder of the physical examination was normal. Complete blood count and basic metabolic panel were within normal limits, and electrocardiogram showed sinus rhythm. C-reactive protein (CRP) was elevated to 7.9 mg/dL. Chest radiograph was unremarkable. CT head showed left basal ganglia and corona radiata hypodensities consistent with recent infarction. CT thorax revealed a hypoattenuating 3.7 x 2.4 cm lesion in the left atrium. Transesophageal echocardiogram (TEE) confirmed a large (5 x 3.2 cm), irregular, gelatinous mass, with frond-like, mobile edges attached to the fossa ovalis, and broad 1 cm stalk. This mass prolapsed into the mitral valve orifice during diastole, likely representing a left atrial myxoma.

Treatment
Four days after presentation to TJUH, the patient underwent robotic-assisted excision of the myxoma. There were no intraoperative complications, and post-procedure TEE revealed resolution of the left atrial myxoma without mitral valvular insufficiency. The patient required pressors and inotropic support for 2 days post-operatively for persistent hypotension. He was discharged home in stable condition on post-operative day #3.

Discussion
Myxomas, the most common type of benign primary cardiac tumor, account for approximately one-third of benign tumors of the heart. They occur across all age groups, more commonly in women and during the third through sixth decades. 90% of cases are sporadic, while the remainder are transmitted in an autosomal dominant fashion. This inheritance typically occurs as part of the Carney syndrome complex that includes myxomas, lentigines/pigmented nevi, and endocrine overactivity. The NAME (nevi, atrial myxoma, myxoid neurofibroma, and ephelides) and LAMB (lentigines, atrial myxoma, and
Most myxomas arise in the left atrium from the interatrial septum near the fossa ovalis.1,4,14 They are gelatinous structures comprised of myxoma cells in a glycosaminoglycan-rich stroma, often pedunculated on a fibrovascular stalk.1,4,15 They arise from multipotent mesenchymal cells that persist from embryonic cardiac septation and have been found to produce vascular endothelial growth factor (VEGF), which is implicated in the early stages of tumor growth.14,16

Depending on location, myxomas can cause the signs and symptoms of corresponding valvular disease; atrial myxomas can mimic atrophicventricular (AV) valve stenosis due to valve obstruction, while ventricular myxomas can cause outflow obstruction similar to subaortic or subpulmonic stenosis.5,13 Diastolic murmurs result from obstruction of the filling ventricle, while systolic murmurs arise when valve closure or outflow is interrupted.1 The characteristic “diastolic tumor plop,” a low-pitched sound during early to mid-diastole, is thought to represent the physical impact of the tumor hitting the AV valve or ventricular wall.1 Repetitive trauma to the valve may also cause damage and regurgitation due to a “wrecking ball” phenomenon.17 Congestive heart failure (CHF) may result from outflow of cardiac flow and/or impaired contractility from direct invasion of the myocardium (myocardial damage may also cause arrhythmias, heart block, pericardial effusion or tamponade).2,18,19 Symptoms may provide a clue to the tumor’s location: left-sided tumors may present with dyspnea on exertion, orthopnea or flash pulmonary edema; right-sided tumors may present with syncope, sudden death or right heart failure.1,18-21 Of note, these symptoms can be sudden and/or positional due to the effect of gravity on the tumor’s position.1,12,18,19 Fragments of myxomas may embolize and cause signs of peripheral or pulmonary emboli, as well as fever, weight loss, malaise, arthralgias, rash, digital clubbing, and Raynaud’s phenomenon.1,2,20-28 Laboratory abnormalities associated with myxomas include anemia, leukocytosis, thrombocytopenia, elevated erythrocyte sedimentation rate (ESR) and CRP.1,2,22 Rarely, myxomas may become infected; the incidence of cerebral and systemic emboli from infected myxomas is greater than that from non-infected myxomas.25 Management of these patients is often complicated by bacteremia, septic shock, disseminated intravascular coagulation (DIC), multi-organ failure, and cerebral infarction.30

Echocardiography is useful in diagnosing myxomas; tumor size, shape, and attachment can be assessed, all of which assist in surgical planning for excision.1,3,13,16 TEE offers superior imaging compared to transthoracic echocardiography (TTE) owing to the proximity of the esophagus to the heart and use of high frequency transducers.31 Cardiac CT and MRI offer noninvasive imaging options that can also help evaluate the characteristics of myxomas.1,12 In the past, cardiac catheterization and angiography were routinely performed prior to excision; their role has diminished in favor of noninvasive imaging due to the additional risk of tumor embolization during catheterization.1,12

Definitive treatment for a myxoma is surgical excision; medical therapy is only indicated for management of concomitant CHF and/or arrhythmias.1,3,14 Septal defects and/or valvular damage that occur during surgery may require repair.33,34 A potential complication of excision is fragmentation and embolization of part of the tumor.23,34 While thrombolytic therapy is reasonable for stroke secondary to blood clot emboli from cardiac myxomas, it has little effect on emboli composed of actual tumor.24 Overall post-surgical prognosis is excellent, with a 3% rate of operative mortality.1,13,33,34 Recurrence is rare in sporadic cases (1-2%) and usually due to inadequate resection; familial myxomas recur in 12-22% of cases and are likely due to multifocal lesions.1,2,19,27 Follow-up includes routine semi-annual echocardiography. Screening of first-degree relatives is appropriate due to the possibility of familial inheritance.1

Key Points

Although an uncommon cause of stroke, cardiac myxoma should be considered in the differential diagnosis. Definitive treatment is surgical resection, which offers excellent cure rates with rare recurrence and low mortality. Medical management is supportive. Once a cardiac myxoma has been identified, arrangements for surgical resection should be made immediately.

References

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“Cows at 13,000 ft, Peru” photograph by Andrew Zabolotsky
NEWLY DIAGNOSED AIDS WITH MULTIPLE OPPORTUNISTIC INFECTIONS DESPITE A RECENT NEGATIVE RAPID HIV TEST
Soham Vakil, MD, Rene Daniel, MD, PhD, William Short, MD, MPH

Background
Human Immunodeficiency Virus (HIV) is a fairly prevalent disease in the United States, with an estimated 1 million persons infected with HIV-1. Despite a decrease in Acquired Immunodeficiency Syndrome (AIDS), the prevalence of HIV is increasing, which has led to recent changes in HIV testing guidelines. Newly diagnosed patients should ideally be linked to care and receive intervention and antiretroviral therapy (ART) allowing them to maintain a near normal life expectancy.

Case Presentation
The patient is a 23-year-old African American male with no significant past medical history. He presented to the emergency department (ED) with fevers, weakness, worsening right-sided chest pain, and shortness of breath associated with a productive cough. When he presented with similar symptoms two weeks ago, he was treated for pneumonia with azithromycin. Symptoms initially improved but then worsened five days prior to returning to the ED. He had odynophagia for the last three weeks causing him to avoid solid foods. Additionally, he reported loss of vision in his right eye for two months which started as blurriness but progressed to only appreciating light versus dark. Left eye vision was intact.

He took no chronic medications and denied drug allergies. Surgical and family history was non-contributory. He rarely drank alcohol and denied tobacco or drug use. He is homosexual and became sexually active at the age of fourteen with inconsistent condom use. He reported a negative rapid HIV test at a local clinic one month ago and his last sexual contact was three months prior to presentation.

Investigations
On physical exam, the patient’s vitals were temperature of 97.6°F, heart rate 101 bpm, blood pressure 133/76 mmHg, respiratory rate 18 bpm, pulse oximetry 98% on room air. Head and neck exam revealed oral thrush and a nonreactive right pupil. Confrontation of visual fields revealed lack of vision in all four quadrants of the right eye. Eyes were anicteric and without conjunctival injection. Cardiovascular exam revealed mild tachycardia but was otherwise normal. Lungs were clear to auscultation. Abdomen exam was unremarkable. He had no lymphadenopathy and the rest of his physical exam was normal.

Lab work was significant for a hemoglobin of 11.6 g/dL, mean corpuscular volume of 78 fl, RDW 15.5%, and lactate dehydrogenase of 581 IU/L. Comprehensive metabolic panel was within normal limits. Chest X-ray revealed patchy bilateral perihilar interstitial infiltrates, more progressed compared to two weeks prior. A rapid HIV test in the ED was positive. CT of the chest showed bilateral patchy, confluent areas of ground glass opacity with perihilar predominance involving all lobes relatively sparing the bases.

Differential Diagnoses
Given his newly diagnosed HIV infection, differential diagnosis included community acquired pneumonia (CAP), Pneumocystis jirovecii pneumonia (PCP), opportunistic viral pneumonia, fungal pneumonia, Mycobacterium infection. His odynophagia was thought to be secondary to esophagitis, likely from Candida albicans, Cytomegalovirus (CMV), or Herpes Simplex Virus (HSV). Possible causes of vision loss included CMV retinitis, toxoplasma retinochoroiditis, and Varicella Zoster Virus Retinitis.

Treatment
Infectious Disease (ID) was consulted, and he was started on empiric moxifloxacin to cover for CAP, including atypical pathogens. He was also started on IV pentamidine for possible PCP. Pentamidine was used secondary to a hospital shortage of IV trimethoprim-sulfamethoxazole (TMP-SMX). Additionally, he was received IV ganciclovir to empirically treat CMV retinitis and possible CMV or HSV esophagitis. He was started on fluconazole to treatthrush and possible candida esophagitis.

His rapid HIV antigen/antibody combination test was positive and confirmed by Western Blot. His CD4 count was 41 cells/mcL, establishing a diagnosis of AIDS. The genotype revealed wild type HIV-1 with a viral load of 3.68 million copies/mL.

Upon admission, Ophthalmology performed a dilated eye exam, which revealed total retinal necrosis of the right eye. There was necrosis and fibrosis of the macula, peripheral retinal necrosis, as well as “frosted branch” retinitis and hemorrhage with “brush fire” appearance. These exam findings combined with a CD4 count less than 50 cells/mcL were consistent with CMV retinitis, and visual prognosis was poor given diffuse necrosis that progressed for two months. Exam of the left eye revealed mild cotton wool spots which could represent either early CMV retinitis versus HIV retinopathy. For induction treatment, he was continued on IV ganciclovir (eventually changed to oral valganciclovir).

His respiratory symptoms slowly began to improve with antibiotics. Bronchoscopy revealed minimal non-purulent secretions. Cultures from bronchoalveolar lavage (BAL) were negative for acid fast bacilli, respiratory viruses (including...
influenza A, B), and bacteria. Fungal culture showed light growth of Candida albicans, and cytology with silver stain was positive for PCP. Treatment was narrowed to IV pentamidine until he was able to tolerate oral treatment doses of TMP-SMX.

He was maintained on fluconazole for thrush. For his esophagitis, endoscopy was deferred as he was already on fluconazole for Candida infection as well as IV ganciclovir for treatment CMV retinitis, which would also treat concomitant CMV or HSV esophagitis.

**Outcome And Follow-Up**

His symptoms began to improve significantly. After his esophagitis resolved, he was transitioned to oral medications to complete treatment of his multiple opportunistic infections. He was discharged from the hospital to finish treatment at home and follow up with his ID physician later that week to initiate ART.

**Discussion**

This case illustrates that despite improved testing techniques, it is still possible for patients to present with new diagnoses of HIV in late stages. Moreover, false negative screening tests are still possible, and patients can present with new HIV/AIDS via multiple simultaneous opportunistic infections. Additionally, it reinforces treatment of various opportunistic infections.

This patient presented with a CD4 count of 41 cells/mcL but had a negative HIV test one month prior. This represents either seronegative chronic HIV infection or chronic infection with a false negative enzyme immunoassay (EIA) and failure to detect the antibody. Alternatively, it may be an atypical instance of acute infection prior to seroconversion with the CD4 count falling dramatically low before recovering to the typical 600-700 cells/mcL. The latter scenario of an acute infection would place the primary HIV infection at roughly 6 weeks prior to admission, which is less likely since visual symptoms began at least 8 weeks prior to admission.

A final possibility is fulminant HIV. Given his long standing risk factors and several months of visual symptoms (which occur at advanced immunosuppression), he likely had chronic HIV that was not detected.

The CDC recommends use of rapid HIV tests so more patients obtain their results. Many outpatient facilities use the third generation EIA, capable of detecting HIV antibodies as early as three weeks after infection. All commercially used tests have excellent sensitivities (>99%) for detection of HIV antibodies, and many can detect them even before the traditional Western blot confirmation test can, yielding pseudo-positive results that require repeat testing. Although these screening tests have excellent performance, their sensitivities are not 100%. There are several reported incidences of false negative EIA tests secondary to immune dysfunction and impaired humoral response, delay to seroconversion following initiation of ART, as well as fulminant HIV infection.

This case demonstrates the need for better access to care and earlier intervention. Unfortunately, this young man’s retinal necrosis was so advanced that he will likely never recover vision in his right eye. Had his HIV been diagnosed earlier, his multiple infections and vision loss may have been prevented. Due to an increasing prevalence of HIV, the 2006 revised CDC guidelines for HIV testing recommend screening for patients in all settings in an opt-out fashion, at least annual testing for those at higher risk, and screening to become overall more routine and not require separate consent. A new US Preventative Services Task Force (USPSTF) draft recommends screening all adults age 15 to 65, with more frequent testing in high risk individuals.

PCP usually occurs in HIV patients with CD4 counts less than 200 cells/mcL. Patients typically develop fever, progressive cough, nonproductive cough, chest discomfort, and uncommonly blebs, cysts, and pneumothorax. Severe cases are characterized by hypoxemia. Imaging usually demonstrates diffuse, bilateral, interstitial infiltrates. Diagnosis requires induced sputum or BAL histopathologic confirmation. Treatment of choice is TMP-SMX orally or parenterally in severe cases and when patients cannot tolerate oral medications. In cases of drug intolerance, IV pentamidine is the preferred treatment. Patients with moderate-severe disease, PaO2 less than 70 mmHg or A-a gradient > 35 mmHg should receive corticosteroids. Treatment should last 21 days, then TMP-SMX should be decreased to prophylactic dosing. Additionally, ART should be initiated within two weeks if not already started.

CMV disease is usually in patients with HIV and CD4 counts less than 50 cells/mcL. CMV retinitis is a necrotizing retinitis that often begins unilaterally, but without treatment, viremic dissemination causes bilateral retinitis. Symptoms include scotoma, floaters, and visual field defects. Visual acuity decreases with central retinal lesions. Diagnosis is made by an ophthalmologist during a dilated eye exam with recognition of characteristic fluffy yellow-white retinal lesions and possible intra-retinal hemorrhage. Treatment for mild disease is typically oral ganciclovir. Moderate-severe disease is treated with intraocular implant of ganciclovir plus oral ganciclovir or IV ganciclovir alone. Induction phase is 14-21 days followed by maintenance with lower dose valganciclovir and regular ophthalmologic exams to detect relapse or immune recovery uveitis. Maintenance can be discontinued after six months of sustained quiescent retinitis and CD4 counts over 100 cells/mcL.

Esophagitis is characterized by odynophagia and retrosternal pain. In HIV patients, it is reasonable to empirically treat for candida, especially with the presence of oral thrush, and perform endoscopy if symptoms do not improve after 3-5 days. Treatment of choice for candida esophagitis is systemic treatment for 14-21 days with fluconazole. CMV esophagitis is diagnosed by endoscopy and biopsy and is treated with IV ganciclovir or oral valganciclovir if tolerated for 21 days or until symptoms resolve. HSV esophagitis is treated with IV acyclovir (orally if tolerated) for 14-21 days.
Key Points

In accordance with revised guidelines, HIV testing should be routine, particularly in patients who are high risk. Clinical judgment should increase index of suspicion for further HIV testing such as nucleic acid amplification, as there are rare cases of seronegative AIDS as well as false negatives despite excellent sensitivities.

References


“Flower Vase”
painting by Mahmoud Gaballa

“Pretty in Pink”
photograph by Rina R. Shah
AN INTERESTING CASE REPORT OF DIABETIC MYONECROSIS

Manjula Nagaraja, MD and Jim Zhang, MD

Case Presentation

A 49-year-old male with a history of ischemic cardiomyopathy, New York Heart Association class II heart failure with an ejection fraction of 35% status post biventricular implantable cardiac defibrillator (ICD), end stage renal disease on dialysis, diabetes mellitus II, and pancreatitis complicated by pseudocyst presented with a sudden onset of left thigh pain with a palpable mass. He denied trauma to the site, numbness, tingling, weakness, fevers, or chills. Review of systems was otherwise negative. Vital signs at presentation were as follows: temperature 98.8°F, pulse 77 beats per minute, blood pressure 150/88 mm Hg, respiratory rate 18 breaths per minute, and oxygen saturation of 96% on 2 liters of nasal cannula. He was notably uncomfortable on exam. The left thigh was edematous on the lateral side and there was tenderness over the distal, lateral portion of the anterolateral left thigh. No tenderness in the calf was noted. He had full range of motion at the hip, ankle, and knee. Straight leg test was negative and pinprick sensation was decreased.

Laboratory tests revealed leukocytosis with a white count of 23.1, slight anemia with a hemoglobin of 9.4. Chem 7 revealed BUN of 33 and creatinine of 4.1. Hemoglobin A1c was 8.0 and CPK was 82. Coags were normal but ESR was elevated at 98.

Radiographic studies included x-ray of the left femur, which revealed no fracture or dislocation. Chest x-ray on admission demonstrated a right dialysis catheter, low lung volumes with mild background pulmonary edema and cardiomegaly. Lower extremity ultrasound was negative for deep vein thrombosis. MRI of the left thigh was not obtained due to his ICD. CT scan of the left thigh showed heterogeneously decreased enhancement of the quadriceps particularly within the vastus lateralis; skin thickening with infiltration of the subcutaneous fat, possibly representing cellulitis in the appropriate clinical setting; diffuse atherosclerotic disease with moderate stenoses of the left femoral artery at the level of the adductor hiatus and the left popliteal artery (Figure 1).

Differential Diagnosis

The patient presented with a left thigh mass containing inflammatory and infectious features. The differential includes: superficial and deep vein thromboses, pyomyositis, myositis ossificans, traumatic muscle rupture, muscle hemorrhage, fasciitis, osteomyelitis, abscess, soft tissue neoplasm (primary lymphoma or sarcoma), granulomatous lesions involving TB or sarcoid, calciphylaxis. A rare but important diagnosis on the differential should include diabetic myonecrosis, which is what our patient had.

Figure 1. CT Scan of Left Thigh
Biopsy showed increased variation in the fiber diameter, increased interstitial fibrosis, and relative type II fiber atrophy. There was no evidence of a neurogenic process or malignancy.

Discussion

Skeletal muscle infarction is a rare and unusual complication of diabetes mellitus. Most patients have advanced end organ damage by the time of presentation. Typical clinical presentation of diabetic myonecrosis includes abrupt onset of pain and swelling in the affected muscle. Patients have subsequent partial resolution and appearance of a palpable painful mass. The quadriceps muscle group is most commonly affected; calf involvement is rare. Bilateral involvement has been reported in a few cases. The muscles most frequently affected are the vastus lateralis (24%) and vastus medialis (22%).

Most laboratory values are nonspecific. Elevated body temperature was not always reported. Creatinine kinase enzymes were often normal in reported cases. About one-third of the patients had leukocytosis; three quarters had ESR > 50. Of known cases, the majority (75%) had a hemoglobin A1C greater than 7%, suggesting poor glycemic control. An ultrasound should be performed to evaluate for deep vein thrombus and abscess collection. MRI is most sensitive and is the diagnostic modality of choice. In approximately 57% of cases, however, diabetic myonecrosis was confirmed by biopsy. Currently, because of complications of biopsy in diabetic patients, physicians tend to eschew invasive methods. Biopsy should be reserved for cases with an atypical presentation.
MRI can show an increased signal from the affected muscle area in T2 images that are hypointense areas on T1 images. Other features can include diffuse enlargement with foci of hemorrhage. Pathologic features most commonly showed muscle fiber necrosis and inflammatory infiltrates. Findings at later stages include replacement of necrotic muscle fibers by fibrous tissue. Microvascular abnormalities can include luminal narrowing and intramural calcifications or perhaps fibrinoid occlusion. The etiology of diabetic myonecrosis remains controversial. There are two proposed mechanisms, microvascular disease and hypercoagulability. Extensive arterial occlusive disease has been identified in many patients. The theory suggests diabetic microangiopathy and/or arteriosclerosis lead to ischemia of muscle, which results in an intense inflammatory response, edema and hyperemia. Some authors suggest that acquired hypercoagulability might be to blame. This latter theory is supported by detection of antiphospholipid antibodies in several cases.

Optimal treatment of diabetic myonecrosis is uncertain. Most patients received bed rest and analgesics. Therapeutic modalities that may be beneficial include antiplatelet agents and anti-inflammatory agents. Some authors recommend anticoagulation therapy. Short term prognosis is good as symptoms usually resolve within 8 to 12 weeks. Approximately 42-48% of cases re-occur usually on the same side. Contralateral recurrence is associated with a poorer prognosis. Most of the patients diagnosed with diabetic myonecrosis will eventually die from long-term complications of diabetes. The mean mortality rate was 10% within two years from diabetic myonecrosis onset.

References
Overview of Diuretic Strategies in Edematous States
Kedar Mahajan, MD

Introduction

Considering potential physiologic causes of volume overload in clinical practice, such as heart failure, renal failure, nephrotic syndrome, or portal hypertension, may yield insight into directing therapy beyond switching from oral to intravenous diuretic therapy. Appropriate oral therapies that achieve effective diuresis may reduce costs, address shortages of intravenous loop diuretics, reduce the need for unnecessary inpatient admissions by facilitating outpatient management, allow earlier optimization of outpatient regimens, and decrease the length of hospital stay.

Congestive Heart Failure

Decreased responsiveness to oral diuretics in either high or low output heart failure has been described. Goldman’s Cecil Medicine identifies factors such as gut edema, hypotension, reduced renal blood flow, and adaptive changes in the nephron. Bowel wall edema from elevated systemic venous pressures in heart failure may decrease bioavailability of diuretics while increased renal afterload from venous congestion and intrinsic renal compromise from interstitial pressures impairs diuresis. “Adaptive changes” are seen in long term loop diuretic use and include hypertrophy and hyperplasia of the distal convoluted tubule cells and increased Na+/Cl- - cotransporter activity which both contribute to increased sodium reabsorption. This adaption is partially addressed by blocking the reabsorption with thiazide/thiazide-like (e.g. hydrochlorothiazide or metolazone) diuretics and decreasing Na+/Cl- - cotransporter upregulation by inhibiting effects of aldosterone (e.g. spironolactone or eplerenone).

Optimal outpatient management of diuresis in heart failure is often difficult. Doubling the oral dose of diuretics (furosemide, torsemide, and metolazone) does not affect left ventricular systolic or diastolic function, has been shown to improve symptoms and 6-minute walk distance after a 24 day endpoint. Detrimental effects of high-dose diuretics in systolic dysfunction have been associated with increased mortality raising controversy, but confounding factors such as diuretic resistance or heart failure severity have made these links uncertain. The superior pharmacodynamic profile of torsemide (see Table 1) and its anti-aldosterone and vasorelaxation effect likely contributes to its better performance in improving left ventricular function, reduction of mortality, frequency/duration of heart-failure related hospitalization, quality of life, exercise tolerance and New York Heart Association functional class compared with furosemide. Synergy of loop-diuretics with potassium sparing or thiazide diuretics is efficacious in persistent edematous states. Additionally, inadequate tissue perfusion, signaled by increasing blood urea nitrogen or serum creatinine, can be addressed during diuresis in heart failure with inotropes or vasodilators.

Renal Disease

Patients with renal insufficiency benefit from loop diuretics since they retain their utility at a creatinine clearance (CrCl) < 5 mL/min while distal tubule diuretics lose their efficacy at a CrCl < 40 mL/min. However, thiazides and thiazide-like diuretics (e.g. metolazone), provide synergistic effects when administered thirty min prior to a loop diuretic to inhibit compensatory distal tubular reabsorption, which avoids having to increase loop dosages and limits long-term exposure to high-dose diuretics.

Higher doses of diuretics are required with a fall in the glomerular filtration rate, whether in chronic kidney disease (CKD), acute kidney injury, or hypoperfusion states. Drug secretion into the lumen of the nephron is diminished with retention of competing anions in renal failure and fewer functioning nephrons limit the maximal response of the drug. Moderate CKD can require 80 mg of intravenous furosemide (or bumetanide 2-3 mg, or torsemide 20-50 mg) while 200 mg may be required with severe CKD (or bumetanide 8-10 mg, or torsemide 50-100 mg).

Renal tubular secretion of furosemide is typically normal in nephrotic syndrome but since the diuretic is bound to urinary albumin, the lack of active drug blunts the diuretic response. If urinary albumin exceeds 4 g/L, 50-66% of the drug is bound to albumin and inactive. Appropriate measures include increasing doses, frequency, and using thiazides in conjunction with loop-diuretics. Avoidance of renal vasoconstriction mediated by non-steroidal anti-inflammatory drugs (NSAIDs) also improves diuretic responsiveness.

Portal Hypertension

Limited cardiac output in heart failure decreases loop diuretic secretion into the tubular lumen from decreased renal perfusion, while cirrhosis through renal vasoconstriction. The mainstay diuretic in managing moderate-volume ascites in cirrhosis is either spironolactone (50-200 mg/day) or amiloride (5-10 mg/day) with low doses of furosemide (20-40 mg/day) to supplement natriuresis if peripheral edema is present. The recommended daily weight loss in these patients without and with peripheral edema is up to 1 lb and 2 lbs respectively to prevent pre-renal failure. Patients with large-volume ascites and marked abdominal discomfort impairing activities of daily living can ideally undergo therapeutic paracentesis or attempt maximum doses of spironolactone (400 mg/day) and furosemide (160 mg/day). These patients typically present with urinary sodium...
<10 mM and normal free-water excretion and serum sodium. When free-water excretion is impaired, dilutional hyponatremia develops spontaneously or with increased fluid intake.

Patients with anasarca can have 2-3 L of fluid removed daily without reduction in plasma volume whereas patients with isolated ascites (no peripheral edema), can only have 300-500 mL/day of ascitic fluid mobilized daily without risking azotemia. The azotemia will improve after ceasing diuresis and fluid repletion whereas hepatorenal syndrome, often mistakenly linked to diuretic use, will continue to worsen. Similar to patients in acute or chronic heart failure, rapid diuresis in cirrhotic patients leads to decreased cardiac output. Diuretic-resistant ascites is defined by either inability to mobilize ascites despite sodium restriction (24-hour urine with <78 mEq sodium or a random urine sodium < urine potassium) and maximum oral diuretics (spironolactone 400 mg/day and furosemide 160 mg/day) or prohibitive diuretic-related complications (progressive azotemia, hepatic encephalopathy, or progressive electrolyte imbalance) in the absence of NSAIDs. Ceasing beta-blockers, angiotensin receptor blockers, or angiotensin converting enzyme inhibitors, can improve blood pressure, tissue perfusion, renal function, and diuretic responsiveness.

**Discussion**

Compounding renal insufficiency with reduced intestinal motility, perfusion, mucosal edema and tolerance to oral diuretics may also project a need for intravenous therapy; however, awareness of the pharmacokinetics and dynamics of diuretics will often provide solutions. All diuretics need to attain a minimal rate of tubular excretion before a response is attained. Minimal response at a given dose indicates the dose was effective in achieving the minimal rate but the effect was short-lived; a twice daily regimen can achieve the desired urine output. However, no response following a diuretic suggests doubling the dose (maximum furosemide dose 320-400 mg PO or 160-320 mg IV) for diuresis. Between the minimum drug excretion rate required for initiating diuresis and a plateau where further drug excretion does not produce additional output, lies the critical curve where drug excretion correlates to the extent of natureis.

Tolerance exists even with consecutive multiple intravenous doses of furosemide in healthy individuals where natureis/diuresis decreases with compensatory increased renin and decreased atrial natriuretic peptide. Outpatient diuretic tolerance can be compounded by renal compensatory mechanisms or an impaired natriuretic response to furosemide if on a low sodium diet. A few weeks of a diuretic dose will activate sodium retaining forces (e.g. renin-angiotensin II-aldosterone, norepinephrine, or reduction in system blood pressure) to achieve steady-state in sodium intake and excretion. However, poor adherence to sodium restriction on the other hand will prevent net fluid loss despite adequate diuresis; greater than 100 mEq sodium (2 g sodium = 88 mEq) in a 24-hour urine collection suggests non-compliance.

Approaches that use higher doses of the drug, increased frequency, or synergy with other diuretics are required to overcome sodium retention. Substantial responses in diuretic naïve patients are likely due to a lack of these adaptations. Acute decompensated patients on outpatient doses of furosemide doses ≥120 mg/day benefit from initial bolus doses inpatient while outpatient regimens with lower doses responded better to initial continuous dosing. Other loop diuretics such as bumetanide and torsemide boast of superior bioavailability (Table 1) and can be considered first-line agents over furosemide in certain cases. In heart failure patients, torsemide has been shown to decrease left-ventricular remodeling, rates of hospitalization, and mortality.

### Table 1. Pharmacodynamics and kinetics of common diuretics

<table>
<thead>
<tr>
<th></th>
<th>Onset (min)</th>
<th>Peak (hours)</th>
<th>Duration (hours)</th>
<th>½ (hours)</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide (PO)</td>
<td>30 – 60</td>
<td>1 – 2</td>
<td>6 – 8</td>
<td>0.5 – 2*</td>
<td>47 – 64</td>
</tr>
<tr>
<td>Furosemide (IV)</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide (PO)</td>
<td>10</td>
<td>1</td>
<td>4 – 6</td>
<td>1 – 1.5</td>
<td>59 – 89</td>
</tr>
<tr>
<td>Torsemide (PO)</td>
<td>60</td>
<td>1 – 2</td>
<td>6 – 8</td>
<td>3.5†</td>
<td>80</td>
</tr>
<tr>
<td>Ethacrynic acid (PO)</td>
<td>30</td>
<td>2</td>
<td>12</td>
<td>2 – 4</td>
<td></td>
</tr>
<tr>
<td>Metolazone (PO)</td>
<td>60</td>
<td></td>
<td>≥ 24</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Spironolactone (PO)</td>
<td>3 – 4</td>
<td></td>
<td>48-72</td>
<td>1.3‡</td>
<td></td>
</tr>
</tbody>
</table>

* End-stage renal disease: half-life (½) increases to 9 hours
† Cirrhosis: half-life (½) increases to 7-8 hours
‡ Active metabolites have the following half-lives (½); canrenone: 10-23 hours; 7-alpha-spirolactone: 7-20 hours

Loop diuretic equivalency: furosemide 40 mg PO = furosemide 20 mg IV = bumetanide 1 mg PO/IV = torsemide 20 mg PO/IV = ethacrynic acid 50 mg PO (sulfonamide alternative)

(Adapted from Lexi-Comp)
and mortality over furosemide. When compared to furosemide, bumetanide was more effective in reducing edema in patients with nephrotic syndrome and dyspnea in heart failure. Certain localized edematous states secondary to venous insufficiency, moderate-severe lymphedema, or malignant ascites require caution against depleting plasma volume when using diuretics.

Given the multifactorial causes of diuresis failure, exploring the nature of the edema state, utilizing a different diuretic agent or considering an additional agent, changing the route, frequency (Table 1), or the dose, can be attempted. The bioavailability of a diuretic will influence the dose required for a response while the plasma half-life will determine frequency of administration.

References


“Hold On, West Yellowstone, Montana” photograph by Andrew Zabolotsky
A BENIGN CAUSE OF WIDENED MEDIASTINUM: A CASE OF MEDIASTINAL LIPOMATOSIS
Natasha Fonseka, MD, Ewa Ruel, MD

Introduction

We report a patient with a widened mediastinum secondary to a rare and benign condition known as mediastinal lipomatosis (ML). ML is caused by accumulation of adipose tissue within the mediastinum. Case reports associate ML with obesity, diabetes, Cushing’s syndrome, steroid use while other cases remain idiopathic.1-4 We report a patient with Glioblastoma Multiforma (GBM) on chronic steroids, who was found to have ML on imaging despite lack of obesity or Cushing’s syndrome. This case provides significant educational benefit in approaching a patient with a widened mediastinum.

Case Presentation

A 59-year-old male with a history of recurrent GBM status post stereotactic radiation and ongoing chemotherapy presented to the hospital with lethargy, altered mental status and expressive aphasia consistent with ongoing progression of his malignancy. The patient was not obese (weight 72.1 kg; height 6’1”, body-mass index 21), non-diabetic, and had been on a daily dose of 2-8mg of dexamethasone intermittently (equivalent to prednisone 25-50mg daily) for approximately a year and half for GBM.

On admission, the patient was in no acute distress and denied abrupt or sharp onset of thoracic or abdominal pain. Physical exam revealed a well healed scalp scar from previous GBM resection, expressive aphasia, and chronic right sided weakness. Despite chronic steroid use, there were no physical manifestations of Cushing’s syndrome such as round face, fat pad, or purple stria. He had equal blood pressures in both arms and intact pulses bilaterally. The patient’s fasting glucose was within normal limits.

A plain chest radiograph demonstrated widening of the mediastinum, which was new compared to a study 6 months earlier (Figure 1). A follow up chest CT with contrast showed anterior-superior mediastinum lipomatosis (Figure 2). The pericardium and other surrounding structures were not involved. Mediastinum and hila were within normal limits on chest CT performed 7 months prior. The diagnosis of ML was made by CT. Since the patient remained asymptomatic, no further workup was required. Although steroids have been associated with ML, Neuro-Oncology deemed the benefits of steroids outweighed the risks. Therefore, the patient continued steroid treatment and was discharged home with Neuro-Oncology follow up.

Discussion

 Mediastinal Lipomatosis is a benign cause of mediastinal widening secondary to mature adipose deposition. Although our patient remained asymptomatic with ML, symptoms

Figure 1. CXR: Apparent widening of the superior mediastinum. Mild atelectasis in the left midlung is noted.

Figure 2. CT scan with contrast: Anterior-superior mediastinum lipomatosis.
may include dyspnea, cough, and chest pain. Physical exam findings range from a benign exam to decreased breath sounds, obesity, or associated signs of Cushing’s syndrome. Unlike most case reports reviewed, our patient did not have physical exam signs of obesity or steroid excess. The patient, however, was on chronic steroids, which may be associated with ML. Though the time course is unknown for development of fat accumulation, this patient appears to have developed ML within 6-7 months.

In most case reports, ML is identified by an incidental mediastinal widening on chest radiographs. Although ML is considered benign, it does have certain clinical implications. Kashikar et al report a patient presenting with progressive shortness of breath who was ultimately found to have segmental atelectasis of the lung related to ML. In the case presented by Peek et al, ML caused right hemidiaphragm paralysis secondary to phrenic nerve compression and mimicked cardiomegaly on CXR. ML can also cause low voltages on electrocardiograms. A rare complication of ML is superior vena cava compression, which can cause difficulty with central venous catheterization. In one case, a primary mediastinal large B-cell lymphoma was found within mediastinal lipomatosis. A more significant complication is laryngeal compression secondary to excess adipose tissue in the mediastinum leading to airway compromise and right ventricular outflow tract obstruction.

**Imaging**

The study of choice for diagnosis of ML is CT or, less often, MRI. Initial CXR will show a widened mediastinum with increased luency. A follow up CT reveals a collection consistent with fat (attenuation of 50 to 100 Hounsfield units). The adipose tissue can extend from the superior mediastinum to the diaphragm and may involve the heart and lungs. Interestingly, CT may also show incidental heart involvement with a characteristic dumbbell shape within the interatrial septum. However, of those studied with interatrial septum lipomatosis, no patient had evidence of electrocardiogram or other cardiac abnormalities, again emphasizing the benign nature of this diagnosis.

**Conclusion**

In contrast to medical emergencies and malignancy, mediastinal lipomatosis is a rare but benign cause of mediastinal widening on CXR. Symptoms caused by mediastinal lipomatosis include dyspnea, cough and arrhythmias, but most people are asymptomatic. The diagnosis is made by CT once acute conditions have been ruled out. Since the prevalence of obesity and use of steroids is increasing, it is important to understand the presentation, diagnosis, and treatment of mediastinal lipomatosis as we will likely see more cases of ML in the future.

**References**

7. Prasanta Raghab Mohapatra, Ashok Kumar Janmeja. Asymptomatic Mediastinal Lipomatosis
Metastatic Lip Cancer of Unknown Primary
Jonathan Dunn, MD, Jerry Hsieh, MD

Background
As housestaff, we seldom have the chance to admit a patient with cancer of unknown primary. Even if a patient presents with metastatic cancer, it is frequently evident what the primary cancer is based on epidemiology and imaging. However, in this case we have the unique opportunity of describing a metastatic cancer that presented as a lip carcinoma with several possible primary sources. Our goal is to guide the reader through the thought process involved with determining the primary malignancy in patients presenting with metastatic disease.

Case Presentation
A 54-year-old female with a 30-pack-year smoking history presented to the emergency department with pain and swelling of the right lower lip. The symptoms started one month ago with mild to moderate pain, and progressed within one week to significant swelling. She had developed a lip abscess two weeks prior that was incised and drained, but now presented with worsening drainage, swelling, and pain. She also had fevers and a non-productive cough for one month.

Investigation
On admission to the hospital, the patient was afebrile and had normal vital signs. Her right lower lip was noted to be indurated, with no fluctuance. There was no area of warmth or erythema surrounding the area of induration. Admission labs were within normal limits. Initial chest x-ray revealed consolidation within the right middle lobe and right lower lobe, as well as a moderate right pleural effusion. Maxillofacial CT with contrast revealed an organized rim-enhancing fluid collection within the soft tissues overlying the right mandible with overlying skin ulceration and surrounding inflammatory changes in the adjacent subcutaneous tissues.

Hospital Course
The initial differential diagnosis of the patient’s lip lesion included abscess, cellulitis, and malignancy. On admission, she was empirically treated for cellulitis and community acquired pneumonia. On hospital day 2 she was taken for a lip biopsy, which revealed ulcerated lesions with clusters of markedly atypical cells, most consistent with an ulcerated squamous cell carcinoma (SQCC). Immunohistochemistry stains showed that the tumor cells were positive for cytokeratin CK7 and negative for CK20, TTF1/Napsin, CK5/6 and mucicarmine. These were not consistent with a cutaneous SQCC as will be discussed later on. These results necessitated a metastatic workup to determine the primary source. A CT of the chest was obtained which showed a large right hilar mass, a new spiculated 7mm nodule in the inferior left lower lobe, and new mediastinal and hilar adenopathy. It also showed a large hypodense lesion with irregular margins within the right hepatic lobe. Based on these findings, a fine needle aspiration of the lung was obtained. The immunohistochemistry of the lesion matched that of the lip. These findings favored a diagnosis of primary lung cancer with metastasis to the lip, but could also represent either unknown primary or synchronous malignancies. Primary squamous cell carcinoma of the lip was deemed unlikely since these cancers are most often CK7 negative. Based on these findings, the decision was made by the primary oncologist to go forward with treatment of primary lung cancer, and platinum based chemotherapy was initiated.

Discussion
In the initial approach to a cancer of unknown primary, an evaluation of immunohistochemical markers can help narrow the list of possible cancers. The first step is often to stain for cytokeratins, specifically CK7 and CK20. The patient tested positive for CK7, and negative for CK20, which could indicate any of the following cancers: non-small cell lung, small cell lung, breast, endometrial, nonmucinous ovarian, mesothelioma, and squamous cervical carcinoma. In general, CK7+/CK20- strongly favors lung carcinoma. After a metastatic workup with imaging that yielded a lung and liver nodule, it was thought that the lip lesion was most metastatic from the lung.
Further analysis of the lesion involved lung cancer specific markers. Napsin and TTF1 are markers for lung adenocarcinoma (ADC) and both used in conjunction have 74% sensitivity and 87% specificity for ADC. These were both negative indicating a low likelihood of lung ADC. Additionally, p63 and CK5/6 markers were analyzed, which are used for distinguishing SQCC from ADC of the lung. ADC does not express either marker, whereas SQCC has approximately 75% chance of positive expressivity. Virtually all ADC and SQCC will not express CK20.

Metastatic carcinomas tend to be poorly differentiated, as is the case with this patient. Unfortunately, the immunohistochemistry of this particular carcinoma does not strongly favor ADC or SQCC; however, the histology more closely resembles poorly differentiated SQCC. At this time, the diagnosis favors a lung SQCC metastatic to the skin of the face.

Key Points
A thorough pathological examination is important in the diagnosis and treatment of tumors of unknown primary. Important components of this examination include cytokeratin markers CK7 and CK20, as well as other markers such as TTF1, Napsin, CD5/6 and mucicarmine. Further analysis depends largely on the clinical picture. For our patient, a closer look at her long smoking history along with the information gathered from cytopathology favored a diagnosis of lung cancer, and appropriate treatment was given.

References
Sudden Onset Blindness in a Patient with Mixed Connective Tissue Disease

Chris Terry, MSIII, Prachi Thanawala, MD, Erika Villanueva, MD

Case Presentation

A 66-year-old Caucasian female recently diagnosed with mixed connective tissue disease presented with acute onset vision loss in the left eye. The patient first noted a “hazy-shower” that caused blurry vision with loss of peripheral vision. Her vision progressively worsened over a four-day period, resulting in complete blindness in the left eye and the onset of blurry vision in her right eye. She denied any eye pain, discharge, photophobia or similar symptoms in the past. The patient did note a very mild headache for four days but denied any other symptoms.

Investigations

The patient was admitted for workup of left eye vision loss. Rheumatology was consulted for concern of autoimmune vasculitis, and the patient was started on IV methylprednisolone (1g daily). There was a concern for giant cell arteritis (GCA). Therefore bilateral temporal artery biopsies were obtained. The biopsy specimens showed no signs of GCA; however some ophthalmic artery occlusion was noted. There was concern for further thromboses, so MRI, MRA, and MRV of the head, CT of the chest, abdomen and pelvis, ultrasound of the carotid arteries, and trans-esophageal echocardiogram were performed. However, all of these imaging studies were non-diagnostic.

The patient had an Orbital Duplex Scan that showed significantly reduced blood flow to both eyes. Laboratory testing for autoimmune markers were significant for a positive rheumatoid factor (RF) and positive anti-cyclic citrullinated protein (anti-CCP) antibody (Ab). An ANA screen was positive with a titer of 1:80. Anti-ssDNA and anti-dsDNA antibodies were both moderately elevated. All other studies were non-diagnostic including anti-Smith Ab, RNP Ab, anti-SS-A Ab, anti-SS-B Ab, C-reactive protein, erythrocyte sedimentation rate, cryoglobulins, C-ANCA, P-ANCA.

Differential Diagnosis

Vasculitides are defined by the presence of inflammatory leukocytes in vessel walls with reactive damage to mural structures and may occur as a primary process or secondary to another underlying disease.1 There was initial concern for GCA due to the age of onset, presence of headaches, and absence of other symptoms. However, the bilateral temporal artery biopsies were negative. Essential cryoglobulinemic vasculitis was also considered; however it was ruled out based on the absence of serum cryoglobulins.

Given the patient’s past medical history and positive ANA, the medical team suspected an underlying connective tissue disorder. Additionally, due to the absence of serum ANCAs, the differential diagnosis was narrowed to a non-ANCA vasculitides. An important differential to bear in mind is systemic lupus erythematosus (SLE), a chronic, autoimmune connective tissue disorder affecting multiple organ systems often with a relapsing and remitting clinical course. Ocular manifestations, occurring in up to one third of patients, result from localized ischemia.2 3 Lupus retinopathy is one of the most common vision-threatening complications of SLE, occurring in up to 29% of patients.4

Another etiology to consider is rheumatoid arthritis (RA). Blood vessel inflammation is a central feature of RA.5 The mean onset of vasculitic symptoms is 13.6 years after the initial diagnosis of RA, and patients typically have developed rheumatoid nodules.10,11 The two principal ocular manifestations of rheumatoid vasculitis are episcleritis and peripheral ulcerative keratitis.12,13 The presence of an elevated RF and positive ANA, as well as a past medical history of nodular episcleritis, led to a high clinical suspicion for rheumatoid vasculitis.

Treatment

Rheumatology and Ophthalmology agreed to continue the IV methylprednisolone. On hospital day four, the patient was given cyclophosphamide (750 mg/m2) to be dosed monthly. This decision was based primarily on two critical studies investigating the efficacy and safety of pulse IV cyclophosphamide.

In mildly progressive ocular inflammation, therapy is often initiated with immunomodulatory agents prior to pulse IV cyclophosphamide. However, with failed immunomodulatory therapy or rapidly progressing inflammation at presentation, initiation of pulse IV cyclophosphamide is warranted. In 2004, Durrani et al. demonstrated the control of inflammation and steroid-sparing effect of pulse IV cyclophosphamide in 38 patients with severe ocular inflammation of diverse etiologies.14 Cyclophosphamide is a non-specific alkylating agent that exerts a cytotoxic effect on rapidly proliferating cells. It has shown remarkable safety in the rheumatologic and dermatologic literature when used IV for limited periods.15,16

Outcome and Follow-up

The patient continued on methylprednisolone (1g daily) for a total of eight days. On hospital day nine, her daily dose of methylprednisolone was decreased to 250 mg. At this time, her vision was stable in the right eye; however she still had complete loss of vision and light perception in her left eye. On hospital day ten, her steroid dose was adjusted to prednisone...
(100 mg daily), which she would continue until her next dose of cyclophosphamide. The patient had a repeat Orbital Duplex scan on hospital day ten which showed stable parameters in the central retinal artery of the right eye and improved flow in the temporal vessel of the short posterior ciliary system in the left eye. On hospital day 11, the patient was medically stable for discharge with close follow up with Ophthalmology, Retina Clinic, and Rheumatology.

**Discussion**

The initial differential diagnosis of sudden-onset vision loss includes infectious etiologies, primary ocular disorders, systemic vasculitides, connective tissue diseases, malignancy, and idiopathic processes. This patient’s past medical history and clinical presentation were most consistent with a vasculitis secondary to an underlying connective tissue disease. Ultimately, the patient had symptoms suggestive of several different connective tissue diseases and was discharged with a diagnosis of non-ANCA autoimmune vasculitis.

**Key Points**

Patients presenting with sudden onset vision loss suspected to be due to vasculitis warrant urgent diagnostic work-up to confirm the diagnosis. Although making a final diagnosis is a challenge due to the non-specific nature of clinical symptoms and lack of precise diagnostic modalities, early identification of vision loss secondary to an underlying connective tissue disease is critical in guiding management and maintaining visual acuity. Early initiation of steroids is the mainstay in preventing further vision loss while maintaining stability with immunomodulating drugs is an emerging treatment modality.

**References**

A 19 Year Old Male With HIV Presents With Diffuse Lymphadenopathy
Brian Curtis, MD, Subhashini Sellers, MD, Jay Sellers, MD, Jack Bruminhent, MD

Background
In 1872, Moritz Kaposi first described “an idiopathic multiple pigmented sarcoma of the skin,” now identified as Kaposi’s sarcoma (KS). While multiple forms of KS exist, over 95% of the cases diagnosed in the US since 1981 are of the AIDS associated variety. Kaposi originally described KS as skin lesions that can progress to visceral involvement. However, in a small number of cases, KS can appear in the viscera without skin involvement. These alternate presentations of KS are difficult to diagnose; therefore, it is critical to recognize them when considering differential diagnoses, particularly in patients with HIV.

Case Presentation
An 18-year-old African American male with a history of HIV presented with progressive worsening of diffuse and painful lymphadenopathy for five weeks prior to admission. The patient was diagnosed with HIV in 2010 and due to insurance issues, was never treated with highly active antiretroviral therapy (HAART). His last CD4 count (approximately two weeks prior to admission) was 411 and he had no history of opportunistic infections. He first noticed swelling in his neck, under his armpits and in his groin five weeks prior, which had become progressively more painful. The patient denied fevers, chills or weight loss, but did report significant night sweats and episodes of hemoptysis with clots. He denied shortness of breath or chest pain. He also denied recent travel, history of incarceration, homelessness or exposure to active tuberculosis infection.

On admission, the patient’s physical exam revealed numerous palpable, mobile and tender lymph nodes in the cervical, axillary and inguinal regions bilaterally. There was no overlying erythema and no skin lesions noted elsewhere. His lungs were clear to auscultation bilaterally. The remainder of his physical exam was within normal limits. His labs upon admission were notable for a hemoglobin of 9.4 and a platelet count of 9,000. The remainder of his labs were within normal limits. A chest x-ray demonstrated no consolidation or infiltrates.

Hospital Course
The differential diagnosis for the HIV patient presenting with diffuse lymphadenopathy includes lymphoma, mycobacterium avium intracellular infection, tuberculosis with extrapulmonary involvement, fungal infection, Castleman’s disease, Kaposi’s Sarcoma, leukemia, infectious mononucleosis secondary to EBV or CMV, Bartonella infection (cat scratch disease), toxoplasmosis and secondary syphilis. Malignancy is a significant concern with the co-existing anemia and thrombocytopenia. He underwent a CT of the chest (Figure 1), abdomen and pelvis (Figures 2 and 3). Given his complaints of hemoptysis, the patient was placed on respiratory isolation and TB was ruled out by sputum acid fast bacilli stain and culture.

Figure 1. CT of the chest with IV contrast demonstrates ground glass opacity in the right upper lobe and bulky enhancing adenopathy in the bilateral axilla.

Figure 2. CT of the abdomen with IV contrast shows bulky enhancing intra- abdominal and para-aortic lymph nodes.
Rapid plasma reagin and monospot tests were also negative and repeat CD4 count was 194. The history, laboratory results and radiological findings required excisional lymph node biopsy for definitive diagnosis, but this was limited by the patient’s severe thrombocytopenia. Hematology was consulted and determined the thrombocytopenia likely represented HIV associated ITP, for which he was treated with IVIG and started on HAART. He was started on romiplostim to stimulate platelet production.

On day 4 of his admission, the patient underwent a left inguinal lymph node excisional biopsy. Pathology was consistent with KS (Figures 4-7). It was assumed that his hemoptysis represented pulmonary involvement, although this could not be confirmed by bronchoscopy in the setting of thrombocytopenia. Although first line treatment for HIV-associated KS is HAART, the patient’s extensive and symptomatic disease required additional therapy. He received radiation for his bulky cervical adenopathy; however, he developed stridor during treatment and was intubated for airway maintenance. His ICU course was complicated by ventilator acquired pneumonia and he required a tracheostomy for continued airway maintenance. He was eventually weaned from the ventilator and started on liposomal doxorubicin on the general floor. After a nearly two month hospitalization, he was deemed stable for discharge home with a plan to continue HAART, weekly romiplostim, and chemotherapy as an outpatient.

The patient was seen for follow up three weeks after discharge. His hemoptysis had resolved and his lymphadenopathy had decreased in size and was less painful. He continued to receive doxorubicin every other week and he required romiplostim for persistent thrombocytopenia. He no longer required supplemental oxygen and ENT planned to decannulate his tracheostomy.

**Discussion**

The Hungarian dermatologist Moritz Kaposi first described classic KS in 1872, as a rare, slow growing cutaneous tumor that mainly affects 50 to 70-year-old Jewish Mediterranean and Eastern European males. Since then, other varieties have been described including the African or endemic, and the immunosuppressed forms. In 1981, a fulminant and disseminated form of the disease appeared alongside HIV/AIDS. In fact, early in the epidemic, 48% of AIDS patients in the US presented with KS. KS typically begins with cutaneous lesions, which are usually dark patches, papules, plaques or nodules. Diagnosis requires biopsy with histopathology illustrating a multicentric angioproliferative spindle cell tumor that stains positive for the endothelial markers CD31 and CD34. Positive stain for HHV-8 is also necessary but not sufficient for diagnosis, as the virus is also associated with multicentric Castleman’s disease and primary effusion lymphoma in HIV patients.

Although the vast majority of patients with KS present with skin lesions, the disease can involve the viscera, most commonly the oral mucosa, lung, liver, spleen, lymph nodes and the GI tract. Patients in later stages of disease can also experience fevers, weight loss and night sweats. Visceral involvement usually progresses from cutaneous disease, but in a small number of cases, it can be the primary site of involvement. This is seen
in KS cases involving the lymph nodes. Direct cutaneous invasion into nodes does not appear to worsen prognosis, but KS presenting solely with generalized lymphadenopathy is recognized as a disease more common in children and young adults that is associated with a worse prognosis.\(^4\)

Regardless of the stage of KS, first line treatment is HAART. This has been shown in several trials, including one in which 80% of patients naïve to HAART with cutaneous disease showed regression with HAART alone.\(^5\) The utility of HAART extends to prevention as well, as demonstrated by the sharp decrease in AIDS and KS incidence with anti-retroviral therapy introduction in the 1990s. In fact, the incidence of KS decreased from 30/1000 patient-years prior to 1995 to 0.03/1000 patient-years in 2001.\(^2\)

Other modalities of treatment include radiation therapy and cytotoxic drugs. Radiation therapy for local disease can be an excellent option, with some series reporting 68-90% resolution of lesions, although the response in the epidemic form is less durable than in other forms of KS.\(^6,7\) Patients with more disseminated disease can be treated with systemic chemotherapy. Liposomal doxorubicin has been reported to have significantly higher response rates and possibly fewer side effects than other regimens including doxorubicin, bleomycin and vincristine.\(^8,9\)

Based on these studies, liposomal doxorubicin is now considered first-line treatment for advanced KS. Paclitaxel has also shown promising results and is considered second-line therapy.\(^9\)

**Conclusion**

As KS is a heterogeneous disease, it must always be considered in the workup of patients with HIV/AIDS. As demonstrated by our case, patients can present with normal CD4 counts, lack skin lesions, and present with symptoms secondary to visceral involvement, including adenopathy, hemoptyisis, gastrointestinal bleeding, and systemic symptoms. While KS is rarely a cause of death, it is not curable and can be disabling. Current management options are often able to symptomatically alleviate and improve quality of life.

**References**

A Devastating Storm
Eve Merrill, MD

Case Report

A 26-year-old female with no significant medical history presented with palpitations and shortness of breath. Two weeks prior, she experienced rhinorrhea and congestion. Vital signs on admission were temperature 96.6°F, heart rate 252 beats per minute, blood pressure 127/74 mmHg, respiratory rate 24 breaths per minute, oxygen saturation 98% on room air. On exam, the patient was tachycardic and had a large, homogenous thyroid without any palpable nodules. The rest of her physical exam was unremarkable.

Laboratory data revealed total bilirubin 4.4 mg/dL, aspartate aminotransferase 245 units/L, alanine aminotransferase 263 units/L, thyroid stimulating hormone (TSH) 0.02 mIU/L, free thyroxine (T4) 5.5 ng/dL, and free triiodothyronine (T3) 21.4 pg/mL. Electrocardiogram revealed supraventricular tachycardia. Computed tomography angiogram of the chest revealed a grossly enlarged thyroid, a left lower lobe infiltrate, and no evidence of pulmonary embolism. The patient was cardioverted to sinus rhythm and was started on a continuous infusion of diltiazem. She then became hypotensive and tachypneic and was subsequently intubated. Thionamide medications, including methimazole and propylthiouracil, for the patient’s hyperthyroid state were initially held due to acute liver failure.

On the second day of admission, the patient developed rapid atrial fibrillation and was started on an esmolol infusion. Shortly thereafter, she became bradycardic and had a cardiac arrest with successful resuscitation. She then had a transvenous pacer placed as her asystolic event was attributed to a long conversion pause. Echocardiogram showed an ejection fraction of 10% with severe global systolic dysfunction, likely representing a stress-induced cardiomyopathy compounded by ischemia from the cardiac arrest.

In light of her rising liver function tests (transaminitis greater than 1000 units/L), the patient was started on methimazole, potassium iodine, and high-dose hydrocortisone for her severe hyperthyroid state. Ultrasound revealed an enlarged, heterogeneous thyroid with increased vascularity and serum studies showed anti-TSH receptor antibodies. Once her thyroid levels and liver function improved, propylthiouracil was used instead of methimazole. The patient also developed acute kidney injury requiring continuous venovenous hemodialysis. As she continued to clinically deteriorate, she was started on Extracorporeal Membrane Oxygenation (ECMO). The plan was to ultimately have the patient undergo a thyroidectomy once she became hemodynamically stable. Unfortunately, the patient had uncontrollable bleeding from her ECMO graft site and passed away on hospital day six.

Discussion

Thyroid storm is a state of severe hyperthyroid crisis (thyrotoxicosis) that causes organ dysfunction. Excess thyroid hormone produces a massive sympathetic (adrenergic) response and can damage the heart, liver, lungs, and central nervous system. Interestingly, the severity of thyroid dysfunction in thyroid storm does not correlate with thyroid levels. Thus, one cannot use thyroid levels alone to distinguish between hyperthyroidism and thyroid storm. Instead, there is scoring system developed by Burch and Wartofsky in 1993 to help establish a diagnosis of thyroid storm. Diagnostic criteria includes a point scale for varying degrees of cardiovascular dysfunction (including tachycardia and atrial fibrillation), heart failure, thermoregulatory dysfunction, central nervous system dysfunction, gastrointestinal-hepatic dysfunction, and a precipitant history event. A score below 25 makes thyroid storm unlikely, while scores between twenty-five and forty-four supports the diagnosis and a score of 45 of more is highly suggestive. Our patient had a score of 85.

Thyroid storm usually develops after an inciting factor in a patient with undertreated or undiagnosed hyperthyroidism. Precipitating stressors include infection, surgery, trauma, and a cardiovascular event. Other possible triggers include discontinuation of hyperthyroid medications or exposure to iodine, including intravenous contrast or amiodarone. The underlying hyperthyroid state is most commonly due to Graves’ disease, but other causes of hyperthyroidism include toxic adenoma, toxic multinodular goiter and Hashimoto’s thyrotoxicosis. Our patient likely had undiagnosed Graves’ disease and an upper respiratory tract illness as her inciting event.

Medical treatment of thyroid storm aims to stop thyroid hormone production within the gland, inhibit the release of thyroid hormone, and inhibit conversion of T4 to T3. In addition, supportive treatment for adrenergic symptoms and management of end organ dysfunction are crucial. Mainstays of treatment include beta-blockers, thionamide (propylthiouracil or methimazole), iodine, steroids and for definitive therapy, thyroidectomy. Propranolol is the first line beta-blocker because it provides anti-adrenergic effects and also inhibits the peripheral conversion of T4 to T3. Propylthiouracil is the thionamide of choice in severe, life-threatening thyroid storm as it blocks peripheral conversion of T4 to T3. Methimazole is recommended for severe non-life threatening thyroid storm as it has a longer half-life than propylthiouracil, normalizes T3 more rapidly, and has less hepatotoxicity. Despite our patient’s critical hyperthyroid state, she was initially started on methimazole because of her severe liver failure. She was transitioned to propylthiouracil once her thyroid hormone levels improved and her liver function stabilized. Mortality associated with thyroid
storm is predicted to be twenty to thirty percent, making it crucial to diagnose early.

References


"Rock Polishing” photograph by Soham Vakil
A 19-year-old Vietnamese female with no significant past medical history presented to the emergency department (ED) with fevers, sore throat, generalized myalgias, arthralgias, and a worsening lower extremity rash for the past two weeks. Approximately one week after the onset of constitutional symptoms, the patient noticed a rash developing on the anterior surface of her legs. Three days prior to hospitalization, her primary care physician prescribed cephalexin for her, but she didn’t recall what it was for. When her symptoms continued to worsen the next few days, she presented to the ED. In the ED, she also complained of abdominal tenderness. She had no previous hospitalizations, and her vaccinations were up to date. She also had a small tattoo noted on her neck that she reported receiving at a reputable place four years ago. She was sexually active with her boyfriend, and did not regularly use condoms. However, she denied any genitourinary symptoms.

Upon presentation, the patient had a fever and mild tachycardia. However, she was in no acute distress. Physical examination revealed diffuse palpable petechiae along the anterior part of both lower legs. The patient also had a developing rash over the anterior arms bilaterally. The rash spared her palms and soles. Abdominal exam revealed right upper quadrant (RUQ) tenderness with mild hepatomegaly. The rest of the exam was normal. On labs, patient was found to have a microcytic anemia, normal white blood cell and platelet count. Urinalysis revealed mild proteinuria and hematuria. However, the patient had normal renal function. Ultrasound of the kidneys revealed normal-appearing kidneys. Further work-up revealed mildly elevated ALT (98), AST (76), INR (1.86), and ESR (55). With the liver abnormalities, a RUQ ultrasound was also done, which revealed mild hepatomegaly but was otherwise normal. Screens for possible viral (including viral hepatitis, Monospot), bacterial (anti-streptolysin O titers, cultures), and autoimmune (antinuclear antibody, C-reactive protein) causes were all normal.

The clinical picture of palpable purpura, oligoarthralgia, abdominal pain and renal involvement as demonstrated by the microscopic hematuria, and further evaluations from Rheumatology, Infectious Disease, and Nephrology led to Henoch-Schonlein purpura (HSP) as the most likely diagnosis in this patient. The exact etiology of the HSP in this patient however was unknown. The most likely triggers were either a previous viral infection or medication-induced.

Skin biopsy was not obtained because the clinical picture was deemed enough to diagnose HSP. The patient demonstrated gradual improvement with supportive care and no further work-up was necessary. The elevated liver enzymes and INR also normalized. Despite the patient’s proteinuria, her renal function was normal so a renal biopsy was deemed unwarranted. On hospital day four, the patient was discharged with instructions to follow up with her primary care physician for any recurring symptoms.

**Discussion**

Henoch-Schonlein purpura (HSP) is a small-vessel vasculitis characterized by palpable purpura (without thrombocytopenia), abdominal pain, and arthritis. It is a syndrome predominantly seen in children; the highest occurrence of HSP is in patients between the ages of 3 and 5. Ninety percent of HSP cases are in children under the age of ten. However, HSP can be seen at any age, though the occurrence in adults is rare and reported in 3.4-14.3 cases per million. The precise etiology of HSP is unknown. The proposed triggers are generally infectious; an upper respiratory infection often precedes HSP symptoms in 90% of cases. Other proposed infectious agents include group A Streptococcus, MRSA, H. pylori, Parvovirus B 19, Hepatitis B, HIV, Stenotrophomonas maltophilia. In adults, a wider variety of antigenic stimuli have also been suggested to predispose to HSP: vaccinations, insect bites, food allergies and drugs. Medication-induced HSP is particularly more common in adults and has been seen in association with ACE-inhibitors, ARBs, NSAIDs, and antibiotics.
Whatever the antigenic stimuli may be, the cross reactivity between the offending agent and small vessel endothelial cells leads to a leukocytoclastic vasculitis. Immunoglobulin A (IgA) has been found to be the key mediator of this reaction.\(^2\) Immune complexes and chemotactic factors activate polymorphonuclear leukocytes causing inflammation and eventually necrosis of vessel walls. IgA complex depositions accumulate primarily in the skin, intestinal mucosa, joints and kidneys—precisely the organ systems behind the classic clinical features of HSP.\(^3\)

The main clinical features seen with HSP are palpable purpura, abdominal pain, arthritis, and renal insufficiency. A retrospective analysis of 250 adult patients with HSP reported a purpuric rash in 96% of cases, arthritis in 61%, gastrointestinal disease in 47%, and renal disease in 32%.\(^3\) The classic skin lesions of HSP start as multiple small, painless, erythematous macular lesions that combine into palpable purpura. The rash is symmetrical and more prominent in dependent areas of the body such as the lower extremities. The arthritis/arthralgia seen in HSP is migratory and oligoarticular. The arthritis is non-deforming and the joints are not usually swollen or tender. Gastrointestinal involvement often presents as colicky pain with or without bleeding from the large or small bowel. A potentially severe complication is intussusception. Renal disease is considered the most serious manifestation of HSP, its involvement can range from microscopic hematuria to fulminant nephrotic syndrome.

The diagnosis of HSP is clinical. The European League Against Rheumatism and Pediatric Rheumatology European Society criteria include one mandatory criterion and at least one of four minor criteria. The mandatory criterion is palpable purpura predominantly in the lower limbs. In addition, there must be one of the following: diffuse abdominal pain, IgA deposition in any tissue biopsy, arthritis/arthralgia, or renal involvement. Urinalyses are often abnormal and may reveal anything from microscopic hematuria to nephrotic range proteinuria. Inflammatory markers (C-reactive protein, erythrocyte sedimentation rate) are typically elevated. The diagnosis can be supported by a tissue biopsy that shows vasculitis with IgA immunofluorescence.\(^2,3\) There will also be perivascular infiltration of neutrophils.\(^2\) In cases of uncertain diagnosis or severe renal disease a renal biopsy may be performed.

Treatment is symptom-directed. NSAIDs are used in mild cases for joint pain. Colchicine can be used in cases of severe skin lesions. In pediatric HSP, no guidelines exist for the management of GI and renal involvement of the disease, and far fewer recommendations exist for adults. Glucocorticoids have been used to treat GI symptoms successfully, as they have been proven to shorten the duration of these symptoms. Corticosteroids can also be used in patients with renal involvement, and in severe disease can decrease proteinuria significantly.\(^1\) It should be noted, however, that there is little evidence to support the use of glucocorticoids to prevent renal disease once the diagnosis of HSP is established. 6 Leukopheresis, cytotoxic agents and immunoglobulin have been used in refractory cases.\(^2,3\)

References

**Paraneoplastic Acral Vascular Syndrome**

Daniel M. Kopolovich, MSIII, Dean D. Laganosky, MSIII, Allison A. Greco, MSIV, Emma Weaver, MD, Rahul Malhotra, MD, Phoebe Holmes, MD, John Stewart, MD

**Introduction**

Cases of rheumatologic phenomena coinciding with malignancy have been well-documented in the medical literature. These syndromes may be associated with common autoimmune markers, potentially masking the underlying diagnosis of malignancy. The association between malignancy and its coinciding rheumatologic manifestations is poorly understood. These paraneoplastic symptoms are more prevalent in high-stage adenocarcinomas of the lung, breast, and ovary. Possible mechanisms may include cytokine derangements, blood hyperviscosity, and circulatory disruption. While some evidence suggests that control of the primary tumor alleviates its associated paraneoplastic symptoms, other proposed therapies include heparin, prednisone, aspirin, and vasodilatory agents. Efficacy is limited due to association of these syndromes with high-grade malignancy. We describe the case of a patient presenting with paraneoplastic acral vascular syndrome (PAVS) in association with primary ovarian carcinoma.1,2

**Case**

The patient is a 57-year-old female with a history of Hashimoto’s thyroiditis and migraines, who presents with an ulcerating rash of the fingertips and a tender discoloration of the plantar aspect of both feet. The rash began four weeks prior to presentation as a purple discoloration of the fingertips, progressing to a desquamating, palmar rash with distal phalangeal ulceration and necrosis of the fingertips. Almost simultaneously, the patient experienced purple discoloration of the soles of her feet bilaterally and described a sensation of “standing on marbles.” She denies similar episodes in the past as well as sick contacts. She reports experiencing excessive stress in preparing for her daughter’s wedding, exposure to a new type of dryer sheet, and a recent manicure/pedicure. The patient was recently treated with two medrol dose packs, minocycline, nitroglycerin paste (which had to be discontinued due to hypotension), and aspirin. Following treatment, the patient had no relief of symptoms.

Review of systems was remarkable for bilateral knee pain, painful mouth ulcers, a non-tender, erythematous scaling rash on the elbows, back, and right thigh. She denied fever, weight loss, fatigue, night sweats, change in appetite, or abdominal swelling. She reported allergies to DEET (rash and trouble breathing) and Demerol. Recent skin testing suggested sensitivity to wheat, corn, and soy. Family history was significant for a mother with giant cell arteritis, father who passed away from melanoma and a sister with breast cancer. The patient also had two daughters, one with Raynaud’s syndrome and celiac disease, and another with Sjogren’s syndrome. The patient was a middle school math teacher and had no occupational exposures. Social history was unremarkable.

**Physical Exam**

Physical exam revealed unremarkable vital signs. The patient’s right hand was notable for purple discoloration of the distal 2nd through 5th digits and necrotic ulcerations of the distal 2nd and 3rd digits (Figure 1). The left hand had purple discoloration of the distal 1st through 5th digits. Both hands had slight peeling of the palmar surface, not extending past the wrist. There was mild swelling of the metacarpal-phalangeal joints as well as proximal inter-phalangeal joints bilaterally. Purple discoloration of the anterior plantar surfaces of bilateral feet was also noted. Neurologic exam was intact. Patient had 2+ radial, posterior tibial and dorsalis pedis pulses bilaterally, and no leg edema. Faint crackles were auscultated posteriorly in bilateral lower lobes of the lungs. No cervical, supraclavicular, axillary or inguinal lymphadenopathy was palpated.

Lab values revealed the following: C-Reactive Proteins 10.9 (H), Rheumatoid Factor: 16.9 (H), ANA (homogenous 1:160, speckled 1:160), Anti-Ro 8.0 (H), Anti-cardiolipin IgM 76 (H), Aldolase 11.7 (H). CA-125 118 (H) CA 15.3 (CA 27.29) 46 (H). Blood

![Figure 1. Right Hand Rash](image-url)
count, coagulation profile, chemistry profile, liver function tests, lipid profile and urinalysis were unremarkable. Additionally, ESR, Anti-double stranded DNA, Anti Scl-70, c-ANCA, p-ANCA, atypical p-ANCA, anti-MPO, Antiproteinase-3, Jo-1 antibody, Lyme panel, viral hepatitis panel, EBV/CMV PCR, cold agglutinins, SPEP/UPEP, beta-2 glycoprotein, Celiac panel, Lupus anticoagulant, RNP, CPK, heavy metals, CEA, and CA 19.9 were also normal. Chest radiograph showed a pulmonary interstitial prominence with predilection for the lung bases.

CT chest/abdomen/pelvis showed patchy ground glass opacities bilateral lower lobes, likely airspace filling process, of uncertain significance. No interstitial lung disease. Diffuse retroperitoneal adenopathy, extending from the diaphragm down through the common iliac and external iliac territories and a cystic area in the left adnexa. Another lymph node in the right supraclavicular region was also seen and a fine needle biopsy of this node was performed. Cytology was consistent with an adenocarcinoma of ovarian origin. (Figures 2 & 3)

MRI of the abdomen and pelvis revealed a 5.0 cm solid and cystic left adnexal mass, lesions of the left ileum consistent with bony metastases, and extensive peritoneal carcinomatosis.

**Discussion**

This patient was diagnosed with paraneoplastic acral vascular syndrome (PAVS) in association with primary ovarian carcinoma. PAVS is an infrequently described phenomenon characterized by acrocyanosis and subsequent necrosis of the distal extremities secondary to malignancy. Most common associations are adenocarcinoma of gastrointestinal and pulmonary origin; however, ovarian cancer has been implicated in a number of cases. Of these, the majority are found to be metastatic at the time of diagnosis. In one literature review it was shown that PAVS affects the hands in 94% of patients and the feet in only 30%. The mean age of onset is 54.4 years old and vasculitis precedes the diagnosis of malignancy by an interval of 1-38 months with a mean of 10 months.

A number of authors have previously described atypical features that may raise suspicion for an underlying neoplastic versus primary rheumatologic pathology. Age greater than 50 years at presentation, atypical involvement of the digits, as well as poor response to steroids and vasodilating agents may indicate an underlying malignancy. In contrast to primary rheumatologic disorders, which occur more frequently in young women, these conditions occur with equal frequency in men and women.

Several proposed mechanisms for PAVS include: (i) ischemia from tumor antigen immune complex deposition in the small vessels of the digits, (ii) tumor infiltration into the cervical plexus resulting in the release of vasoconstrictor substances, (iii) direct endothelium invasion by the tumor cells, and (iv) hypersensitivity reaction. However, these mechanisms are not consistent between patients. In one study, the pathology of the digits showed leukocytoclastic small vessels, which was histologically different from the vascular involvement normally seen in other diseases such as Rheumatoid arthritis, SLE, and Takayasu vasculitis. Fibrinoid necrosis and intimal proliferation were also noted. Other findings included disruption of the endothelium and invasion of the vessels by neutrophils.

Treatment options for addressing the symptoms of PAVS include steroids, IV prostacyclin, lower molecular weight Heparin, aspirin, topical nitroglycerin, and calcium channel blockers. More definitively, PAVS was found to resolve with cancer treatment. In another study of 22 patients, clinical remission of malignancy corresponded with the disappearance of PAVS.
summary, small vessel disease refractory to traditional therapies warrants increased clinical suspicion for metastatic malignancy so as not to delay definitive treatment.

References
A 47-YEAR OLD FEMALE WITH MUSCULAR RIGIDITY, NEW-ONSET DIABETES AND HYPOTHYROIDISM
Michael A. Valentino, MD, PhD

Background
This case highlights a rare but devastating neurologic condition, Stiff Person Syndrome (SPS). While symptoms of muscular rigidity and spasms are associated with numerous neuromuscular conditions, the association between SPS, autoimmune diabetes, and other autoimmune disorders such as thyroiditis, pernicious anemia, and vitiligo, could aid in the early diagnosis of this debilitating condition.

Case Presentation
A 47-year-old African American female presented with six months of progressively worsening rigidity and spasticity of her axial muscles and extremities. The patient was in good health until one and a half years prior to admission when she lost consciousness while driving and was subsequently diagnosed with epilepsy. Her daughter was a passenger in the car and suffered a brief coma. Over the next year, the patient started having anxiety with increasingly more frequent and severe panic attacks. Six months prior to admission, she developed muscle stiffness and painful spasms that were so severe, she had difficulty ambulating and eventually became bed-bound. Magnetic Resonance Imaging (MRI) of the brain and spine did not reveal any pathology. Additionally, during the past year she was diagnosed with diabetes, which was unusual given her thin body habitus (Body-Mass Index of 20.9).

Investigations
The patient was admitted to the hospital for further work-up of her neuromuscular symptoms. On physical exam, her abdomen was tightly flexed and rigid, almost “board-like.” Musculoskeletal exam revealed significant spinal lordosis with tight contraction of the abdominal and paraspinal muscles. She also had several muscle contractures including bilateral externally rotated and adducted shoulders, bilateral elbow flexion, left wrist flexion, bilateral knee extension, bilateral ankle plantar flexion, and flexion of the left fingers (Figure 1a-b). There was no joint effusion or erythema. Neurologic exam revealed cranial nerves II-XII to be grossly intact. She had hypertonicity of the upper and lower extremities, abdominal, and paraspinal muscles, as well as intermittent myoclonic jerks of the limbs and neck that could be elicited by auditory or tactile stimuli. She had normal reflexes and no motor, sensory or cognitive deficits. In addition, telemetry monitoring revealed wide fluctuations in blood pressure (109/63 - 181/109 mmHg) and heart rate (104-140 beats per minute). Admission labs were significant for an elevated erythrocyte sedimentation rate, C-reactive protein and thyroid stimulating hormone (Table 1).

Figure 1A, B. Representative X-rays showing upper extremity contractures
Differential Diagnosis

Neurology was consulted to evaluate the patient’s undiagnosed neuromuscular disorder. The differential diagnosis included Stiff Person Syndrome (SPS), neuromyotonia (Isaac’s syndrome), and chronic inflammatory demyelinating polyneuropathy (CIDP). However, there was also a suspicion of a psychological etiology to her symptoms. She had blood tests sent for anti-glutamic acid decarboxylase (GAD) 65, anti-voltage gated potassium channel, and anti-GM1 ganglioside antibodies to evaluate for SPS, neuromyotonia, and CIDP, respectively. Her anti-GAD65 antibody level was above the upper limit of detection. She was also found to have markedly elevated anti-islet cell and anti-thyroid peroxidase antibodies to evaluate for SPS, neuromyotonia, and CIDP, respectively. Her anti-GAD65 antibody level was above the upper limit of detection. She was also found to have markedly elevated anti-islet cell and anti-thyroid peroxidase antibodies. Her elevated anti-GAD65 antibody level, clinical presentation, and concurrent autoimmune diabetes and thyroiditis led to the diagnosis of SPS. She was evaluated for the paraneoplastic variant of SPS with anti-amphiphysin antibody, a paraneoplastic antibody panel, and Computed Tomography (CT) of the abdomen and pelvis, which were all negative.

Outcome & Follow-up

Her hospital course was complicated by esophageal dysmotility causing aspiration pneumonia, Pseudomonas bacteremia, and ventilator-dependent respiratory failure. She was weaned from the ventilator and discharged to rehabilitation with plans of implanting a baclofen pump.

Discussion

Stiff person syndrome is a rare central nervous system (CNS) disorder characterized by progressive rigidity of the axial and proximal musculature with intermittent superimposed spasms. The age of onset of SPS is typically the fifth decade, and the disorder affects twice as many females as males. Two symptoms are key to the characterization of SPS: (1) stiffness of axial and proximal limb muscles due to continuous contraction and co-contraction of agonist and antagonist muscles and (2) superimposed intermittent painful spasms. In the classic form of this disorder, patients will experience aching and tightness in the neck and axial musculature and will develop hyperlordosis due to simultaneous contraction of abdominal and paraspinal muscles. The rigidity will spread to involve the proximal muscles of the lower extremities and is often asymmetric at onset. Along with progressive stiffening of the musculature, patients also experience intermittent, sudden painful spasms which can be triggered by visual, auditory, or tactile stimuli, as well as emotional stress. In some cases, individuals can identify

<table>
<thead>
<tr>
<th>Table 1. Pertinent lab values</th>
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<tr>
<td><strong>Lab</strong></td>
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<tr>
<td>CRP</td>
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<tr>
<td>ESR</td>
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<tr>
<td>Hemoglobin A1C</td>
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<tr>
<td>TSH</td>
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<tr>
<td>Free T4</td>
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<tr>
<td>Free T43</td>
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<tr>
<td>Vitamin B12</td>
</tr>
<tr>
<td>Anti-Amphiphysin Ab</td>
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<tr>
<td>Anti-GAD65 Ab</td>
</tr>
<tr>
<td>Anti-Islet Cell Ab</td>
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<tr>
<td>Anti-Thyroglobulin Ab</td>
</tr>
<tr>
<td>Anti-Thyroid Peroxidase (TPO) Ab</td>
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<tr>
<td>TSH Receptor Ab</td>
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</table>

Treatment

She was started on a regimen of GABA-ergic and anti-spasticity medications including high-dose diazepam, tizanidine, baclofen, and dantrolene. She was then initiated on a five-day course of intravenous immunoglobulin (IVIG) with no relief in her symptoms. Joint manipulation under anesthesia was unsuccessful. Botulinum toxin injections mildly improved her range of motion.
a major stressful life event that preceded the onset of their psychological and neuromuscular symptoms. The association between the exacerbation of the patient’s symptoms and emotional stress often leads to psychiatric evaluation. Early in the course of the disease, a patient's neuromuscular symptoms may be non-specific, and the psychological features of anxiety and depression may dominate the clinical picture. This often leads to a diagnosis of a psychogenic movement disorder as their neuromuscular symptoms progress. Frequently, the misdiagnosis of a psychogenic movement disorder can be reinforced by the exacerbation of the patient’s symptoms by emotional stress and the improvement of symptoms with benzodiazepines. Finally, patients may suffer paroxysmal autonomic dysfunction, dysphagia from esophageal dysmotility, and seizures.

Case reports have demonstrated an association between SPS and diabetes, but a major breakthrough in understanding the pathophysiology of SPS came in 1988 when Solimena et al identified antibodies against glutamic acid decarboxylase (GAD) in the serum and cerebrospinal fluid (CSF) of a patient with SPS and diabetes. GAD is the rate-limiting enzyme involved in the synthesis of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS (Figure 2). The hypothesis that the loss of GABA-signaling in the CNS is the cause of SPS was supported by magnetic resonance spectroscopy showing a selective reduction in GABA in the sensorimotor cortex of patients with SPS.

Beyond anti-GAD antibodies, other autoantibodies targeting GABA synthesis, transport, and signaling have been recognized in patients with SPS (Table 2). More recently, antibodies targeting GABAA receptor-associated protein (GABARAP), have been identified in up to 70% of patients with SPS. A variant of SPS that occurs as a paraneoplastic syndrome has also been identified. This syndrome is most commonly associated with breast cancer but also has been observed in colon, lung, thymus cancers, as well as Hodgkin’s lymphoma. Autoantibodies against amphiphysin and gephyrin have been identified in the serum of patients with paraneoplastic SPS.

Clinical criteria for diagnosing SPS were last revised in 2009 as new discoveries regarding the pathophysiology of the disorder were made (Table 3). Beyond these diagnostic criteria, clinical response to diazepam is often included in the clinical criteria for the diagnosis of SPS.

Table 2. Autoantibodies associated with stiff person syndrome

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Function of Target Protein</th>
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<tbody>
<tr>
<td>Anti-GAD65</td>
<td>Rate-limiting enzyme in the synthesis of GABA</td>
</tr>
<tr>
<td>Anti-Amphiphysin</td>
<td>Synaptic vesicle protein involved in the recruitment of dynamin to sites of clathrin-mediated endocytosis which is involved in retrieving vesicle membrane from axon terminals after exocytosis of GABA</td>
</tr>
<tr>
<td>Anti-Gephyrin</td>
<td>Tubulin-binding protein involved in the clustering of GABA, and glycine receptors at the postsynaptic membranes of inhibitory synapses</td>
</tr>
<tr>
<td>Anti-GABAA Receptor-Associated Protein (GABARAP)</td>
<td>Linker protein between gephyrin and GABAA receptors which is involved in postsynaptic clustering and stability of GABA receptors at the post-synaptic membrane</td>
</tr>
</tbody>
</table>

Table 3. Dalakas diagnostic criteria for stiff person syndrome

<table>
<thead>
<tr>
<th>Criterion</th>
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<tr>
<td>Muscular rigidity in the limbs and axial (trunk) muscles, prominent in the abdominal and thoracolumbar paraspinals leading to a fixed deformity (hyperlordosis)</td>
</tr>
<tr>
<td>Continuous co-contraction of agonist and antagonist muscles, confirmed clinically and electrophysiologically</td>
</tr>
<tr>
<td>Episodic spasms precipitated by unexpected noises, tactile stimuli, or emotional upset</td>
</tr>
<tr>
<td>Absence of any other neurologic disease that could explain the stiffness and rigidity</td>
</tr>
<tr>
<td>Positive anti–glutamic acid decarboxylase (or amphiphysin) antibodies assessed by immunocytochemistry, Western blot, or radioimmunoassay</td>
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</table>

SPS is strongly associated with a variety of other autoimmune disorders, and the presence of these co-morbidities can be helpful in correctly diagnosing SPS. Autoimmune diabetes occurs in up to 35% of patients with SPS. In addition to anti-GAD antibodies, islet-cell antibodies have also been detected in the serum of patients with SPS and diabetes. Other autoimmune disorders, including thyroiditis, pernicious anemia, and vitiligo, have also been observed in patients with SPS. Patients with SPS presenting with these co-morbid autoimmune conditions have elevated levels of their respective autoantibodies, including thyroglobulin antibodies, thyroid peroxidase antibodies, and gastric parietal-cell antibodies.

Historically, the mainstays of treatment for SPS were GABA-enhancing medications and anti-spasticity drugs. However, as the autoimmune pathogenesis of SPS was identified, the utility of immunotherapy for SPS was investigated and has been validated. Currently, treatment of SPS consists of a combination of GABA-ergic and anti-spasticity medication as well as immunotherapy (Table 4).

### Table 4. Treatment options for patients with stiff person syndrome

<table>
<thead>
<tr>
<th>GABA-Enhancing Drugs</th>
<th>Benzodiazepines (e.g. diazepam, clonazepam, alprazolam, lorazepam)</th>
<th>diazepam: 5-100 mg; clonazepam: 2.5-6 mg; alprazolam: 2-4 mg; lorazepam: 6 mg</th>
<th>Central GABA&lt;sub&gt;A&lt;/sub&gt; agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptic drugs (e.g. vigabatrin, valproate, gabapentin, levetiracetam, tigabine)</td>
<td>vigabatrin: 2-3 g; valproate: 0.6-2 g; gabapentin 3600 mg; levetiracetam: 2000 mg; tigabine: 6 mg</td>
<td>Augmentation of GABA signaling</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antispasticity Agents</th>
<th>Baclofen</th>
<th>10-60 mg</th>
<th>GABA&lt;sub&gt;B&lt;/sub&gt; agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tizanidine</td>
<td>6 mg</td>
<td>Central α2-adrenergic action; inhibits norepinephrine release</td>
<td></td>
</tr>
<tr>
<td>Dantrolene</td>
<td>200-400 mg</td>
<td>Dissociates excitation-contraction coupling and blocks release of Ca&lt;sup&gt;2+&lt;/sup&gt; from the sarcoplasmic reticulum</td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin A</td>
<td>–</td>
<td>Neuromuscular junction blocking; prevents acetylcholine exocytosis</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Immunotherapies</th>
<th>IV immunoglobulin</th>
<th>2 g/kg</th>
<th>Immunosuppression/modulation</th>
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<tbody>
<tr>
<td>Rituximab</td>
<td>2 g (in two divided doses)</td>
<td>B-cell depletion</td>
<td></td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>5-6 passes</td>
<td>Immunosuppression/modulation</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Up to 60 mg</td>
<td>Immunosuppression/modulation</td>
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</tr>
<tr>
<td>Immunosuppressive agents (e.g. azathioprine, methotrexate, mycophenylate mofetil)</td>
<td>azathioprine: 2.5-3 mg/kg; methotrexate: 15-20 mg; mycophenylate mofetil: 2-3 g</td>
<td>Immunosuppression/modulation</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: Dalakas MC. Stiff person syndrome: advances in pathogenesis and therapeutic interventions. Curr Treat Options Neurol 2009;11:102-10

### Key Points

This patient’s case displays many of the clinical features classically observed in SPS. There was a prodrome of severe anxiety and she was able to identify a significant psychological stressor that triggered her functional decline. She developed progressive stiffness of the axial muscles leading to hyperlordosis and then developed stiffness of the extremities with the lower extremities locked in extension and upper extremities locked in flexion. She also had painful spasms elicited by auditory or tactile stimuli and she displayed autonomic instability on telemetry. She had markedly elevated anti-GAD65 antibodies and had co-morbid autoimmune disorders (autoimmune thyroiditis, latent autoimmune diabetes of adults) with associated circulating autoantibodies. Finally, she showed clinical improvement after treatment with diazepam.

Unfortunately, our patient did not display any clinical improvement following treatment with IVIG. However, in the clinical trial that demonstrated benefit of IVIG therapy for patients with SPS, bedridden patients were excluded. Thus,
this case highlights the importance of early diagnosis of this severely debilitating neurologic condition, as the least disability is observed in patients treated early in the course of their disease.

References


“Sulfur and Steam, Yellowstone” photograph by Andrew Zabolotsky
A Case Study of Pseudo-Neuropathic Pseudogout

Christina C. Lindenmeyer, MD, Adam Sobel, MD, Levon Nazarian, MD, Steven Mandel, MD, Steven M. Raikin, MD, Homyar Karanjia, DPM

Background

This interesting case highlights the clinical progression of a rare disease process and the important role of a multi-disciplinary team in achieving a diagnosis and successful management plan.

Case Presentation

A 76-year-old male with a history of coronary artery disease, hypertension and hyperlipidemia presented as an outpatient with left foot pain and swelling. He had spent a week bicycling in Colorado one month prior to presentation. The pain was initially localized to the plantar surface of his foot and progressed to involve the lateral and dorsal aspects of the foot, as well as his great toe. The pain was accompanied by swelling of the midfoot without erythema and he was unable to bear weight. His podiatrist prescribed Ibuprofen and a foot brace for empiric treatment of tendinitis. An outpatient MRI demonstrated extensive bony edema and synovial enhancement within the midfoot, as well as severe superficial edema and peroneal tendinitis with mild subluxation. The patient was sent to the emergency department to be evaluated for osteomyelitis.

On exam, the patient was afebrile with normal vital signs. The left foot was warm and edematous without erythema or discrete fluid collection. There were no ulcers or breaks in the skin. The dorsal portion of the foot was exquisitely tender to palpation. The ankle had decreased active and passive range of motion. Pedal pulses were equal, and sensation was intact. Initial chemistries were significant for an erythrocyte sedimentation rate (ESR) of 81 mm/hr and C reactive protein (CRP) of 1.1 mg/dL. Foot and ankle x-rays were negative for fracture or dislocation. Venous ultrasound of the lower extremities was negative for deep venous thrombosis.

The patient was evaluated by orthopedic surgery and was diagnosed with severe bony stress and trauma from his prolonged bike trip. A full rheumatologic evaluation was normal. A fluid collection amenable to arthrocentesis was not identifiable. Based on imaging and physical exam, the Infectious Disease team did not feel there was evidence of osteomyelitis. The patient was prescribed high-dose Ibuprofen and a foot brace for empiric treatment of tendinitis. An outpatient MRI demonstrated extensive bony edema and synovial enhancement within the midfoot, as well as severe superficial edema and peroneal tendinitis with mild subluxation. The patient was sent to the emergency department to be evaluated for osteomyelitis.

Two weeks after discharge, rheumatology aspirated three milliliters of straw-colored fluid from the left ankle, which contained calcium pyrophosphate crystals, consistent with pseudogout. An ultrasound four months later demonstrated improvement in the left talonavicular and tarsometatarsal joint synovitis, and a small tibiotalar joint effusion with persistent chondrocalcinosis. The patient’s outpatient orthopedic surgeon confirmed the diagnosis of pseudogout, with associated pseudo-neuropathic joint disease. The patient is currently being maintained on low dose scheduled Naproxen and Methotrexate as an outpatient. He is no longer wearing an orthopedic boot, and is progressively regaining his mobility.

Outcome and Follow-up

Two weeks after discharge, rheumatology aspirated three milliliters of straw-colored fluid from the left ankle, which contained calcium pyrophosphate crystals, consistent with pseudogout. An ultrasound four months later demonstrated improvement in the left talonavicular and tarsometatarsal joint synovitis, and a small tibiotalar joint effusion with persistent chondrocalcinosis. The patient’s outpatient orthopedic surgeon confirmed the diagnosis of pseudogout, with associated pseudo-neuropathic joint disease. The patient is currently being maintained on low dose scheduled Naproxen and Methotrexate as an outpatient. He is no longer wearing an orthopedic boot, and is progressively regaining his mobility.

Discussion

This case highlights the importance of an evolving differential diagnosis, based on physical exam, laboratory and radiological tests. The initial outpatient differential diagnosis included severe multifocal stress response, osteomyelitis, and early neuropathic change, and evolved to include reflex sympathetic dystrophy, osteoporosis and finally pseudogout with associated neuropathic joint disease.
Calcium pyrophosphate dehydrate (CPPD) crystal deposition, and ensuing crystal-induced synovitis, is an important pathologic entity that is part of a spectrum of disease. This includes pseudogout, or acute attacks of CPPD synovitis, chondrocalcinosis, or radiographically evident deposition of CPPD crystals, and CPPD arthropathy, or chronic joint disease that typically accompanies CPPD crystal deposition. This disease process has important epidemiologic implications, as estimates suggest an age-related rise in prevalence of related chondrocalcinosis.1 CPPD crystal formation is thought to initiate near the surface of chondrocytes and may be related to purely elevated levels of calcium, pyrophosphate, or local cartilage matrix changes that enhance calcium or pyrophosphate levels. Most cases are idiopathic, but some are associated with an underlying disorder. Hemochromatosis, hyperparathyroidism, hypophosphatemia, hypomagnesemia, familial hypocalciuric hypercalcemia, Gitelman’s syndrome, gout, and hypothyroidism have been shown to be associated with CPPD. Joint trauma or joint instrumentation is also an important etiology.2,3

Definitive diagnosis of CPPD crystal deposition disease is made by synovial fluid analysis. Microscopy of aspirated fluid will demonstrate the presence of positively birefringent CPPD crystals. CPPD crystal deposits can be imaged by plain film radiography as linear radiodensities in joint cartilage, ligaments and joint capsules.4 Ultrasound imaging can also be used to diagnose CPPD deposition disease. CPPD crystals will appear as hyperechoic bands along the cartilage surface or as hyperechoic spots in the fibrocartilage.5 There are few cases of CPPD crystal deposition disease associated with severe joint degeneration resembling neuropathic arthropathy and Charcot joint. This rare condition that has been termed “pseudo-neuropathic joint disease.” It has been speculated that acute episodes of pseudogout and chondrocalcinosis can precede the development of Charcot arthropathy through cartilaginous microfractures, which results in the shedding of CPPD crystals into the joint cavity and progressive joint destruction.6-8

In patients with acute CPPD crystal arthritis, the CPPD crystals should be removed by arthrocentesis. Intra-articular injection of glucocorticoids is recommended in patients with no more than two involved joints. When more than two joints are involved, administration of oral non-steroidal anti-inflammatory (NSAID) medications is recommended. For patients in whom NSAIDs are contraindicated, colchicine can be used, and in patients for whom NSAIDs and colchicine are contraindicated, systemic glucocorticoids or immunomodulators such as methotrexate can be used. Joint immobilization is the mainstay of therapy for pseudo-neuropathic joint disease in order to prevent the development of microfractures and joint collapse.9

Key Points

Pseudo-neuropathic pseudogout is a rare disease process that can be difficult to elucidate. The key to diagnosis is arthrocentesis of the involved joint and the identification of calcium pyrophosphate crystals in the synovial fluid. Ultrasound is a
sensitive and specific technique for identifying chondrocalcinosis in a patient with suspected neuropathic joint disease. The mainstay of treatment is NSAID therapy.

References

“Half Dome” photograph by Soham Vakil
Background

Sickle cell crises are commonly treated at our institution given its large sickle cell patient population and well-established hematology department. While pain management is a crucial aspect to these patients’ care, it is important to remember that a vaso-occlusive crisis can be life threatening. Many organs can be at risk, including the lungs (acute chest syndrome), brain (stroke), eyes (retinopathy) and as in our case, the liver. We hope this case report can become incorporated in future differential diagnoses pertaining to sickle cell crises.

Case Presentation

A 48-year-old black female with a past medical history of sickle cell anemia, HIV on antiretroviral therapy, pulmonary hypertension on 4L of home oxygen, lymphocytic interstitial pneumonitis, chronic obstructive pulmonary disease, remote history of deep vein thrombosis, and pulmonary embolism, presented to the emergency department with complaints of shortness of breath, increased abdominal girth and lower extremity swelling for four days. She also complained of lower back and leg pain typical of her sickle cell crises. Her prescribed medications included tenofovir/emtricitabine, atazanavir, ritonavir, folic acid, oxycodone/acetaminophen, oral hydromorphone, and furosemide. Her social history was significant for smoking one fourth of a pack of cigarettes daily.

Investigations

On presentation her vitals were temperature 98.1°F, blood pressure 106/48 mmHg, heart rate 87 beats per minute, and respiratory rate 19, with an oxygen saturation of 88% on 4L of oxygen by nasal cannula. Her physical exam revealed scleral icterus, diffuse abdominal pain most pronounced in the right upper quadrant to palpation, hepatomegaly and abdominal distention. She did not have any lower extremity edema. Her initial labs showed a total bilirubin of 49.4 (mg/dl), direct bilirubin 42 (mg/dl), AST 165 (IU/L), ALT 110 (IU/L), alkaline phosphatase 434 (IU/L), ammonia level 150 (mcmol/L). Her coagulation studies were partial thromboplastin time (PTT) 32, and an international normalized ratio (INR) of 1.9. She also was found to have a hemoglobin of 6.6 g/dL (down from 9 g/dL three days prior to presentation), white blood cell count of 13.6 (B/L) and platelet count of 276 (B/L). Additionally, the Hemoglobin S (HgS) percentage was 90%. Her creatinine was 2.8 (mg/dL), urea nitrogen 74 (mg/dL), potassium 6.2 (mmol/L), bicarbonate 6 (mmol/L), anion gap of 25. Her other serum electrolytes were within normal limits. Her lactate dehydrogenase was 1405 (IU/L) and haptoglobin <10 (mg/dL). Her ABG showed a pH of 7.2, pCO2 24 (mm Hg), pO2 91 (mm Hg). Lactate was 8.4 (mmol/L). Her CD4 count was 432. A limited abdominal ultrasound showed cholelithiasis with gall bladder sludge, but normal wall thickness and no pericholecystic fluid. The liver measured 22.1 cm in sagittal length consistent with hepatomegaly, but showed normal echogenicity and texture. There was no intra or extrahepatic bile duct dilatation. Renal ultrasound showed no hydronephrosis. An echocardiogram showed a pulmonary artery systolic pressure of 90 mm Hg, normal left ventricle systolic function, right ventricle enlargement and decreased function, but no significant changes from a prior echocardiogram.

Differential Diagnosis

Table 1 highlights our initial broad, problem-based, differential diagnosis. In terms of the workup of her liver failure, the differential was narrowed by the aforementioned lab findings and imaging. The abdominal ultrasound did not show signs of biliary obstruction or thrombus. Hepatitis panels and initial screening for medication induced liver failure were negative. Given her initial liver function elevations and lactic acidosis, it was thought that a vaso-occlusive hepatic crisis was most likely the etiology of her liver failure. Tenofovir, known to cause a severe lactic acidosis, was initially held. The patient was empirically started on broad-spectrum antibiotics, but with negative bacterial cultures and lactic acid resolution following appropriate intervention, the vaso-occlusion from sickled red blood cells (RBC) leading to end organ ischemia was believed to be the most likely etiology. Likewise, this would also explain the pathogenesis behind her renal failure.

The patient was admitted to the medical intensive care unit. A femoral pheresis catheter was urgently placed and she received six units of red blood cell exchange transfusion. Her Hemoglobin S percentage decreased to 42% from 90% after the transfusion and her hemoglobin increased to 9.4 (g/dL), while total bilirubin decreased to 36.3 (mg/dL) and direct bilirubin 29.4 (mg/dL).

Outcome and Follow-up

Once stabilized, the patient was transferred to the general medicine floor for routine care. Her hospital course included episodic shortness of breath and hypoxia, which improved with diuresis. Five days after presentation, her total bilirubin reached a nadir of 9.4 (mg/dL), with a direct bilirubin of 6 (mg/dL) and...
AST / ALT levels of 76 (IU/L) and 140 (IU/L) respectively. Her creatinine stabilized at 1.6 (mg/dL) from a peak of 3.2 (mg/dL) at time of discharge.

Discussion

Sickle cell disease (SCD), as a hemoglobinopathy, can cause widespread sickling and vaso-occlusive events in all organ systems. Although not as commonly seen, liver involvement can be life threatening. Sickle cell hepatopathy has been a term used to generally describe varying etiologies of liver dysfunction in sickle cell patients. Multiple blood transfusions subject patients to increased risk of infectious processes, such as hepatitis B and C, and iron overload. Chronic hemolysis also causes sickle cell patients to be more prone to development of pigmented gallstones, which can lead to acute cholecystitis and/or biliary duct obstruction. Hepatic sequestrations can cause hepatic enlargement and rapidly falling hemoglobin. These complications can present similarly to acute sickle hepatic crisis and need to be excluded to make a diagnosis.1-4

Acute sickle hepatic crisis has been seen in about 10% of patients with SCD. Common presenting symptoms include right upper quadrant pain, low-grade fever, tender hepatomegaly, jaundice and elevated liver function tests. The pathogenesis stems from sickle cell thrombi in the sinusoidal space leading to ischemia. In a more extreme form, this can lead to intrahepatic cholestasis, which is rooted in widespread ischemia secondary to a massive sickled RBC load leading to hepatocyte edema and obstructive biliary outflow.5 AST/ALT levels can run in the thousands, with total bilirubin levels reported as high as 300.6 Coagulopathy is common and worsens as hepatocyte necrosis spreads. Histological hallmarks include sickle cell thrombi within sinusoids that can lead to bile plugs formation in canulici, inflammatory cell infiltration and hepatocyte edema/necrosis from prolonged ischemia. Such hepatic damage makes the prognosis of sickle cell intrahepatic cholestasis poor. Of the limited published cases report, mortality from intrahepatic cholestasis is greater than 50%.5

The cornerstone treatment for intrahepatic cholestasis is rapid HgbS fraction reduction. While there are no specific studies looking at target fractions in acute hepatic sickle cell crises, previous studies focusing on stroke risk in sickle cell patients show risk reduction with HgsS fractions less than 30%.6 Reduction can be achieved through exchange transfusion using pheresis, which allows for better fluid management and avoids rapid changes in volume that can impact intravascular viscosity. Additional supportive treatment includes hydration, pain management, coagulopathy correction, and electrolyte monitoring.

Liver transplantation has been proposed as a therapeutic option in patients with fulminate failure from an acute crisis.7 However, transplantation experience is very limited. Only 18 transplant cases have been reported in the literature.7 Hepatic vascular re-thrombosis and associated phenomenon (i.e. neurovascular injury) from post-operative sickle cell crises add to the inherent morbidity/mortality risk.7 Consequently, the overall mortality rate in SCD patients with acute hepatic failure undergoing transplant is 60%.6 Optimization of post-operative management will improve as transplantation is considered early in patients where fatal hepatic failure is anticipated.

Given the clinical presentation of our patient, she showed signs of ischemia with an elevated lactate, liver and kidney failure. Her hepatitis panels were negative, and ultrasound showed no signs of obstructive disease. Given her significant direct hyperbilirubinemia, it was thought that she was suffering from acute intrahepatic cholestasis causing liver and renal failure. This was confirmed by her immediate improvement after red blood cell exchange transfusion. This case reiterates the need for early detection of liver involvement in sickle cell disease. Early management with exchange transfusion usually prevents potentially fatal liver failure.1

Key Points

- Acute sickle cell hepatic crisis is an uncommon, but potentially fatal sequela of sickle cell disease if not diagnosed early in the disease course.
- Common findings include profound jaundice, hepatomegaly, high AST / ALT, total bilirubin and renal failure.
- Primary therapy is aimed at rapid reduction of the HgbS fraction through exchange transfusion via pheresis.
- Liver transplantation is a possible option in patients with fulminant hepatic failure.

References

A 73-Year-Old Female With Palpitations
Kevin Curl, MD, Jacqueline Kraft, MD, Malinda Wu, MSIII, Carlos Fernandez-Ortega, MSIII

Background
Atrial fibrillation is a commonly encountered clinical problem. Although a large percentage of patients have no clearly identifiable precipitant, secondary atrial fibrillation is a well-documented clinical entity.1

Case presentation
A 73-year-old female with a history of obstructive sleep apnea, hypertension, and chronic obstructive pulmonary disease presents with complaints of intermittent palpitations, substernal squeezing chest pressure, and shortness of breath for two weeks. Her most recent episode occurred on the bus, prompting her to come to the emergency room for evaluation. Further questioning revealed mild weight loss and diarrhea over the prior few weeks. Home medications included amlodipine, baby aspirin, albuterol as needed, and ciprofloxacin for a recently diagnosed URI.

Investigation
Vital signs were temperature 99.4°F, blood pressure 140/70, heart rate 154, respiratory rate 14, with oxygen saturation of 95% on room air. Physical exam revealed scattered bilateral rhonchi, irregularly irregular tachycardia, and mild lower extremity edema. Electrocardiogram (ECG) showed atrial fibrillation with a ventricular rate of 137 bpm and non-specific ST/T wave changes. Initial laboratory studies showed negative cardiac markers, normal blood counts, and normal basic metabolic panel. Transthoracic echocardiogram on hospital day 1 was remarkable for a normal ejection fraction (65%) without segmental wall motion abnormalities, severely dilated left atrium (left atrial volume Index 43 cc/m2), mild left ventricular hypertrophy, and no significant valvular abnormalities. Further lab studies revealed a thyroid-stimulating hormone (TSH) less than 0.01mIU/mL and free thyroxine (T4) of 4.1 ng/dL (0.7-1.7 ng/dL). Endocrinology was consulted and recommended empirically starting methimazole 10 mg three times a day along with further thyroid laboratory investigation, and a thyroid ultrasound. Total triiodothyronine (T3) was 325ng/dL (90-180ng/dL), free T3 was 15.3pg/dL (2-4.4 pg/dL), and thyroid ultrasound revealed a rounded homogeneous thyroid without any dominant nodules greater than1cm. A thyroid uptake scan (Figure 1) exhibited rapid iodine turnover consistent with Graves’ disease. Eventually, thyroid stimulating immunoglobulin returned at a level of 620% (normal <140%) and anti-thyroid peroxidase antibody level was 530.5 units (0-100 units).

Treatment
The patient’s heart rate was initially controlled with intravenous beta-blockers. She was fully anticoagulated for her new-onset atrial fibrillation. The patient’s rate control improved with oral metoprolol in addition to methimazole. She spontaneously converted to sinus rhythm on treatment day 3 of this regimen. Her heart rhythm remained in sinus throughout the rest of her hospitalization, and she was discharged with a enoxaparin to warfarin. She was asked to follow-up with endocrinology as an outpatient to discuss further treatment options for her hyperthyroidism, including possible radioactive ablation.

Outcome and follow-up
The patient has been seen in follow-up in the cardiology clinic. Office exam and ECG revealed frequent atrial ectopy and it is possible that this patient has subclinical paroxysmal atrial fibrillation episodes. She is rate controlled with metoprolol and is anticoagulated with warfarin, which she is to continue for three months. After three months, a one week outpatient telemetry will be ordered to assess her burden of atrial fibrillation. Should she be free of atrial fibrillation, the possibility of discontinuing her warfarin and maintaining her on aspirin mono-therapy will be discussed with the patient.

Figure 1. Thyroid uptake scan showing diffuse thyroid uptake without a dominant “hot” nodule. These findings are consistent with Graves’ disease.
Discussion

Atrial fibrillation is the most common arrhythmia in patients with thyrotoxicosis. Prevalence of atrial fibrillation in hyperthyroidism ranges between less than 2% to 20%.\(^1,2\) Increasing age, male sex and structural heart disease, such as ischemic heart disease, congestive heart failure and valvular disorders (especially mitral valve prolapse), are associated with increased risk of atrial fibrillation in patients with hyperthyroidism.\(^3\) While it is common for hyperthyroid patients to develop atrial fibrillation, less than 1% of all atrial fibrillation patients have hyperthyroidism.\(^4\)

The mechanism by which hyperthyroidism predisposes to atrial fibrillation has not been clearly identified.\(^1\) Thyroid hormone shortens cardiomyocyte refractory period by upregulating the transcription of β-adrenergic receptors, resulting in an increased cAMP that subsequently accelerates diastolic depolarization and increases heart rate. Thyroid hormone shortens the action potential duration of isolated rabbit pulmonary vein cardiomyocytes, which decreases refractoriness and facilitates the genesis of reentrant circuits, thereby increasing the arrhythmogenic activity of pulmonary vein cardiomyocytes.\(^5\)

The cardiovascular manifestations of hyperthyroidism are best corrected by treating the underlying thyrotoxicosis with either antithyroid drug therapy or radioactive iodine thyroid ablation.\(^1\) Pharmacotherapy with methimazole or propylthiouracil can provide a more rapid reduction in serum T4 and T3 than radioactive iodine ablation and is often utilized to prevent the potential thyrotoxicosis exacerbation that can occur with therapeutic doses of radiiodine.\(^6\) Methimazole is typically preferred to propylthiouracil, except during the first trimester of pregnancy, because it can more rapidly reverse thyrotoxicosis and has fewer side effects. Both serum T4 and T3 should be monitored in the treatment of thyrotoxicosis because serum T3 concentrations may remain elevated even with normalization of serum T4.\(^7\) In comparison with the importance of serum T3 and T4 values, serum TSH values may be misleading during the initial period of treatment.\(^8\)

Patients under 60 years of age without preexisting heart disease and short duration thyrotoxicosis typically spontaneously convert to normal sinus rhythm within 6 weeks; the frequency of conversion decreases in older patient populations, who frequently require interventions.\(^9\) The treatment of atrial fibrillation in thyrotoxicosis should be limited to rate control, as cardioversion and normal sinus rhythm cannot be reliably maintained while thyrotoxicosis persists.\(^1\) Patients who experience atrial fibrillation as a complication of thyrotoxicosis are at increased risk of thromboembolism, and should be anticoagulated according to non-valvular atrial fibrillation guidelines. Because thyrotoxicosis is associated with increased plasma clearance of vitamin K-dependent coagulation factors, the dose of warfarin required to achieve full anticoagulation in these patients is lower.\(^10\)

Key Points

Patients presenting with arrhythmias should be screened for thyroid dysfunction. These arrhythmias are best corrected with treatment of underlying thyroid disease. Atrial fibrillation secondary to thyrotoxicosis should be treated with rate control, as cardioversion cannot reliably maintain sinus rhythm.

References

A Young Female Who Develops Tachycardia and Orthostatic Intolerance Following a Recent Infection
Michael A. Valentino, MD, PhD

Case Presentation

The patient is a 20-year-old female with a history of asthma and anxiety with panic attacks who presented with palpitations and lightheadedness/pre-syncope. The morning of admission, she was attending a seminar and experienced an acute onset of palpitations. The palpitations started while she was seated and worsened upon standing. They were associated with lightheadedness, shortness of breath, and chest tightness. A nurse attending the seminar recommended that she go to the emergency room.

On presentation to the emergency department (ED) her vital signs were: Temperature: 99.2°F, Blood pressure (BP): 140/98; Heart rate (HR): 140; Respiratory rate (RR): 16; Oxygen saturation: 100% on room air. She reported that she had experienced prior panic attacks but that this episode was persistent and significantly more intense in comparison. She also reported that a few days prior to presentation she had completed a prolonged course of antibiotics for tonsillitis. Her only medications were oral contraceptive pills (OCPs) and dextroamphetamine/amphetamine (Adderall®). She reported taking her Adderall® as prescribed, most recently on the day prior to presentation. She denied other stimulant or illicit drug abuse. Her family history was significant for anti-phospholipid antibody syndrome (APS) in her mother.

Investigations

On physical exam, she was in no acute distress. She had moist mucous membranes and no conjunctival pallor. Her cardiac exam was remarkable only for tachycardia. The rest of her exam was unremarkable. Orthostatic vitals were checked revealing a BP of 130/75 and HR of 90-110 beats per minute (bpm) while sitting and a BP of 145/97 and HR of 130-150 bpm while standing, with associated lightheadedness and shortness of breath.

Differential Diagnosis

The differential diagnosis included cardiac tachyarrhythmia (e.g. supraventricular tachycardia, atrial flutter/fibrillation), dehydration, anemia, hyperthyroidism, hypoglycemia, pharmacologic stimulant abuse, infection, and pulmonary embolism. An electrocardiogram (ECG) revealed sinus tachycardia (Figure 1) with no significant ST-T wave changes. Labs drawn on admission revealed normal blood counts and chemistries, and her thyroid panel revealed an elevated thyroid stimulating hormone but normal free T3 and free T4 levels. A urine drug screen was positive for amphetamines, consistent with her reported use of Adderall® the day prior to presentation. Given the acuity of onset of her symptoms, her family history of APS, and her OCP use there was a high suspicion for pulmonary

Figure 1. Patient’s admission ECG
Fatigue is also a common symptom, and many patients have surgery or trauma. Initial work-up was negative and her orthostatic tachycardia continued, the Electrophysiology service was consulted. Their differential diagnosis included: amphetamine-induced tachycardia, other exogenous stimulants, and inappropriate sinus tachycardia. However, given the patient’s orthostatic tachycardia with normal BP, her age, gender, and recent infection, the most likely diagnosis was postural orthostatic tachycardia syndrome (POTS).

**Outcome and Follow-up**

On the second day of the patient’s admission, her tachycardia improved. Her HR while ambulating peaked in the 110s associated with only mild shortness of breath. The decision was made not to treat with beta-blockers or calcium channel blockers since she remained hemodynamically stable and only minimally symptomatic. She was instructed to discontinue the Adderall® and avoid any other stimulants, including caffeine. She was to follow-up with Electrophysiology at Thomas Jefferson University Hospital and to schedule an outpatient tilt table test.

**Discussion**

Orthostatic intolerance is defined as cerebral hypoperfusion or sympathetic activation while standing, relieved by recumbency. POTS is a clinical syndrome characterized by orthostatic intolerance without orthostatic hypotension. The accepted definition of POTS is orthostatic intolerance with a rise in HR of >30 bpm within 10 minutes of head-up tilt or standing, or a HR of >120 bpm while upright, without orthostatic hypotension.

The majority of patients with POTS are young females, with an average age of 30 years. The most common symptoms are those related to cerebral hypoperfusion and sympathetic activation. Fatigue is also a common symptom, and many patients have poor exercise tolerance. While most patients cannot identify an inciting event, some patients recall an antecedent viral illness, while others associate the onset of symptoms with recent surgery or trauma.

Several pathophysiologic mechanisms have been proposed to underlie POTS. About 50% of patients with POTS have regional autonomic denervation, typically in the lower limbs. Sympathetic denervation of the lower extremities, as demonstrated by a quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test, and impaired norepinephrine spillover in the lower extremities in response to various stimuli, can cause loss of vasomotor tone and pooling of blood in the legs. This can cause a decrease in preload upon standing and a reflexive increase in sympathetic stimulation of the heart in order to maintain cardiac output. The cause of this peripheral sympathetic denervation is still unclear, but ganglionic (α3) acetylcholine receptor (AChR) antibodies have been demonstrated in ~15% of patients with POTS indicating a possible autoimmune mechanism.

Another subset of POTS is characterized by a hyperadrenergic state with elevated plasma norepinephrine levels (>600 pg/mL) and a rise in BP on standing. In a recent study, 29% of patients with POTS had elevated plasma levels of norepinephrine upon standing, and these patients benefited the most from β-blockade.

In some patients, hypovolemia may also contribute to the manifestation of POTS. Dysfunction of the renin-angiotensin-aldosterone system has been implicated as a cause of the hypovolemia observed in some patients with POTS, as these patients lack a compensatory increase in circulating renin and aldosterone despite low plasma volume.

Several investigations should be made to establish the diagnosis of POTS including: orthostatic vitals (head-up tilt or standing), QSART response, thermoregulatory sweat test, supine and standing norepinephrine measurements, and 24-hour urine sodium excretion (surrogate marker for plasma volume).

Pharmacologic treatments for POTS are aimed at increasing plasma volume (fludrocortisone, erythropoietin), enhancing venous return to the heart (midodrine, octreotide), or counteracting a hyperadrenergic state (β-blockers, clonidine, pyridostigmine, disopyramide). Nonpharmacologic treatments for POTS include high salt intake, water repletion, small frequent meals, regular exercise, and compression stockings. Typically, treatment is tailored toward the suspected underlying mechanism determined from autonomic testing.

**Key Points**

POTS is a disorder that is most common in young females and characterized by orthostatic intolerance without a decline in blood pressure. The syndrome may have several etiologies, which include peripheral denervation with lower extremity pooling of blood, a hyperadrenergic state, and low plasma volume. In a significant number of patients, the symptoms of POTS are manifested shortly after an infection, as occurred in our patient’s case, or following other stressful events such as surgery or trauma. Initial work-up includes ruling out common etiologies for tachycardia, including: cardiac tachyarrhythmia, anemia, stimulant abuse, dehydration, pulmonary embolism, and hyperthyroidism. The patient should have orthostatic vitals measured or undergo a formal tilt table test. An increase in HR of >30 bpm or a HR of >120 bpm upon standing, without orthostatic hypotension, correlates with a diagnosis of POTS. The patient should then undergo autonomic testing as outlined above to determine the etiology of the patient’s orthostatic intolerance and determine the most appropriate therapy.
References


"Pier"
photograph by Rajan Singla
Metastatic Uveal Malignant Melanoma: A Case Report

James Walter, MD, Rebecca Matro MD, and Daniel Quirk, MD, MPH

Case Report

A 77-year-old woman presented with a chief complaint of one day history of severe, acute abdominal pain. The patient described the pain as “intense,” non-radiating, and located primarily in the left upper abdominal quadrant. The pain was associated with nausea and multiple episodes of non-bilious, non-bloody emesis. She denied melena and hematochezia. On physical examination, her abdomen was soft and exquisitely tender in the left upper quadrant and epigastric regions. Aside from trace lower extremity edema, the remainder of her physical examination was unremarkable. Laboratory results at the time of admission were notable for: hemoglobin 10.8 g/dL, alkaline phosphatase 459 U/L, aspartate transaminase 56 U/L, and alanine transaminase 66 U/L.

The patient’s past medical history was significant for hypertension, gastroesophageal reflux disease, papillary thyroid carcinoma, and right eye uveal melanoma. The ocular melanoma was treated 16 years ago with radioactive plaque followed by transpupillary thermal therapy. The patient was diagnosed with metastatic disease to her liver approximately 6 years prior and she had received several rounds of hepatic radiation and chemotherapeutic embolizations. The patient’s oncologist closely monitored her for disease progression through regular abdominal imaging studies.

An esophagogastroduodenoscopy revealed a normal esophagus, numerous hyperpigmented flat to slightly raised lesions throughout the stomach, particularly in the proximal body and fundus (Figures 1, 2), and a 2 mm lesion in the duodenal bulb. Histopathology and immunohistochemical staining of these lesions confirmed metastatic malignant melanoma (Figure 3).

Discussion

The incidence of cutaneous malignant melanoma is rising at a rate faster than that of any other malignancy.1 Melanoma is notorious for its aggressive ability to metastasize to nearly every part of the body, with the liver, lung, and bone being the most common sites.2 With specific regards to uveal melanoma (UM), it is the second most common form of melanoma.3 Unlike the cutaneous form, UM’s incidence rate has remained stable over the years. UM can arise anywhere within the uveal tract (iris, ciliary body and choroid) and spreads hematogenously. Hematogenous spread is favored over lymphatic spread due to the lack of sufficient lymphatic drainage.4,5

Melanoma’s particular affinity for metastasizing to the gastrointestinal (GI) tract has been well described in the literature. GI involvement has been found in up to 60% of primary cutaneous malignant melanoma patients at autopsy and is commonly associated with invasive visceral organ disease. Given the highly vascularized nature of the small bowel, it is the most common site of GI tract metastasis. Stomach involvement comprises approximately 20% of GI tract metastasis cases. Antemortem diagnoses of GI metastasis are made in only 1% - 4% of patients with malignant melanoma. Such a diagnosis can go clinically undetected until years after the initial diagnosis.6,7
Endoscopically, metastatic melanoma can be polypoid in nature, is frequently ulcerated, and is either pigmented or amelaontic. Large polypoidal lesions can be obstructive in nature and can act as lead points for intussusception. Submucosal nodules with similar characteristics have also been seen.

Symptoms of GI melanoma metastasis tend to be inconspicuous and nonspecific. Patients may report vague abdominal pain, weight loss, nausea/vomiting, and/or malaise. Anemia may also be seen as a result of slow, chronic blood loss from ulcerated lesion sites giving rise to melena. Such symptoms should raise suspicion in patients with a known history of melanoma. However, with a median survival time of less than six months after confirmed GI involvement, the prognosis is generally very poor.

References
Easing the Pain: An Argument for Prescribing Opiates in Continuity Clinic
Lindsay Wilde, MD

Continuity clinic can be painful. The patients are often non-adherent, the no-show rate is high, and the paper-electronic records hybrid system is less than ideal. Added to that is the stress of caring for patients with a variety of medical issues and the burden of being expected to prescribe opiates for them. Given all of the difficulties associated with opiate prescribing, including the potential for abuse, limited continuity with providers, and poor overall adherence to medical advice, it has been proposed that these medications should no longer be prescribed at our resident clinic, and many residents support this plan. However, implementing a blanket moratorium on opiate prescribing would violate several of the fundamental principles of our medical training.

According to U.S. Food and Drug Administration data, approximately one hundred million new opiate prescriptions were written in the year 2009. Of these prescriptions, general internists were responsible for writing about fifteen percent of them, including both immediate and extended release formulations. So, if opiate use is so fraught with problems, why are physicians prescribing so many of them? This is likely because they are some of our most effective medicines and many of our patients need immediate relief from acute pain.

There is a wealth of evidence that has shown opiates to be effective in the management of acute pain. Eliminating opiate prescribing in our continuity clinic would limit our ability to provide comprehensive treatment to those patients with acute pain needs. Similarly, it would deprive patients of adequate pain control in the acute setting. In the spirit of practicing evidence-based medicine, as well as upholding the core value of beneficence, it is our responsibility to prescribe opiates to those patients for whom the benefits outweigh the potential risks.

The ability to prescribe the full range of medications for pain management is also a necessity for the residency program. Residency training is designed to broaden the knowledge and experience of new physicians. This includes an education in appropriate pain management strategies. In fact, the Accreditation Council for Graduate Medical Education lists education in the use of common medications, including pain medications, as a requirement for the accreditation of all internal medicine residency programs. While didactic sessions are useful and necessary in fulfilling this requirement, there is no substitute for first-hand clinical experience. Learning to partner with patients in the clinic in order to manage their pain and seeing their response to different therapies is an integral part of our preparation for future practice. Regardless of our career path, we will all be caring for patients who are in pain, and it is imperative to know how to care for them. Continuity clinic is one place where we must gain this knowledge.

It is without question that our current method of prescribing opiates in clinic is imperfect. However, simply suspending the practice would deprive us of a valuable quality improvement opportunity. Reviewing the pain management literature, creating an educational curriculum, developing a prescribing policy, and implementing evidence-based monitoring practices would not only serve as an important educational exercise, but it would also help to alleviate many of the stressors that we face in continuity clinic on a daily basis.

As residents, it is imperative that we remain dedicated to expanding our medical knowledge and implementing evidence-based practices in order to provide our patients with the highest level of medical care. Learning to uphold these fundamental principles during our training will help to ensure that we continue to do so for the duration of our medical careers. Therefore, we should rethink the way we prescribe opiates in clinic and, instead of prohibiting the practice altogether, commit ourselves to improving what we do, both for the sake of our education and for our patients.

References
Chronic pain is one of the most common complaints a primary care physician faces while in practice. As resident physicians at Jefferson Hospital Ambulatory Practice (JHAP), it is a frequently addressed concern, which ultimately leads to the question of whether or not opiates should be prescribed at JHAP to those patients who have failed non-narcotic alternatives.

The hesitation most physicians have in prescribing such medications is the potential for abuse, addiction and diversion. The Drug Enforcement Administration (DEA) shares these concerns and consequently monitors and restricts the prescription of opioids, stimulants and anxiolytics by requiring a separate license. Most resident physicians choose to not obtain a DEA license because of the cost, but also due to the convenience of not having the responsibility that comes from prescribing controlled substances.

In a European study evaluating the prescribing habits of general practitioners, nearly a quarter refused to prescribe opioids for persistent non cancer pain. Both prescribers and non prescribers expressed concern over risks of opioids and believed to be inadequately trained in treating chronic pain. To alleviate such concerns, an institution sponsored training program in treating chronic pain and assistance in obtaining a DEA license would perhaps foster an environment that is more conducive to prescribing narcotics at JHAP.

Even with appropriate training and the understanding that these medications have a potential for abuse and diversion, misuse of opiates is a common occurrence and growing problem. In a prospective cohort study, the one-year incidence of opioid misuse among patients enrolled in a chronic pain disease management program within an academic internal medicine practice was 32%.

Practicing in a tertiary care center allows us to utilize resources that would otherwise be inaccessible in a community setting. The Jefferson Pain Center is one of those resources dedicated to providing comprehensive, pain-focused evaluation and treatment of chronic pain. Referral to such a center would allow patients to be treated by physicians trained specifically to deal with their concerns in a setting with established guidelines and protocols.

In light of such concerns for abuse, lack of training and appropriate licensure, and the availability of alternative resources at Thomas Jefferson University Hospital, the utilization of such alternative resources for treatment of chronic pain would be most appropriate for a resident physician practice such as JHAP.

References

The Graduate Medical Education (GME) committee is composed of all Jefferson residency and fellowship program directors, as well as ten selected housestaff members. The committee meets monthly to discuss a wide array of topics, including Accreditation Council for Graduate Medical Education compliance, duty hours violations, and program reviews. One recently covered topic was the timeliness of discharge summary dictations. Implementing changes to improve transitions of care remains a focus of all healthcare systems. Jefferson is attempting to take an innovative approach to this issue, and discharge summaries are only one of the areas being examined.

The current policy requires housestaff to dictate the discharge summary within 14 days of discharge. Delinquent summaries receive a monetary fine on a weekly basis. Attending physicians have up to 120 days from discharge to finalize the summary, which is currently not in line with the Joint Commission mandate of finalized summaries within 30 days of hospital discharge. With increasing emphasis on early outpatient follow-up, many primary care physicians are seeing patients prior to having access to the discharge summary. Because of the disparity between the current policy and goal of timely clinical follow-up, Jefferson is examining the current timeline to address this issue.

At its September meeting, the committee heard a proposal to alter the required time of finalizing the discharge summary to 17 days. Members discussed the appropriate allocation of the seventeen days between housestaff and attending physicians. Housestaff members were encouraged to voice their opinion about changing the current 14 days to 10 or possibly 7 days. The official recommendation of the committee was to preserve the current 14 day policy for housestaff, while making necessary adjustments to the attending policy.

After significant discussion and review by multiple hospital subcommittees, the official policy was announced at the January 22nd, 2013 GME committee meeting. The time for house staff will remain unchanged at 14 days, and the attending policy will change to 30 days from hospital discharge. Punitive measures for delinquent attending finalized discharge summaries will increase, including suspension and revocation of admitting privileges. This policy was officially implemented in April 2013. Undoubtedly, improving healthcare provider hand-off will remain an area of focus throughout the healthcare system. The Jefferson discharge summary policy will likely remain a target for improvement in the future.
I was clearly out of place. I came to the highlands of Guatemala during my fourth year of medical school to study Spanish, work in a rural clinic, and experience a different way of life. For a month, I lived with a Guatemalan family, ate plantains with every meal, and generally tried to immerse myself in the rich Mayan culture surrounding me. Almost a year later, my Spanish is fading fast. The handful of days I spent in volunteer clinic is a distant memory at this point. Why did I go there again?

I was the epitome of an outsider. I came down with Montezuma’s revenge, just like all of my American classmates who traveled there with me. Despite its location in tropical Central America, Guatemala is an exceptionally mountainous country and despite all the warnings from the program’s director about the cool climate, I severely under packed. That left me living, eating, and sleeping in my one Patagonia fleece. As a tall American, I towered over the local people and fit very poorly in nearly all things Guatemalan. I rode buses with my knees under my chin and my head on the ceiling.

The coup de grace occurred while I was walking down a street near my Guatemalan family’s home. One of the storefronts was doing construction that involved scaffolding above the sidewalk, which I had safely avoided, until now. This time, I walked smack into a wooden beam at full clip. I was jolted backwards and fell flat on my back. I had taken the impact right over the bridge of my nose, where luckily I had been wearing a pair of sturdy sunglasses. I’m convinced that were I not wearing them, I would have broken my nose or knocked out some teeth. In any case, this beam of wood—at over six feet above the ground—was much too high to bother the locals as they all passed under it with ease. Again, I was out of place—and fortunate to escape with only some minor cuts and a bad headache.

I realized then that it was this feeling of foreignness, of not belonging, that came to define my experience there. Living in a foreign place freed me to approach my time in Guatemala as something altogether different. I didn’t want to and really couldn’t compare it to my American life because that would be like comparing apples and oranges. The value was in recognizing this disparity and taking Guatemala for what it was. It took me several weeks, but I turned the corner while I still had the chance to enjoy my time there. Accepting the discomfort is what allows us to grow.

Mayan culture fascinated me, and I rekindled my love of learning languages that had fallen by the wayside for a decade. I took pleasure in exploring a new diet and helped my host family’s children with their English homework. Interactions with Guatemalan medicine showed me new approaches to familiar problems, and the crippling limitations of third world countries.

I don’t know if I will ever have another opportunity to immerse myself in a different culture, but the future holds many more challenges to my comfort zone. When I flew out of Guatemala, I knew in my heart that I would never return—or that if I did, it wouldn’t be the same. Still, that didn’t change what I learned and how I felt while I was there. I was too tall, yes, but that’s precisely what allowed me to make the most of it.
**Doximity**  
**Price:** Free  
**Platform:** iOS, Android  
**What It Does:** Doximity is a professional network for physicians. It offers a comprehensive medical directory with 140,000 doctors. Additionally, the app gives a free fax number to everyone who joins, allowing you to securely receive medical records directly into your phone.  
**Likes:** Allows you to quickly and easily receive medical records and look up contact info for doctors.  
**Dislikes:** Not possible to print the records that you receive.

**ECG Source**  
**Price:** $1.99  
**Platforms:** iOS  
**What It Does:** This app lists the criteria for different EKG diagnoses and provides a full searchable list of ECG diagnoses and criteria. It also has many sample EKG’s, a quiz and video tutorials.  
**Likes:** Good reference app.  
**Dislikes:** Videos are too simplistic and the quiz only offers 4 sample questions.

**GoodRx**  
**Price:** Free  
**Platforms:** iOS, Android  
**What it Does:** This app enables you to find out the price of any medication without insurance at local pharmacies.  
**Likes:** Enables providers to find affordable medications for patients.  
**Dislike:** Some prices reflected are after a coupon associated with the app, although these can be printed for patients on the GoodRx website.

**Heart Failure Trials**  
**Price:** $2.99  
**Platforms:** iOS, Android  
**What It Does:** The app summarizes pertinent trials that are relevant for the treatment of heart failure. It organizes the trials by EF, class of medication, and name of medication. It gives a comprehensive summary of the trial, including methods, inclusion/exclusion criteria, results and more.  
**Likes:** Well organized, comprehensive.  
**Dislikes:** Possibly too advanced for medical students.

**QX Calculate**  
**Price:** Free  
**Platforms:** iOS, Android, BlackBerry  
**What it Does:** This app provides a repository of calculators, equations, and scores that are split by specialty.  
**Likes:** Easy to use calculators while on rounds.  
**Dislike:** Can be hard to find certain calculators.
Cover Art

*Photograph:* “Philadelphia Skyline, South Street Bridge” by Andrew Zabolotsky

*Front Cover:* Editors of Jefferson Forum 2013
(from left to right): Erika Villaneuva, MD, Eve Merrill, MD, Brian Curtis, MD, Christina Lindenmeyer, MD, Rina R. Shah, MD, Harkirat Singh, MD, Mariam Kabir, MD, Mitul Kanzaria, MD, Natasha Fonseka, MD, Andrew Zabolotsky, MD