Welcome to the Forum!

It is bittersweet to write my final Message from the Program Director for the Forum. This publication is one example of the passion, talent, creativity and scientific inquisitiveness of our Jefferson residents. As a completely resident run journal, what follows in this journal helps prove to me that the future of medicine is in good hands.

In my time as program director, we have seen many changes in the healthcare landscape, both nationally and locally at Jefferson. We have launched the Milestone evaluations in the Next Accreditation System for the ACGME and are embarking on major curricular reform at the UME level to better align training as a continuum. We are having real and meaningful conversations about quality, safety and value and thinking critically about those aspects of our care of patients. Wellness is a concept that no longer only conjures yoga and crystals, but is taking shape in our curriculum to train doctors who can cope with the difficult situations they watch their patients endure every day and the stressors that being a physician piles onto their lives. The new EMR is increasingly seeming like a reality and more of our patients are insured and taking ownership of their health.

As I prepare for the next step in my career, I marvel at what our residents are capable of and it makes my heart burst with pride when I watch them in action! I will always strive to be a meaningful part of the education of our residents and hope to continue to make Jefferson an ever stronger place to learn to practice medicine. I leave you in good hands and you will all remain in a special place in my heart for all we’ve been through together!

Never stop trying to be the best at what you do!

All the best,

Gretchen Diemer, MD, FACP
Associate Professor of Medicine
Program Director Internal Medicine
Associate Dean for GME and Affiliations
Dear Students, Residents, Faculty, and Friends of the Forum,

We are excited to present you with the 16th annual edition of The Medicine Forum. This work is a culmination of months of effort on the part of medical students, residents, fellows and faculty to share clinical pearls from the last year of their experiences.

Amongst the greatest strengths of medical professionals and patients alike is the ability to tell stories. Stories, and how they are told form the basis of medical care. The way in which a particular patient’s story unfolds has a lasting impact on physicians, trainees, other medical staff, and perhaps most importantly, on future patients. Stories of patient cases formed the earliest beginnings of evidence-based medicine. There is a Babylonian tablet dating earlier than 6000 B.C.E. which describes a case of “dropsy”, for the instruction of patients of this condition.¹ Stories told amongst practitioners of medicine date back to the first published medical journal, the Acta Medicorum Berolinensium, from Berlin in 1722.²

In today’s era of information technology, the amount of information collected, analyzed and reported in medicine is beyond the scope of any one physician to even be aware of, let alone to read. In 2001 alone, the total number of articles indexed on MEDLINE was over 400,000.³ Burgeoning topics in how the evidence base is gathered in medicine include the use of Big Data analytic methods to provide patients and physicians with real time data on outcomes as a tool of medical decision making. While these efforts are in progress, the art and the science of medicine continue to rely upon experience from patient stories, both our own, and from those of others.

In the Forum this year, we present a collection of stories, namely patient cases, which highlight the process of differential diagnosis, novel associations, and medical decision making. We would like to thank our contributors for their commitment to scholarship, our editorial staff for their attention to detail, the Media department for the artistic expertise, and the Department of Medicine for funding support. We hope you will enjoy reading the stories presented here, and that they will be instructive in your future practice.

From the Editors-in-Chief,

Anusha G. Govind, MD
Loheetha Ragupathi, MD
Michael A. Valentino, MD, PhD

¹ Squire S. Medical Journalism and Scientific Progress. JAMA. 1928;91(25):1990-1993
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A Case of Ipilimumab Induced Hypophysitis

Eric Shiffrin, MD and Melinda Ukrainski, MD

INTRODUCTION

Ipilimumab (Yervoy®) is a human monoclonal antibody that has been shown to significantly improve survival in cases of metastatic melanoma. Ipilimumab blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4), a protein receptor on the surface of T-cells, resulting in their activation, proliferation and an anti-tumor response. Commonly reported immune-related side effects of ipilimumab are enterocolitis, dermatitis, and hepatitis. However, different endocrinopathies, including autoimmune hypopituitarism, have become emerging clinical entities in patients taking ipilimumab. We present a case of ipilimumab induced hypophysitis in a 62-year-old male presenting with fatigue and hypotension.

CASE PRESENTATION

A 62-year-old male with a history of melanoma metastatic to the lung and brain status-post frontal craniotomy and whole brain radiation, as well as a recent diagnosis of hypothyroidism, presented from the oncology office with hypotension after receiving his fourth dose of ipilimumab therapy. The patient had a routine blood pressure check after the chemotherapy infusion and was found to be hypotensive at 80/58 mmHg. He reported increasing fatigue over the past week. He denied chest pain, shortness of breath, dizziness and headache. He was given one liter of normal saline solution, but remained hypotensive and was directly admitted to the hospital.

On physical exam, the patient was tachycardic to 102 beats per minute with a regular rhythm, clear lungs, and positive orthostatics. Laboratory studies were significant for a thyroid stimulating hormone of <0.02 uIU/mL (normal range = 0.3 – 5 uIU/mL), free T4 of 1.2 ng/dL (normal range = 0.7 – 1.7 ng/dL), follicle stimulating hormone of 0.9 mIU/mL (normal range 1.5 – 12.4 mIU/mL), adrenocorticotropic hormone (ACTH) of <9 pg/mL (normal range 9 – 46 pg/mL), total testosterone of 4 ng/dL (normal range 250 – 1100 ng/dL), and a free testosterone of 0.4 pg/mL (normal range 35 – 155 pg/mL). His white blood cell count, hemoglobin and electrolytes were within normal limits. A noon cortisol was 0.3 mcg/dL (normal A.M. range 16 – 20 mcg/dL and P.M. range 2 – 12 mcg/dL).
MRI findings in ipilimumab-induced hypophysitis are non-specific and are typically characterized by a diffuse enlargement and homogeneous enhancement of the pituitary gland. Less commonly, heterogeneous enhancement has also been described. While it is common to have radiographic evidence of hypopituitarism, a normal MRI is possible. Follow-up imaging often shows resolution of abnormal findings after hormone replacement.

Pituitary hormone replacement with corticosteroids is critical to treatment, assuming ACTH is low. Either high dose or physiologic replacement dose corticosteroids are needed. Current recommendations advocate for high dose (1-2 mg/kg/day of prednisone or equivalent) steroids for moderate to life threatening symptoms. However, it is not clear whether initial high doses of corticosteroids are beneficial in treating hypophysitis. While they may play a role in reducing inflammation, they do not improve neuro-endocrine function compared to physiologic doses. However, high doses of corticosteroids may increase morbidity through side effects.

Mineralocorticoid replacement is not needed since the renin-angiotensin-aldosterone system is still intact. It should be at the discretion of the oncologist and endocrinologist as to whether ipilimumab should be continued based on the condition of the patient and response to hormone replacement. Hormone deficiencies can improve, although corticotroph function seems to be the least likely to recover. Many doctors recommend close monitoring for hormone abnormalities in patients receiving ipilimumab, especially after the third infusion.

DISCUSSION

Endocrine-related adverse events were reported in 8.5% of patients in a recent phase III trial designed to evaluate ipilimumab as an adjuvant therapy following resected stage III melanoma, with hypophysitis encompassing 5.1% of these events. The majority of patients who develop hypopituitarism do so after the third or fourth dose of ipilimumab, suggesting a possible cumulative effect. Adverse events have limited the duration of use of the drug in patients who could have clinical benefit from additional therapy.

The mechanism of hypopituitarism is likely from ipilimumab’s immunomodulatory effect on activating T-cells, resulting in a lymphocytic hypophysitis. It has also been shown that some pituitary cells express CTLA-4, the receptor target of ipilimumab. Therefore, it remains unclear whether the adverse effects are caused by T-cells acting against antigens shared by tumor cells and normal cells or from a direct antibody effect on CTLA-4 receptors on pituitary cells, or both. Presenting symptoms are related to a pituitary mass effect and consequent hormone deficiencies.

Clinical manifestations may be non-specific as they depend on the extent of hormone deficiencies. Additionally, it is often difficult to recognize many of these symptoms in patients undergoing chemotherapy, but there should be a low threshold to consider hypophysitis in a patient taking ipilimumab. Typical symptoms include fatigue, headache, and loss of libido. Other symptoms could include cold intolerance, visual disturbances, hypotension, hypoglycemia and hyponatremia. Our patient reported fatigue, but his diagnosis only became apparent after hypotension was noted.

KEY POINTS

Hypophysitis is a well recognized side effect of ipilimumab therapy. A high clinical suspicion for hypopituitarism in patients receiving the drug is imperative due to the non-specific symptoms and potentially life threatening consequences. Corticosteroids should be promptly initiated as soon as secondary adrenal insufficiency is detected. While ipilimumab has many side effects, the drug has improved survival in metastatic melanoma and remains an important treatment option.
REFERENCES


INTRODUCTION
Takotsubo cardiomyopathy (TC), also known as stress cardiomyopathy, and broken heart syndrome is characterized by transient left ventricular (LV) apical akinesis with symptoms mimicking acute coronary syndrome. The first case was described by Sato et al. in Japan.¹ The Japanese word “takotsubo” translates to “octopus pot” describing the shape of the left ventricle during systole. TC can be triggered by a “broken heart” including death of a loved one, constant anxiety, surgery, or critical illness etc. Prevalence is around 2% to 3% with over 90% in postmenopausal women aged between 58 and 75. Its pathogenesis remains unclear. Some postulated that excess catecholamine released during stress can induce an exaggerated sympathetic response precipitating severe, reversible LV dysfunction in patients without coronary disease.² Whether there is a genetic component is not well understood. There are a few reported cases of Takotsubo in family members, one case of two sisters and another mother-daughter pair.³⁴ Recurrence of the syndrome in the same patient, although rare, can occur and suggests a genetic predisposition.³

Majority of patients regain normal ventricular function within one to four weeks if they survive the acute episode. Hospital mortality rates range from 0 to 8%. However, one major complication is the risk of intraventricular thrombus formation and systemic embolization. Data is lacking to guide anticoagulation for LV thrombus prevention in patients with stress cardiomyopathy.

CASE PRESENTATION
Mrs. S is a 62 year old woman with a prior history of TC with full recovery, hyperlipidemia, and gastroesophageal reflux disease presented with chest pain radiating to her left shoulder. She was under significant financial stress during that week. Her pain was unrelieved with aspirin or sublingual nitroglycerin. In the emergency room, her electrocardiogram showed ST segment elevations in leads V2-V6 (Figure 1) with Troponin T 1.49ng/mL. She was immediately started on heparin and nitroglycerin drips and rushed to the catheterization laboratory. Coronary angiography did not reveal significant coronary disease but incidentally found elevated pulmonary

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Figure 1. Mrs. S’s initial EKG showing ST segment elevations in leads V2-V6.
wedge pressures. Upon transfer to the cardiac intensive unit, Mrs. S became hypotensive and norepinephrine was started. Her transthoracic echocardiogram (TTE) revealed moderately decreased LV systolic function with an estimated ejection fraction (EF) of 35%, with segmental wall motion abnormalities, mid and distal akinesia of the LV and hyperkinesis of basal LV. There was a late-peaking LV outflow tract gradient of 77 mm Hg consistent with severe, dynamic left ventricular outflow tract (LVOT) obstruction.

She had a prior episode of TC when her husband passed away three years ago. She also has a twin sister who suffered from TC a year ago when she lost her job. Unlike Mrs. S, she did not fully recover and required long term heart failure management.

DIFFERENTIAL DIAGNOSIS
Takotsubo was at the top of our differential given the patient’s personal and family history and recent financial stress. The lack of significant coronary disease on LHC clinched the diagnosis of stress cardiomyopathy.

OUTCOME AND FOLLOW-UP
Mrs. S was diagnosed with TC with LVOT obstruction complicated by cardiogenic shock. The LVOT obstruction made treatment particularly difficult given that inotropes can worsen the obstruction. Due to tachycardia, she was switched from norepinephrine to phenylephrine. On day 2, Mrs. S developed hypoxia and was intubated and rushed to cath lab for intra-aortic balloon pump insertion. However, the procedure was aborted when her right heart catheterization numbers and vital signs improved. She continued to recover on supportive care and was successfully extubated on day 8. Her repeat TTE showed recovery of systolic function (EF 70%) but revealed a 2.3 x 1.1 cm LV apical thrombus. Heparin drip and warfarin were initiated. On day 9, patient reported blurry vision and a left visual field defect that were persistent despite wearing her glasses. Although her head CT scan was negative for mass effect or stroke, her head MRI revealed a recent punctate infarction in the right occipital lobe. In addition, on day 11, Mrs. S developed intractable back pain and a CT Abdomen and Pelvis showed new wedge-shape perfusion defects in the right kidney consistent with infarcts.

DISCUSSION
This case has multiple teaching points. First, it is one of the few cases of a patient with a recurrence of Takotsubo as well as a twin sister who suffered from the same syndrome suggesting a possible genetic predisposition to stress cardiomyopathy. Second, it emphasizes the risk of intraventricular thrombus formation and systemic embolization in patients with TC and raises the important discussion on whether these patients should receive prophylactic anticoagulation.

Familial cases of stress cardiomyopathy are very rare. One case reports a 64 year old female diagnosed with TC when presented with sudden chest pain, elevated cardiac enzymes and ST elevations. Her elder sister developed TC one year prior with similar presenting symptoms. There are also several other reports of sisters with TC. Studies on genetic polymorphisms for Takotsubo have been inconclusive. One study found an association between patients with TC and beta 1 adreno-receptor gene polymorphisms, suggesting possible genetic disease modifiers for developing TC. However, a large Australian study did not find any association between functional variants in the G-protein-coupled receptor kinase 5 genes or the β1-adrenergic receptor with the occurrence of the syndrome. More research is also needed to understand the risk and prevention of thromboembolism in TC patients. In a Japanese study of 21 patients with Takosubo, they found that 3 patients (14%) suffered thromboembolism, one of which had a LV thrombus. They recommended prophylactic anticoagulation for TC patients with severe wall motion abnormality to prevent cardioembolic stroke.

There are scant data on criteria for prophylactic anticoagulation to prevent thromboembolism in TC. In patients with myocardial infarction, it has been found that reperfusion therapy and anticoagulant therapy lowers the risk of thrombus formation, which would also lower the risk of thrombus embolization. In a 1993 meta-analysis in patients who had an anterior MI, the odds ratio of LV thrombus in patients treated with fibrinolytic was half compared to no fibrinolytic therapy. The same study also showed that initiating heparin early and for more than 48 hours lowered the rate of thrombus formation. In a randomized control trial, high dose (12,500 units) subcutaneous unfractionated heparin given every 12 hours for 10 days was associated with lower incidence.
of LV thrombus compared to low dose (5,000 units). (11 versus 32 percent). Amongst patients who already developed a LV thrombus, anticoagulation with warfarin lowers the risk of thrombus embolization. An observational study of 43 patients with LV thrombus after MI found no embolic events in the 25 patients treated with anticoagulation compared to 7 of 18 untreated patients having an embolic event, all occurring within 4 months. Although no studies have been done on patients with stress cardiomyopathy, it would be reasonable to initiate anticoagulation in patients with severe LV dysfunction to prevent thrombus.

KEY POINTS

1. Familial and recurrent cases suggest a genetic predisposition to Takotsubo cardiomyopathy.
2. Patients suffering from stress cardiomyopathy with severe LV dysfunction may benefit from early anticoagulation to prevent thromboembolism.

REFERENCES

INTRODUCTION

Tick-borne infections were first formally recognized over a century ago, but it was only in 1990 that the first case of human granulocytic anaplasmosis (HGA), a tick-borne infection caused by *Anaplasma phagocytophilum*, was identified.1,2 Like other tick-borne infections, HGA presents as a nonspecific febrile illness. The most common clinical features are fever, headache, myalgia and malaise.2 This case report presents a rare but serious complication of HGA – acute respiratory distress syndrome (ARDS).

CASE PRESENTATION

A 49-year-old female with no past medical history presented to her local emergency department with complaints of fevers, headache, neck pain, myalgia, and malaise. She denied symptoms of upper respiratory tract infection, diarrhea, dysuria, rashes, and bleeding or bruising. She worked as an administrative assistant and lived on a farm in a rural area of Pennsylvania. She was in a monogamous relationship. She drank alcohol socially, and she was not known to use any illicit drugs.

Her vital signs were temperature of 102 degrees Fahrenheit, pulse of 100 beats per minute, oxygen saturation of 98% on room air, and respiratory rate of 18 breaths per minute. On physical examination, she appeared fatigued but was alert and oriented to person, place, and time. There were no focal neurologic deficits. Her oropharynx was clear. Her neck was supple with full range of motion. Brudzinski and Kernig test were negative. Her lungs were clear to auscultation. Cardiac exam revealed tachycardia but no murmurs, rubs, or gallops. Her abdomen was soft and non-tender. There were no stigmata of liver disease. She had no rashes and no cutaneous bleeding. There were no palpable lymph nodes.

Laboratory evaluation revealed a white blood cell count of 2 x 10^9/L (normal range = 4-11 x 10^9/L), platelet count of 43 x 10^9/L (normal range = 140-400 x 10^9/L), and hemoglobin of 11 g/dL (normal range = 14-17 g/dL). Her liver function panel revealed an aspartate aminotransferase (AST) of 923 U/L (normal range = 7-42 U/L) and alanine aminotransferase (ALT) of 946 U/L (normal range = 1-45 U/L). Her bilirubin and alkaline phosphatase were mildly elevated. The patient was admitted for Systemic Inflammatory Response Syndrome (SIRS). She was empirically started on vancomycin and piperacillin-tazobactam. On her first day of admission she developed hypoxemic respiratory failure. A chest x-ray showed bilateral airspace opacities without evidence of volume overload. Mechanical ventilation was initiated and doxycycline was added. She was transferred to Thomas Jefferson University Hospital for management of ARDS.

DIFFERENTIAL DIAGNOSIS

The patient’s high fevers and acute onset of symptoms suggested an infectious etiology. Cerebrospinal fluid testing was negative for viral, fungal, and bacterial pathogens. Bronchoalveolar lavage was lymphocyte-predominant, and testing for viral, fungal, and bacterial respiratory pathogens was also negative. A right upper quadrant abdominal ultrasound was unremarkable. Given that she lived on a farm with deer nearby and the laboratory findings of leukopenia, thrombocytopenia, and elevated liver enzymes, there was concern for a tick-borne infection. Blood tests for Lyme, Ehrlichia, Babesia, and Rocky Mountain Spotted Fever (RMSF) were negative. Serum IgM and IgG for Anaplasma were negative, but Anaplasma DNA testing via real time polymerase chain reaction (PCR) was positive.

OUTCOME AND FOLLOW-UP

The patient was ventilated per the ARDS protocol, with a tidal volume of 6 mL/kg. Once the diagnosis of HGA was confirmed, vancomycin and piperacillin-tazobactam were discontinued and doxycycline, the treatment of choice for Anaplasma, was continued. After three days in the medical intensive care unit the patient was successfully extubated. At the time of discharge her blood cell counts had normalized and her liver enzymes were improving. Her chest x-ray demonstrated resolution of the bilateral airspace opacities. The patient was discharged home to complete a 14-day course of oral doxycycline.

**Acute Respiratory Distress Syndrome from Tick-borne Human Granulocytic Anaplasmosis Infection**

Vedang Patel, MD
DISCUSSION
HGA is characterized by a febrile illness that most often presents with headache, myalgia, and fatigue. The first case of HGA in a human was in 1990 when a Wisconsin man died two weeks after being bitten by a tick. In the United States, the Centers for Disease Control and Prevention has recorded 2135 cases between 1994 and 2002, the last year for complete data. The incidence of HGA is rising and cases are often unreported. ARDS, the most serious complication seen in this patient’s clinical course, has been reported in less than 1% of cases of HGA.

ARDS is characterized by hypoxemic respiratory failure, radiographic evidence of bilateral airspace opacities without volume overload, and an arterial oxygen pressure (PaO2) to inspired oxygen fraction (FiO2) ratio of less than 300 mmHg. Sepsis, aspiration, pneumonia, and trauma are the most common causes of ARDS. Patients require high levels of oxygen supplementation during the first several days, and clinical improvement usually depends on treatment of the underlying cause. Unlike traditional mechanical ventilation strategies that use 10 to 15 mL/kg of tidal volume, a low tidal volume approach of 6 to 8 mL/kg has been shown to decrease mortality and improve clinical outcomes in patients with ARDS. The consequences of ARDS include impaired gas exchange, decreased lung compliance, and pulmonary hypertension. Thus, it is imperative to make a diagnosis of the underlying cause and to begin immediate treatment.

The diagnosis of HGA is often difficult because symptoms develop days after the tick bite but seroconversion takes 2 to 4 weeks. If testing for antibodies is being considered, 2 serum samples should be taken at least 2 to 3 weeks apart and a 4-fold rise in antibody titer is needed to make the diagnosis. A Wright- or Giemsa-stained peripheral blood smear may provide early diagnosis by detecting morulae in neutrophils. Confirmation of HGA now often relies on PCR testing, but PCR is not readily available at all facilities. Therefore diagnosis often relies on clinical signs and symptoms, and treatment should not be delayed for confirmation of diagnosis. HGA infection is most common in the spring and summer months. The vector for transmission is the deer tick *Ixodes scapularis*. The highest incidence in the United States is in the northeast and north central states. Laboratory findings suggestive of HGA are leukopenia (present in 50% of cases), thrombocytopenia (94%), and transaminitis (90%).

had all of the common laboratory features, presented in late spring, and lived in the northeast United States.

The treatment of choice for adults with HGA is doxycycline at a dose of 100 mg orally every 12 hours for 7 to 14 days. In patients who are pregnant or have a tetracycline allergy, rifampin at 300 mg twice daily may be substituted. Symptoms start to resolve within 24 to 48 hours, and in patients who do not show clinical improvement a co-existing *Babesia* infection should be considered. Treatment with doxycycline and a low tidal volume mechanical ventilation strategy were pivotal to this patient’s favorable outcome.

KEY POINTS
Headache, myalgia, and fatigue are the most common symptoms of HGA. Seroconversion takes two weeks so PCR testing is the test of choice for diagnosis. If suspicion for HGA is high, treatment with doxycycline should not be delayed for confirmation of diagnosis. ARDS is a very rare complication of HGA. Treatment with doxycycline and a low-tidal volume mechanical ventilation strategy were essential for the favorable outcome in this patient.

REFERENCES
Chronic Idiopathic Intestinal Pseudo-Obstruction: A Working Diagnosis

Ankush Kalra, MD and Anthony J DiMarino, MD

INTRODUCTION
Chronic intestinal pseudo-obstruction (CIP) is a rare and disabling motility syndrome, yet one that demands an extensive review of digestive motility and peristaltic pathophysiology. Primarily a disorder of the small intestine, CIP was first described by Dudley and colleagues in 1958; it is defined by severe signs and symptoms of intestinal obstruction (abdominal pain and distention, nausea, vomiting, and constipation), in addition to radiographic evidence of dilated bowel in the absence of a true, mechanical obstruction. Symptoms are often slowly progressive and diagnosis requires the presence of symptoms for at least six months. A 2013 national survey in Japan estimated the prevalence of CIP at 0.8 to 1.0 per 100,000, with an incidence rate of 0.21 to 0.24 per 100,000. In the same survey, the mean age at diagnosis is 63.1 years for males and 59.2 for females. CIP encompasses an extensive differential diagnosis, a complex, multidisciplinary work-up, and a vast array of potential treatment options based in intricate pathophysiology.

CASE PRESENTATION:
RC is a 75-year-old male who presented with recurrent small bowel obstructions (SBOs) between August and September 2014. He has no chronic medical conditions, and his past medical history is significant only for a community-acquired pneumonia and pleural empyema at age 50. His surgical history is significant only for a right inguinal hernia repair at age 7. Initially, his symptoms began in April 2014 and were mild, limited to constipation relieved with over the counter laxatives. After two brief admissions for SBOs that resolved with nasogastric tube decompression, RC presented on September 9, 2014 with a distended, tympanitic abdomen with absence of bowel sounds and minimal tenderness to palpation. A computed tomography (CT) scan demonstrated multiple dilated loops of small bowel with a transition point in the proximal ileum. A nasogastric tube was again placed but the obstruction persisted clinically and on repeat X-Rays. During an exploratory laparoscopy on September 15, 2014, the right colon and entire small bowel were palpated. No transition zone or small bowel abnormality was found and the peritoneal surfaces of all abdominal organs appeared normal. Ultimately, an ileocecectomy was performed and RC underwent a thorough diagnostic workup.

DIFFERENTIAL DIAGNOSIS:
While CIP is a rare and elusive diagnosis, it is not one of exclusion. It is a clinical diagnosis typically confirmed by endoscopic or radiologic exclusion of a mechanical obstruction. In the case of RC, the lack of mechanical obstruction was confirmed by manual palpation of the entire small bowel and colon. The rest of the workup focused on the etiology of CIP, which may be either idiopathic or secondary. Secondary CIP was ruled out with lab testing for collagen vascular diseases, hypothyroidism, diabetes, porphyria, and celiac disease, as well as a lack of any iatrogenic factors. A thorough paraneoplastic work-up was unremarkable; Ho, Yu, and neuronal nuclear antibodies were negative, CT scan of the thorax ruled out thymoma, thyroid ultrasound revealed benign nodules, and testicular ultrasound demonstrated no masses. The ileocecectomy specimen demonstrated small bowel mucosa with prominent reactive lymphoid hyperplasia. While nonspecific, this pathology is most consistent with an inflammatory neuropathy.

OUTCOME/FOLLOW-UP:
An exploratory laparotomy performed on September 24, 2014 demonstrated significantly dilated small bowel at the ligament of Treitz. There was no evidence of mechanical obstruction such as mass, adhesions, stricture, kinking, or intussusception. Palpation of the colon was normal minus significant transverse colon dilation. Ileocecectomy was performed and a gastrostomy tube was also placed for venting. With continued symptoms and radiographic pseudo-obstruction after ileocecectomy, RC was started on total parenteral nutrition (TPN). After failure of stool softeners, laxatives, and prokinetic lubiprostone, treatment with prokinetic linaclotide was initiated. Moderate success
was achieved with the addition of somatostatin analog octreotide and antibiotic rifaximin, as RC began to move his bowels. Acetylcholinesterase inhibitor neostigmine was also administered with successful movement of the bowels within less than five minutes, further supporting a neuropathic etiology. Ultimately, RC was discharged on October 14, 2014 with linaclotide, octreotide, polyethylene glycol, and TPN. Significant progress was made over the ensuing months, as he began to tolerate oral intake, discontinued TPN, and had his medications tapered. Currently, RC only takes linaclotide twice weekly and maintains a gastrostomy tube for intermittent venting. He has returned to his normal lifestyle and has daily, formed bowel movements without symptomatic or radiographic evidence of bowel obstruction.

DISCUSSION:
Reflecting on the case of RC, it can be said that the true mechanism of his return to health remains uncertain. CIP is classified using three histological categories: neuropathies (either inflammatory or degenerative), myopathies (smooth muscle fibrosis), and mesenchymopathies (dysfunction of the pacemaker interstitial cells of Cajal). Inflammatory neuropathies are the most common cause of CIP, defined by myenteric plexus ganglionitis and encompassing etiologies such as paraneoplastic syndromes, infections, and connective tissue disorders. Interestingly, most case reports describe CIP as the first presentation of another disease, most commonly small cell lung cancers, lupus, and scleroderma. While the appropriate screening tests were done for these conditions, one 2012 case report describes CIP as the initial manifestation of an atypical, seronegative systemic sclerosis. Octreotide has been used with much success in CIP secondary to scleroderma. Gastrointestinal transit studies have demonstrated that, while octreotide has been proven to slow intestinal transit by inhibiting intermittent, low-amplitude contractions, it enhances short burst, high amplitude contractions. A 1991 study demonstrated that scleroderma patients with an inability to generate migrating motor complexes were able to produce 3.6 complexes every three hours after administration of 100 micrograms of octreotide. The stasis associated with CIP is believed to generate a cycle of small intestinal bacterial overgrowth (SIBO) that leads to mucosal inflammation and further dysmotility, and this might explain why RC developed transverse colon dilation later on in his course. While rifaximin and other antibiotic regimens are often used to treat SIBO, it has been demonstrated that 50 micrograms of octreotide every evening for three weeks will reduce breath hydrogen excretion, a marker of SIBO, from 25 to 4 parts per million. Therefore, the SIBO that is both a contributor to and consequence of CIP may be successfully treated by targeting small intestinal motility. As CIP generally has a chronic, relapsing course and overall poor prognosis, it is important to regularly monitor these patients and remain vigilant about pursuing further workup and therapies with any change in clinical status.

KEY POINTS:
The case of RC is a complicated one defined by uncertainty and a multitude of diagnostic and therapeutic interventions. While he is currently symptom free and maintained only on linaclotide twice weekly, history tells us that this case may soon be revisited and a more certain diagnosis obtained. While there is a need for physicians to become knowledgeable about CIP, the medical community must continue to inquire about targeted therapies. It is essential that these stories be shared. The pathophysiological basis of treatments used in these cases continues to be a key focus of research.

REFERENCES
Eculizumab for Gemcitabine-Induced Hemolytic Uremic Syndrome: A Novel Therapy for an Emerging Condition

Raphael Karkowsky, MD and Kinjal Parikh, MD

INTRODUCTION
Atypical hemolytic uremic syndrome (aHUS), a thrombotic microangiopathy (TMA), is a disease characterized by hemolytic anemia, thrombocytopenia, and renal impairment. Gemcitabine, a commonly used chemotherapy, is emerging as a cause of aHUS. Although rare, the morbidity and mortality can be significant. Few studies have explored the use of eculizumab, an anti-C5 monoclonal antibody as a potential therapy for gemcitabine-induced aHUS.

CASE PRESENTATION
A 45 year old Caucasian male with metastatic urothelial carcinoma was started on weekly gemcitabine (1000 mg/m² per dose) to treat recurrent disease. During his seventh cycle, he was hospitalized for hypertension, acute kidney injury, and anemia. Laboratory data at that time revealed a hemoglobin of 6.2 g/dL (reference range 14.0-17.0 g/dL) and a platelet count of 70 x 10⁹/L (reference range 140-400 x 10⁹/L). Hemolysis was suggested by an elevated lactate dehydrogenase (LDH) of 420 IU/L (reference range 125-240 IU/L), undetectable haptoglobin, and the presence of schistocytes on the peripheral smear (see Figure 1). Creatinine was elevated to 2.8 mg/dL (reference range 0.7-1.4 mg/dL) and an ADAMTS-13 (A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) returned as normal. The patient was diagnosed with gemcitabine-induced aHUS. Gemcitabine was discontinued, and the patient was started on steroids. Two weeks later, he presented with generalized tonic-clonic seizures, uncontrolled hypertension, and worsening renal failure. His labs on admission showed continued hemolysis and thrombocytopenia. In light of the patient’s poor response to steroids, the decision was made to start eculizumab.

DIFFERENTIAL DIAGNOSIS
Gemcitabine-induced aHUS is often a difficult diagnosis to make. In this case, it was distinguished from thrombotic thrombocytopenic purpura (TTP) by normal levels of ADAMTS-13. Furthermore, normal coagulation studies and the lack of bleeding made disseminated intravascular...
coagulation unlikely. Bone marrow biopsy showed trilineage, hypercellular hematopoiesis, suggesting peripheral destruction rather than myelosuppression from chemotherapy (see Figure 2). Idiopathic thrombocytopenic purpura was a less likely diagnosis, as the presence of schistocytes suggested microangiopathy.

OUTCOME AND FOLLOW-UP
The patient was started on ecuizumab and received a course of six doses. His treatment was complicated by a multifocal pneumonia that developed four days after receiving his second dose. His labs two months after starting treatment showed an improved platelet count of 118 x 10^9/L. Although he remained anemic, his labs did not show evidence of further hemolysis (see figure 3). The patient’s creatinine remained elevated at 6.2 mg/dL, and he was started on renal replacement therapy (RRT). The patient died three months after initiation of eculizumab therapy secondary to complications of his underlying malignancy.

DISCUSSION
The vast majority of HUS are preceded by a bout of infectious diarrhea, usually due to Escheria coli; 90% of cases are not, and are therefore termed atypical.1 This atypical form of HUS is associated with factors such as human immunodeficiency virus infection, malignancy, organ transplantation, pregnancy, or medications, including anti-neoplastic drugs.1,2 Recently, gemcitabine, a 2’,2’-difluorodeoxycytidine, has surfaced as a cause of atypical HUS. The incidence of gemcitabine-induced aHUS ranges from 0.015 to 1.4% per current case series reviews.

Pathologically, aHUS is identical to the typical form. Histology generally shows arteriole and capillary thickening, a swollen endothelium, and proteinaceous deposits in the subendothelium. A blood smear will typically show schistocytes. The kidneys are most commonly involved, but the brain, lung, pancreas, and gastrointestinal tract may be affected as well. Dysregulation of the alternative complement cascade leads to the formation of the final membrane-attack complex (MAC) and subsequent endothelial injury, which plays a pivotal role.1

The most agreed upon treatment for gemcitabine-induced aHUS remains discontinuation of the drug. Other therapies, such as therapeutic plasma exchange (TPE), demonstrate less reliable effectiveness, as shown in a recent meta-analysis by Gore and colleagues, which concluded that the use of TPE is not associated with an improved rate of recovery.8 Recent case reports have also suggested a potential role for splenectomy9 or rituximab7. Novel therapies such as Complement Factor H, a regulatory protein in the alternative complement...
The safety of eculizumab is still being determined. In this case, the patient developed multifocal pneumonia just days after receiving his second dose of eculizumab. Inhibition of MAC formation by eculizumab reduces defense against encapsulated organisms, specifically those that cause pneumonia. Therefore, it is reasonable to suspect, that eculizumab may have served as a risk factor in our patient’s development of this complication.

Only a few studies have investigated the treatment of gemcitabine-induced HUS with eculizumab. Similar to the studies by Starck and colleagues and Legendre and colleagues, this case study highlights eculizumab’s effectiveness in improving microangiopathy and the resultant thrombocytopenia and hemolysis in aHUS. Those studies, although promising, were somewhat confounded by prior use of TPE, which was not true in our case. Lohr and colleagues’ case series, seemed to suggest that eculizumab is an effective therapy for the kidney damage sustained in aHUS. In our case study, however, the patient did not demonstrate the same improvement in kidney function, and his kidney disease ultimately progressed to the point of needing RRT. The role of eculizumab in treating aHUS and its efficacy is still being defined.

KEY POINTS
The above case demonstrates eculizumab’s partial effectiveness in treating the microangiopathy in gemcitabine-induced aHUS. Although the patient demonstrated recovery in platelet count and resolution of his hemolysis, he showed only limited improvement in renal function. Moreover, the patient’s course of therapy was complicated by pneumonia, which along with infections from other encapsulated organisms, may represent a possible side effect of the medication. Further research, specifically, larger scale prospective studies, are needed to better assess the degree of efficacy and safety of eculizumab for gemcitabine-induced TMA.

REFERENCES
Metformin Associated Lactic Acidosis

Jinyu Zhang, MD, Ravi Sunderkrishnan, MD, Samantha Brackett, MS4, Maham Qureshi, MD, Keithe Shensky, MD, Rakesh Gulati, MD

INTRODUCTION
Metformin is a first line oral medication for diabetes mellitus shown to decrease cardiovascular morbidity and mortality. Though the prevalence of metformin-associated lactic acidosis (MALA) is low, mortality is high, ranging from 25-50%. Therefore, it presents a diagnostic challenge that is critical to identify, particularly in patients with renal impairment at baseline. Traditionally patients with creatinine greater than 1.5 mg/dL have been excluded from using metformin; however, metformin might be acceptable in some patients with chronic kidney disease (CKD).

CASE PRESENTATION:
A 69 year old female with a past medical history of diabetes mellitus, hypertension, breast cancer, and no chronic kidney disease was sent to the hospital by her rehabilitation facility secondary to her being found unresponsive. This was in the presence of decreased appetite and impaired mobility limiting her ability to feed herself in the 2 weeks prior to hospital admission. Her medications included metformin, insulin glargine, anastrozole, and hydrochlorothiazide. She had nausea and vomiting the night prior to admission. Despite her decreased oral intake, she continued taking her full dose of metformin and insulin throughout that two week period.

On arrival to the emergency room, her vitals were rectal temperature 90.6°F, heart rate 66 beats per minute, blood pressure 60/40 mmHg, respiratory rate 25 breaths per minute, and oxygen saturation 88% on room air. Her Glasgow Coma Scale was 2 with physical exam findings significant for limited withdrawal to noxious stimuli. Her initial labs were significant for bicarbonate of 2 mEq/L (normal range 24-32 mEq/L), potassium of 6.7 mEq/L (normal range 3.5-5.0 mEq/L), blood urea nitrogen of 110 mg/dL (normal range 7-26 mg/dL), creatinine of 9.7 mg/dL (normal range 0.7-14mg/dL) with a baseline of 0.7 mg/dL 2 months ago, and lactate of 26 mmol/L (normal range 0.5-2.2 mmol/L). A venous blood gas was significant for a pH of 6.65. Plasma metformin level was not available.

DIFFERENTIAL DIAGNOSIS
The differential was broad including septic shock, toxin ingestion, cardiogenic shock, and intracranial abnormality. Drug toxicity was ruled out as her urine drug screen and alcohol level were negative. Severe sepsis was ruled out when cultures (urine, blood, bronchoalveolar lavage) were negative. CT chest, abdomen, and pelvis did not show any source of infection. CT head was within normal limits. A transthoracic echocardiogram did not show significant abnormalities. Given her elevated anion gap metabolic acidosis with concomitant osmolar gap, a diagnosis of MALA was made.

OUTCOME AND FOLLOW UP
Patient was intubated and admitted to the medical intensive care unit. She was empirically started on broad-spectrum antibiotics, stress dose steroids, intravenous fluids, and vasopressors for presumed septic shock. Given her low bicarbonate level, a bicarbonate drip was started, and nephrology was consulted for acute renal failure and metabolic acidosis management. The nephrology team initiated her on continuous veno-venous hemofiltration (CVVH) therapy. She had 3 days of CVVH, after which she was transitioned to intermittent hemodialysis. Patient’s urine output gradually improved throughout her hospital stay. Upon discharge, she was alert, oriented, and conversing appropriately.

DISCUSSION
Metformin is renally cleared and therefore accumulates in states of decreased creatinine clearance. It also inhibits mitochondrial electron transport, thereby increasing anaerobic metabolism and lactate production. It has been proposed that in acute kidney injury, metformin levels accumulate, contributing to worsening lactic acidosis, which further compounds nausea and vomiting, and thereby reducing renal perfusion. The incidence of MALA is thought to be 1-5 cases per 100,000 patient years but can be as high as 30 cases per 100,000 patient years. Mortality ranges from 25-50%.

The 5 characteristics highly suggestive of MALA are: severe acidemia (pH < 7.1) with an anion gap greater than 20 mEq/L (normal anion gap ≤ 12 mEq/L), very low serum
bicarbonate (7 +/- 4 mEq/L), markedly elevated lactic acid (12.4 +/- 8 mmol/L), history of metformin ingestion, and history of renal insufficiency. With infectious and other drug toxicities ruled out in this patient, MALA was the most likely cause of her lactic acidosis as the patient met all 5 aforementioned points. We propose that this patient, in the presence of decreased oral intake in the weeks prior to her presentation, developed acute kidney injury, which decreased her ability to clear metformin. Consequently, she started developing lactic acidosis, which likely worsened any nausea or vomiting, further exacerbating her acute renal failure leading to anuria.

Given the lack of randomized control trials in the study of MALA, much of the existing literature on MALA are case series, retrospective studies, and observations. The goal in the acute management of MALA is to provide airway, breathing, and circulatory support and to correct the underlying acidosis with possible intravenous bicarbonate and/or renal replacement therapy. A retrospective analysis study compared cases of severe acidosis with \( pH < 7.0 \) secondary to MALA and lactic acidoses of other origins. Despite the \( \text{pH} \) being lower in the former group, the mortality was 100% in the latter group as compared to 50% in the former. This shows that despite a greater degree of acidosis and renal failure in MALA patients, early recognition and aggressive medical therapy including renal replacement therapy improves the survival.

A recently published retrospective study looked at the incidence of MALA in those with and without impaired renal function. The 77,601 identified patients were divided into different groups based on glomerular filtration rate (GFR): normal, mildly reduced, moderately reduced, or severely reduced. They found an incidence of 10.37 per 100,000 patient years. What is more significant is that they severely reduced. They found an incidence of 10.37 per 100,000 patient years. What is more significant is that they found a significant difference in the development of MALA among the 4 groups. This calls for more awareness amongst general internists such that impending signs of toxic drug accumulation, which can be successfully removed by renal replacement therapy. Furthermore, though our patient did not have any CKD at baseline, she should have been counseled on stopping her metformin during periods of poor appetite or dehydration. Physicians need to be comfortable and knowledgeable with using metformin alongside medications that interfere with renal hemodynamic regulation such as angiotensin-converting enzyme inhibitors, aldosterone receptor blockers, and nonsteroidal anti-inflammatory drugs.

**KEY POINTS**

Metformin is currently a first-line agent in the management of diabetes. Though it can cause metformin-associated lactic acidosis, the prevalence is relatively low. High clinical suspicion is, however, important. In those taking metformin and presenting with lactate greater than 15 mmol/L and \( \text{pH} \) less than 7, MALA must be strongly considered. To prevent MALA, patients on metformin should be counseled on its use in states of potential kidney injury such as volume depletion as was the case in our patient. Overall, patients who have MALA should receive aggressive resuscitation methods including fluid repletion, airway protection, vasopressors, intravenous bicarbonate, and/or renal replacement therapy depending on the severity of the acidosis.

**REFERENCES**

Nephrotic Syndrome: Is HIV Associated Nephropathy on Your Differential?

Jad Al Danaf, MD, Jeffrey Marbach, MD, Sharon Li, MS4, Emily Stewart, MD

CASE DESCRIPTION

A 30-year old African American female with no significant past medical history initially presented to our emergency department with three days of sore throat, dysphagia, fever, fatigue, nausea and vomiting. She denied ear pain, rhinorrhea, shortness of breath or any sick contacts. Her social history was negative for tobacco, alcohol and illicit drug use. She works as a security officer, lives with her family and is sexually active only with her husband. On initial examination she was febrile to 101.9° F, with a heart rate of 100 beats per minute, blood pressure of 143/99 mmHg, respiratory rate of 18 breaths per minute and an oxygen saturation of 99% on room air. Her only pertinent physical examination findings were a mildly erythematous oropharynx without exudates, mildly swollen uvula and right tonsil, bilateral tender swollen sub-mandibular lymph nodes and reduced breath sounds on auscultation of the right lower lung base. She was routinely tested for HIV, ruled out for group A strep, and discharged home with the diagnosis of viral pharyngitis on supportive care.

Following the identification of a presumptive positive rapid HIV screening test with evidence of HIV-1 p24 antigen and a reactive HIV-1 antibody on the multispot HIV 1 / 2 antibody test she was called to return to the ED for counseling regarding a positive HIV test. She reported continuation of her prior symptoms with worsening dysphagia, as well as new complaints of bilateral lower extremity edema to the knees. Initial laboratory testing revealed an elevated serum creatinine (Cr) of 2.2mg/dL (0.7-1.3 mg/dL) up from <1.0mg/dL one-year prior, with an estimated Creatinine clearance (CrCl) of 43.4 ml/min using the modified Cockcroft-Gault equation. She was admitted for further workup. A trial of IV fluid hydration overnight worsened her symptoms and additional labs demonstrated hypoalbuminemia, 4+ proteinuria with 1+ blood, and a urine protein/creatinine ratio of 17mg/mg (<0.2 mg/mg), consistent with nephrotic syndrome. Her CD4 count was 115 cells/mm3 (500-1500 cells/mm3) with an HIV viral load of 117,148 copies/ml. Based off negative labs for syphilis, hepatitis panel, ANA, complement C3/C4, and diabetes, findings were felt to be consistent with HIV Associated Nephropathy (HIVAN). The patient underwent renal biopsy to confirm the diagnosis and was started on abacavir, darunavir, dolutegravir, lamivudine and ritonavir. Pathology results were consistent with HIVAN with tubulointerstitial nephritis and collapsing glomerulonephropathy and electron microscopy showed diffuse epithelial cell injury with effacement of foot processes and segmental collapse of glomerular capillary loops. Her serum Cr peaked at 2.78 on day 7 of her admission. Her serum Cr and urea-nitrogen steadily improved after just one week of HAART therapy leading to a 42% reduction in serum Cr (Figure 1). Additionally, due to her un-resolving dysphagia the patient underwent esophagogastroduodenoscopy, which was unremarkable. However, she subsequently had esophageal manometry, which was consistent with diffuse esophageal spasm for which she was started on diltiazem.

DISCUSSION

HIV-associated nephropathy (HIVAN) is an aggressive form of collapsing focal segmental glomerulosclerosis and tubulointerstitial lesions that is observed predominantly in African Americans. The first descriptions of this disease manifestation were among African-American and Haitian immigrants with advanced HIV illness, which serve to highlight the racial disparity and genetic susceptibility to HIVAN. The era of highly active antiretroviral therapy (HAART) has reduced the incidence of HIVAN; however, HIVAN remains the 3rd leading cause of end stage renal disease (ESRD) among blacks between the ages of 20-64 years old, with an estimated 90% of patients with ESRD attributed to HIVAN being of African-American descent. Although incompletely understood it has been postulated that the pathogenesis of HIVAN involves several factors, including direct HIV infection of glomerular and tubular epithelial cells and upregulation of host cellular pathways involved in apoptosis and cell cycle arrest. As previously mentioned, current therapy involves initiation of HAART, along with renal replacement therapy and renin-angiotensin system inhibitors as warranted.
Ultimately, HIV prevention remains the best approach to impact the epidemiology of HIVAN. In this case report, it was not clear for exactly how long the patient had HIV, however if it was a recent transmission it would have been a rare case of HIVAN in the setting of sub-acute HIV infection. Additional high quality studies and randomized clinical trials are needed to establish treatment beyond HAART for HIVAN, taking into account the recent progress in the understanding of the pathogenesis of HIVAN in the existing body of literature. Furthermore, it is still not clear which of the combination antiretroviral therapies (cART) available are effective in treating HIVAN and to what extent they are achieving survival and morbidity reductions.

SUMMARY
This case serves as an example of an uncommon yet dangerous complication of HIV. In the setting of nephrotic syndrome, screening for HIV infection and ruling out HIVAN in HIV-infected individuals is essential. HIVAN may be the first manifestation of HIV-1 infection in an otherwise asymptomatic patient and preservation of renal function in African Americans with chronic kidney disease and HIV is dependent upon its prompt recognition and early treatment. Early recognition and treatment of HIVAN has the potential to delay the onset of ESRD and improve mortality associated with complications of HIV.

REFERENCES
Persistent Fever and Pancytopenia: Lupus Flare vs Macrophage Activation Syndrome

Amy McGhee, MD

INTRODUCTION

Macrophage activation syndrome (MAS), first named in 1993, is a subcategory of hemophagocytic lymphohistiocytosis (HLH), characterized by prolonged fever, hepatosplenomegaly, pancytopenia, liver dysfunction, and most notably hyperferritinemia. MAS, in particular, is the term used to describe secondary HLH, or HLH caused by rheumatologic conditions. Secondary HLH can also be associated with other systemic autoimmune diseases, underlying malignancy, infection, or medications and can be a life-threatening complication. MAS is characterized by unwarranted proliferation and stimulation of T cells and benign macrophages leading to an excessive inflammatory state with hypersecretion of cytokines. This, in turn, leads to phagocytosis of normal blood cells and injury to the organs containing these macrophages (liver, spleen, bone marrow, lymph nodes). With regard to rheumatologic conditions, MAS is most often seen associated with juvenile idiopathic arthritis (incidence of 7-13%) while it is much less commonly seen in systemic lupus erythematosus (SLE) with an incidence of 0.9-4.6%. The etiology is unknown, although there are hypotheses.

CASE PRESENTATION

A 53 year old female with SLE complicated by lupus nephritis and lupus anticoagulant initially presented with a syncopal episode. While walking out of the rheumatologist office, she felt faint and had an assisted fall to the floor with transient loss of consciousness. The patient reported approximately 1-2 months of decreased oral intake, weight loss, daily fevers to 102-103°F, lightheadedness, dry cough, and 1 week of rash on her upper chest. During this time, her rheumatologist adjusted her SLE medications, attributing her symptoms to a SLE flare. Work up during this admission (labs listed in Table 1) ruled out sepsis as a source of fever. It was determined that her symptoms and lab abnormalities were likely secondary to a lupus flare given her fever, rash, constitutional symptoms, and pancytopenia in the setting of SLE that was difficult to control. Early macrophage activation syndrome (MAS) was also on the differential given the elevated ferritin level. Her symptoms improved with pulse dose steroids and resuming mycophenolate mofetil for immunosuppression. The plan was to change this to cyclosporine as an outpatient to prevent MAS.

Before switching to cyclosporine however, the patient was readmitted for recurrent fevers, fatigue, diarrhea, and worsening lab abnormalities. On admission, her physical exam was significant for fever to 102.4°F, tachycardia, and dry mucus membranes. Labs are shown in Table 2. The most remarkable finding was a ferritin of 11,741 which was a significant increase from 4,542 during her last admission. The patient underwent a bone marrow biopsy, which demonstrated increased macrophages with hemophagocytic activity, confirming a diagnosis of MAS.

DIFFERENTIAL DIAGNOSIS

In an SLE patient with recent flare 4 months ago, a recurrent lupus flare was highest on the differential as the patient reported joint pain, skin rash, fevers, weight loss, and fatigue. Infection is also high on the differential for a patient on chronic immunosuppression who presents with fever. An infectious workup was undertaken including a Right upper quadrant ultrasound, chest CT, blood cultures, urine cultures, respiratory viral panel, and transthoracic echo, all of which were negative for infection. Anti-dsDNA antibodies were unexpectedly normal and complement levels were unremarkable which made a SLE flare less likely.

During the initial admission, the hyperferritinemia, an acute phase reactant, was thought to be elevated in the setting of a lupus flare or infection. However, the dramatic increase to 11,741 upon readmission raised suspicion for MAS. Multiple case reports have described this diagnostic difficulty in distinguishing between MAS and a SLE flare. It has been reported that elevation of ferritin (greater than or equal to 500ug/L) and LDH can help differentiate as this represents activation of the mononuclear phagocyte system. Hyperferritinemia has a sensitivity and specificity of almost 100% for distinguishing between a SLE flare and MAS. Lastly, a bone marrow biopsy is usually diagnostic for MAS if there is still uncertainty.
Table 1. Labs for first admission.

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<th>Lab</th>
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<tr>
<td>WBC (B/L)</td>
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<td>AST (U/L)</td>
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<td>Platelets (B/L)</td>
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<td>Alk phosphatase (U/L)</td>
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<td>Lactate (mmol/L)</td>
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<td>Iron Binding Capacity (mcg/dL)</td>
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<td>Iron Saturation (%)</td>
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<td>C3 complement (mg/dL)</td>
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<td>PT (sec)</td>
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<tr>
<td>INR</td>
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<td>Anti-dsDNA Ab (IU)</td>
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<td>Albumin (g/dL)</td>
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<td>Vitamin B12 (pg/mL)</td>
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<td>Folate (ng/mL)</td>
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Table 2. Labs upon second admission.

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<td>Platelets (B/L)</td>
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<td>Alk phosphatase (U/L)</td>
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<td>Ferritin (ng/mL)</td>
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</table>
OUTCOME AND FOLLOW-UP
Once the diagnosis of MAS was confirmed, the patient was treated with cyclosporine, anakinra (IL-1 receptor blocker), and high dose steroids. These were uptitrated until the ferritin, leukopenia, and liver function tests began to improve. Interestingly, in the work-up of the patient’s pancytopenia, her EBV studies showed a positive VCA IgG and ENA IgG so the patient was also treated with IVIG in case an EBV infection was contributing to the MAS. The patient was discharged home after a month-long hospitalization. In the next nine months, her medications were all gradually tapered and she had a concordant improvement in ferritin, blood counts, and symptoms.

DISCUSSION
There remain many uncertainties surrounding MAS including its etiology, treatment, and prognosis. In one case study of a patient with SLE and MAS, the patient tested positive for numerous antibodies (ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, and peripheral ANCA antibodies). It was hypothesized that the overwhelming amount of autoantibodies and immune complexes bound to normal blood cells trigger phagocytosis of those cells. It is possible that the quantity of these autoantibodies and the increased complement activity during a SLE flare can trigger MAS.

Once the diagnosis of MAS is made, it is important to initiate therapy quickly as it can be a life-threatening illness. The cornerstone of therapy is high dose steroids. Multiple case reports also discuss the importance of immunosuppressant medications, such as cyclosporine A and cyclophosphamide in patients who do not respond to steroids, such as the patient in this report. One study, in particular, demonstrated 54% of patients with MAS from systemic autoimmune disease who received only high dose steroids were resistant to this treatment and the majority of patients who were treated with both steroids and immunosuppression had good treatment response. Another case report demonstrated the fairly rapid improvement in labs and clinical condition of a young man who was treated with cyclosporine when he did not respond to steroids. IVIG is another treatment option which is especially useful in patients who are suspected to have an underlying viral infection. Further, the next line of treatment if both steroids and immunosuppression are not effective is biologic agents, such as anakinra and rituximab. Anakinra is an IL-1 receptor blocker that has been used effectively in patients with MAS secondary to SLE which did not respond to steroids, IVIG, and cyclosporine. There is also evidence that rituximab is effective in treating resistant MAS. The patient in this case study did not respond appropriately to pulse dose steroids, cyclosporine, or IVIG, so she was started on anakinra and did well after a few weeks on this regimen.

Further, prognosis is another area of uncertainty in MAS. There have been no prognostic indicators established yet but there is evidence suggesting the level of certain cytokines can be associated with a worse prognosis and that ferritin levels may help predict outcome. Multiple studies have found no correlation between ferritin levels and the severity of disease or outcome; however, serial ferritin levels may shed more light on prognosis. The patient in this case report had a ferritin of 4500 on initial admission, which increased to 11,000 on her subsequent admission indicating lack of response to therapy. Once anakinra was added and titrated, her symptoms improved and her ferritin slowly decreased over the course of weeks. She was safely discharged home with close follow up.

KEY POINTS
MAS is a potentially life-threatening complication of rheumatologic diseases, characterized by excessive activation of benign macrophages which lead to the phagocytosis of normal blood cells and injury to surrounding tissues. Common clinical manifestations include fever, pancytopenia, liver dysfunction, hepatosplenomegaly, and hyperferritinemia. Diagnosis can be difficult as the signs and symptoms of MAS can mimic an infection or SLE flare. However, hyperferritinemia and elevated LDH are characteristic of MAS and may help distinguish and guide treatment decisions. If uncertainty remains, a bone marrow biopsy can usually establish the diagnosis. The best treatment options at this point include high dose steroids, immunosuppression, IVIG, and biologics depending on the patient’s laboratory and clinical response.
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**Pulmonary Mucormycosis in a patient with Acute Myeloid Leukemia**

Jonathan Pan, MD, Margaret Kasner, MD, Sheel Patel, MD, Gretchen Diemer, MD

**INTRODUCTION**

Mucormycosis is a rare fungal infection that is common amongst uncontrolled diabetics and immunocompromised patients. The most common clinical presentation is rhino-orbital-cerebral infection, which typically affects diabetics with ketoacidosis. Less commonly, pulmonary mucormycosis can occur in patients with hematologic malignancy, solid organ transplant and patients taking steroids or deferoxamine. The following report describes a 25-year-old male with Acute Myeloid Leukemia (AML) who developed a pulmonary mucormycosis infection. With a mortality rate of about 87%, this case represents a favorable outcome for a rare and often lethal diagnosis.

**CASE DESCRIPTION**

A 25-year-old male with no past medical history presented to the hospital after two weeks of fatigue, shortness of breath and epistaxis. Lab work revealed leukocytosis with 43% blasts, anemia and thrombocytopenia. A bone marrow biopsy confirmed the diagnosis of AML. After admission, the patient developed persistent fevers and CT scan demonstrated ground-glass opacities in bilateral lung fields. Blood and sputum cultures, respiratory viral panel and acid fast studies were negative and the patient was started on antifungals and broad spectrum antibiotics. Bronchoscopy with bronchoalveolar lavage did not reveal an infectious source. The patient underwent induction chemotherapy with idarubicin and cytarabine, which was initially well tolerated. However, he soon developed neutropenic fever, hypoxia, and a non-productive cough. The treatment was broadened from vancomycin, zosyn and micafungin to meropenem and ambisome. Cultures remained negative during this time and subsequent imaging revealed right-middle and left-upper lobe consolidations with a central lucency.

**OUTCOME AND FOLLOW UP**

A CT-guided biopsy of the pulmonary consolidation was performed. Pathology revealed granulomatous inflammation with necrosis and silver stain showed sparsely septate hyphae consistent with mucormycosis. High-dose ambisome was initiated and the patient began to demonstrate signs of clinical improvement. He was discharged on a six-week course of intravenous ambisome. Follow-up imaging showed improvement of the consolidations and the patient was switched to oral posaconazole for six additional weeks.

**DISCUSSION**

Mucormycosis is a rare opportunistic fungal infection caused by fungi in the mucorales order, including mucor, rhizopus and absidia. These fungi are ubiquitous in nature, commonly found in soil and decaying matter and released via airborne spores. Histologically, hyphae are seen in broad, irregular branches with few septations, as opposed to aspergilli, which have acute branching angles and many septations. Comprising a unique category of angioinvasive molds, tissue infarction is a hallmark of the disease process. Risk factors include diabetes, hematologic malignancy, solid organ or stem cell transplant, immunocompromised state, iron overload and treatment with deferoxamine. While incidence is difficult to estimate due to mucormycosis not being a reportable disease, it is estimated that approximately 500 cases occur in the US each year. As rhino-orbital-cerebral infection is the most common clinical manifestation in diabetics, pulmonary mucormycosis is more commonly seen with hematologic malignancy, transplant patients and steroid or deferoxamine use. It is caused by direct inhalation of spores into bronchioles and alveoli, which presents as a rapidly progressing pneumonia with or without hemoptysis. Clinical presentation is similar to that of other angioinvasive molds such as aspergillus or fusarium, and diagnosis is therefore obtained by culture and pathology. Imaging can show non-specific findings such as focal consolidation, nodules, masses, or pleural effusions. A halo sign on CT scan, which shows ground...
glass attenuation surrounding a nodule, is characteristic of pulmonary aspergillus. A reverse halo-sign, on the other hand, shows focal ground glass attenuation within a ring of consolidation and is more commonly seen with mucormycosis. As cultures are typically negative, tissue diagnosis is often pursued. A biopsy with silver stain will typically reveal broad, irregular, branching hyphae.

In cases where pulmonary mucormycosis is localized to a single lobe, surgical excision can be performed. However, first line treatment for pulmonary mucormycosis remains high-dose, intravenous amphotericin B. Liposomal amphotericin is preferred due to improved efficacy and safety, although renal function and electrolytes must nonetheless be carefully monitored. Treatment should be initiated for several weeks until the patient clinically improves. At this time, amphotericin may be switched to oral posaconzale, which is often continued for several months until attainment of both clinical and radiographic resolution.

KEY POINTS
This case represents a rare and difficult diagnosis of pulmonary mucormycosis in a patient with hematologic malignancy. While a rapidly progressive disease with a high mortality rate, the patient in this case experienced a favorable outcome. Diagnosis was made only after invasive testing and successful treatment was achieved with an extended course of high dose intravenous ambisome.

REFERENCES
A Retinal Tear Induced By Pazopanib Therapy: A Case Report

Raza Hasan, MD

INTRODUCTION
The management of renal cell carcinoma has undergone major transformation in recent years. With the onset of innovative surgical treatments and systemic medications – there has been an overall decrease in mortality. The systemic medications that target the vascular endothelial growth factor (VEGF) protein have created the most potent effects, especially when treating metastatic renal cell carcinoma. These prove to be important treatments since renal cell carcinoma has become the seventh most common cancer in men, with a general prevalence of 2-3%. With more advancement in knowledge about renal cell carcinoma, research has shown the utility of pazopanib (Votrient), a specific tyrosine kinase inhibitor, targeting multiple receptors; its action is primarily to block angiogenesis and tumor growth, such as VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-A, PDGFR-B, FGFR-1, and FGFR-3. Targeting these specific receptors helps pazopanib to achieve an overall clinical benefit rate of greater than 90%, creating long-lasting disease control for patients.

CASE PRESENTATION
A 63 year old Caucasian female with a past medical history of migraine headaches, dyslipidemia and depression was diagnosed with clear cell type Renal Cell Cancer, in late 2004. She underwent a laparoscopic nephrectomy in 2005 and a kidney mass measuring 9 x 7 x 4 cm was removed, revealing T2 disease with Furman Grade 2 disease. The patient was followed for years and had a CT scan of her chest in June of 2012 - where multiple bilateral pulmonary nodules were identified, the largest nodule was a 1.5 x 1.2 cm nodule at the right middle lobe. CT-guided biopsy was attempted, however was not diagnostic. Therefore, the patient underwent a right upper lobe wedge resection in October of 2012, which confirmed metastatic renal cell cancer to the lung. A PET/CT scan was also performed, and ruled out any evidence of abdominal or bone metastatic disease. Additional therapeutic options were discussed with the patient, such as high-dose interleukin-2 infusion to achieve durable remission and then potentially start targeted therapy when needed. At the time when she was diagnosed with metastatic disease, the patient was in optimal health and was an excellent candidate for high-dose interleukin-2 treatment because she only had pulmonary nodules, without evidence of metastatic disease elsewhere in her body. She was agreeable and finished three cycles of high-dose interleukin-2 treatment along with Stereotactic Body Radiation Therapy. The patient was finally started on targeted therapy with a multi-tyrosine kinase inhibitor in June of 2013. Pazopanib 400mg daily was started and titrated up to 600mg daily, which is considered optimal therapy. However, this patient began to have significant diarrhea without relief from Lomotil and other antidiarrheal medication regimens. Her dose was decreased to 400mg daily which resulted in a decreased amount of diarrhea - one to two times a day which was tolerable. Additionally, a few months after the onset of pazopanib treatment, the patient began having blurry vision, a symptom which was very worrisome.

DIFFERENTIAL DIAGNOSIS
The patient’s blurry vision was the main symptom of concern – her vision had been gradually worsening since the start of pazopanib therapy. Therefore, it was suspected that the systemic therapy was a plausible causal agent of the blurry vision. Upon visiting the ophthalmologist, she was diagnosed with Rhegmatogenous Retinal Tear OD. Her past ocular history was negative for any prior chronic diseases. On exam, the patient had retinal detachment, superotemporal (horseshoe) tear. Furthermore, the patient’s left eye exam was remarkable for nuclear sclerosis. It was likely determined that the pazopanib caused a tear in the retina, thus further leading to detachment.
OUTCOME AND FOLLOW-UP
To treat the pazopanib induced retinopathy, the patient had a pneumatic retinopexy performed on August 19, 2014 and was started on Maxitrol 0.1% 1 drop OD, four times a day. Post operatively, she had decreased complaints of blurry vision. However, because of this adverse event along with intractable diarrhea, the patient was switched from pazopanib to Sutent 37.5mg daily. The Patient is currently doing well – the blurry vision has not worsened and is slowly improving after stopping pazopanib.

DISCUSSION
The usage of pazopanib is a common treatment in metastatic renal cell carcinoma. A multitude of studies have shown that “pazopanib demonstrated significant improvements in progression-free survival and response rate compared with placebo in patients with advanced or metastatic RCC.” Furthermore during these studies, there were no reports of patients developing other systemic abnormalities; the medication demonstrated acceptable safety and tolerability. However, as pazopanib is an oral angiogenesis inhibitor targeting specifically VEGF receptor, it is important to evaluate other locations in the body that might be affected secondary to inhibiting VEGF receptors.

A recent study was published evaluating the ocular effects of Sorafenib – as it was shown that many cancer signaling molecules, such as VEGF, were also expressed in ocular tissue. Sorafenib and Pazopanib have similar pathways, both specifically targeting VEGF proteins and thus both affecting the ocular tissue. Furthermore, there have been studies analyzing the effect of pazopanib in mice retinal tissues – specifically studying pazopanib’s effect on inhibiting choroidal neovascularization. It was shown that pazopanib primarily down-regulates the VEGF release in the retina and impairs VEGF-induced signaling and chemotaxis. Thus, a clear link is illustrated between pazopanib and its effect on retinal tissue. Furthermore, studies have shown that if pazopanib is “orally administered, [it] has good bioavailability to the retina/choroid” further giving proof to its profound effect on the retina and likely impact on treating ocular abnormalities, such as choroidal neovascularization by inhibiting angiogenesis.

However, analysis of the link between pazopanib and retinal tears is important to be determined – in order to understand the findings in this case. Case reports of retinal effects from Sorafenib have been reported, likely secondary to a similarity between the VEGF receptors targeted in systemic RCC and in ocular tissue; similarly a comparison can be drawn between pazopanib and its effects on ocular tissues. With pazopanib’s large bioavailability in ocular tissues, and its direct effect on VEGF receptors – there can be a correlation made between pazopanib and retinal tears developing after initiating chemotherapy. Retinal tears occur when the retinal tissue begins to peel away from supporting tissue. Rhegmatogenous retinal detachment, the type of retinal attachment the patient in above case had, occurs primarily when a small retinal tear allows for fluid to pass from vitreous space into subretinal space where the retinal pigment epithelium (RPE) is located. Studies have illustrated that these tears are often preceded by anti-VEGF therapy, stating that an “increased risk of developing a retinal pigment epithelium tear after anti-VEGF therapy” is common in many patients. This occurs because following the administration of anti-VEGF therapy, there is rapid involution and contraction of the neovascular tissue that is attached to the undersurface of the retinal pigment epithelium. Those forces will cause a contractile force of the RPE forcing a tear on the retinal tissue. Given the pathophysiology of retinal tears and its relationship with anti-VEGF therapy – it is highly probable that the repeated administration of pazopanib in therapeutic doses for RCC can lead to strain of the retinal pigment epithelium, inducing a tear and further progressing onto a rhegmatogenous retinal detachment.

KEY POINTS
This case illustrates a risk with using VEGF inhibitors, such as pazopanib, due to the possibility of retinal damage causing tears leading to detachment. As in our case, there is an increased amount of anti-VEGF being used in renal cell carcinoma cases at therapeutic doses. With the increased usage, guidelines may be required for annual ophthalmology screening to monitor for retinal abnormalities. Furthermore, follow up will be required to determine if discontinuing the pazopanib and starting Sutent helped deter further ocular abnormalities. Overall, it should be recommended to discontinue pazopanib if any blurry vision or vision changes are noted.
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Rising Prevalence of *Pneumocystis jirovecii* Pneumonia Amongst the Non-HIV Immunosuppressed

Zachary Jones, MD and Anusha Ganesh, MD

**INTRODUCTION**

Fungal Pneumonia caused by *Pneumocystis Jirovecii* (PCP) has long been associated with morbidity and mortality in HIV-positive patients. With the widespread use of high dose corticosteroids and biologic therapies, the prevalence of PCP infection in the non-HIV immunosuppressed population has increased significantly. A lack of formalized prophylaxis guidelines in these specific populations has lead to increasing rates of preventable infection and death.

**CASE PRESENTATION**

The patient is a 63-year-old man, admitted to the hospital for persistent shortness of breath following a seven-day course of Levofloxacin taken as an outpatient. Two months prior, the patient was found by his hematologist to have a hemoglobin level of 5.5g/dL, and was diagnosed with autoimmune hemolytic anemia. He was started on a 12 week Prednisone taper following an initial blood transfusion. Three weeks prior to admission, the patient began to develop shortness of breath worse with ambulation, a non-productive cough, and he denied fevers. At time of admission, the patient was taking Prednisone 40mg daily.

The patient’s past medical history was significant for Hodgkin’s Lymphoma in 2001 treated with Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD) and radiation therapy, with recurrence in the nasopharynx and lung requiring further ABVD cycles and left pneumonectomy in 2005. Patient also had renal cell carcinoma requiring nephrectomy in 2007. Social history was significant for a 5-year pack history of cigarette smoking. Family history was significant for myocardial infarction in his father at age 69.

Vital signs at presentation were temperature of 99.4 F, blood pressure of 157/70, pulse of 105 beats per minute and oxygen saturation of 90% on room air. Pertinent positive physical exam findings were sinus tachycardia and diffuse wheezing in all right lung fields and lack of breath sounds on the left. Patient was resting comfortably and able to answer questions without distress. On admission, patient had a normal white blood cell count and a hemoglobin level of 9.8g/dL. Computed tomography scan of the thorax showed mild diffuse, nonspecific ground glass opacities.

![Cross Section CT scan with ground glass opacities.](image1)

![Coronal Cut of CT scan demonstrating severe interstitial pneumonia cut from day 9 of hospitalization.](image2)

![Sagittal cut from CT scan demonstrating interstitial pneumonia from day 9 of hospitalization.](image3)
DIFFERENTIAL DIAGNOSIS

The differential diagnoses for shortness of breath in this specific patient with previously treated hematologic malignancy currently on chronic steroids is vast, including pulmonary infection, Chronic Obstructive Pulmonary Disease (COPD), or volume overload. Also, two components of ABVD regimen can cause side effects producing symptoms of shortness of breath: Adriamycin can cause cardiomyopathy and subsequent congestive heart failure, and Bleomycin can cause pulmonary fibrosis. Further possible diagnoses include pulmonary embolism and opportunistic infection given his steroid use.

OUTCOME

The patient was initially started on Moxifloxacin and given Furosemide intravenously. The patient’s Ventilation/Perfusion scan was negative for embolism, echocardiogram revealed no systolic dysfunction, and HIV antibody, Antinuclear antibodies, perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic-ANCA (c-ANCA) and rheumatoid factor were negative. The patient’s respiratory viral and sputum culture were also negative. A right heart catheterization completed on day 6 of hospitalization revealed pulmonary hypertension. Bronchoscopy was performed on day 10 due to worsening hypoxia and worsening radiographic evidence of interstitial process on antibiotics and diuretics (Figure 1,2,3). Bronchoalveolar lavage demonstrated presence of Pneumocystis jirovecii.

The patient was started on Trimethoprim/Sulfamethoxazole (Bactrim). On day 15, the patient required continuous Bilevel Positive Airway Pressure (BiPAP) for worsening hypoxia and was transferred to the Intensive Care Unit. The patient was transitioned to intravenous Bactrim and his Prednisone dose was increased. On day 23, the patient required intubation and suffered pulseless electrical activity and return of spontaneous circulation was not achieved after 20 minutes of cardiopulmonary resuscitation.

DISCUSSION

Pneumocystis pneumonia (PCP) is a life threatening disease caused by the fungus Pneumocystis jirovecii previously classified as Pneumocystis carinii. While PCP is historically associated with HIV and CD4 counts less than 200/µL, there have been increasing case reports in HIV negative patients treated with high dose steroids, Methotrexate, Tacrolimus, Infliximab and Etanercept. In the HIV negative population, PCP has a higher likelihood of causing fulminant pulmonary disease more likely requiring mechanical ventilation.

In a study looking at those with Adult T Cell Leukemia treated with corticosteroids, there was a 16.6% overall risk of PCP infection without prophylaxis. In a small case series of patients with Giant Cell Arteritis treated with high dose Prednisone, 85% presented on admission solely with dyspnea, 43% required mechanical ventilation, and 29% died. The documented PCP mortality rate ranges from 51% - 80% in HIV negative patients. In a review of neurology literature, up to 90% of patients were treated with high dose corticosteroids prior to diagnosis with PCP. In a Cochrane review of immunocompromised patients without HIV, thirteen trials showed a reduction of 85% in incidence of PCP when prophylaxis was administered. Across multiple specialties, no firm prophylaxis guidelines have been set. It is generally accepted that any patient on greater than or equal to Prednisone 20 mg per day for greater than 4 weeks should be considered for PCP prophylaxis with Bactrim. There was found to be no statistically significant difference when comparing once daily versus three times weekly dosing of Bactrim for prophylaxis.

The diagnosis of PCP can be delayed due to nonspecific radiographic findings and vague symptoms at time of presentation, as seen with our patient who was not diagnosed until day 10 of hospitalization. Novel serologic markers that detect PCP have been described, with B-1,3 Glucan approaching 100% sensitivity but lacking specificity with regards to detecting PCP. Another marker, KL-6, is a glycoprotein elevated in interstitial pneumonitis caused by PCP, which is elevated in the HIV population, but has not been shown to reliably detect the disease in non-HIV patients. In the non-HIV immunosuppressed, the mainstay of diagnosis involves direct sampling via bronchoalveolar lavage and should be considered early in hospital stay for any patient at risk for PCP.
Once a diagnosis is made, PCP treatment is similar regardless of reason for immunosuppression. Bactrim is the gold standard of therapy with Dapsone, Atovoquone, or Pentamidine used when Bactrim cannot be tolerated. Duration of treatment is not well established in non-HIV patients but should extend to at least 14 days in contrast to the minimum of 21 days for the HIV positive. In patients with HIV and an A-a gradient greater than 35 mmHg or a PaO2 less than 70mmHg, corticosteroids should given. In contrast, adjunctive high dose corticosteroids increased mortality in the non-HIV immunocompromised and are not recommended.

**KEY POINTS**

Pneumocystis pneumonia is a devastating disease of both HIV and non-HIV patients alike. While there are no formalized guidelines, any patient on a corticosteroid dose greater or equal to Prednisone 20 mg per day for more than 4 weeks should be on prophylaxis. In doing so, the rates of PCP can be drastically lowered in these patient populations preventing undue burden of disease.

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Sinus Histiocytosis: An Uncommon Presentation of an Uncommon Condition
Allison Greco, MD and Gregory Kane, MD

INTRODUCTION
Rosai–Dorfman Disease (RDD), also known as Sinus Histiocytosis with Massive Lymphadenopathy (SHML), is a rare, benign, proliferative disorder of macrophages and monocytes that was first described by Rosai and Dorfman in 1969. The vast majority of patients present with painless bilateral cervical lymphadenopathy during childhood or young adulthood. The condition is self-limited and rarely requires medical treatment. Involvement of extranodal sites such as eyelids, eye sockets, skin and subcutaneous tissue, gastrointestinal tract, upper airways and central nervous system have been infrequently described. Mediastinal involvement is extremely rare, and there are few cases reported in the literature.

Here, we present a case of a 61-year-old female with a history of mediastinal sinus histiocytosis with massive lymphadenopathy.

CASE PRESENTATION:
A 61-year-old female with history of hypercholesterolemia and vitamin D deficiency was referred to the Pulmonary clinic for evaluation of an abnormal chest radiograph which was concerning for a right-sided pleural effusion (Figure 1). The patient noted two to three weeks of increasing dyspnea on exertion, chest tenderness, a dry cough, and decreased exercise tolerance. She denied fevers, chills, night sweats, and weight loss. She reported a 10-pack-year smoking history, but denied other occupational exposures. There was no family history of pulmonary disease or malignancy. Vital signs were normal, and physical examination was notable only for decreased breath sounds in the lower one-third of the right lung and reproducible sternal tenderness.

Upon further review of her past medical history, the patient stated that she had similar symptoms several years ago and was subsequently noted to have an abnormal mass and lymph nodes near her esophagus in 2010. She underwent mediastinoscopy with biopsy of these nodes at that time, which was complicated by esophageal perforation and emergent esophageal stent placement. She was told pathology at that time was benign and received limited follow up.

ACT of the thorax from initial presentation in 2010 revealed an abnormal 10 cm, soft tissue mass in the subcarinal region (Figure 2A). There was a mild, right-sided pleural effusion with atelectasis in the right lower lobe. Nineteen biopsy specimens obtained during mediastinoscopy, including 19 excisional lymph node biopsies, were negative for malignancy and demonstrated pathology consistent with sinus histiocytosis with anthracosis.
Follow up imaging obtained after esophageal stent placement showed atelectasis in the right-lower lobe (Figure 2B).

Interestingly, a CT of the thorax from 2011 revealed complete resolution of the subcarinal mass, with persistent scarring in the right lower lobe (Figure 3).

Figure 2. A CT scan of the thorax obtained in 2010 depicts a 30.8 x 32.8mm mass concerning for malignancy (A). Biopsies of this mass obtained via mediastinoscopy revealed histology consistent with sinus histiocytosis. This procedure was complicated by esophageal perforation and esophageal stent placement, as pictured here (B).

Figure 3. A CT of the thorax obtained in 2011 demonstrates interval removal of the esophageal stent, as well as resolving right lower love atelectasis and scarring. There is resolution of the subcarinal lymphadenopathy.

Figure 4. A non-contrast CT of the Thorax obtained in 2014 demonstrates resolution of the mediastinal mass as well as stable right lower lobe scarring without evidence of pleural effusion. These findings account for the right lower lobe opacity seen on plain chest radiograph (Fig. 1).
**DIFFERENTIAL DIAGNOSIS:**
Differential diagnosis for the patient’s radiographic findings at the time of current presentation included chylothorax given the patient’s history of mediastinal instrumentation, malignancy, and persistence of sinus histiocytosis with lymphadenopathy. Additionally, the presence of chest discomfort and shortness of breath indicated a possible cardiac etiology including valvular or ischemic heart disease.

**OUTCOME AND FOLLOW UP:**
Laboratory testing revealed normal metabolic panel, hepatic function panel, cell counts with differential, and inflammatory markers. An echocardiogram revealed normal left ventricular function without evidence of valvular disease or pulmonary hypertension.

A CT of the thorax revealed absence of consolidation, mass, and lymphadenopathy. There was no pleural effusion. There was an area of slightly improved scarring in the right lung base, accounting for the abnormal right lower lobe finding on plain chest radiography (Figure 4).

Pulmonary function testing revealed slight restrictive physiology with a decreased diffusion capacity that corrected when adjusted for volume loss caused by right lower lobe scarring.

Our hypothesis was that the patient suffered from Rosai Dorfmann disease in 2010 and that her biopsies and esophageal perforation caused the observed x-ray and CT findings that are stable to this current evaluation. As the patient’s pulmonary workup was benign, she was encouraged to undergo further cardiac workup, including stress testing.

**DISCUSSION:**
Sinus histiocytosis with massive lymphadenopathy is primarily a benign proliferation of monocytes and macrophages that affects the cervical lymph nodes in children and young adults. Here we present a case of a 61-year-old female with mediastinal lymphadenopathy and histologic changes suggestive of SHML.

Review of the literature reveals several case reports of more typical SHML. Most patients not only present with painless, enlarged, cervical lymph nodes but may also have fever and an elevated erythrocyte sedimentation rate (ESR). Involvement of extranodal sites such as eyelids, eye sockets, skin and subcutaneous tissue, have been described. In the rare reported cases of mediastinal SMHL, patients may have pleural effusion or develop reactive or interstitial lung disease.

The presence of SHML can be identified histologically by the presence of large polyclonal histiocytes with abundant eosinophilic cytoplasm and infrequent mitoses. They generally demonstrate the expression of the S-100 protein.

While our patient’s pathology did not specifically comment on the presence of the above histologic markers, perhaps the most notable factor that suggests the presence of SHML is the disease course; here we are able to examine serial imaging studies, which demonstrate complete resolution of massive mediastinal lymphadenopathy over the course of four years. A self-limited clinical course has previously been described, with the majority of patients receiving surgical debulking and systemic treatment with corticosteroids or chemotherapy only when organ systems become compromised.

**KEY POINTS:**
Sinus histiocytosis with massive lymphadenopathy is primarily a benign proliferation of monocytes in macrophages that typically affects the cervical lymph nodes in children and young adults. It typically involves a self-limiting clinical course that rarely requires treatment.

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Sudden Vision Loss During Hemodialysis

Andrew W. Panakos, MD

INTRODUCTION
Catheter-related blood stream infections (CRBSIs) are a common and unfortunate consequence of prolonged vascular access in hemodialysis patients. Metastatic infections are feared sequela of bacteremia, and include endocarditis, osteomyelitis, septic arthritis, epidural abscess, and endophthalmitis. The following is a case of *Serratia* endophthalmitis originating from a tunneled-dialysis catheter.

CASE PRESENTATION
A 47 year-old Caucasian female with a history of end stage renal disease on hemodialysis, Type 2 diabetes mellitus, and hypertension was undergoing her routinely scheduled hemodialysis session when she experienced “flashes of hot pink” in her left eye. The hemodialysis session was terminated, and the patient returned home. When she awoke the next morning she noticed a large black spot obscuring vision in her left eye as well as pain in the affected eye. The patient presented to Wills Eye Emergency Department that day. She denied any recent fevers, chills, pain, or erythema at the catheter site. She did, however, report that her left-sided chest wall tunneled dialysis catheter had been manipulated and tubing had been exchanged the day prior because of concerns that it was clogged. The patient was transferred to Thomas Jefferson University Hospital (TJUH) for further care.

Initial vital signs revealed a temperature of 98.6 degrees Fahrenheit, heart rate of 88 beats per minute, respiratory rate of 21 per minute, blood pressure of 160/94 mmHg, and 95% oxygen saturation on room air. Physical exam was significant for a diffusely erythematous left sclera with a hazy cornea and a small hypopion occupying the bottom third of the pupil (Figure 1). Her left pupil was sluggishly reactive to light. The patient’s visual acuity exam of the left eye revealed 20/60 vision (20/20 in right eye). Her left chest wall port site was non-erythematous with no palpable fluctuance or drainage. There was no tenderness to palpation in this area. Cardiac exam revealed a grade II/VI systolic ejection murmur most prominent at the right upper sternal border. There were crackles at both lung bases and bilateral 2+ lower extremity pitting edema to the shins. There were no splinter hemorrhages or other skin changes. The patient’s admission laboratory values were notable for a white blood cell count of 16,200 cells/microliter (normal range 4,000-11,000) with 92% neutrophils (normal range 40-73%) and a hemoglobin of 7.5 g/dl (normal 12.5-15) decreased from a baseline of 9 g/dl. A chest x-ray was normal.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis for sudden vision loss is broad and can be divided into media disruptions, retinal problems, and neural visual pathway disturbances. Examples of media problems include keratitis, hyphema, lens changes, vitreous hemorrhage, uveitis, and endophthalmitis. Retinal pathology includes vascular occlusion, retinal detachment, and acute macular problems. Neural visual pathway disruptions can involve the optic nerve, chiasm, and retrochiasm.
OUTCOME AND FOLLOW-UP

The patient’s indwelling central venous access, elevated white blood cell count, and physical exam findings raised suspicion for an infectious cause of vision loss. A culture of the patient’s vitreous fluid resulted as “many gram negative coccobacilli” five hours after being drawn, virtually clinching the diagnosis of bacterial endophthalmitis. The final culture revealed *Serratia marcescens*. Blood cultures drawn upon admission to TJUH grew gram negative bacilli one day after collection, and subsequently also speciated as *Serratia marcescens*. An ultrasound of the eye, also known as a “B scan”, was performed by Ophthalmology and showed a large subretinal abscess and dense vitritis.

Her tunneled dialysis catheter was kept in place for 48 hours to allow her to receive two more dialysis sessions due to concern for refractory fluid overload. Subsequently, the catheter was removed and she was given a three day line holiday before replacement once her blood cultures had cleared. Of note, cultures from the catheter tip also grew gram negative bacilli.

The patient was noted to have a systolic ejection murmur upon admission. It was unknown whether this was a new finding. Considering her evidence of metastatic infection, endocarditis was a concern (particularly involving the aortic valve). However, a transthoracic echocardiogram revealed no abnormalities involving the aortic valve or other vegetations. The patient’s murmur resolved with red blood cell transfusion, thus it was felt that her initial murmur was a flow murmur related to anemia.

The patient was initially treated broadly with intraocular vancomycin, ceftazadime, moxifloxacin, and prednisolone, as well as intravenous vancomycin and piperacillin-tazobactam. Oral moxifloxacin was added on day 3 for its vitreal penetration. Intravitreal tobramycin and atropine eye drops were also added on day 5. Sensitivities returned and subsequently the patient’s non-ocular antibiotics were de-escalated to only oral ciprofloxacin.

Despite these interventions, the patient suffered progressive vision loss and eye swelling (Figure 2). Oral prednisone was added but did not significantly improve her ocular symptoms. Ten days after presentation, the patient underwent enucleation of her left eye for progressive swelling, pain, and fear of refractory ocular infection which could spread beyond the orbit. An ocular implant was inserted during the same surgery. She was discharged on both oral and ocular ciprofloxacin as well as ocular moxifloxacin and a Medrol dose pack.

The patient was discharged on both oral and ocular ciprofloxacin as well as ocular moxifloxacin and a Medrol dose pack.
DISCUSSION
The most important modifiable risk factor for tunneled CRBSI is duration of catheter usage. One study found a 35% and 48% incidence of CRBSI at three and six months, respectively. The type of vascular access for hemodialysis patients also has an effect on the risk of infection. The relative risk of blood stream infection of a tunneled dialysis catheter compared with an arteriovenous fistula is 10:1. Additionally, the relative risk of a non-tunneled vs. tunneled dialysis catheter is 3:1. Other risk factors for CRBSIs include previous CRBSI, recent surgery, diabetes mellitus, iron overload, immunosupression, and hypoalbuminemia.

Five techniques recommended by the Institute for Healthcare Improvement to prevent primary blood stream infections include effective hand hygiene, maximal barrier precautions at insertion, cutaneous antisepsis with chlorhexidine, optimal insertion site selection, and prompt removal when the catheter is no longer necessary. Microorganisms reach circulation in one of three ways: 1) colonization of insertion site (most common), 2) colonization of hubs, junctions, and other connectors—with subsequent access when these are manipulated, and 3) contamination of infused fluid.

Endophthalmitis is a potential metastatic complication of CRBSIs. Endophthalmitis refers to a bacterial or fungal infection within the eye, including involvement of the vitreous and/or aqueous humors. Of note, endophthalmitis is not caused by viruses or parasites; eye infections due to these organisms are termed “uveitis”. Endophthalmitis is further divided into exogenous and endogenous causes. Exogenous endophthalmitis refers to infections that occur due to external factors such as trauma, surgery, or corneal infection. These account for the majority of cases of endophthalmitis. In contrast, endogenous endophthalmitis occurs due to seeding of the eye from within the body, typically through the choroid, which supplies blood to the retina.

KEY POINTS
Catheter related blood stream infections are a common and often avoidable occurrence. The incidence of CRBSIs in end stage renal disease patients is directly related to the amount of time the catheter is left in place. CRBSIs should be suspected in any patient with central venous access who presents with fevers/chills or any signs of metastatic infection. Endogenous endophthalmitis is a potential metastatic manifestation of a CRBSI. Urgent ophthalmic consultation, intracocular and systemic antibiotics/antifungals, as well as catheter removal are the mainstays of treatment.

REFERENCES
The Rare Case of Streptococcus Pyogenes Pneumonia and Its Sequelae

Fern Martin, MD and Gloria Francis, MD

INTRODUCTION

Group A Streptococcus (GAS) or Streptococcus pyogenes is an aerobic gram-positive coccus that causes a multitude of infections that range in severity. GAS most commonly infects the soft tissues, which results in infections such as cellulitis, erysipelas, necrotizing fasciitis and myositis. These deep soft tissue infections are also the most common source of GAS bacteremia. Other common infections caused by GAS include pharyngitis, rheumatic fever and glomerulonephritis. Patients with a severe GAS infection can develop streptococcal toxic shock syndrome, which consists of GAS bacteremia in conjunction with shock and organ failure. Here we present a case of severe GAS pneumonia complicated by toxic shock syndrome and purpura fulminans, a rare complication of disseminated GAS infection.

CASE PRESENTATION

A 57-year-old male with a history of gastric adenocarcinoma status post partial gastrectomy presented with a two-day history of shortness of breath and chest tightness. He denied any associated fevers, cough, sputum production, pharyngitis, diarrhea or dysuria. In the emergency room, he was afebrile (although he had been taking acetaminophen-oxycodone tablets every 4 to 6 hours for his chest pain) with a heart rate of 123 bpm, blood pressure 78/49 mmHg, respiratory rate 21-27 bpm, and pulse oximetry of 94% on a non-rebreather. Physical exam revealed right upper lobe rales, as well as egophony and sinus tachycardia. There was no evidence of pharyngeal erythema, exudates, or ulcers. Pertinent lab work on admission included a creatinine of 2.3 mg/dL and a lactate of 9.0 mmol/L. Computed tomography (CT) of his chest was consistent with pneumonia in the right upper lobe with patchy areas of consolidation in the right middle and lower lobes. The patient received ceftriaxone, azithromycin and five liters of normal saline. He was admitted to the medical intensive care unit (MICU) for severe sepsis secondary to community-acquired pneumonia.

INVESTIGATIONS AND TREATMENT

After fluid resuscitation and antibiotic initiation, the patient’s vital signs improved to a heart rate of 102 bpm and blood pressure of 116/72 mmHg. On hospital day 2, the patient had a temperature of 103.1°F, heart rate 108 bpm, blood pressure 91/60 mmHg, respiratory rate 35 bpm, and pulse oximetry of 90% on a non-rebreather. The patient was intubated for acute hypoxic respiratory failure. His rapid influenza test was negative and gram stain from blood cultures revealed gram-positive cocci in chains. The team presumed that the patient had a Streptococcus species pneumonia with subsequent bacteremia. Over the next twelve hours, the patient continued to be hypotensive and a norepinephrine infusion was started. He subsequently developed acute oliguric renal failure, which required hemodialysis. Blood cultures grew Streptococcus pyogenes, but despite appropriate intravenous (IV) antibiotics and vasopressors, the patient remained hypotensive and his lactate rose to 12.2 mmol/L. On hospital day 3, his bilateral dorsalis pedis, posterior tibialis, and left radial pulses were absent. He developed areas of ecchymoses on his lower extremities that evolved into indurated, well-demarcated purple papules with erythematous borders. The patient was diagnosed with purpura fulminans given his vascular thromboses and disseminated intravascular coagulopathy. He was started on clindamycin and given a dose of intravenous immunoglobulin for presumed toxic shock syndrome secondary to GAS bacteremia. His overall status continued to worsen, as he developed ischemic limbs, shock liver and worsening mental status. Vascular surgery was emergently consulted and felt the patient would require amputations of all distal extremities if he were to recover hemodynamically. On hospital day 5, the patient’s pupils were minimally responsive and he had temperatures of 107°F. It was felt the patient had a cerebral event and a CT scan of the head was ordered. He had a witnessed seizure in the radiology department and developed atrial fibrillation that ultimately became asystole. No cardiopulmonary resuscitation (CPR) was initiated as the patient was made do not resuscitate (DNR) by his family. The patient was pronounced dead in the MICU, and his family was notified.
DISCUSSION

GAS is an aerobic gram-positive beta-hemolytic coccus that causes an array of diseases in all age groups. In patients over the age of forty, risk factors for developing GAS bacteremia include burns, surgical procedures, trauma, nosocomial transmission, chronic steroid use, cardiac disease, diabetes melitus, peripheral vascular disease, malignancy and immunosuppression. Early recognition of GAS bacteremia is important to improving survival. GAS bacteremia can lead to shock and organ failure, such as renal failure, acute respiratory distress syndrome, hepatic failure and diffuse capillary leak syndrome. Streptococcal toxic shock syndrome (TSS) can be caused by any streptococcal species, but it is most commonly associated with GAS. The mortality rate for patients with GAS bacteremia is approximately 35 percent; however once TSS develops, the mortality rate is 79 percent.

In addition to aggressive fluid resuscitation, GAS TSS must also be treated with IV antibiotics. GAS is susceptible to beta-lactam antibiotics, but there is a high failure rate in invasive infections. Beta-lactams, such as penicillin G, inhibit cell wall synthesis, but can be overwhelmed by a large inoculum size. Clindamycin should be added to the antibiotic regimen to suppress toxin production by inhibiting protein synthesis. Intravenous immune globulin (IVIG) can also be used as an adjunctive therapy. Though data on using IVIG in patients with streptococcal TSS is limited, it is believed that IVIG helps by raising antibody levels in patients with invasive infections. A study conducted by Carapetis et al. examined eighty-four patients with invasive GAS infections. The primary outcome of mortality was compared across patients who received clindamycin as a single adjunct versus patients who received dual adjunct therapy with clindamycin and IVIG. Patients treated with clindamycin often had more severe disease but lower mortality (15% versus 39%). Patients who received IVIG in addition to clindamycin had an even lower mortality rate, at 7%.

Our patient presented with common features of GAS TSS, including shock and multi-organ failure, as well as rarer manifestations, such as purpura fulminans and limb ischemia. Purpura fulminans is most commonly seen in children with invasive group B beta-hemolytic streptococcal infections, but it has also been reported in association with GAS. In adults, purpura fulminans is most commonly associated with Neisseria meningitidis, followed by streptococcal species. In asplenic adults, purpura fulminans is associated with Streptococcus pneumoniae bacteremia. It can also occur in individuals with inherited or acquired deficiencies in the Protein C or Protein S anticoagulant pathway. Purpura fulminans is rarely reported in adults with GAS bacteremia who have functioning spleens. Purpura fulminans is a severe, life-threatening syndrome in which disseminated intravascular coagulation (DIC) leads first to hemorrhagic skin infarcts and progresses to limb ischemia. When purpura fulminans is due to sepsis, the vascular lesions causing the classical skin findings also involve a variety of organs, including the kidneys, lungs, and adrenal glands. The mortality rate associated with purpura fulminans is typically greater than 50 percent.

The pathogenesis of sepsis-induced purpura fulminans involves bacterial endotoxin mediated disturbances of procoagulant and anticoagulant activities in vascular endothelial cells. Anticoagulant factors become widely consumed, leading to a state of DIC. The initial clinical manifestation of purpura fulminans is typically a petechial, purpuric rash. Other clinical features include the classical manifestations of sepsis, such as fevers and hypotension. The characteristic petechial rash typically develops 12-24 hours after onset of infectious symptoms, which in the above patient included shortness of breath and chest tightness. As hemorrhagic skin infarction progresses, the petechiae coalesce to form purpuric ecchymoses. Hemorrhagic bullae can then form and develop into dry gangrene.

Treatment is mainly supportive and also targets the bacterial trigger of purpura fulminans. The majority of affected patients require intensive care unit monitoring for aggressive fluid resuscitation, inotropic support, mechanical ventilation, and/or hemodialysis. Surgery can be performed to debride necrotic tissue, but most affected patients eventually require amputations of ischemic limbs. Various therapies have been proposed to target the coagulation pathway deficiencies associated with purpura fulminans, but none have showed any significant clinical efficacy. Recombinant activated protein C has been described as a promising adjunctive therapy in a number of case studies and retrospective studies; however, no randomized controlled trials have been performed to demonstrate its effectiveness.
REFERENCES


INTRODUCTION

Tumor lysis syndrome (TLS) is a potentially life threatening complication of cancer treatments that typically occurs in highly proliferative malignancies. It is rare in patients with multiple myeloma (MM) given the disease’s indolent nature and is estimated to occur in less than 1% of cases. Increasing reports of TLS have been described in MM, particularly in treatment regimens containing bortezomib, the first available proteasome inhibitor. Here we describe a case of a newly diagnosed light chain multiple myeloma resulting in tumor lysis syndrome following the first dose of combination therapy with bortezomib, cyclophosphamide and dexamethasone.

CASE REPORT

A 68 year old man presented with 6-8 weeks of gradually worsening lower back pain and fatigue. In addition, he reported symptoms of severe constipation, nausea, night sweats, dysuria, right sided rib pain, and a 30 lb weight loss. On examination, he had tenderness to palpation along the lower thoracic spine, para-spinal muscles and lower anterior ribs bilaterally. He was found to have deranged renal function with a serum creatinine of 2.75 mg/dl, corrected serum calcium of 11.9 mg/dl, macrocytic anemia with hemoglobin of 11.4 g/dl (MCV 102) and urinalysis with trace protein but a urine protein to creatinine ratio of 9.6. The liver function tests were normal. An X-Ray of his thoracic and lumbar spine revealed a T12 compression fracture.

Subsequent labs revealed hypogammaglobulinemia and beta-2 microglobulin elevation of 19.53 mg/L (normal 1.31-2.6 mg/L). Serum protein electrophoresis had a monoclonal lambda light chain spike measuring 14,520 mg/L. 24 hour urine studies showed 11.5g of protein and 12.1g lambda light chains. A skeletal survey showed a questionable lucent lesion in the right 10th posterior rib. He underwent a bone marrow biopsy which showed 45.9% plasma cells. FISH probe was negative for common cytogenetic abnormalities including 13q deletion. The patient was diagnosed with lambda light chain multiple myeloma, International Staging System (ISS) stage III.

For treatment, the day 1 cycle included bortezomib 1.3mg/m2, cyclophosphamide 300mg, and dexamethasone 40mg. Prior to starting chemotherapy, his serum creatinine had improved to 2.5 mg/dl with normal serum electrolytes. Calcium remained elevated at 11.2mg/dl despite hydration. His care was transferred to the Veteran’s Hospital’s Community Living Center for the duration of his chemotherapy.

24 hours after his first dose of chemotherapy, he re-presented to the emergency room with hypoxia, hypotension, tachycardia, and tachypnea. No fever was observed. Initial laboratory values were as follows: potassium 5.5 mmol/L, serum uric acid 22.7 mg/dL, serum phosphorous 8.2mg/dL, bicarbonate 20mmol/L with anion gap of 17, serum calcium 8.3mg/dL, lactate 1.7mmol/L, LDH 1147 IU/L, and serum creatinine 3.41 mg/dL. He met clinical and laboratory criteria for tumor lysis syndrome (TLS) based on the Cairo-Bishop definition (Table 1). For TLS treatment the patient was started on IV fluid hydration with bicarbonate supplementation, allopurinol 200 mg daily and given a dose of rasburicase 0.15 mg/kg. The patient was admitted to the ICU and closely monitored.

<table>
<thead>
<tr>
<th>TABLE 1: CAIRO-BISHOP DEFINITION OF TUMOR LYSIS SYNDROME (TLS) IN ADULTS</th>
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<td>Laboratory TLS: ≥2 of the following serum abnormalities, developing within 3 days before or 7 days after initiation of chemotherapy</td>
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<tr>
<td>-Uric acid ≥ 8 mg/dL or 25% increase from baseline</td>
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<td>-Potassium ≥ 6 meq/L or 25% increase from baseline</td>
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<tr>
<td>-Phosphorous ≥ 4.5 mmol/dL or 25% increase from baseline</td>
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<tr>
<td>-Calcium ≤ 7 mg/dL or 25% decrease from baseline</td>
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Clinical TLS: Laboratory TLS AND ≥1 of the following criteria

-Creatinine >1.5x upper limit of normal
-Cardiac arrhythmia or sudden death
-Seizure
DIFFERENTIAL DIAGNOSIS
Differential diagnosis of new onset lower back pain in this elderly man included multiple myeloma, metastatic prostate cancer, lumbar strain, hyperparathyroidism and severe constipation secondary to an underlying malignancy of the colon.

OUTCOME AND FOLLOW UP
Over the course of several days, the patient’s TLS labs normalized and he was discharged back to the Veteran’s Community Living Center for rehabilitation. Per oncology’s recommendation, he was treated again with bortezomib, cyclophosphamide and dexamethasone. He was re-admitted to the hospital approximately 2 weeks later with altered mental status and dehydration. Tumor lysis labs at this time were normal. During this hospitalization, the patient and his family made the decision to withhold further treatment and enter home hospice.

DISCUSSION
Tumor lysis syndrome (TLS) is a complication carrying a high morbidity and mortality most commonly occurring secondary to cell lysis caused by chemotherapy with the subsequent release of intracellular potassium, phosphate, and nucleic acids into the bloodstream. Characteristic laboratory findings include hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia and elevated LDH. Clinically, patients can present with nondescript symptoms such as nausea and vomiting, or life threatening cardiac arrhythmias, renal failure, seizures, or sudden death. TLS is most frequently associated with highly proliferative neoplasms such as non-Hodgkins lymphoma and acute lymphocytic leukemia, while plasma cell dyscrasias such as multiple myeloma are classified as typically having a <1% risk.\(^1\)

Multiple myeloma is characterized by a low proliferative index with less than 1% plasma cells engaging in cellular proliferation.\(^2\) As a result, TLS is a rare complication of chemotherapy in the treatment of multiple myeloma. It is believed to have a higher likelihood of occurrence in patients with a high tumor burden, especially if treated with bortezomib in combination with other agents. The definition of high tumor cell burden is not clear in the literature, but it is believed to be correlated with increased serum lactate dehydrogenase and Beta-2 microglobulin levels (≥ 5.5 mg/dL) as well as diffuse bone marrow disease, multiple lytic lesions, hypercalcemia (>12 mg/dL) and positive C reactive protein.\(^3\) TLS has also been cited to occur in monotherapy treatment with bortezomib, steroids, or thalidomide.\(^2\) Additional risk factors associated with the development of TLS in multiple myeloma include high proliferative activity, immature plasma cell morphology, and poor cytogenetics.\(^2,4\) Case reports by Hung Chang et al associate higher rates of TLS in light chain myeloma with pre-existing renal insufficiency prior to chemotherapy, a presentation similar to our patient. Nonetheless, not enough data exists to have clear understanding of the risk factors and whether certain types of multiple myeloma carry a higher risk.

Since the introduction of bortezomib, there have been several other case reports of patients with multiple myeloma developing tumor lysis syndrome with a reported incidence of 1.4%.\(^3\) As a reversible inhibitor of the 26S proteasome, bortezomib’s impact on the transcriptional factor NF-kB is thought to be the mechanism of rapidly induced cancer cell apoptosis.\(^1\) In a case series, Sezer et al. reviewed 496 cases of multiple myeloma treated with bortezomib in three phase II multi-center trials and found that the criteria for tumor lysis syndrome was fulfilled in 7 cases (1.8%). TLS caused renal failure leading to dialysis occurred in three cases, with one patient subsequently dying from renal failure. When a timeline was explicitly described, the earliest TLS case occurred on day 5 following bortezomib administration, making our patient’s presentation one day after treatment even more atypical. Additionally, in two of the cases, TLS did not occur on initial exposure to bortezomib, but rather during retreatment with bortezomib in combination with dexamethasone.\(^5\)

Since the majority of reported cases of TLS typically occur very early in the course of treatment with bortezomib, patients are at the highest risk during the first cycle of therapy. Therefore, it is important to closely monitor patients receiving bortezomib, particularly those with higher tumor burden. Concomitant use of thalidomide or dexamethasone, such as in our patient, tends to increase the likelihood of tumor lysis syndrome.\(^2\) Chim in his article suggests TLS prophylaxis with hydration and alkalinization in patients with a high tumor burden who are being started on a treatment with bortezomib.
CONCLUSION
Although rare, tumor lysis syndrome (TLS) is a potentially severe complication in the treatment of multiple myeloma. After initiation of treatment, patients should be closely monitored, particularly those with a high tumor burden receiving bortezomib. There is a need for further studies and case reports to identify incidence and predicting factors that may lead to TLS in patients treated for multiple myeloma.

REFERENCES
The patient is a 64 year old man with active primary central nervous system B-cell lymphoma who was hospitalized for management of a right lower extremity traumatic injury complicated by a calf hematoma. During the hospital stay, the patient was diagnosed with a provoked left lower extremity deep vein thrombosis (DVT) and treated initially with therapeutic dosing of enoxaparin. Five days after low molecular weight heparin (LMWH) initiation, gradual development of tense, well-circumscribed bullae were noted to appear on his arms and hands bilaterally, ranging from 0.5 cm to 1.5 cm in diameter. These lesions were both nonpruritic and nontender with no significant surrounding erythema (Figure 1). Bullae were located distal to the site of enoxaparin injections. Aside from a normocytic normochromic anemia related to chronic medical conditions, results of platelet counts, creatinine levels, and coagulation profiles remained unremarkable. A shave biopsy of one of the lesions revealed an intraepidermal collection of red blood cells without evidence of thrombotic or vasculitic changes (Figures 2 & 3). Enoxaparin dose was reduced several days after lesion onset due to increasing calf hematoma size, in an effort to balance anticoagulation benefit for the DVT with risk...
of continued bleeding into the hematoma. The bullae started to regress approximately two weeks after onset, eventually crusting over. The patient was eventually discharged home.

We present a case of hemorrhagic bullous dermatosis, which is a rare type of cutaneous reaction to heparins with only a handful of cases reported in the literature. Delayed-type (type IV) hypersensitivity and immune-mediated (heparin-induced thrombocytopenia) mechanisms are the most common causes of cutaneous complications attributed to heparin products. Type IV cutaneous hypersensitivity reactions are non-antibody mediated and typically occur several days to weeks following drug exposure. They may manifest as isolated or multiple erythematous plaques with papulovesicles or scaling. Heparin-induced thrombocytopenia, on the other hand, can induce skin erythema that progresses to hemorrhage and subsequent tissue necrosis. Several unusual and rare dermatologic manifestations have been reported in the literature with a broad differential diagnosis including pustulosis, toxic epidermal necrolysis, arthus reaction, baboon syndrome, hypereosinophilia, and calcinosis cutis. There have only been ten cases reported in the literature regarding the clinical setting and course of hemorrhagic bullous. Mechanisms underlying the pathogenesis of these lesions have not been clearly elucidated, although a hypersensitivity reaction has been suspected. The histopathology of the bullae reveal intraepidermal collections of red blood cells without any thrombotic or vasculitic changes. Direct immunofluorescence and heparin platelet factor 4 have all been negative in prior case reports. Only one of the ten cases has reported unfractionated heparin as an inciting agent for hemorrhagic bullous, while the remaining have been from LMWH. The age range of affected patients in case reports were 50-90 years old with several having a history of malignancy.

Hemorrhagic bullous seems to take a clinically benign course with no patient report of pain or pruritis. The onset of bullae in our case is consistent with the reported 5 to 21 day window of lesion development reported in the literature. The association between lesion regression and discontinuation of heparin treatment seems to be unclear given that about half of the patients’ bullae reported thus far regress despite continuation of heparin therapy with no changes in dosing. Although the resolution of bullae in our patient occurred several days after enoxaparin dose reduction, it is hard to differentiate whether lesion regression occurred directly due to medication management or the natural history of these seemingly benign, self-limiting, bullae.

REFERENCES
INTRODUCTION
Pneumothorax ex vacuo (“without vacuum”) is a type of pneumothorax that can develop in patients with large pleural effusions. Unlike spontaneous or tension pneumothoraces, pneumothorax ex vacuo does not require chest tube placement. Careful recognition of this type of pneumothorax may save patients and physicians from an unnecessary procedure, and limit patient risk of infection, bleeding and further lung injury.

CASE REPORT
An 81 year old woman with a history of osteoarthritis, depression, and remote smoking history, presented to her primary care provider complaining of progressive cough, dyspnea, and 30 lb unintentional weight loss. An outpatient chest radiograph revealed total opacification of the right lung. She was admitted to the hospital for further management. Computed tomography showed a large right pleural effusion with partial collapse of the right lung, bilateral pulmonary nodules, and obliteration of the right lower lobe bronchus. A diagnostic thoracentesis showed an exudative effusion, and cytology was consistent with primary lung adenocarcinoma. Bronchoscopy revealed an aerated right upper lobe, and endobronchial biopsy was unrevealing.

Due to worsening hypoxia, a PleurX drainage catheter was placed, and one liter of pleural fluid was removed daily. Lungs were monitored with post-drainage radiographs, and the patient improved clinically. Five days after PleurX placement, however, she was noted to develop right upper lobe atelectasis and a right apical pneumothorax with no tracheal deviation (Figure 1). In the setting of collapsed lung due to sudden atelectasis, this represented pneumothorax ex vacuo. Her management continued unchanged and she was safely discharged to a rehabilitation facility with pneumothorax ex vacuo and PleurX catheter in place.

Figure 1. Portable chest radiograph demonstrating right upper lobe atelectasis (white arrow head) with pneumothorax ex vacuo (white arrow), in the setting of right pleural effusion and right-sided PleurX catheter.

Pneumothorax ex vacuo: A pneumothorax ex vacuo was traditionally thought to develop when a mucus plug, foreign body, or extrabronchial mass obstructs a bronchus causing acute lobar collapse. The sudden lobar collapse generates a negative intrapleural pressure that draws gas—mainly nitrogen—from the neighboring tissues and blood into the adjacent pleural space. More recently, pneumothorax ex vacuo is also thought to develop when a lung is unable to re-expand following drainage of pleural fluid. The seal between the visceral and parietal pleura remains intact at the sites of the aerated lobes, causing the pneumothorax ex vacuo to surround only the collapsed lobe, distinguishing it from both tension and spontaneous pneumothoraces. Boland et al. and Ponrartana et al. demonstrate that chest tubes are not beneficial for asymptomatic patients with malignant lung parenchymal disease and pneumothorax ex vacuo. Malignant infiltration of the lung tissue leads to poor lung compliance and unresponsiveness to chest tubes. One hypothesis is that malignant cells create a fibrinous peel limiting re-expansion of the lung, while...
another suggests that chronic atelectasis, interrupted blood flow, and pulmonary edema decrease production of pulmonary surfactant prohibiting lung re-expansion after pleural fluid drainage. Observation is appropriate and sufficient in asymptomatic patients. If there is concern for trapped lung, Pien et al. found that PleurX catheter placement is an effective treatment.

**KEY POINTS:**

Pneumothorax ex vacuo develops in the setting of sudden acute lobar collapse, and persists from an inability of the lung to re-expand. Unlike tension or spontaneous pneumothoraces, it only surrounds the atelectatic lobe and does not surround the lobe(s) that are healthy and aerated. Unlike spontaneous and tension pneumothoraces, pneumothorax ex vacuo should be observed without chest tube placement in the asymptomatic patient.

**REFERENCES**


Cartoon by Eugene Han, MD