The **Medicine** Forum

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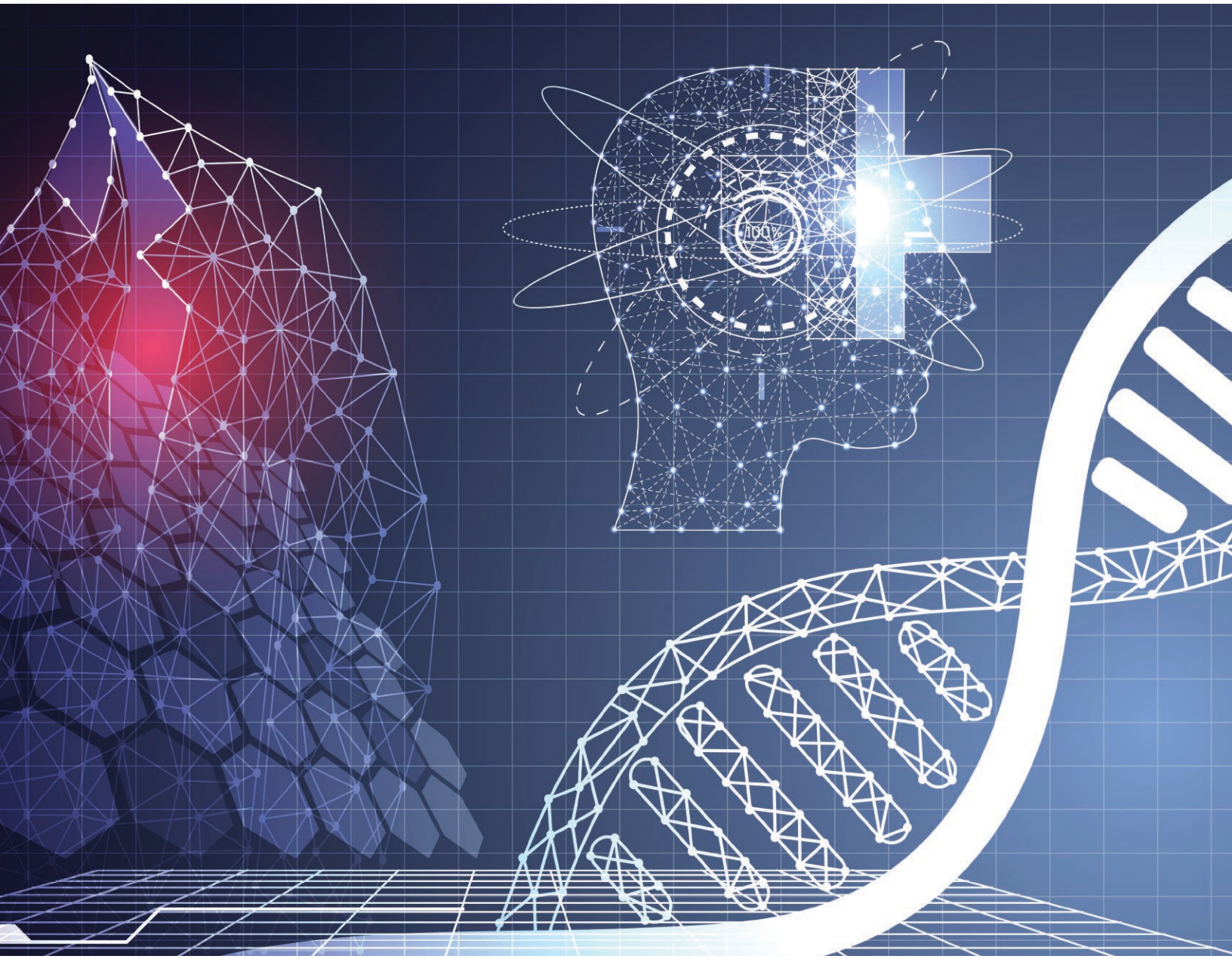

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FROM THE DESK OF THE RESIDENCY PROGRAM DIRECTOR

To Friends of the Department of Medicine

It has been another wonderful year in the Jefferson Internal Medicine Residency Program. Our program continues to train the best and brightest residents in the country. This publication is just one example of the passion, dedication and creativity our residents continue to provide to the Jefferson Community. The residents are not just outstanding clinicians but excel in all aspects of medicine including: research, humanities and medical education.

Like every year, this year has seen changes in our training model as health care delivery across the country continues to evolve. Besides being one of the worst winters on record with our hospital bursting at the seams with patients, we have also implemented a new training schedule called block scheduling. This schedule has allowed us, as a program, to address work compression in the hospital while prioritizing education in outpatient care delivery. The Graduate Medical Education office in conjunction with our residents and medicine faculty leadership is working to utilize the new EPIC EMR to optimize patient care handoffs to improve safety and communication. The residents are thought leaders in delivering outstanding care to our patients across the spectrum and continue to challenge all of us to provide quality, cost effective, safe care to our patients daily.

This journal, now in its 19th edition, continues to exemplify the perseverance, inquisitiveness, and talent of our Internal Medicine residents. Congratulations to the Editors and all of the residents who contributed to another amazing edition of the Forum. I hope you will enjoy reading it!

Emily Stewart, MD, FACP
Associate Professor of Medicine
Program Director Internal Medicine Residency

FROM THE EDITORS

Dear Students, Residents, Faculty, and Friends of the Forum,

We are delighted to present you with the 19th annual edition of *The Medicine Forum*. Here in the birthplace of our nation, we like to think of *The Medicine Forum* as being of the housestaff, by the housestaff and for the housestaff. Undeniably, this publication would not be possible without the countless hours dedicated by our residents, students, fellows and faculty.

At its core, *The Medicine Forum* is about the expansion of our knowledge base and the betterment of our clinical practice. In sharing our experiences with each other, we all improve the care that we deliver our patients. With this objective in mind, we are particularly excited to present you this year with a quality improvement article on transitions of care. Dr. Turner and his colleagues tackle the handoff processes between the intensive care units and the inpatient medicine services in an effort to make these transitions safer for critically ill patients.

This year, we chose to highlight the opioid epidemic which has become the greatest public health crisis of our generation. Working in the heart of Philadelphia, we see the consequences of this epidemic every day. We see it in our clinics, in our emergency department, and on our inpatient medicine services. Everyday, we care for young patients with devastating complications of this disease. We struggle with the challenges of treating addiction in the hospital and facilitating the transition to outpatient care. In this edition, we talk to a team of multi-disciplinary providers about the role of providers in this epidemic and how to best care for these patients as we move forward. How we identify and respond to this crisis will define our generation of medicine.

As always, thank you for reading the *The Medicine Forum*. We hope you will continue to support us in the years to come.

Sincerely,

Neha Bansal Etherington, MD
Anita Modi, MD
Debbie Chen, MD
Brianna Shinn, MD
Colin Thomas, MD

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Clinical Image: Halo Sign

Brandon Menachem MD, and Alan Gandler MD

CASE PRESENTATION

A 68-year-old man with no significant past medical history was transferred to our hospital for evaluation of newly diagnosed acute leukemia. His bone marrow biopsy showed acute undifferentiated leukemia. He was initiated on standard induction chemotherapy with cytarabine and idarubicin. His hospital course was complicated by neutropenic fever secondary to Fusobacterium bacteremia. He was started on antibiotic therapy with intravenous cefepime and oral metronidazole. Intravenous vancomycin was added in the setting of recurrent intermittent fevers. On hospital day 20, he developed minimal hemoptysis, pleuritic chest pain, and recurrent fevers. A CT scan of the chest showed a right upper lobe band-like opacity. Due to concern for possible invasive aspergillosis, he was started on oral voriconazole. Serum galactomannan was negative. Given the patient's thrombocytopenia, tissue diagnosis was deferred. Repeat CT of the chest two weeks later showed an interval increase in the right upper lobe spiculated mass with surrounding ground glass "halo" (Figure 1). A presumptive diagnosis of pulmonary aspergillosis was made in the setting of prolonged neutropenia, classic symptomatology, and rapid growth of the mass suggestive of an infectious process, as well as the halo sign on CT. He was discharged on voriconazole with plans for repeat imaging in several weeks and possible tissue diagnosis at that time.

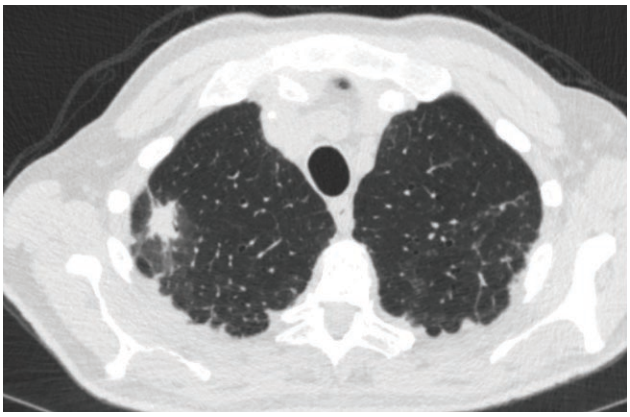

Figure 1: The halo sign, as seen in our patient, is a nodule surrounded by ground glass representing angioinvasive pulmonary infection

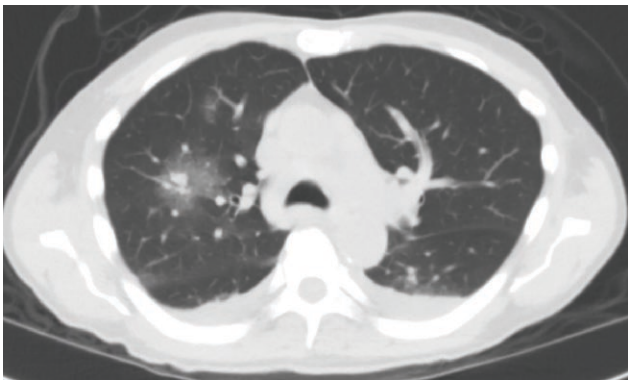

Figure 2: A second case of the halo sign, often seen in early pulmonary aspergillosis and aiding in prompt diagnosis in the correct clinical setting.

DISCUSSION

Members of the fungal genus Aspergillus have been implicated as the causal organisms in a spectrum of distinctive pulmonary pathologies in humans, including allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis, and invasive aspergillosis. The extent of infection is largely determined by differences in the host immunity-microbe interaction. Invasive aspergillosis primarily occurs in the setting of immune compromise, most commonly with acute leukemia, recent hematopoietic stem cell transplant, neutropenia, solid organ transplant on immunosuppression, and chronic granulomatous disease. Pulmonary symptoms typically include dyspnea, cough, and fever unresponsive to broad-spectrum antibiotics. Pleuritic chest pain and hemoptysis can occur due to vascular invasion. If uncontrolled, Aspergillus can spread hematogenously and seed all organ systems.

Diagnosis can be difficult since the only definitive tests are biopsy with positive histopathology or positive cultures from a normally sterile location. Since biopsy is often not performed, infection must often be presumed on the basis of clinical suspicion, respiratory culture data, and biomarkers such as galactomannan. A positive respiratory culture is not sufficient for diagnosis since Aspergillus is a common colonizer. In addition, negative cultures do not rule out infection. In immunocompromised or neutropenic hosts, fever may be the only presenting symptom. Patients with persistent fevers despite an appropriate course of empiric antibiotics (10-14 days) should be assessed for potential fungal infection. In patients for whom aspergillosis is suspected, CT scan may help in identifying early invasive disease and, as some studies suggest, lead to earlier initiation of

antifungal therapy and better overall outcomes. The earliest findings on CT are pulmonary nodules and the classic halo sign.

The halo sign is a nodule with surrounding ground glass opacity. It is thought to represent a central area of infarction and coagulative necrosis with surrounding alveolar hemorrhage due to angioinvasion and local pathogen spread. Although statistics vary between reports, one of the largest cohorts included 235 patients with proven or probable invasive disease, of which 94% had a macronodule and 60.9% had a positive halo sign. The halo sign is not pathognomonic for invasive aspergillosis, as it has also been described with other angioinvasive organisms including pulmonary Mucormycosis and Pseudomonas. However, Aspergillus is the most common pathogen in those at risk for invasive fungal infection. Aspergillosis may also present as a bronchopneumonia, which may be indistinguishable from other more common causes. Treatment consists of a 6 to 12 week course of voriconazole.

This article serves to provide several examples of the halo sign as seen in patients with acute leukemia and neutropenic fever (Figures 1 and 2). Prompt identification of this characteristic radiographic finding and initiation of early treatment for invasive pulmonary aspergillosis is important as mortality rates from untreated infection range from 29-90% depending on patient characteristics.

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Massive Pneumoperitoneum

Harry Wang, MD

CASE PRESENTATION

A 72-year-old man with a past medical history of pancreatic adenocarcinoma status post biliary and duodenal stent placement presented to the emergency department for one week of cramping abdominal pain in the setting of a surveillance abdominal/pelvis computed tomography (CT) scan done two days prior to admission that showed massive pneumoperitoneum (Figure 1). The patient felt bloated but otherwise had no complaints on presentation. His physical exam was significant for marked abdominal distension with mild diffuse tenderness on palpation, normal bowel sounds, and no peritoneal findings of guarding or rebound. Given concern for perforated viscus causing pneumoperitoneum, he was started on intravenous antibiotics and antifungal therapy. Repeat CT scan on admission demonstrated patent biliary and duodenal stents and no definite source of perforation. The patient remained hemodynamically stable throughout his hospitalization; he continued to have regular bowel movements daily and eventually tolerated a diet. His abdominal distension and pain gradually improved without any surgical intervention, and he was discharged home six days after admission to complete 7 days of oral fluconazole, levofloxacin, and metronidazole. It was thought that this patient most likely had a perforated viscus that sealed off. A CT scan two months later showed complete resolution of the pneumoperitoneum.

DISCUSSION

Pneumoperitoneum is caused by perforated intra-abdominal viscus in about 90% of cases, often requiring acute laparotomy/laparoscopy for source control and intravenous antibiotics for 4-8 days to prevent contamination of the peritoneal cavity.[1] However, there are reported cases of pneumoperitoneum without peritonitis that resolve with conservative treatment.[2] These cases of "spontaneous" pneumoperitoneum illustrate the importance of recognizing peritoneal signs and deferring surgical intervention for those who would otherwise have a benign clinical course.

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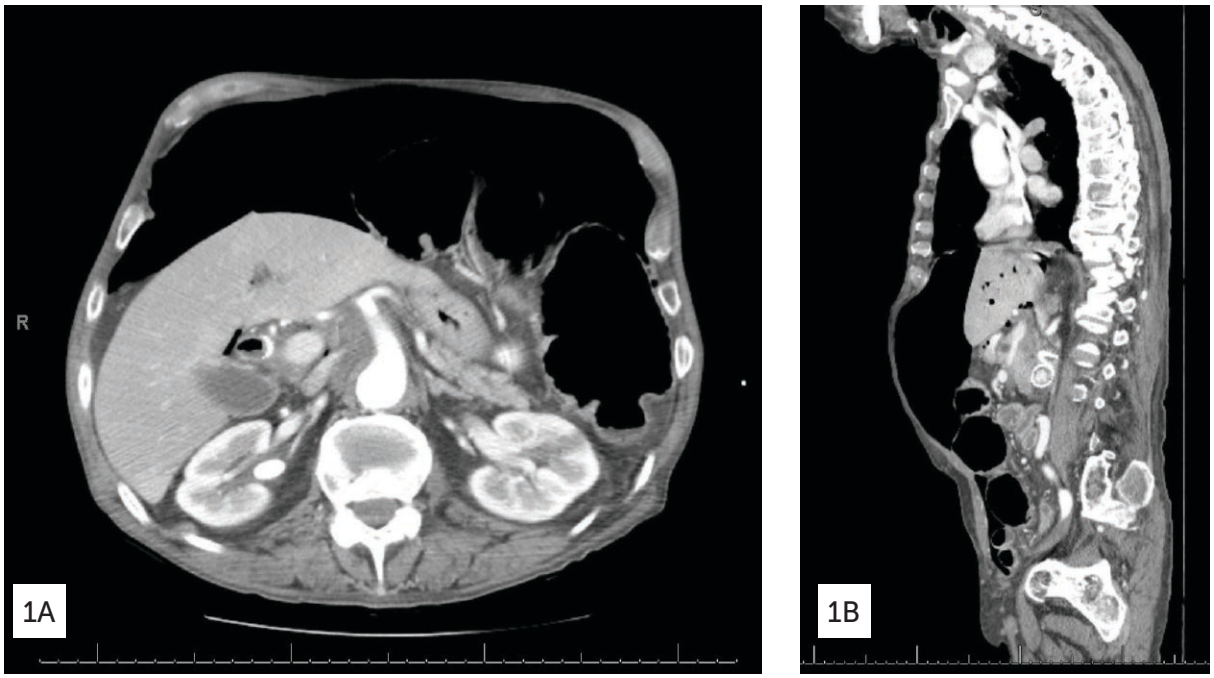

Figure 1. CT abdomen/pelvis with contrast in the axial (1A) and sagittal plane (1B) showing massive pneumoperitoneum.

Roth Spots in Bacterial Endocarditis

Michael A. Weintraub, MD

CASE PRESENTATION

A 30-year-old female with a history of intravenous drug use presented to the hospital with left wrist pain. Physical exam revealed a left volar ulnar wrist abscess with purulent drainage, a holosystolic murmur heard best at the apex radiating to the axilla and Janeway lesions on the right hand and bilateral feet. A transthoracic echocardiogram revealed a 20 mm mobile vegetation on the mitral valve along with valve perforation and severe regurgitation consistent with bacterial endocarditis.

On eye exam, Roth spots (Figure 1) were noted bilaterally. Roth spots are present in less than 2% of all infective endocarditis cases and are composed of immune complex microthrombi that lead to a localized vasculitis. Roth spots are one of the immunologic phenomena that make up the modified Duke criteria in endocarditis but they also appear in other conditions such as leukemia and diabetes. The patient continued to develop more Roth spots, however she did not experience any vision changes.

Brain MRI revealed multiple septic emboli and abscesses. CT angiogram of the head revealed multiple foci of contrast outpouchings consistent with mycotic aneurysms. Her course was complicated by a spontaneous mycotic aneurysm rupture which required endovascular coiling.

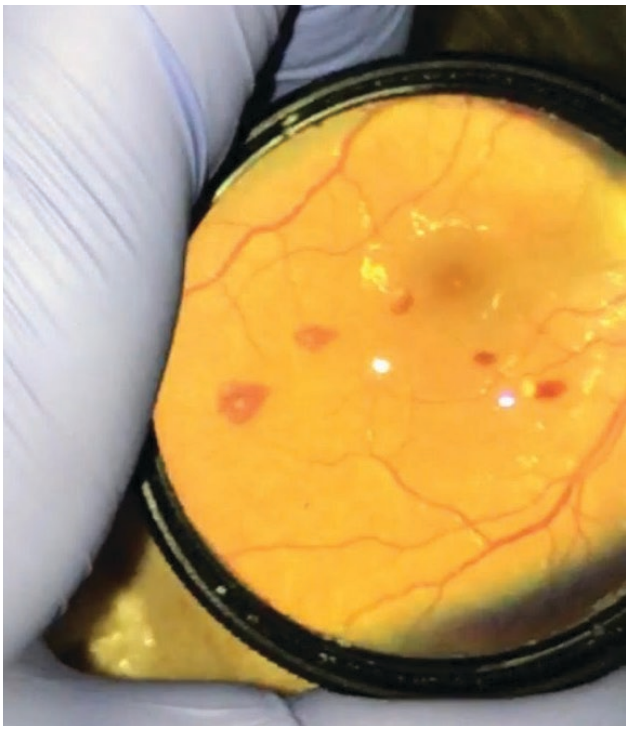

Figure 1. Roth spots are white-centered retinal hemorrhages. Roth spots were noted bilaterally on our patient's eye exam.

DISCUSSION

In endocarditis, surgical valve repair is indicated in the setting of embolic events therefore she ultimately underwent bioprosthetic mitral valve replacement. The mitral valve culture was positive for *propionibacterium acnes*, a rare cause of endocarditis (1% of cases). Wrist abscess cultures grew *clostridium perfringens* and *streptococcus viridans* which suggested polymicrobial endocarditis. However, polymicrobial endocarditis was thought to be less likely since the mitral valve cultures only grew *P. acnes*.

As a member of normal skin and mouth flora, the pathogenic potential of *P. acnes* is often overlooked. It is a fastidious organism that presents commonly with negative blood cultures, as seen in our patient. The majority of patients with *P. acnes* endocarditis are middle-aged males with prosthetic cardiac devices. This case is unique given the patient's demographics, the causative organism, and the classic exam findings seen in endocarditis.

Sharon Li, MD

Acute Aortic and Mitral Valve Insufficiency Precipitated by Infective Endocarditis

Raj Patel, MD, Tatiana Bekker, MD, and Daniel Kramer, MD

INTRODUCTION

Acute severe valvular regurgitation is a medical emergency requiring prompt recognition and diagnosis. Both mitral and aortic valve rupture, if left untreated, inevitably lead to advanced heart failure, cardiovascular collapse, and death. As such, rapid diagnosis is critical and surgical valve repair or replacement is a life-saving intervention. We present a case of a patient with both mitral valve and aortic valve bacterial endocarditis who developed acute valvular rupture, regurgitation, and cardiovascular collapse.

CASE PRESENTATION

A 63-year-old male with no prior medical history presented to an outside hospital with shortness of breath, fatigue, and unexplained 30 pound weight loss over three months. He noted some chills, but otherwise denied fevers, night sweats, chest pain, or palpitations.

On admission to the outside facility, he was noted to be hypoxic and admitted to the intensive care unit (ICU) for respiratory failure. Chest computed tomography (CT) was unrevealing. There was concern for a non-ST elevation myocardial infarction (NSTEMI) for which a cardiac catheterization was performed. No coronary disease was noted on that study; however, it did reveal severe aortic insufficiency and severe mitral regurgitation with an ejection fraction of roughly 60%. Blood cultures from admission showed Gram positive cocci in chains. No vegetations were noted on transthoracic echocardiogram (TTE) or subsequent transesophageal echocardiogram (TEE). The patient was transferred to Thomas Jefferson University Hospital (TJUH) for further management of his valvular disease.

On presentation to TJUH, his physical examination was notable for the following: thin male in mild respiratory distress, without jugular venous distension. Rales were present bilaterally on auscultation of the lungs. Cardiac findings included tachycardia with a grade II/VI diastolic decrescendo murmur heard at Erb's point as well as a grade III/VI holosystolic murmur at the cardiac apex radiating to the axilla. A repeat TTE was done showing a calcified mobile echodensity on the mitral valve with mitral insufficiency and a mobile calcified echodensity on the aortic valve with a flail leaflet and moderate to severe aortic insufficiency. His admission chest x-ray showed radiographic evidence of pulmonary edema. Blood cultures from the outside hospital grew *Streptococcus gallolyticus subsp. pasteurianus* (formerly *Strep. bovis*). Repeat blood cultures at TJUH were without growth, but the patient had been on antibiotics.

He was initially treated with diuretics for his edema, but remained in mild respiratory distress. As such, he was transferred to the cardiac ICU on hospital day 1 for closer monitoring. As he was relatively hemodynamically stable, appropriate preoperative work up was started and he was planned for non-emergent cardiac surgery on hospital day 8. On hospital day 5 however, his respiratory status rapidly worsened. He initially improved with bilevel positive airway pressure, but eventually decompensated, requiring intubation. Immediately after intubation, he became hypotensive, necessitating pressors. His post intubation chest radiograph was notable for acute pulmonary edema.

OUTCOME AND FOLLOW-UP

Cardiothoracic surgery was called and the patient was taken for emergency cardiac surgery. Intraoperatively, the right leaflet of the aortic valve was noted to be prolapsed and perforated. This was ultimately excised. The mitral valve was noted to have endocardial lesions involving the coapting surfaces of both anterior and posterior leaflets, and was also excised. Tissue valves were implanted to replace the damaged aortic and mitral valves. Operating room cultures of valvular tissue showed Gram positive cocci on staining, but the organism was deemed non-viable on repeat subculture.

Post-operatively the patient completed a 4-week course of intravenous (IV) antibiotics. His course was complicated by renal failure requiring dialysis and ventilator dependent respiratory failure requiring tracheostomy and percutaneous endoscopic gastrostomy (PEG) tube placement. Most recently he was seen as an outpatient and was doing well from a cardiac standpoint. He was no longer on dialysis and both tracheostomy and PEG tube had been removed. He was noted to be gaining weight and was able to walk multiple blocks without becoming short of breath.

DISCUSSION

The primary mechanisms by which acute aortic regurgitation develops are endocarditis, aortic dissection, and trauma. Acute regurgitation presents as a distinct entity, quite different than the chronic form when the ventricle has time to compensate for increased volume. In acute aortic regurgitation there is a large reflux of volume into an unprepared left ventricle. This reflux of volume into a relatively small left ventricle rapidly increases the left ventricular end diastolic pressure. Eventually this pressure is transmitted to the left atrium and pulmonary circulation, precipitating pulmonary edema. Additionally, there is decreased cardiac output, which is exacerbated by two mechanisms. The rise in end diastolic pressure mediates a premature closure of the mitral valve thus shortening diastolic filling time. Furthermore, the drop in cardiac output will lead to a compensatory tachycardia that will also decrease diastolic filling time.[1]

Patients typically present with signs of acute cardio-vascular collapse (profound hypotension, pallor, cool extremities) and acute pulmonary edema. Of note, due to the acute volume and pressure overload, a functional mitral regurgitation murmur may develop in the setting of acute aortic regurgitation. However, this is different from an organic cause of mitral regurgitation. It does not warrant any intervention on the mitral valve and should improve with repair of the aortic valve.[1-3]

Organic causes of acute mitral regurgitation, such as endocarditis, do however require rapid intervention to correct the valvular defect. Acute mitral valve rupture leads to an acute regurgitation of fluid into a normal sized, relatively small left atrium. This leads to acute pulmonary edema and decreased forward flow.[1-3]

Definitive treatment of acute valvular insufficiency is surgical repair. Temporizing medical measures can be of limited benefit—primarily intravenous vasodilators, such as nitroprusside, which promote forward flow by reducing afterload.[3] Inotropic agents such as dobutamine can help as well.

The most common cause of acute valvular regurgitation is endocarditis. Some studies show that it accounts for >56% of cases of acute aortic regurgitation.[2] However, encountering multi-valvular disease is overall less common and has been estimated to account for only 15% of all cases of all infective endocarditis.[4] The proposed mechanisms theorize that there is secondary infection of the mitral valve from either direct extension of the aortic valve infection or a jet of regurgitant infected material that progresses to a satellite infection.[5] Cases of multi-valvular endocarditis tend to be more complex and the majority (~70%) require surgical intervention.[4]

KEY POINTS

Our patient presented with subacute, multivalvular endocarditis with evidence of valvular insufficiency on presentation. He initially appeared well compensated without significant respiratory compromise. However, the fragility of his valves placed him in a high-risk position. Upon acute valvular rupture he rapidly decompensated and required emergency cardiac surgery. Acute valvular insufficiency is a medical emergency. Rapid identification and triage, with referral for surgery, is a life-saving intervention.

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Cat Scratching Your Valve: An Elusive Case of *Bartonella* Endocarditis

Ritu Nahar, MD and Evan Caruso, MD

INTRODUCTION

Bartonella Henselae is an uncommon, but significant cause of "culture-negative" endocarditis. While six *Bartonella* species have reportedly caused infective endocarditis (IE) in humans, the vast majority of cases are secondary to either *B. quintana* or *B. henselae*. The epidemiologic features of patients predisposed to *Bartonella* endocarditis are varied. Alcoholism, body lice infestation, and homelessness have been associated with *B. quintana* endocarditis, while *B. henselae* endocarditis has been linked to prior valvular disease and cat exposure.[1-4] Patients with *Bartonella* endocarditis have clinical manifestations similar to those seen with traditional forms of subacute bacterial endocarditis. However, the rarity of the disease compounded by limitations of diagnostic testing make this entity a diagnostic challenge. This case exemplifies a classic presentation of *Bartonella* endocarditis while highlighting the systemic repercussions of inadequate source control and challenges associated with surgical intervention.

CASE PRESENTATION

A 53-year-old female with a history of dysautonomia status post pacemaker over 10 years ago, membranoproliferative glomerulonephritis (MPGN), and chronic pulmonary embolism (not on anticoagulation) presented to an outside hospital with two years of fatigue, weakness, and weight loss complicated by unexplained fevers for 2 weeks. The patient was initially treated with broad spectrum antibiotics, but fevers persisted. Infectious work-up at outside hospital was negative. Upon delving further into her social history, the patient endorsed extensive contact with cats, assisting in kitten birthing 6 months prior to presentation. Physical exam revealed a 2/6 systolic murmur at the left lower sternal border that was louder with inspiration. On transthoracic echocardiography, a 2.2 x 1.9 echodensity was visualized adjacent to the tricuspid valve in close proximity to the right ventricular (RV) pacemaker lead with smaller echodensities on the atrial side of the RV pacemaker lead. Broad-spectrum antibiotics were initiated but the patient continued to spike fevers as high as 104° F. Blood cultures remained sterile despite prolonged incubation periods. Transesophageal echocardiography 5 days later demonstrated progression of lesions, now revealing a 3.9 x 2.5 cm mass stemming from the RV pacemaker lead. On the 5th hospital day, the patient developed severe pleuritic chest pain. Computed tomography (CT) of the chest demonstrated wedge shaped peripheral opacities suspicious for lung infarct from septic emboli versus thromboemboli.

DIFFERENTIAL DIAGNOSIS

Patients with valvular/pacemaker vegetations in the absence of overt bacteremia typically result from marantic endocarditis secondary to a noninfectious etiology or culture-negative endocarditis from an infectious source.[5] Marantic vegetations (nonbacterial thrombotic endocarditis) refers to a spectrum of lesions generally seen in the setting of hypercoagulable states, malignancy, and rheumatologic conditions including systemic lupus erythematosus (Libman-Sacks endocarditis). Interestingly, our patient had a history of pulmonary embolism diagnosed the year prior in the setting of antithrombin deficiency which, compounded by her biopsy proven MPGN, raised concern for a possible thrombotic endocarditis or verrucous endocarditis.

The leading causes for negative cultures in infective endocarditis include prior antimicrobial treatment as seen with our patient and insufficient microbiological techniques. While HACEK organisms (*Haemophilus aphrophilus; Actinobacillus actinomycetemcomitans; Cardiobacterium hominis; Eikenella corrodens;* and *Kingella kingae*) were conventionally believed to be culture-negative, they have since been more successfully cultured with the assistance of modern culture systems.[6] Instead, the predominating causative agents of blood culture-negative endocarditis are fastidious organisms such as zoonotic agents and fungi. *C. burnetii* and *Bartonella* species are two such pathogens with prevalence based on exposure to epidemiological risk factors. Of note, *T. whipplei* may also be an underappreciated source of culture-negative IE with *Mycobacteria* being a rarer cause.[7]

Our patient underwent a thorough rheumatologic and infectious work-up. Her extensive kitten exposure combined with iatrogenic interruption of her valve (pacemaker placement) significantly increased the risk for a possible *Bartonella* infection. Diagnostic tests for culture-negative endocarditis include unique culturing

techniques, molecular tests including polymerase chain reaction (PCR) and serologic assays, and lastly direct histopathology staining of valvular tissue. She was found to have positive *Bartonella* serology with an elevated *Bartonella henselae* immunoglobulin G (IgG) level at 1:512. Interestingly, her *B. Quintana* IgG was also 1:512 likely secondary to cross-reactivity, which is common between IgG among *Bartonella* species. Of note, the recommended cutoff for definitive positivity in patients with suspected *Bartonella* endocarditis is a titer of ≥1:800 for IgG antibodies to either *Bartonella henselae* or *Bartonella quintana*.[8] Diagnosis was eventually confirmed by positive blood PCR for *Bartonella*.

OUTCOME AND FOLLOW-UP

The patient was started on doxycycline (given continued symptomatic fevers) and deemed appropriate for pacemaker and lead removal. The decision was also made to initiate anticoagulation given evolving lung infarcts on CT. Management was complicated by heparin resistance requiring antithrombin concentrate pre- and intra-operatively. On hospital day 10, the patient underwent successful cardiopulmonary bypass surgery for pacemaker and associated mass removal. Of note, the patient was not a candidate for percutaneous lead extraction due to the size of her vegetation; thus, earlier detection may have precluded necessitating surgical intervention. Post-operatively she was initiated on a 6-week course of doxycycline, rifampin, and ceftriaxone. Gentamycin was avoided given her renal impairment from MPGN. Upon confirmation of *Bartonella* blood PCR, ceftriaxone was discontinued and the patient completed a 6-week course of oral doxycycline and rifampin.

DISCUSSION

This case highlights the importance of eliciting epidemiologic risk factors when working up fevers of unknown origin. Systemic complications our patient endured from lack of prompt intervention include recurrent hospitalizations and septic lung emboli. Additionally, *Bartonella* endocarditis is associated with development of immune-complex glomerulonephritis.[9] Thus her MPGN may also in fact be a manifestation of her untreated endocarditis. Blood cultures for *Bartonella henselae* are seldom positive, potentially a result of intraerythrocytic sequestration of the pathogen. Therefore, specialized culturing, molecular assays, and histopathological evaluation of valvular tissue are generally required to establish the diagnosis.

Medical management for *Bartonella* endocarditis is comprised of dual therapy with doxycycline and gentamicin. Gentamicin may be replaced by rifampin if the patient has renal impairment. Ceftriaxone can be added for additional coverage of culture-negative endocarditis if definitive diagnosis of Bartonella has not been established.[10] Of note, our patient had actively evolving lung infarction from septic emboli and recurrent symptomatic fevers resulting in hemodynamic instability, thus surgical removal of the pacemaker and leads was indicated. While endocarditis is an established predisposing factor for decreased heparin responsiveness during cardiopulmonary bypass, the mechanism of this phenomena and how this alters management pre and intra-operatively is an area of research requiring further evaluation.[11]

KEY POINTS

Recognizing and appropriately diagnosing *Bartonella* endocarditis is critical in preventing systemic complications via earlier surgical intervention for source control augmented with adequate antibiotic coverage.

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Case Report: Coexistence of Papillary Thyroid Cancer and Thyroid Lymphoma

Christine Mathai, MD and Edward Ruby, MD

ABSTRACT

We describe a case of a 75-year-old female found to have concurrent papillary thyroid cancer and diffuse large B cell lymphoma of the thyroid.

CASE PRESENTATION

A 75-year-old female presented to the hospital with weakness and a 35-lb weight loss over a 6-month period. She was found to have a new diagnosis of Type 2 diabetes and was evaluated by endocrinology. Physical exam was notable for a palpable right sided thyroid nodule. Thyroid stimulating hormone (TSH) was normal. Thyroid ultrasound confirmed a 4 x 4.8 cm nodule in the right lobe. Fine needle aspiration (FNA) of the nodule revealed atypia of undetermined significance, but the sample tested positive for BRAF and NRAS mutations, concerning for papillary thyroid cancer. She underwent total thyroidectomy. Pathology revealed a combination of multifocal papillary carcinoma, diffuse large B-cell lymphoma (DLBCL) of the thyroid, and chronic lymphocytic thyroiditis. Post-thyroidectomy, she was started on oral levothyroxine to maintain a euthyroid state.

Follow-up positron emission tomography/computed tomography (PET/CT) scan showed no fluorodeoxy-glucose (FDG) uptake in the neck, chest, abdomen, and pelvis. Several 2-3 mm nodules were found in both upper lobes of the lung, some of which demonstrated minimal cavitation which were nonspecific and likely infectious or inflammatory in origin. Metastatic disease in the lung was considered unlikely given the upper lobe predominance. Her DLBCL was characterized as stage IE.

She followed up with medical oncology for management of her DLBCL. She was initiated on standard of care for her disease, including a combination of chemotherapy with 3 cycles of R-CHOP and local radiation, which reportedly has a 90-95% 5-year overall survival rate for stage I extra-nodal DLBCL.[1] She is following with endocrinology for her stage I papillary thyroid cancer, now status-post total thyroidectomy, and continues to take levothyroxine for thyroid replacement. After her treatment for lymphoma is complete, the need for radioactive iodine (RAI) treatment would be discussed further between oncology and endocrinology.

DISCUSSION

Papillary thyroid cancer is the most common thyroid cancer, making up 70-80% of diagnosed thyroid cancers.[2] The BRAF V600E mutation, which activates the mitogen-activated protein kinase (MAPK) signaling pathway, is found in 40- 45% of papillary thyroid cancers.[3] BRAF mutation screening is typically performed with FNA biopsies of thyroid nodules to aid in the diagnosis of papillary thyroid cancer. However, this mutation is found in other thyroid malignancies as well, including thyroid lymphomas. In one study reviewing 33 thyroid lymphomas of various types, 8 of the 33 lymphomas were positive for a BRAF mutation, including the V600E mutation, D594G mutation, and K601N mutations.[3] Of note, the presence or absence of the BRAF mutation did not change outcomes. These patients were treated with a combination of surgery, radiation, and/or chemotherapy with an overall 33% mortality from their respective thyroid lymphoma.

In comparison to papillary thyroid cancer, primary thyroid lymphomas are rarer, accounting for less than 5% of all thyroid cancers or 2 cases per million.[2,4] Primary thyroid lymphomas are typically B-cell in origin and affect middle-aged to older individuals, primarily women. They usually present as rapidly growing neck masses and less commonly present with compression symptoms or B type symptoms. Patients usually present with Stage I disease. Diffuse large B-cell lymphoma is the most common subtype of thyroid lymphoma; mucosa-associated lymphoid tissue (MALT) lymphomas are the second most common.[4] Of thyroid lymphomas, MALT lymphomas tend to be more indolent in nature with a favorable prognosis. MALT lymphomas localized to the thyroid gland tend to respond well to total thyroidectomy and radiation but about 40% of diffuse B-cell lymphomas evolve from MALT lymphomas.[2] The 5-year survival of diffuse B-cell lymphoma is less than 50% with treatment, including chemotherapy and radiation.[2] This increases the importance of early diagnosis of thyroid lymphoma.

There is an association between papillary thyroid cancer and MALT lymphoma in the setting of Hashimoto's thyroiditis.[2] MALT lymphomas in particular are difficult to distinguish from Hashimoto's thyroiditis on FNA biopsy as they are histologically similar. Hashimoto's thyroiditis has been associated with 10-58% of cases of papillary thyroid

cancer and more than 90% of cases of thyroid lymphoma.[2] However, the co-occurrence of papillary thyroid cancer and thyroid lymphoma is very rare.[2] This case demonstrates that as a clinician, one must be aware of the possibility of multiple concurrent thyroid malignancies.

Of note, our patient was never diagnosed with thyroiditis prior to her presentation, but had evidence of chronic thyroiditis on final pathology. Because of the association of thyroid malignancy in patients with Hashimoto's thyroiditis, there should be adequate surveillance in patients with a history of Hashimoto's thyroiditis for papillary thyroid cancer as well as thyroid lymphoma. Some studies suggest performing a thyroid ultrasound at the initial visit for patients diagnosed with Hashimoto's thyroiditis to screen for thyroid malignancy.[5] Although, the risks and benefits of this type of surveillance would likely need to be studied further. In addition, testing for BRAF, NRAS and a growing list of other genetic mutations, particularly in patients with atypia of undetermined significance on FNA biopsy, is becoming more prominent in the identification of thyroid malignancies.[6] These mutations are frequently present in papillary thyroid cancer, but are also seen in thyroid lymphoma, making it important to consider thyroid lymphoma in the differential diagnosis when these mutations are detected in thyroid FNA samples.[7]

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Octreotide-Induced Hypoglycemia in a Cirrhotic Patient

Debbie Chen, MD

INTRODUCTION

Hepatorenal syndrome (HRS) is characterized by functional renal impairment in patients with end-stage liver cirrhosis and no parenchymal kidney disease. It is due to splanchnic vasodilation, which results in renal vasoconstriction with consequent reduction in renal plasma flow and glomerular filtration rate.[1] In the United States, treatment is with a combination of octreotide, midodrine, and human albumin to increase the effective blood volume and subsequently improve renal function.[2] While octreotide, a long-acting somatostatin analog, is used to induce splanchnic vasoconstriction in this setting, it also affects the secretion of insulin and glucagon.

CASE PRESENTATION

A 44-year-old man with a history of Roux-en-Y gastric-bypass and alcoholic cirrhosis complicated by ascites and esophageal varices status-post banding was transferred from an outside hospital for management of hepatic encephalopathy, which clinically improved with lactulose and rifaximin administration. He was recently diagnosed with acute on chronic kidney injury from presumed type 2 hepatorenal syndrome, and started on octreotide, midodrine, and albumin. His hospital course was complicated by persistent symptomatic hypoglycemia that required him to be on a continuous dextrose 50 percent in water infusion, and a high-carbohydrate diet.

Laboratory Studies: When the patient was symptomatically hypoglycemic with a blood glucose level of 43 mg/dL, he concurrently had elevated levels of serum insulin (25 mcIU/mL), C-peptide (10.38 ng/mL), and pro-insulin (52 pmol/L).

Radiological Findings: Abdominal ultrasound and magnetic resonance imaging studies showed no gross evidence of a pancreatic mass. The initial somatostatin receptor scintigraphy showed increased activity in the region of the pancreatic head and uncinate process with focal uptake in the dome of the liver. However, a repeat somatostatin receptor scintigraphy about two weeks later showed resolution of the previously noted increased activity. Intra-arterial calcium stimulation with hepatic venous sampling showed no evidence of elevated insulin levels, significant vascular disease, or a hypervascular region. All of these studies were unrevealing for evidence of a neuroendocrine tumor.

CLINICAL MANAGEMENT

The patient was briefly treated with high-dose octreotide (up to 200mcg every 8 hour), hydrochlorothiazide, and diazoxide when the etiology of his hypoglycemia was thought to be a result of excess insulin secretion. The hydrochlorothiazide and diazoxide were discontinued in the setting of hyperkalemia and worsening kidney function. There was no appreciable improvement in the patient's blood glucose levels until the octreotide was discontinued and high-dose steroids was initiated. The patient was weaned off of all continuous dextrose infusion about three weeks after he last received octreotide, and was subsequently discharged home one week later on prednisone 5mg once daily. As an outpatient, the patient was tapered off of prednisone.

DISCUSSION

In the evaluation of hypoglycemia in patients without diabetes, it is essential to first distinguish between those that meet criteria for Whipple's triad from those who do not, as the former group requires further laboratory workup. Whipple's triad consists of a low plasma blood glucose concentration with concurrent symptoms of hypoglycemia, and symptomatic improvement after the blood glucose level is raised.

In our patient who had documentation of Whipple's triad, the differential for the etiology of his hypoglycemia included an insulinoma, nesidioblastosis, and side effect of octreotide administration. Nesidioblastosis after gastric-bypass surgery causes hyperinsulinemic hypoglycemia as a result of pancreatic islet cell hypertrophy.[3] Laboratory evaluation was consistent with those expected in an insulinoma given elevated levels of serum insulin, C-peptide, and pro-insulin when the patient's blood glucose level was 43 mg/dL. However, repeat octreotide scans and portal venous sampling did not yield evidence of a neuroendocrine tumor.

Octreotide inhibits insulin secretion, and is thus indicated in the treatment of sulfonylurea-induced hypoglycemia. However, paradoxical hypoglycemia with octreotide use has been described in case reports of patients with an insulinoma and a proinsulinoma.[4-7] In our patient, octreotide-induced hypoglycemia is the most plausible explanation for his persistent hypoglycemic state, which spontaneously resolved without additional intervention after discontinuation of octreotide.

CONCLUSION

This is the first reported case of hypoglycemia from octreotide use in a cirrhotic patient being treated for hepatorenal syndrome. This rare side effect cannot be reliably predicted, thus necessitating close supervision and glucose monitoring during octreotide therapy.

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Sharon Li, MD

Liver Abscess Turned Metastatic Infection in an Otherwise Healthy Patient: A Case Report

Samik Shah, MD, Ritu Nahar, MD, and Neha Etherington, MD

INTRODUCTION

The most common type of visceral abscesses are liver abscesses, which have a mortality rate of at least 2.5 percent.[1,2] Most liver abscesses are polymicrobial, containing both facultative and anaerobic enteric pathogens, and develop secondary to another infection such as peritonitis and cholangitis, or from hematogenous spread.[2-4] Liver abscesses are sometimes associated with systemic diseases such as colorectal cancer and diabetes mellitus.[5,6] Rarely, as in our case presentation, primary liver abscesses occur spontaneously in patients with no identifiable precipitating or predisposing conditions.

CASE PRESENTATION

A 54-year-old Chinese-American woman with no significant past medical history presented to the emergency room with two weeks of subjective fevers and chills that worsened two days prior to presentation. She denied shortness of breath, chest pain, abdominal pain, nausea, vomiting, diarrhea, and dysuria. She had no prior surgeries and took no medications. She did not use tobacco, alcohol, or illicit drugs and she worked in a restaurant. She immigrated to the United States from China in the 1990s, and recently traveled to China six months prior to admission.

In the emergency room, she was febrile to 101.6°F, tachycardic to 128 beats/minute, and hypotensive to 85/53 mmHg. Physical exam revealed cervical lymphadenopathy. She was not jaundiced, had no abdominal tenderness or distension, and had a non-focal neurologic exam. Laboratory studies were notable for an elevated leukocyte count 15.2 B/L, aspartate aminotransferase 142 IU/L, alanine aminotransferase 189 IU/L, alkaline phosphatase 295 IU/L, and total bilirubin 1.3 mg/dL. Abdominal ultrasound showed nonspecific gallbladder wall thickening and sludge without biliary ductal dilatation or pericholecystic fluid. Blood cultures were drawn. She was treated with fluid resuscitation and antibiotics (vancomycin, piperacillin-tazobactam, and one dose of tobramycin) for presumed sepsis.

Within 24 hours, blood cultures became positive with gram-negative bacilli, so vancomycin was stopped. Soon after, the patient developed nausea, vomiting, and a brief new oxygen requirement of 2 L/min via nasal cannula. Chest x-ray revealed a new (since admission) small opacity in the left lung base. Respiratory pathogen panel, rapid influenza and respiratory syncytial virus nasal swab, and urine *Streptococcal* and *Legionella* antigens were all negative.

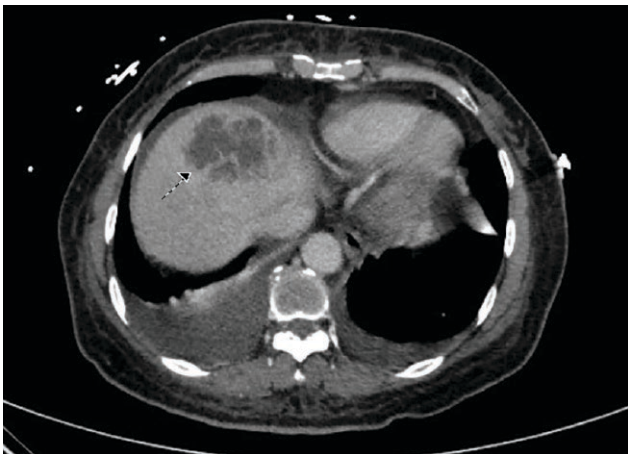

Figure 1. Computed tomography scan of the abdomen with intravenous contrast showing the abscess at the dome of the liver (arrow).

On day three of admission, the initial blood cultures speciated as Klebsiella pneumoniae. On day four, she developed vertigo with left ear hearing loss, tinnitus, nausea, and vomiting. Dix-Hallpike maneuver was positive, but the rest of the neurologic examination was non-focal. Repeat blood cultures were persistently positive for the same organism.

DIFFERENTIAL DIAGNOSIS

The patient presented with sepsis from *K. pneumoniae* bacteremia that was complicated by hypoxia. Even with the hypoxia considered, *K. pneumoniae* is not a common cause of community acquired pneumonia in an otherwise healthy patient, and the patient had sustained bacteremia despite treatment with appropriate antibiotics. Her hypoxia was thus attributed to aspiration due to her emesis. Although a primary source for *Klebsiella* bacteremia may not be identified in up to 30-47 percent of patients, this is more common in nosocomial rather than community acquired infections.[7] Community acquired bacteremia from primary liver abscesses is well-documented in the East Asian population.[8,9] Further, primary *Klebsiella* liver abscesses can rarely be complicated by metastatic brain abscesses.[10] In the setting of our patient's sustained bacteremia with new onset vertigo, she underwent imaging of the brain, abdomen, and pelvis to rule out the presence of abscesses.

OUTCOME AND FOLLOW-UP

Computed tomography (CT) of the abdomen and pelvis showed a 5.3 x 4.6 cm abscess at the dome of the liver (Figure 1). CT of the head showed multiple subcortical ring-enhancing lesions (largest measuring 12 mm) that were concerning for cerebral abscesses. Magnetic resonance imaging (MRI) of the brain similarly showed multiple cerebral abscesses. The cerebral abscesses were determined to be too small for neurosurgical intervention. MRI of the whole spine was unremarkable. Her antibiotics were narrowed from piperacillin-tazobactam to ceftriaxone for better central nervous system penetration. On day five of admission, she underwent liver abscess drain placement with fluid culture positive for *K. pneumoniae*. The liver abscess drain was removed after four days because of decreased output.

After the drain placement, blood cultures cleared and remained negative. Repeat brain MRI performed six days after the initial scan showed that some lesions increased and others decreased in growth, and that there was a new punctate foci of enhancement. Neurological exam remained non-focal. On day 13, she was discharged home to complete a six-week course of intravenous ceftriaxone. Post-discharge imaging shows resolution of the liver abscesses. Unfortunately, she had persistent tinnitus and difficulty hearing on the left side, so she sees an audiologist.

DISCUSSION

This patient's *K. pneumoniae* bacteremia and multiple brain abscesses were likely complications of her 5.3 x 4.6 cm liver abscess since blood cultures became negative after the abscess was drained. The patient had no predisposing conditions including hepatobiliary or colorectal disease, recent intra-abdominal surgery, trauma, or immunocompromising factors. Ko et al. determined the liver to be the primary source in 18% of Taiwanese patients with community-acquired *Klebsiella* bacteremia, as opposed to just 2% in other countries, including the United States and Australia.[11] Among patients with *K. pneumoniae* liver abscesses, Fang et al. found that 23% had septic ocular or central nervous system metastasis, while Cheng et al. found that 12% of patients had some sort of metastatic lesion, also including endophthalmitis, pulmonary abscesses, and central nervous system abscesses.[8,12]

Diabetes mellitus, fatty liver disease, and certain virulence factors found on the specific *Klebsiella* organisms such as a bacterial capsular serotype resistant to phagocytosis, are considered to be risk factors for the pathogenesis of this.[8,9]

In a study of 79 patients with liver abscesses from any organism, the most common presenting symptoms were found to be fever, chills, right upper quadrant abdominal pain, nausea, and vomiting. The most common laboratory abnormalities involved the initial serum albumin (mean 3.1 g/dL, 70% of patients had an abnormal value), leukocyte count (15.4 B/L, 68%), alkaline phosphatase (206.8 IU/L, 67%), and alanine aminotransferase (93.4 IU/L, 54%).[2] Treatment of the liver abscesses involves drainage of the abscess to obtain source control. Antibiotics should be tailored to the sensitivities of the *Klebsiella* species, with a duration of at least a four to six weeks. Follow-up CT imaging is recommended to ensure resolution of the abscesses.

KEY POINTS

This case highlights the importance of a broad differential diagnosis when evaluating a patient with an unknown source of bacteremia. A *Klebsiella* liver abscess should be considered in East Asian patients without an identified source of bacteremia. Early detection to prevent central nervous system metastasis can prevent further devastating complications. The identification of our patient's liver abscess allowed for source-directed therapy with immediate drainage and subsequent resolution of the patient's bacteremia.

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Maggots—Friend or Foe? Treating Myiasis in a Patient with Chronic Wounds

James Harrigan, PharmD, Anita Modi, MD, and Gretchen Diemer, MD

INTRODUCTION

Myiasis, or the infestation of living vertebrates with dipterous (two-winged fly) larvae, can take many forms. Depending on their species, maggots will feed on living or dead tissue, liquid body substances, or even ingested food.[1] The anatomical classification system of such larvae is based on the host location of infestation: sanguinivorous, cavitary, or cutaneous, including furuncular, migratory, or wound.[1] While pathologic myiasis can result in significant morbidity in both humans and livestock, therapeutic myiasis has played an important role in wound debridement for centuries. This article will explore the varying forms of pathologic cutaneous myiasis and the evolving role of therapeutic myiasis by presenting the case of a patient admitted with newly identified infestation of bilateral lower extremity wounds.

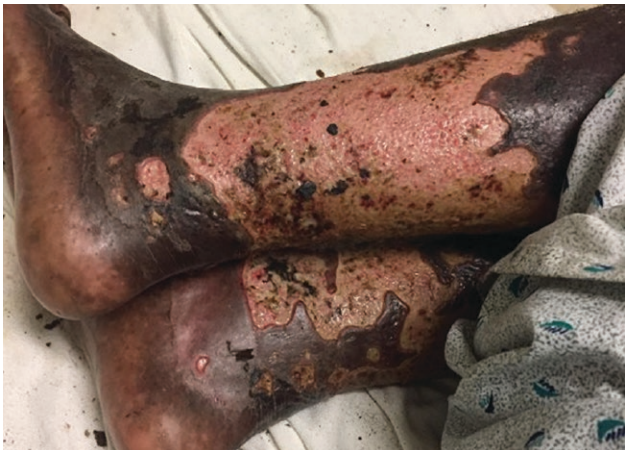

Figure 1. Superficial lower extremity wounds without purulence, edema, erythema, or other evidence of superimposed bacterial infection.

CASE PRESENTATION

The patient is a 59-year-old homeless man with a history of poorly-controlled schizophrenia who presented to the Thomas Jefferson University Hospital (TJUH) Emergency Department with bilateral leg pain. On examination, his legs had multiple areas of superficial ulceration with pale larvae (Figure 1). There was no purulent drainage to suggest superimposed bacterial infection, and his vital signs and laboratory studies demonstrated no signs of systemic illness. The patient was admitted for management of necrotic wounds complicated by myiasis. Surgery was consulted for potential debridement. However, it was noted on inspection that his extremities were devoid of any necrotic tissue to debride. The lack of necrotic tissue was attributed to the maggot infestation. Topical betadine solution was applied and two doses of ivermectin 400 mcg/kg/dose were administered to treat concomitant body lice. Three days after initiation of these therapies, the wounds began to exude purulent and malodorous drainage with evidence of newly developed necrotic tissue. Local wound care with daily dressing changes incorporating Santyl (collagenase), Medihoney, and betadine-soaked gauze were continued for the remainder of the hospital course to prevent further infection.

Table 1: Diptera larval species responsible for varying forms of cutaneous myiasis.

Cutaneous Myiasis	Diptera Larval Species
Furuncle Myiasis	*Dermatobia hominis* *Cordylobia anthropophagia* *Cuterebra s pp.* *Wohlfahrtia vigil* *W opaca*
Migratory Myiasis	*Gasterophilus intestinalis* *Hypoderma spp.*
Wound Myiasis	Facultative parasites *Lucilia seriata* Obligatory parasites *Cochliomyia hominivorax* *Chrysomya bezziana* *W magnifica*

DISCUSSION

Pathologic myiasis is most frequently seen in tropical and travel medicine settings, though maggots can be easily found all over the world, including the United States.[2] Cutaneous myiasis—furuncular, migratory, or wound—is the fourth most reported skin disease in returning travelers.[3] Poor hygiene and low socioeconomic status, which were noted in our patient, serve as risk factors for pathologic myiasis even in developed countries.[4] Wounds most susceptible to pathologic myiasis include neuropathic ulcers, vascular insufficiency

ulcers, psoriasis, hemorrhoids, impetigo, and malignant wounds.[4] Given its prevalence, an understanding of identifying and treating various forms of cutaneous myiasis and superimposed bacterial infections such as tetanus is important.

Furuncular myiasis develops following larval penetration into the healthy exposed skin of travelers or inhabitants of tropical regions, with an incubation period of one to two days. A pruritic, painful, and erythematous nodule forms, with a central dimple facilitating larval respiration and releasing serosanguinous or purulent fluid—and through which a single or multiple larvae can be directly observed.[5] Agitation and insomnia can occur even in localized myiasis, while systemic symptoms of fevers, chills, and lymphadenopathy suggest secondary bacterial infection.

While larvae responsible for furuncular myiasis tend to stay localized within the primary nodule, those of migratory myiasis burrow through the skin and lead to the development of pruritic lesions with raised red borders.[4] These erythematous lesions that are the result of initial larval infestation fade to yellow patches once the larva migrates to a new site. In so doing, larvae can live for months in human skin, rarely penetrating visceral organs and brain and lung parenchyma. Migratory myiasis is typically associated with animal exposures, as the *Diptera* species involved cannot complete their larval life cycles in human hosts and instead relies on cattle and horses as intermediate hosts.

Wound myiasis, such as was seen in our patient, results when flies occupy and lay eggs in open wounds, especially those with necrotic, hemorrhaging, or purulent lesions.[4] Facultative parasites feed only on dead tissue within a wound, excrete antimicrobial and alkaline substances to inhibit bacterial growth, and stimulate granulation—providing utility in wound debridement for centuries.[6] Obligatory parasites, on the other hand, require living tissue for larval development, and are thus prone to cause local destruction, fistula formation, as well as invasion of deep tissue requiring immediate removal.[5] Examination of the wound itself can help determine whether the larvae are facultative or obligatory. Facultative parasites often remain superficial and visible to the naked eye, consuming necrotic tissue on a microscopic level to leave behind clean margins and healthy granulation tissue. Obligatory parasites produce foul-smelling discharge, localized swelling, and deep pockets of infection. Therapeutic myiasis involves the careful selection and sterile harvesting of facultative species, such as *Lucilia sericata*, which will effectively serve to debride, disinfect, and enhance healing at the wound site (Table 1). Clinical indications for the use of therapeutic myiasis include wounds infected with multi-drug resistant bacteria, superficial wounds, non-healing ulcers and burns, and the presence of significant medical comorbidities precluding surgical debridement. Exudate, wound odor, and pain sores have all been demonstrated to decrease with therapeutic myiasis when compared to conventional dressings.[6] All studies to date have used laboratory-bred sterile maggots; no studies to our knowledge have evaluated outcomes in patients presenting with wounds already infested with maggots.

Diagnosis of pathologic myiasis is usually clinical, although dermoscopy and ultrasound have been employed in the detection of larvae within furuncular lesions and along migratory tracts.[4] Peripheral eosinophilia and elevated IgE levels may be observed in patients with chronic or recurrent myiasis, though these values may be normal in the context of acute infestation. Once identified, pathologic larvae should be killed using one of three techniques: application of a toxic substance to the larvae; production of localized hypoxia (i.e. via occlusion of the central dimple with petroleum or paraffin) to force the larvae to emerge from the furuncle; or mechanical/surgical removal of the larvae.[4] Regardless of the mechanism of killing employed, dead larvae should be removed to prevent secondary bacterial infection. Systemic therapy is not recommended for furuncular myiasis in the absence of secondary bacterial infection, as dead larvae may remain trapped within the nodule, resulting in a subsequent inflammatory reaction and development of a nidus.[4] Eradication of obligatory parasites in wound myiasis is similarly performed on a local level, involving application of antiseptic solution or topical ivermectin to the wound. In addition, oral ivermectin or albendazole have been reported to bring migratory larvae closer to the skin surface facilitating subsequent extraction.

KEY POINTS

Therapeutic myiasis has long been employed in controlled settings for the management of chronic, poorly-healing wounds. Enzymes found in the gastrointestinal tracts of some species confer antimicrobial properties to this localized therapy. However, it should be stated that not all maggots are created equal. Obligate larvae feed on all tissues thereby endangering human hosts, while facultative larvae feed preferentially on necrotic tissues—making them ideal therapeutic agents. Despite being used with great regularity for local wound care in ancient cultures, the mere thought of maggots has made many physicians shudder since the advent of germ theory in the second half of the 19th century.[6] While it has yet to be definitively proven in any scientific studies, preserving and identifying maggots that prefer necrotic over living tissue could help debride extensive wounds and allow for timely healing.

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When DeQuervain's DePigments: A Case of Iatrogenic Hypopigmentation

Tatiana Bekker, MD

INTRODUCTION

Localized joint and soft tissue corticosteroid injections are being increasingly utilized to decrease inflammation, improve pain, and recover mobility. Adverse effects from injections are rare, with a 1% incidence of skin depigmentation.[1]

CASE DESCRIPTION

A 58-year-old African American female initially presented to her outpatient primary care clinic with a chief complaint of left wrist pain. She described the pain as localized over the lateral aspect of the radiocarpal joint, non-radiating, and without overlying erythema or edema. The pain had been present for five months. The patient had already tried NSAIDS as well as splinting with minimal relief.

On physical exam, the patients' wrist, hand, and fingers appeared normal to inspection. On palpation, joint spaces were non-tender; however, her Finkelstein's test was grossly positive. This raised suspicion for pathology in the 1st and 2nd extensor compartments consistent with De Quervain's tenosynovitis. All therapeutic options were explained to the patient and she agreed to receive a steroid injection, as this has been shown to have superior outcomes for De Quervain Tenosynovitis.[1,2] Consent was obtained and 10mg triamcinolone was injected in the region of the first extensor compartment just proximal to the radiocarpal joint.[3]

The patient experienced mild symptomatic relief for approximately four weeks. Four months later, she returned to the clinic with skin depigmentation over her left wrist (Figure 1). On exam, her skin was neither pruritic, inflamed, nor painful to palpation. No other areas of depigmentation were appreciated.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acquired skin hypopigmentation includes vitiligo, pityriasis alba, tinea versicolor, post inflammatory causes, and iatrogenic (i.e. from steroids, both injected and less commonly topical).[4] Pityriasis is typically found on the face, neck, and arms and is most commonly associated with a history of atopic dermatitis.[5] Vitiligo is an autoimmune disorder that classically presents with a diffuse bilateral distribution of skin depigmentation and is not limited to skin alone—as hair and mucosal depigmentation may be appreciated as well.[6] Tinea versicolor, a fungal skin infection, presents with multiple diffuse patches as well, most commonly presenting on the trunk.[7] For this specific patient, the localized area of depigmentation and recent steroid injection made iatrogenic cause the most likely etiology.

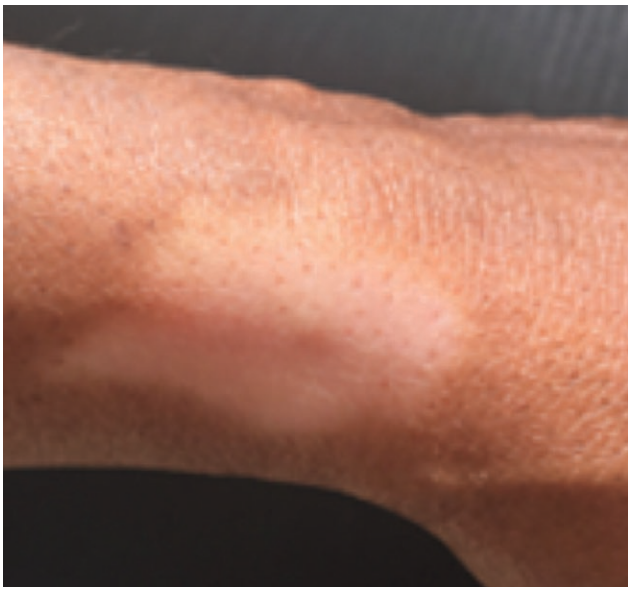

Figure 1. Skin depigmentation over the patient's left wrist.

OUTCOME AND FOLLOW UP

Available therapies for De Quervain's tenosynovitis include rest, non-steroidal anti-inflammatory medications, wrist splinting, steroid injections and a combination of both wrist splinting and steroid injections. This patient was diagnosed with corticosteroid-induced hypopigmentation secondary to her recent injection. Proper anticipatory guidance was provided and the patient was reassured that her normal pigment should return with discontinuation of steroids. The patient was scheduled to follow up in four months for re-evaluation of her wrist.

DISCUSSION

Pigmentation of skin is dependent upon the amount and function of melanocytes. Skin hypopigmentation results from either a decreased number of melanocytes or an injury to the melanocytes' ability to properly transport

melanin to the skin surface. It is hypothesized that steroids likely interfere with melanin synthesis within melanocytes, causing an area of hypopigmentation that is reversible with discontinuation of steroids.[8]

Localized corticosteroid injections are a well-established and effective therapeutic intervention for inflammatory, crystalline, and mechanical arthropathies. In a pooled meta-analysis, injection alone was shown to have a higher cure rate than any other therapeutic avenue, with a reported 83% cure rate.[9] Complications can arise from the process of the injection itself, including local trauma and infection, and those due to the effect of a locally injected steroid, such as post injection flare where there is a local inflammatory reaction that appears and resolves within 24-48 hours after injection, and late skin changes such as atrophy and depigmentation.[1] Depigmentation has been shown to be more likely to occur in dark-skinned individuals and arises between 1-4 months after injection. Time to resolution of hypopigmentation is variable, reportedly taking anywhere between 6-30 months to return to baseline.[10,11] This complication is widely described in the literature. However, it is relatively rare, with an incidence of less <1% of all injection.

KEY POINTS

Hypopigmentation is a well-known complication of steroid injections. Though infrequently encountered and relatively benign, it remains an important complication to explain to patients prior to the procedure.

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Death by Delirium: A 71-Year-Old Male with Poor Post-operative Recovery

William Bradford, MD

INTRODUCTION

Delirium is an acute decline in attention and cognition not better explained by another medical condition.[1] It is multifactorial in origin, with risk factors including advanced age, male sex, baseline decreased cognitive status, sensory impairment, poor baseline functional status, polypharmacy, and multiple comorbid conditions. Acute precipitants for delirium include administration of psychoactive medications (particularly benzodiazepines, narcotics, anticholinergic medications, and general anesthesia), sleep deprivation, major surgery, and new illness or worsening of current illness.[1] Delirium accounts for some 49% of all hospital days in older patients, increases rates of mortality and morbidity, and is associated with lasting cognitive impairment after discharge, even in younger patients.[2]

CASE PRESENTATION

Mr. M was a 71-year-old male Vietnam-War veteran living independently and working as a standardized patient at a local medical college. The patient had a past medical history of cirrhosis due to nonalcoholic steatohepatitis (NASH), multiple sclerosis (MS), atrial fibrillation (AF), and diverticulosis. He presented as a transfer from an outside hospital for management of decompensated NASH cirrhosis precipitated by a mechanical fall, resulting in a right hip replacement eleven days prior. He was admitted to an inpatient hepatology service and shortly after admission, he was noted to have altered mental status. Admission blood cultures were positive for *Klebsiella pneumoniae* and purulent drainage was noted from the hip incision. The patient was taken to the operating room by orthopedic surgery for hip replacement washout and revision and transferred to the surgical intensive care unit (SICU) postoperatively for hypoxic respiratory failure requiring intubation. After an 8 day course in the SICU marked by persistent delirium, the patient was transferred back to the hepatology service for further management.

On arrival to the hepatology service, Mr. M had moderate global weakness, severe dysphagia requiring tube feeds via a dobhoff tube (DHT), and recurrent bouts of symptomatic AF with rapid ventricular response. The patient was maintained on ciprofloxacin for suppression of his prosthetic joint infection. His course over the ensuing days was marked by episodes of disorientation, vivid visual and auditory hallucinations, and alternating somnolence and agitation. His hospital course was further complicated by bilateral lower extremity deep vein thromboses, persistent severe dysphagia, post-traumatic stress disorder with flashbacks, periodic mild hypernatremia, and poor tolerance of physical therapy. He had worsening of his hallucinations, inability to follow commands, and decreased orientation after an EGD for banding of esophageal varices. These symptoms improved slightly after his home baclofen (for multiple sclerosis) was tapered and ceftriaxone was substituted for ciprofloxacin. Head magnetic resonance (MR) imaging, MR angiography and multiple computed tomography (CT) scans showed no evidence of an acute intracranial process or major worsening of his known MS lesions. His blood urea nitrogen (BUN) was within normal limits, and he was maintained on lactulose and rifaximin with stool output at or above goal 3-4/day throughout his stay. On hospital day 53, 39 days after his transfer from the SICU to the floor, he developed lactic acidosis, severe acute kidney injury, and became acutely hypoxic with increased work of breathing. He was offered intubation and further workup for his severe sepsis; however, his decision-maker opted for hospice.

DIFFERENTIAL DIAGNOSIS

Mr. M suffered discrete episodes of altered mental status that were precipitated by anesthesia, sleep deprivation due to late lab draws, nighttime administration of ciprofloxacin and baclofen, and known triggers of his post-traumatic stress disorder (including hospital helicopter landings and thirst). These episodes decreased in frequency with adequate sleep, reorientation measures, control of his thirst, use of atypical antipsychotics, and removal of a fecal management system. His ammonia was elevated initially at 49, at which point he was empirically started on lactulose and rifaximin with stool output at or above goal. He was euglycemic throughout his stay. The patient had no kidney disease or elevated BUN to suggest uremia. Exhaustive brain imaging did not reveal any significant intracranial pathology. Comprehensive infectious workup found no new infection or recurrence of his previous joint infection. Given his critical illness, waxing and waning mental status, and lack of improvement despite correction of other identifiable causes, the diagnosis of delirium was made.

OUTCOME AND FOLLOW-UP

The patient expired two days after transfer to inpatient hospice.

DISCUSSION

Mr. M's unfortunate case illustrates prolonged delirium leading to a cascade of complications that ultimately led to what was likely a hospital-acquired infection resulting in his death. This case highlights the importance of early recognition and aggressive treatment of delirium in hospitalized elderly patients. Although Mr. M predominantly displayed hyperactive delirium, it is estimated that some 75% of delirium cases are the more insidious hypoactive form, which is associated with worse outcomes, possibly because it more often goes undiagnosed and untreated.[3] As the front-line provider for inpatients, the resident physician is able to have a major impact on the recognition and treatment of delirium.

Recognition of delirium begins with clinical suspicion based on risk factors. A bedside diagnostic test, such as the Confusion Assessment Method (Figure 1A), should follow.[1] If the diagnosis of delirium is confirmed, the clinician should perform a thorough evaluation for the underlying cause. The DELIRIUM mnemonic provides a useful approach for this evaluation (Figure 1B).[1] The cornerstone of delirium management is well-integrated care by all members of the healthcare team as well as the patient's family to identify and address all modifiable contributors. Physical restraints, although frequently utilized, are actually associated with increased risk of injury and persistence of delirium after discharge.[4] Their use should be reduced or eliminated on the general wards but may be necessary in the ICU to prevent dislodgement of lines and tubes. Use of a sitter should be considered in lieu of restraints. Pharmacologic treatment with antipsychotics may be required for patients with distressing perceptual disturbances or delusional thoughts but should not be employed without attention to potential underlying reversible causes.

Prevention is the best approach to delirium, with the key components of the prevention strategy established in a 1999 study which showed that reorientation, non-pharmacologic sleep protocol, getting the patient out of bed, encouraging the use of glasses/hearing aids, and encouraging fluid intake result in lower rates of delirium in hospitalized elderly.[5] Some studies also show benefits for elderly patients who receive geriatric consultation early in their hospital stay. More aggressive prevention, especially closer attention to hydration status and more attention to preventing nocturnal awakenings early in his stay, might have prevented such a tragic outcome for Mr. M and other patients like him.

Figure 1A: The Confusion Assessment Method for diagnosing delirium

To diagnose delirium, features 1 and 2 and *either* 3 or 4 are required

1. Acute change in mental status with a fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

Figure 1B: The DELIRIUM mnemonic for underlying causes of delirium

Drugs
Electrolyte disturbances
Lack of drugs
Infection
Reduced sensory input
Intracranial etiologies
Urinary and fecal disorders
Myocardial and pulmonary disorderss

KEY POINTS

- Delirium, especially the hypoactive form, is an under-recognized and preventable complication of hospitalization in elderly patients.
- Advanced age, male sex, baseline cognitive impairment, polypharmacy, and multiple comorbidities are risk factors for development of delirium.
- Reorientation, institution of a non-pharmacologic sleep protocol, getting the patient out of bed, encouraging the use of glasses/hearing aids, and encouraging fluid intake result in lower rates of delirium in hospitalized elderly.
- Antipsychotic medications should only be used when necessary to prevent harm to the patient and should be initiated at a very low dose (0.25 mg IV is the recommended starting dose of haloperidol).

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A Case of Secondary Hemophagocytic Lymphohistiocytosis in an Adult Patient Treated with Concurrent Dexamethasone and Interleukin-1 Receptor Blockade

Vikas Sunder, MD

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) is a rare, life-threatening syndrome of overwhelming inflammation caused by activation and proliferation of T-lymphocytes and hemophagocytic macrophages.[1] This uncontrolled proliferation of macrophages creates a cytokine storm with resultant tissue damage. HLH is associated with clinical and laboratory findings which include fever, cytopenias, hepatic dysfunction, splenomegaly, and marked hyperferritinemia.[1-3] There exists limited epidemiologic data on adult (age ≥ 18 years) cases of HLH, and its incidence is uncertain.[2,4] HLH can be due to inherited mutations causing immune system dysregulation or secondary to underlying malignancy, infection, or rheumatologic condition. Macrophage activation syndrome (MAS) refers to HLH that occurs secondary to rheumatologic diseases.[5] Approximately 8% of HLH cases in adults occur secondary to rheumatologic diseases.[4] The overall 30-day mortality for HLH in adult patients is approximately 44% and can be related to the underlying trigger with malignancy-associated HLH patients having a higher mortality.[4] A key barrier to HLH treatment in adults is delay in diagnosis given the lack of specific laboratory findings to distinguish it from bacterial sepsis.[1,2] The treatment for HLH in adults, beyond early initiation of steroids, remains unclear given its rarity, with much of our understanding of HLH derived from the pediatric literature.[5]

CASE PRESENTATION

A 26-year-old man presented to an outside Emergency Department (ED) with 3 days of fevers to 103°F, headache, and rash on his upper chest and upper extremities. He was discharged home with ibuprofen, but represented to the ED when his fevers did not resolve. The patient had a history notable for Raynaud's syndrome diagnosed as a toddler. Five months prior to admission, he was hospitalized for a pyogenic hepatic abscess for which he underwent percutaneous drainage and a 6-week course of ciprofloxacin and metronidazole. His only complaint was vague right upper abdominal soreness. Vital signs were notable for heart rate of 115 beats/minute and fever to 102.2°F.

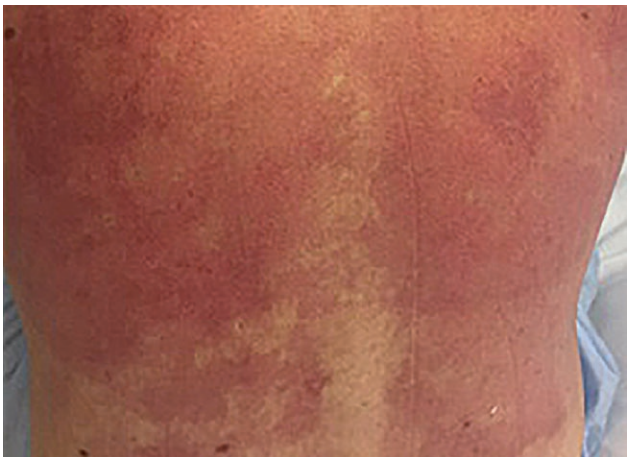

Figure 1. Erythematous rash involving the back.

Physical exam was significant for conjunctival injection and icterus, tachycardia, and blanching erythematous patches involving the chest, upper arms and back (Figure 1). The patient's admission labs were notable for hyperbilirubinemia, transaminitis, thrombocytopenia, and leukopenia with significant bandemia (Table 1).

Table 1: Labs for Admission to the hospital

Lab	Result	Lab	Result
Hemoglobin (g/dL)	13.2 L	AST (IU/L)	480 H
WBC (B/L)	2.8 with 66% bands L	ALT (IU/L)	591 H
Platelets (B/L)	86 L	Total Bilirubin (mg/dL)	3.9 H
BUN (mg/dL)	8	Albumin (g/dL)	3.9
Creatinine (mg/dL)	0.9	ANA titer	>1:640 H
Ferritin (ng/mL)	6881 H	Anti-RNP/SM ELISA (U/mL)	>1562 H
LDH (IU/L)	1064 H	CRP (mg/dL)	12.1 H

Table 2: HLH-2004 Criteria for Hemophagocytic Lymphohistiocytosis Observed in Case	
HLH-2004 Diagnostic Criteria	**Patient**
Fever>38.5 °C	*Temperature 39.2 °C on admission
Splenomegaly	*Present on multiple imaging modalities abdominal ultrasound, CT scan of abdomen
Cytopenia with 2 of following: hemoglobin <9 g/dL, Platelets <100 (B/L), absolute neutrophil count <1000	ANC 2548 on admission, platelet count 81 (B/L)
Hypertriglyceridemia and/or hypofibrinogenemia	Fibrinogen 257 mg/dL, Triglycerides 144 mg/dL (Within normal limits)
Hemophagocytosis in bone marrow, spleen, lymph node or liver	*Bone marrow biopsy with increased number of macrophages with hemophagocytic activity
Low or absent Natural Killer cell activity	Flow Cytometry with NK cells making up 6% of lymphocyte lineage
Ferritin>500 ng/mL	*6881 ng/mL
Elevated soluble CD25 (IL-2) receptor (U/mL)	*3304 U/mL

DIFFERENTIAL DIAGNOSIS

Sepsis was at the top of the differential so the patient was started on broad spectrum antibiotics with daptomycin, aztreonam, and doxycycline to cover for arthropod-borne infection given the high fevers and rash. A computed tomography (CT) scan of the abdomen/pelvis with contrast was performed and showed scarring at the site of the previous hepatic abscess and splenomegaly. The absence of a new hepatic abscess on imaging, along with the patient's upward trending fever curve over the next 2 days while on broad spectrum antibiotics moved the suspected diagnosis towards a non-infectious cause of severe inflammatory disease. The patient's ferritin level dramatically increased from 6,800ng/mL on admission to 10,000ng/mL on day 3. The antinuclear antibody (ANA) titer resulted as >1:640, and Anti-RNP/Sm ELISA was >1562U/mL, concerning for an underlying autoimmune condition. A soluble serum interleukin-2 (IL-2) receptor level was elevated to 3,300U/mL. A bone marrow biopsy showed an increased level of macrophages, some of which contained phagocytized cells. Given the composite of this primary data, along with worsening clinical status, HLH-2004 diagnostic criteria was applied and unified this patient's clinical syndrome as HLH based on meeting five of the eight criteria (Table 2).

OUTCOME AND FOLLOW-UP

Treatment with IV dexamethasone was initiated on day 3 of admission for a suspicion of HLH. Intravenous Immunoglobulin (IVIG) 1g/kg/day for two doses and anakinra 100mg twice daily were also initiated on day 4 of admission given the lab-work suggesting an underlying rheumatologic trigger. Etoposide, a recommended treatment for non-rheumatologic HLH, was not given due to this patient's extensive hepatic disease, pancytopenia, and likely rheumatologic trigger.[6] The patient's fever curve, ferritin level, and transaminases down-trended, and his rash greatly improved over the next few days. Dexamethasone was stopped 30 days after discharge based on improving lab-work and the anakinra is to be continued indefinitely with rheumatology follow-up. 60 days after initial admission, the patient's ferritin level normalized, and he returned to his baseline functional independence.

DISCUSSION

HLH is a life-threatening disease marked by severe uncontrolled inflammation. HLH in adults remains an elusive diagnosis given its non-specific laboratory findings. Studies have shown that marked hyper-ferritinemia >50,000µg/L is not predictive of HLH in adult populations, as opposed to pediatric populations in which it is 90% sensitive and 98% specific.[7] The major obstacle to initiating HLH treatment is a delay in diagnosis as was evident in our case. In our patient, the soluble IL-2 receptor level, which reflects the activation of T-cells, was highly elevated in accordance with cytokine mediated organ dysfunction associated with HLH.[2,5] There is, however, a time delay in obtaining the IL-2 receptor level, which may take 3- 6 days to result. Overall, our patient's presentation was in line with documented cases of adult HLH in that our patient had a fever (93% of cases), splenomegaly (50% of cases), elevated ferritin (98% of cases), and hemophagocytosis seen on bone marrow biopsy (97% of cases).[4,8-11] Given that diagnosis remains a barrier to HLH treatment, future work should focus on developing adult specific diagnostic criteria. In 2014, a research group based in Paris constructed a diagnostic score called the "HScore" which may be used to estimate an individual's risk for reactive hemophagocytic syndrome according to weighted criteria. This tool is freely available online, but it has limitations including non-specific cutoff values for the criteria and it requires further validation in prospective study.[12]

The principle of HLH management is to suppress the unregulated inflammation.[2] There is a more specific HLH-2004 treatment protocol which comes from pediatric literature and includes an initial 8-week course of chemo-immunotherapy with etoposide, dexamethasone, and cyclosporine A upfront for patients who are less than

18 years of age and meet HLH-2004 diagnostic criteria.[6] Early initiation of dexamethasone, which can cross the blood brain barrier, appears to be of benefit in documented adult cases of HLH and was in this case.[2] Treatment of the underlying trigger can often lead to control or resolution of the secondary HLH. Our patient had an unclear but likely rheumatologic trigger and was treated with anakinra, an IL-1 receptor antagonist. The exact role of IL-1 in HLH is unknown, but considering the end-product of HLH is an increased production of cytokines, it would make sense to see IL-1 up-regulation.[1] Anakinra has been used with positive response in patients with HLH secondary to Systemic Juvenile Idiopathic Arthritis, Adult Still's disease, Systemic Lupus Erythematosus, and even Cytomegalovirus infection.[1,3,8,9,11] It is clear that not all adult cases of HLH require initiation of the complete HLH-2004 protocol treatment, which includes chemotherapeutics, as these medications carry harmful side effects.[2] Use of a biological response modifier along with dexamethasone may achieve treatment of secondary HLH in an adult patient as exemplified by this case. Further reporting of successful treatment regimens is crucial to developing trigger specific HLH treatment protocols, given that these patients carry different prognoses based on their underlying cause.[4]

KEY POINTS

- The prompt diagnosis of secondary HLH in adult patients remains elusive in the absence of adult-specific diagnostic criteria. The presence of multiple HLH-2004 criteria along with the progression of laboratory data can be used to support an HLH diagnosis.
- Not all cases of HLH in adult patients require the initiation of HLH-2004 specific therapy. HLH secondary to a rheumatologic trigger may be managed successfully with dexamethasone and IL-1 receptor blockade. Further investigation of HLH treatment in adult patients is needed.

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Resistant *Raoultella Ornithinolytica* Bacteremia in a Patient with New Acute Myeloid Leukemia

Mario Caldararo, MD

INTRODUCTION

Members of the *Raoultella* genus were formerly considered to be *Klebsiella* species until they were differentiated based on phylogenetic Deoxyribonucleic acid (DNA) analysis.[1] Since then, *Raoultella ornithinolytica* has been sparsely implicated in clinically-apparent disease, though more case reports are appearing as of late. Here we report the first documented instance of *R. ornithinolytica* bacteremia in a patient with new acute myeloid leukemia (AML).

CASE PRESENTATION

A 71-year-old man was transferred to our hospital for treatment of newly discovered AML. Prior to transfer, he experienced an aching abdominal pain attributed to pancreatitis and daily episodes of watery diarrhea for five days.

On admission, he had an oral temperature of 102.7°F, pulse of 96 beats per minute, blood pressure of 145/70 mmHg, and oxygen saturation of 97% on room air. Physical exam revealed gray-brown granular material along the gum line of the third tooth that was tender to palpation, tender lymphadenopathy in the right submandibular space and right anterior cervical chain, a grade 2/6 systolic murmur, and no peripheral edema. Abdominal exam revealed tenderness and guarding over the left upper quadrant and epigastrium. The remainder of the physical exam was unremarkable.

Lab work revealed a white blood cell (WBC) count of 25.0 x 10^9/L with 52% blasts, hemoglobin of 7.4 g/dL, and platelets of 36,000 x 10^9/L. Lipase, liver enzymes, and creatinine were within normal limits. There was no acid-base derangement. Nucleic acid amplification testing for *Clostridium difficile* toxin was negative.

Since initial imaging was not available, a computed tomography (CT) scan of the abdomen without contrast was performed showing duodenitis—but not pancreatitis. Further diagnostic workup was deferred to expedite the initiation of chemotherapy for the patient's concomitant AML. Ten days of empiric therapy for *Helicobacter pylori* was completed with clarithromycin 500 mg PO every 12 hours, amoxicillin 1 g PO every 12 hours, and pantoprazole 40 g PO daily.

Hydroxyurea was administered due to a steadily increasing WBC count which peaked at 36.4 x 10^9/L. The patient remained febrile during this time and was considered functionally neutropenic due to his malignancy, therefore was treated for neutropenic fever with piperacillin-tazobactam 3.375 g IV every 6 hours.

On day 6 of his hospitalization, induction chemotherapy was begun with a "7+3" regimen of idarubicin and cytarabine. From approximately day 8 to day 35 of his hospitalization, he remained neutropenic with an absolute neutrophil counts (ANC) in the 0.2-0.3 x 10^9/L range and his piperacillin-tazobactam was continued. His abdominal pain and diarrhea persisted over this time.

On day 14, the patient's fever curves shifted from 100-101 °F to 101-103°F. On day 16, a CT scan of the abdomen with contrast was again performed, showing evidence of ongoing duodenitis without additional pathology. Blood cultures were redrawn on days 15, 16, and 17 and were all negative.

On day 19, FilmArray Blood Culture Identification Panel by BioFireDx identified the family *Enterobacteriaceae* from cultures taken that same day and while the patient was still on piperacillin-tazobactam. The test was negative for *Enterobacteriaceae cloacae* complex, *Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus,* and *Serratia marcescens*; this is the extent of the genera of *Enterobacteriaceae* included in this particular test.

Overnight on day 20, the patient vomited and aspirated in his sleep, developing acute hypoxia to SpO2 of 74% on room air, respiratory rate of 34 breaths per minute, and pulse of 133 beats per minute. A portable chest x-ray showed a possible consolidation in the right lower lobe. Due to the patient's extended hospital stay and immuno-compromised status, vancomycin was added and piperacillin-tazobactam was changed to meropenem.

On day 21, a lactose-fermenting gram-negative rod was identified from the blood culture obtained two days prior. Our lab reported that this most closely resembled *Raoultella ornithinolytica*. Antibiotic susceptibility patterns were remarkable for resistance to piperacillin-tazobactam with MIC >64/4 mcg/mL. The organism was susceptible to amikacin and meropenem (Table 1).

A single 15 mg/kg dose of amikacin was administered. Surveillance blood cultures from days 21-26 were negative for further gram-negative infection. On day 24, a CT scan of the abdomen with contrast was repeated showing

obstruction despite ongoing diarrhea, thickened and inflamed segments of jejunum, and persisting duodenitis. On day 25, the patient was started on bowel rest, and total parenteral nutrition (TPN) was initiated.

Anidulafungin was administered from days 18-29 for concern of indolent fungal infection. The patient became delirious for the remainder of his hospital course. He received treatment with granulocyte colony stimulating factor to help bolster his leukocyte counts. The patient did not defervesce until day 35, at which point his mental status also improved. On day 37, his ANC surpassed 0.5 x 10^9/L. On day 38, meropenem was stopped; TPN was also discontinued as the patient began tolerating an oral diet. He had no further positive blood cultures. On day 40, a repeat chest x-ray demonstrated improvement of his right lower lobe and he was deemed medically stable for discharge to a rehabilitation facility.

DISCUSSION

A case series and literature review of *R. ornithinolytica* infections from four university hospitals in France found bacteremia to occur only in 5% of cases.[2] In the setting of malignancies, there is a 16-patient case series in which 15 had recent underlying malignancies both solid and hematologic,[3] a three-patient case series of bacteremia with underlying gastric and biliary malignancies,[4] and a report of a patient with acute lymphocytic leukemia (ALL) who died of *R. ornithinolytica* sepsis.[5] The literature thus indicates that *R. ornithinolytica* bacteremia tends to occur in patients with active comorbidities, especially malignancies, as in our patient.

Among more resistant *R. ornithinolytica* isolates, a blood culture isolate in New Jersey was susceptible only to amikacin and gentamicin,[6] a blood culture isolate in Brazil was susceptible only to amikacin, gentamicin, ciprofloxacin, and levofloxacin,[5] and other carbapenemase-producing strains were found in China[7] and Turkey.[8] *R. ornithinolytica* has natural susceptibility to cephalosporins, carbapenems, aminoglycosides; intermediate susceptibility to some penicillins, not usually including piperacillin/tazobactam; and resistance to macrolides.[9]

R. ornithinolytica is susceptible to piperacillin-tazobactam a majority of the time.[2-4, 7, 10-11] This case highlights the importance of antibiotic stewardship to prevent the inducible resistance that likely contributed to the failure of piperacillin-tazobactam in this case. Febrile neutropenia presents an especially difficult challenge as these patient scenarios often necessitate very long courses of very broad antibiotics in the absence of identified organisms. Procalcitonin may be of potential value in guiding antibiotic administration in patients with febrile neutropenia. Some data indicate that procalcitonin may be useful in distinguishing infectious from non-infectious etiologies of neutropenic fever, as well as trending values to monitor for response to therapy.[12-14]

This case also emphasizes the importance of rapid diagnostics. The assay used in this case used multiplex polymerase chain reaction (PCR) technology to identify an organism belonging to the family *Enterobacteriaceae* that was specifically not a member of the *Klebsiella* genus or other genera within *Enterobacteriaceae*. This particular pattern should evoke concern for *Raoultella*, a former member of the *Klebsiella* genus which should be considered as virulent and resistance-prone as *Pseudomonas*. By quickly identifying a new organism, which persisted through piperacillin-tazobactam therapy, the assay prompted the switch to meropenem and prevented the patient from succumbing to his bacteremia.

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Abdomen Actin' Up: A Unique Presentation of Disseminated Abdominal Actinomycosis

Arpana Paruchuri, MD, Brianna J. Shinn, MD, and Rino Sato, MD

INTRODUCTION

Abdominal actinomycosis is a chronic, indolent disease characterized by nonspecific symptoms such as fatigue, weight loss, fever, and abdominal pain. *Actinomyces* is a genus of fastidious, gram-positive, non-acid-fast, branching filamentous bacilli characterized by sulfur granules that is normally found in oral flora and inhabits the gastrointestinal (GI) tract.[1] *Actinomyces* infections are relatively rare, however when present, they have the ability to invade multiple organs and disseminate throughout multiple body cavities.[2] Factors that increase the risk of developing actinomycosis include poor oral hygiene, alcoholism, and preexisting dental disease. Intrauterine devices (IUDs) also increase the risk of developing pelvic actinomycosis.[3] Over the past 10-20 years, actinomycosis is being diagnosed with increasing frequency and should be considered in the differential for patients presenting with indolent abdominal symptoms along with risk factors.[4]

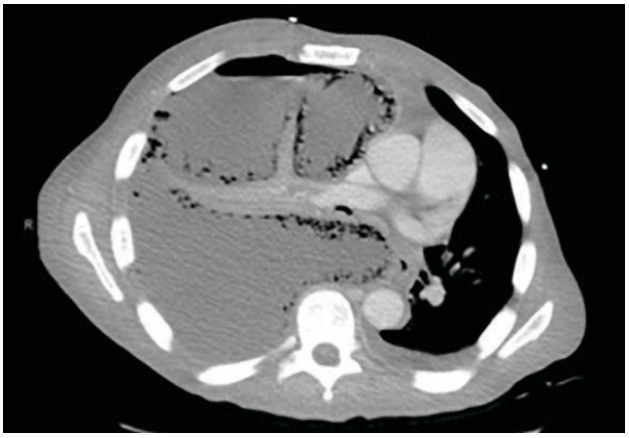

Figure 1. CT Chest demonstrating right-sided pleural effusion with complete collapse of the right lung.

CASE PRESENTATION

A 57-year old male with a history of untreated hepatitis C, treated tuberculosis (TB), and recent incarceration presented to the emergency room with abdominal pain, shortness of breath and weight loss. Of note, he had undergone a liver biopsy two weeks prior to presentation to further evaluate a liver lesion that showed acute and chronic inflammation without evidence of malignancy or infection.

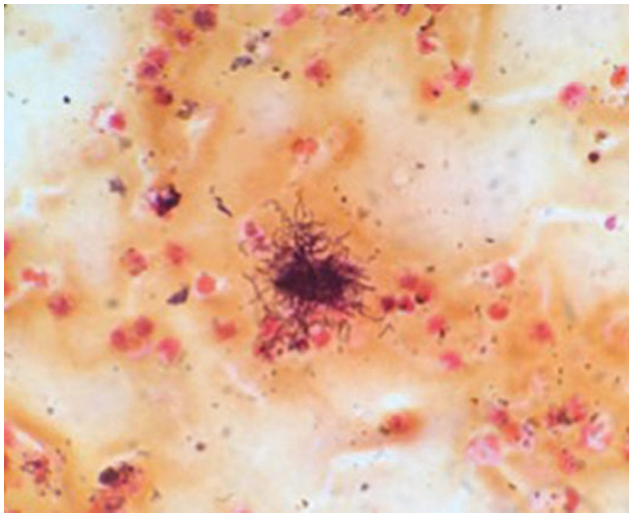

Figure 2. *Actinomyces meyeri* from the patient's abdominal wall abscess.

On exam, he was afebrile, had a blood pressure of 85/70 mmHg, and an oxygen saturation of 84% on room air. The patient had poor dentition, decreased breath sounds bilaterally, and multiple abdominal masses palpable in the left lower quadrant and along the liver border. Labs were remarkable for an elevated lactate of 2.3 mmol/L, hemoglobin of 7.6 g/dL, and albumin level of 1.9 g/dL. His white blood cell (WBC) count and arterial blood gas were within normal limits. Imaging revealed a large right-sided pleural effusion with septations and complete collapse of the right lung (Figure 1), as well as multiple intra-abdominal abscesses with air-fluid levels.

DIFFERENTIAL DIAGNOSIS

Due to his history of previously treated TB, recent incarceration, and recent liver biopsy, the source of infection was thought to be due to TB or a bacterial source introduced from his recent liver biopsy. Given the imaging findings which demonstrated a pleural effusion with septations, the patient had a surgical chest tube placed which drained over three liters of purulent fluid. Based on Light's criteria the pleural fluid was classified as an exudative effusion, with 16,075 WBCs/mm3, Glucose < 2.0 mg/dL, LDH of 4110 IU/L, and a pH of 7.0. Based on these results and the presence of pus in the pleural space, he was diagnosed with an empyema.

OUTCOME AND FOLLOW-UP

After the patient's surgical chest tube was placed, he underwent drainage of the abdominal wall abscesses. Cultures from both the pleural fluid and abdominal abscess fluid grew *Actinomyces meyeri* and the patient was diagnosed with disseminated actinomycosis (Figure 2). The patient ultimately required a video-assisted thoracoscopic surgery (VATS) and decortication during which time he was noted to have a fistulous connection between a hepatic abscess and the right hemithorax. Since the patient's poor dentition was presumed to be the initial source of this infection, he also underwent tooth extraction. He was treated with intravenous Unasyn for six months without transition to oral Penicillin given his complicated presentation. Unasyn was chosen due on its broader coverage and its ability to treat any concomitant infections in this complicated patient. Repeat imaging of his abdomen 2 months after his presentation showed a decrease in size of his intra-abdominal collections.

DISCUSSION

Abdominal actinomycosis is an infection in the abdomen most commonly caused by *Actinomyces israelii*, which is normally an inhabitant of the oral cavity and GI tract.[1] *Actinomyces meyeri*, while a less common cause of abdominal actinomycosis, has a greater propensity for causing disseminated disease.[3] Although *Actinomyces* normally has low virulence, it acquires its pathogenicity through invasion of necrotic tissue or local infections or trauma. As the infection progresses, granulomatous tissue, extensive reactive fibrosis and necrosis, abscesses, draining sinuses, and fistulas can be seen. The most frequent sites of infection include the cervicofacial region (50% of cases), abdominal cavity (20%), and thoracic cavity (15-20%).[2] Patients with abdominal actinomycosis, including our patient, generally present with a chronic, indolent course of nonspecific symptoms such as fatigue, fever, weight loss, and abdominal pain. Physical exam findings may include a palpable abdominal mass, visible sinus tracts, or fistulas and labs can demonstrate anemia and leukocytosis.[5] Culturing abscess fluid is the most effective way to diagnosis an *Actinomyces* infection. Once diagnosed, the treatment of choice is IV Penicillin G for 4-6 weeks followed by Amoxicillin for 6-12 months for large abdominal lesions or draining sinus tracts.[2]

Abdominal actinomycosis is a difficult condition to diagnose due to its rarity, nonspecific symptoms, and its resemblance of more common conditions such as malignancy, Crohn's disease, and tuberculosis.[2] Our patient's case was further complicated by the fact that the infection invaded the thoracic cavity and led to development of an empyema and disseminated actinomycosis. In our patient's case, this invasion of the pleural space was thought to be due to local trauma and direct seeding from the liver biopsy. However, there are cases reports in the literature that describe fistula development between different body cavities allowing for disseminated disease.[3] While fistula development is rare, it is an important complication to be aware of since disseminated disease can be difficult to control and treat.

While abdominal actinomycosis is a relatively rare condition, this case is significant given the rising incidence of this disease over the past 10-20 years. It is important for physicians to be educated about this disease especially given its vague and non-specific symptoms so that it can be included in the differential diagnoses for patients presenting with an insidious onset of abdominal symptoms as well as predisposing risk factors.

KEY POINTS

- While still rare, the incidence of abdominal actinomycosis is increasing.
- Abdominal actinomycosis presents with a chronic, indolent course of nonspecific symptoms similar to other, more common conditions and, should be considered in patients with indolent abdominal symptoms and risk factors including poor dental hygiene, dental disease, and alcoholism.
- The diagnosis is based on abscess fluid culture growing Actinomyces.
- Treatment of actinomycosis is generally with a long course of IV Penicillin G later transitioned to oral Amoxicillin.

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Tenofovir Cons the Kidneys: A Case of Acquired Fanconi

Ritu Nahar, MD and Emma Lundsmith, MD

INTRODUCTION

Proximal (Type 2) renal tubular acidosis (RTA) is a relatively rare diagnosis, especially in adults. It is characterized by a reduction in proximal bicarbonate reabsorption resulting in urinary bicarbonate wasting. Proximal RTA can also be associated with additional defects in proximal tubular function including impaired reabsorption of phosphate, glucose, uric acid, and amino acids. Generalized proximal tubular dysfunction is termed Fanconi syndrome. While there are primary causes of Fanconi syndrome including sporadic and familial sources, this syndrome can also be acquired. Two major culprits include monoclonal gammopathies resulting in increased excretion of immunoglobulin light chains and drug-induced nephrotoxicity to the proximal tubules.[1] Tenofovir disoproxil fumarate (TDF) is one such established nephrotoxic agent associated with Fanconi syndrome, likely because it is excreted through the kidney via active tubular secretion.[2-4] This case demonstrates a classic presentation of tenofovir-induced Fanconi syndrome complicated by respiratory repercussions of hypophosphatemia, and also describes tenofovir alafenamide (TAF), a novel formulation with reduced renal toxicity.

CASE PRESENTATION

A 63-year-old male and active smoker with human immunodeficiency virus (HIV) on Atripla (efavirenz/emtricitabine/TDF), intermittent alcohol abuse for years, severe chronic obstructive pulmonary disease (COPD) on no home oxygen presented with three months of progressive dyspnea on exertion with ambulatory dysfunction. The patient endorsed dyspnea after ambulating 5-10 feet, with associated diffuse body weakness. He noted frequent falls requiring use of a walker. Over the six weeks prior to presentation, he had been treated multiple times for presumed COPD exacerbations with attempts to optimize his triple inhaler therapy. He noted minimal improvement in his respiratory symptoms despite these interventions. Three months prior to presentation, he had been functionally independent.

He was diagnosed with HIV 20 years prior, and had achieved virologic suppression on Atripla without any side effects. His history was also significant for coronary artery disease with non-ST-elevation myocardial infarction in 2012, prior stroke of the corona radiata in 2012, hypertension, and Barrett's esophagus. He endorsed increased alcohol consumption in the last few months to three drinks daily. He was an active smoker using about half a pack of cigarettes per day. He denied recreational drug use.

He reported no history of fever, chills, diarrhea, recent travel, cough, sputum production, chest pain, lower extremity swelling, orthopnea, or paroxysmal nocturnal dyspnea.

On admission, the patient had a blood pressure of 110/70 mmHg with negative orthostatics, oxygen saturation of 96% on room air at rest but 79% with ambulation. He subsequently developed hypoxia at rest as well. On exam, the patient had diffusely decreased breath sounds with no appreciable wheezes, crackles, or rales. He had a regular S1 and S2 with no jugular venous distension or peripheral edema. Neurological exam was grossly unremarkable with 5/5 strength in all extremities and intact sensation.

Labs were significant for serum bicarbonate 16 meq/L, lactate 2.5 mmol/L, magnesium 0.8 mg/dL, phosphate 0.8 mg/dL, albumin 3.6 mg/dL, hemoglobin 8.3 g/dL, CD4 173 with undetectable viral load. Urinalysis revealed 3+ glucose and pH 7.0. Urine phosphate 27 mg/dL and creatinine 43 mg/dL.

Transthoracic echocardiogram demonstrated an ejection fraction of 70% with normal left ventricular size and function. Chest x-ray had no focal consolidation or edema. Computed tomography (CT) angiography of the chest was negative for acute pulmonary embolism. Non-contrast CT head demonstrated no intracranial hemorrhage, masses, or lesions.

DIFFERENTIAL DIAGNOSIS

This patient's constellation of symptoms including progressive shortness of breath, ambulatory dysfunction, normal anion gap metabolic acidosis with hypophosphatemia and hypomagnesemia was initially challenging to unify under one diagnosis.

His primary complaint of progressive shortness of breath had a broad differential. Given his COPD history and new oxygen requirement, progression of his underlying

disease was considered. The timeline of his symptoms and objective physical exam did not support an acute exacerbation. CT angiogram ruled out pulmonary embolism. Given his history of coronary artery disease, heart failure was also considered. However, this was not corroborated by the patient's physical exam and the echocardiogram demonstrated normal ejection fraction. Thus, we hypothesized that the patient's progressive shortness of breath was secondary to hypophosphatemia-induced respiratory muscle fatigue in the setting of severe COPD.

The differential for the patient's ambulatory dysfunction included orthostatic hypotension, ethanol abuse, and a new mass lesion or stroke given his prior cerebrovascular history. His neurological exam was unremarkable, orthostatics were normal, and CT head was unrevealing—making his falls likely secondary to weakness as opposed to an intracranial insult. Thus, there may have been a component of hypophosphatemia-induced muscle dysfunction.

Normal anion gap metabolic acidosis can be caused by renal or gastrointestinal loss of bicarbonate, or with decreased renal acid excretion. Loss of bicarbonate is seen with Type 2 RTAs, diarrhea, carbonic anhydrase inhibitors, and toluene inhalation (glue sniffing).[5]

The patient's severe hypophosphatemia and hypomagnesemia was initially attributed to malnutrition in the setting of alcohol abuse. However persistent deficiencies despite intravenous repletion compounded with the normal anion gap metabolic acidosis suggested generalized proximal renal tubular dysfunction.

OUTCOME AND FOLLOW-UP

Fanconi syndrome was eventually suspected and attributed to TDF. This suspicion was further supported by a urine pH of 7, 3+ glucosuria, and increased fractional excretion of filtered phosphate. Atripla (which contains TDF) was discontinued and the patient was switched to Descovy (emtricitabine and TAF) and Tivicay (dolutegravir).

The patient's generalized weakness, dyspnea, and hypoxia improved with normalization of his serum bicarbonate, phosphate, and magnesium. He was discharged with oral phosphorus and magnesium supplementation. At his most recent pulmonary follow-up, he had normal ambulatory oximetry with increased functionality.

DISCUSSION

Tenofovir disoproxil fumarate, the first approved oral prodrug of tenofovir, has been successfully used in combination antiretroviral therapy for HIV treatment since 2001. However, as seen in this case and established in the literature, TDF can cause clinically significant renal toxicity. This is thought to be secondary to high circulating plasma levels of tenofovir which is then excreted through the kidney via active tubular secretion. Tenofovir alafenamide, a novel oral prodrug of tenofovir, is metabolized to tenofovir intracellularly rather than in plasma. This results in higher intracellular concentrations of the active metabolite compared to TDF. Consequently, the therapeutic dose required for TAF is less than one-tenth of the dose of TDF.[6] The resulting 90% reduction in plasma tenofovir concentrations is believed to be responsible for the improved renal safety demonstrated in several phase 2 and 3 randomized-controlled trials.[7] A recent meta-analysis demonstrated that both TDF-containing regimens and TAF-containing regimens have high and comparable rates of virologic suppression.[8] While promising, the long-term clinical significance of TAF still needs to be assessed in prospective cohorts.

KEY POINTS

This case illustrates the renal side effects of TDF-induced Fanconi syndrome, highlighting the manifestations of hypophosphatemia. Recognizing this potential side effect and switching patients to a TAF-containing regimen is important to prevent renal injury.

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A Case of Eosinophilic Granulomatosis with Polyangiitis

Anita Modi, MD and Lily Ackermann, MD

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (eGPA) is a small- and medium-sized-vessel vasculitis with multi-organ manifestations. Given the rarity of eGPA, patients are often misdiagnosed for decades and may initially present with life-threatening manifestations of late-stage disease. Therefore, it is important to raise awareness of this condition and its associated signs and symptoms. This case report serves to describe a classic presentation of a patient with eGPA, as well as to delineate the diagnostic workup, acute management, and early outpatient follow-up required.

CASE PRESENTATION

A 57-year-old male with a history of recently-diagnosed asthma (on chronic prednisone) presented to the emergency department at our hospital with a month-long history of shortness of breath and fatigue. He denied wheezing and chest tightness typical of his asthma flares, insisting that this isolated dyspnea was similar to the symptoms he experienced two months earlier when he presented to an outside hospital and was diagnosed with symptomatic anemia.

He reported that he was in perfect health until one year prior to presentation when he developed progressively worsening respiratory symptoms. After evaluation by a pulmonologist, he was started on budesonide-formoterol twice daily in conjunction with his rescue inhaler. However, he had persistent symptoms over the subsequent six months, so was ultimately started on prednisone 30 mg PO daily. At the time, he was noted to have an elevated IgE and eosinophil count of 104 IU/mL and 900 cells/uL, respectively. Though he improved dramatically with the addition of systemic steroids, he began to develop generalized fatigue, weakness, chills, night sweats, and migratory polyarthralgias a couple months later. His primary care physician suspected Lyme disease and started doxycycline without symptomatic improvement. He began taking ibuprofen several times a day for the diffuse joint pains. As the patient's shortness of breath and fatigue worsened, a complete blood count was obtained, and his hemoglobin was found to be 6 g/dL. He was admitted to an outside hospital where he received a blood transfusion and underwent an upper endoscopy and colonoscopy which did not demonstrate active bleeding. He was discharged with instructions to avoid further NSAID use.

In the emergency department at our hospital, his hemoglobin was 7.4 g/dL so he received a blood transfusion for symptomatic anemia, which was suspected to be due to an upper gastrointestinal bleed caused by NSAID- and steroid-induced peptic ulcer disease. His chest x-ray demonstrated patchy bilateral airspace opacities throughout both lung fields concerning for multifocal pneumonia. He was also started on ceftriaxone in conjunction with his ongoing doxycycline therapy for treatment of superimposed community-acquired pneumonia. One hour after receiving one unit of blood, the patient developed increased work of breathing with hypoxia that did not improve with diuresis. A computed tomography (CT) scan of the chest without contrast was ordered to delineate possible hemorrhage or atypical infection contributing to his deteriorating presentation. It demonstrated multifocal airspace opacities in a peri-bronchial vascular distribution with relative sparing of the left lower lobe and subpleural spaces, findings consistent with diffuse alveolar hemorrhage (DAH)" and noncardiogenic pulmonary edema (Figure 1).

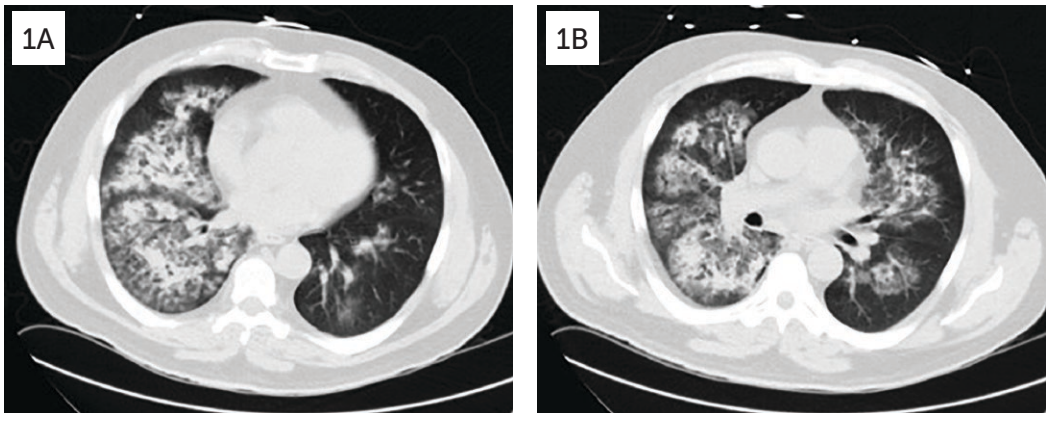

Figure 1. Images from the patient's CT scan of the chest demonstrates multifocal airspace opacities in a peri-bronchial vascular distribution with relative sparing of the left lower lobe and subpleural spaces.

The patient's systemic symptoms and imaging was suspicious for an underlying vasculitis complicated by diffuse alveolar hemorrhage and gastroenteritis. He underwent bronchoscopy which demonstrated diffuse bloody secretions in the right upper lobe and lateral basilar segment of the right lower lobe. Cytology demonstrated marked acute inflammation with no evidence of infection. Differential cell count did not demonstrate eosinophils as would be expected in eGPA, but this may be related to the patient's chronic steroid use pre-procedure. Laboratory studies were significant for positive C-ANCA and PR-3 antibody with a titer of 4.3. In conjunction with the patient's elevated IgE and eosinophilia from six months earlier, this lab work helped to confirm the patient's suspected diagnosis of eGPA.

On further discussion, the patient acknowledged that he had experienced recurrent sinusitis and exercise-induced asthma for one decade prior to initial presentation. His sporadic episodes were managed by his primary care physician until one year prior to admission when he sought evaluation by a pulmonologist and was ultimately started on chronic prednisone, which alleviated his respiratory symptoms and likely palliated his underlying vasculitis.

OUTCOME

The patient was pulsed with intravenous methylprednisolone 1 gram daily for 3 days, followed by oral prednisone 1 mg/kg daily. He also received his first dose of rituximab with the remaining three weekly infusions to be scheduled as an outpatient, and two sessions of inpatient plasmapheresis given his diffuse alveolar hemorrhage. These interventions resulted in prompt alleviation of his respiratory symptoms and migratory polyarthralgias, and he was weaned to room air prior to discharge. Six months after discharge, his prednisone has been tapered to 40 mg daily, his repeat CT scan of the chest demonstrates resolution of focal airspace opacities initially observed in the setting of DAH, and his PR-3 antibody titer is negative.

DISCUSSION

eGPA is characterized by the histological findings of necrotizing vasculitis as well as eosinophilic infiltrates and granulomas in tissues.[1] The American College of Rheumatology has since defined six diagnostic criteria, of which four should be present in a patient with suspected eGPA: asthma, greater than 10% peripheral eosinophilia, neuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophils. Our patient had a long history of recurrent sinusitis and asthma prior to presentation, eosinophilia, and pulmonary infiltrates. The disease progresses over the course of decades, classified into three distinct phases: the prodromal phase that is associated with allergic rhinitis and asthma; eosinophilic infiltration of multiple organs including the lungs and gastrointestinal tract; and granulomatosis resulting in life-threatening disease.[2]

Clinical presentations of eGPA differ based on associated ANCA positivity. ANCA-negative patients typically present with more frequent cardiomyopathy, while ANCA-positive patients present with mononeuritis multiplex and glomerulonephritis. Poorer prognoses can be anticipated for patients with documented gastrointestinal, renal, or cardiac manifestations of the disease, meriting screening endoscopies, urinalyses, and transthoracic echocardiograms of in-patients with newly-diagnosed eGPA.[3] Commonly noted laboratory abnormalities include serum eosinophilia, elevated IgE levels, and P-ANCA of anti-MPO specificity. However, up to 40% of patients with eGPA demonstrate positive C-ANCA of anti-PR-3 specificity. Extravascular eosinophilia (e.g. in bronchoalveolar lavage fluid) and biopsy demonstrating granulomas aid in confirming the diagnosis of eGPA. Despite these objective features, eGPA is essentially a clinical diagnosis based on symptom presentation and the presence of eosinophilia.

Recommendations on treatment of eGPA depend on the severity of disease and organ involvement. Glucocorticoids are first-line treatment for eGPA and those with severe documented gastrointestinal, renal, pulmonary, or cardiac involvement should be prescribed an additional immunosuppressant (e.g. rituximab, cyclophosphamide). Though plasma exchange is not merited for every patient with newly-diagnosed eGPA, it may successfully forestall progressive glomerulonephritis in ANCA-positive patients with severe diffuse alveolar hemorrhage and renal insufficiency.

KEY POINTS

Given the life-threatening complications of this rare condition, it is important to raise awareness about eGPA. This is a classic presentation of eGPA in a patient with a decades-long asthma history, eosinophilia, new lung and gastrointestinal manifestations, and systemic symptoms. His serologies were significant for positive C-ANCA of anti-PR-3 specificity. His clinical course included screening for gastrointestinal, renal, and cardiac involvement as well as initiating steroid therapy, plasmapheresis, and rituximab.

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Use of Venovenous Extracorporeal Membranous Oxygenation Following Iatrogenic Tracheal Rupture

Rajiv Kabadi, MD

INTRODUCTION

Iatrogenic tracheal rupture is a rare complication of endotracheal intubation and has a high risk of morbidity and mortality. Risk factors include female gender, short stature (height less than 160-cm), difficult airway anatomy, underlying connective tissue disorder, chronic obstructive pulmonary disease, use of a rigid stylet, inadequate intubation tube size, cuff over-inflation, emergent intubation and intubation performed by non-anesthesiologists.[1] Early recognition is important and diagnosis requires bronchoscopic confirmation.[2,3] We describe a case where emergent venovenous extra-corporeal membrane oxygenation (VV-ECMO) was utilized in the management of tracheal rupture.

CASE DESCRIPTION

A 46-year-old female smoker with a history of asthma presented to an outside hospital with worsening dyspnea and was found to be in status asthmaticus. She underwent a difficult intubation on hospital day two for hypercapneic respiratory failure. She subsequently developed severe subcutaneous emphysema on her face that spread to her torso, arms and legs (Figure 1). Computed tomography of the chest revealed pneumothoraces, pneumomediastinum, pneumopericardium (Figure 2) and pneumoperitoneum (Figure 3). Bilateral chest tubes and a pericardial drain were placed and she was transferred to our facility for higher level of care.

Bronchoscopy was performed which revealed a 2-cm longitudinal laceration in the membranous wall of the trachea that extended towards the carina. Given these findings, cardiothoracic surgery was consulted. Due to refractory hypoxemic and hypercapnic respiratory failure despite maximal ventilatory support, VV-ECMO was initiated on hospital day three. Due to improvement in oxygenation and ventilation, a right thoracotomy with tracheal repair and pericardial window placement was performed.

The patient was continued on steroids and bronchodilators for management of her asthma exacerbation. VV-ECMO was weaned and the patient underwent ECMO catheter decannulation on hospital day five. She underwent tracheostomy on hospital day fifteen with eventual decannulation prior to being discharged to acute rehab on hospital day thirty-one.

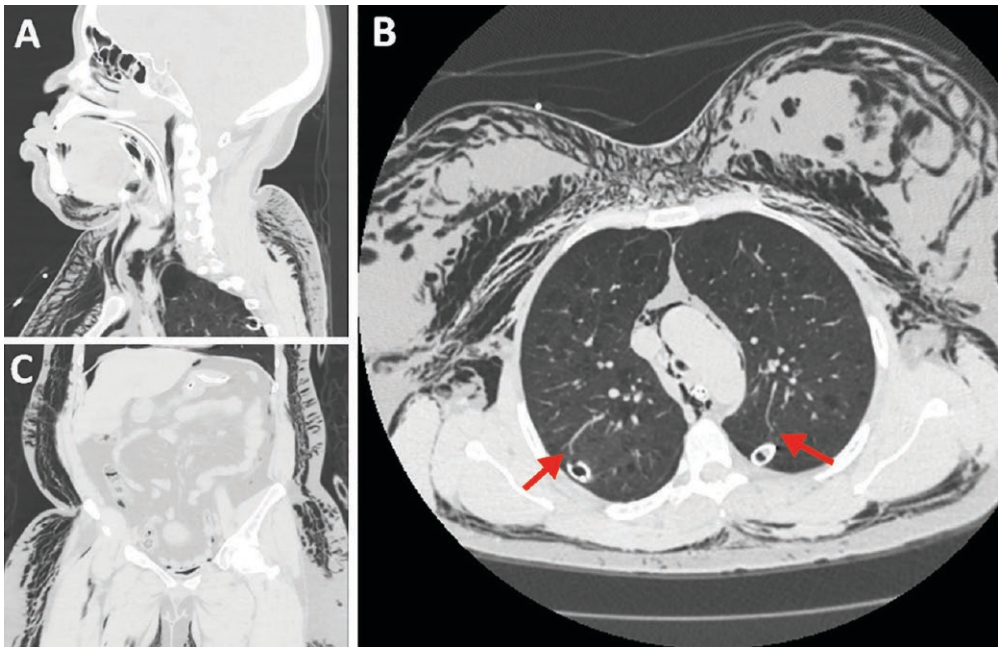

Figure 1. Computed tomographic (CT) imaging demonstrating extensive subcutaneous emphysema (A-C), apical bleb (A), emphysematous changes in the lungs (B) and bilateral chest tubes (B; arrows).

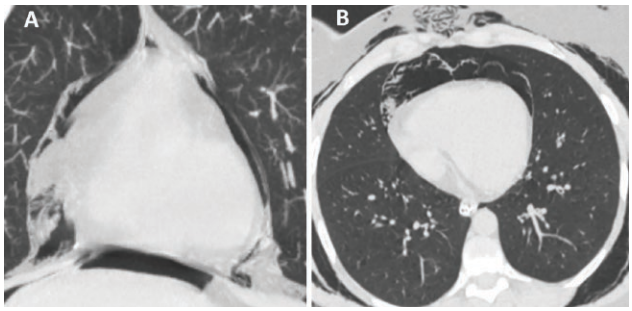

Figure 2. CT imaging demonstrating pneumomediastinum and pneumopericardium (A-B).

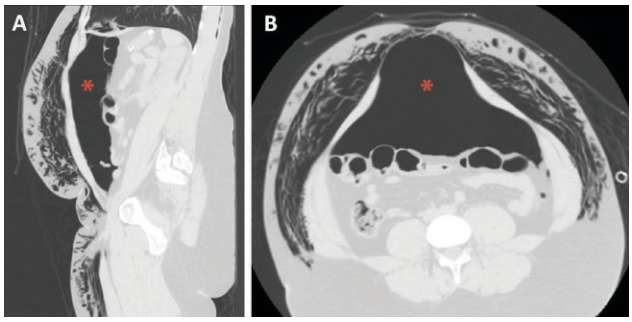

Figure 3. CT imaging demonstrating pneumoperitoneum (marked by red asterixis).

OUTCOME AND FOLLOW UP

The patient was last seen in the pulmonology clinic 6 months after she was discharged and has maintained good functional status. She was continued on standard care treatment for moderate persistent asthma which was well-controlled despite her continued cigarette smoking. Her major complaint at the recent office visit was anxiety rather than cardio-pulmonary symptoms.

DISCUSSION

Tracheal rupture is an uncommon but severe complication of endotracheal intubation. Conservative management should be considered for hemodynamically stable patients without sequela such as progressive air leak, sepsis, or esophageal injury. Non-operative strategies involve non-invasive positive-pressure ventilation for patients who are breathing spontaneously, or endotracheal intubation and fixation distal to the rupture site ("bridging") with low-tidal volume ventilation and permissive hypercapnia for patients with underlying respiratory disease. Additional measures include daily bronchoscopic examinations, post-pyloric feeding, limiting patient movement to specified times, and antibiotic therapy to reduce risks of mediastinitis and ventilator-associated pneumonia.[4] Surgical intervention is reserved for patients with uncontrolled air leaks, active endobronchial hemorrhage, or for patients who have failed conservative measures as evinced by progressive ventilator requirements leading to extreme difficulties in oxygenation and ventilation as was the case for our patient.[1,5] For our patient, VV-ECMO was used as a bridge to surgical tracheal repair in the setting of status asthmaticus and respiratory failure. Further studies should identify patients who will benefit from early surgical management and/or transfer to an ECMO-ready facility.[3]

KEY POINTS

- Tracheal rupture is an uncommon but severe complication of endotracheal intubation.
- VV ECMO may be used as a bridge to definitive management of tracheal rupture in patients with progressive respiratory failure who failed conservative strategies.
- Further studies should identify patients who may benefit from early surgical management and/or transfer to a facility that has ECMO capabilities.

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Fifty Shades of Sarcoidosis: A Case Report of Löfgren Syndrome

Arpana Paruchuri, MD

INTRODUCTION

Sarcoidosis is a multi-organ disorder that is characterized by the presence of noncaseating granulomas in involved organs. It commonly affects young and middle-aged individuals of all races, but is 3-4 times more common in African Americans and typically presents earlier with more severe symptoms.[1] The lungs are affected in 90% of patients and pulmonary disease accounts for the majority of the morbidity and mortality associated with this disease. However, approximately 30% of patients can present with extrapulmonary findings and can have involvement of other organs such as the skin and eyes.[1] The various presentations of sarcoidosis can make it challenging to diagnose and can lead to delays in treatment. Therefore, it is important for clinicians to recognize the wide variety of manifestations of sarcoidosis. In this case report, we present a case of sarcoidosis in a young man with arthralgias and skin lesions.

CASE PRESENTATION

A 44-year-old African American male with a past medical history of hypertension, prior treated syphilis and anal warts presented with a three-week history of a constant, throbbing headache at the top of his head and night sweats. His headache was worse in the morning and improved with nonsteroidal anti-inflammatory drugs (NSAIDs). He noted a month prior that his eyes were red and that his vision had become blurry and he was prescribed glasses. Around that time he noticed a pruritic, tender rash on the ink lines of his tattoos on his upper extremities bilaterally. His tattoos were five years old and he had not had any issues with them prior to this episode. He also noticed tender, hard bumps on his lower extremities bilaterally. He complained of night sweats, chills, rigors, bilateral ankle pain, and weakness but denied any neck pain, photophobia, confusion, chest pain, shortness of breath, and cough. Of note, the patient had been diagnosed with syphilis four years ago when he presented with weakness in his lower extremities. His symptoms reportedly improved after a gluteal injection of an unknown medication. The patient's social history was positive for anal intercourse with his husband but he denied any new partners in the last six months. His husband was HIV positive but the patient reported that they used condoms consistently. On exam, the patient had a temperature of 100.9F, heart rate of 106 bpm, blood pressure of 166/96 mmHg, and oxygen saturation 100% on room air. The only positive findings on physical exam were multiple raised, firm, and tender nodules along the ink-lines of both tattoos on bilateral upper extremities (Figure 1) and three firm, erythematous, non-fluctuating nodules on his lower extremities.

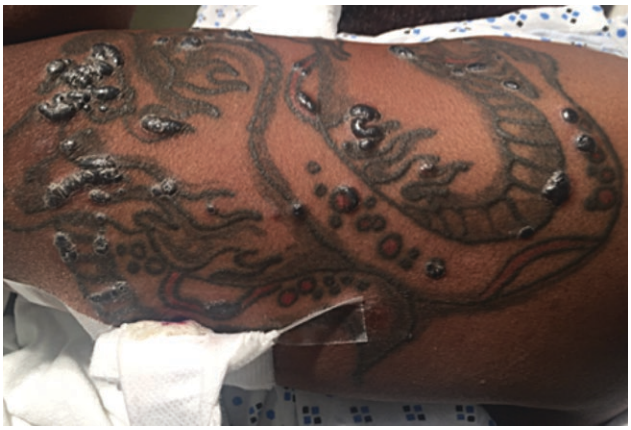

Figure 1. Skin findings of tender firm nodules along the ink-lines of the tattoo on the patient's upper extremity.

DIFFERENTIAL DIAGNOSIS

In a middle-age, African American male with fevers, ankle pain, and new skin findings consistent for erythema nodosum (EN) on his lower extremities, sarcoidosis remained high on the differential despite the lack of pulmonary symptoms. Based on his past medical and social history, human immunodeficiency virus (HIV) and neurosyphilis were also on the differential. Given the patient's symptoms at the time of syphilis diagnosis (lower extremity weakness), the story seemed consistent for neurosyphilis. However, given the fact that he received only an intramuscular injection, it was unclear if he had been treated properly for neurosyphilis which would require IV Penicillin. Given his fever and tachycardia, infection was on the differential as well. During the work-up, the only abnormal labs were an elevated serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and angiotensin-converting enzyme (ACE) level. Blood cultures, HIV, rapid plasma reagin (RPR) test, and sexually transmitted disease (STD) testing were negative. A chest x-ray was unremarkable but a subsequent chest

CT showed bilateral multifocal pneumonia and possible mild hilar lymphadenopathy. A punch biopsy of the tattoo was performed which confirmed the presence of a sarcoidal granulomatous tattoo reaction with negative cultures. Given his clinical presentation of EN, hilar lymphadenopathy, arthralgias and fever the patient was diagnosed with Löfgren Syndrome.

OUTCOME & FOLLOW UP

The patient was discharged the following day with a course of moxifloxacin for pneumonia and prednisone 40 mg daily with a plan to slowly taper. At his one-month dermatology follow up, there was improvement of his skin lesions and headaches. As his prednisone was tapered during the next four months, he reported a return of his headaches and new dyspnea on exertion. He was started on hydroxychloroquine and told to follow up with ophthalmology for clearance to continue this medication. Unfortunately, the patient did not follow up for clearance and hydroxychloroquine was discontinued.

DISCUSSION

This case emphasizes that sarcoidosis is a multisystem disease with a variety of clinical presentations.[2] About 50% of patients diagnosed with sarcoidosis are asymptomatic with a normal lung exam at the time of diagnosis. However, sarcoidosis may present with pulmonary symptoms including non-productive cough, dyspnea, and chest pain along with fatigue, fever, joint pain, and weight loss.[3] The occurrence of sarcoid granulomas on old scars or tattoos is a rare but well-recognized phenomenon and can be the initial presentation of sarcoidosis in some patients.[4] A common presentation of extrapulmonary sarcoidosis is the combination of hilar lymphadenopathy, migratory polyarthralgia, and fever with or without EN, also known as Löfgren syndrome. Sarcoidosis is a diagnosis of exclusion that relies on a combination of symptoms, radiologic findings, histologic evidence of noncaseating granulomas in involved organs, and exclusion of other known causes of granulomatous inflammation such as lymphoma and tuberculosis. In the absence of Lofgren's syndrome, a tissue biopsy of the most accessible lesion is needed for diagnosis. Chest x-ray is the only routine imaging recommended for suspected sarcoidosis and can show bilateral hilar lymphadenopathy and pulmonary infiltrates. Chest CT scans can be used in more atypical presentations. In Löfgren syndrome, EN and arthralgias are managed with NSAIDs. Based on consensus recommendations, only patients with severe pulmonary symptoms are managed with prednisone 20-40 mg/day that is slowly tapered.[3] Since 60% of patients have recurrent symptoms, a maintenance dose of prednisone 10-15 mg/day for 3-6 months is recommended. Extrapulmonary treatment is determined individually and may be managed with a similar steroid taper. In cutaneous disease, topical high-potency steroids are the first-line treatment. Additional systemic therapies include methotrexate and hydroxychloroquine.[3] Patients should follow up with a rheumatologist or pulmonologist. Recognizing that sarcoidosis can affect many organs and present with non-specific symptoms is essential in order to diagnose and treat this disease in a timely fashion.

KEY POINTS

- Common organs affected in sarcoidosis include the lungs, skin and eyes.
- Extrapulmonary sarcoidosis can manifest as Löfgren syndrome which is a constellation of symptoms and objective findings including hilar lymphadenopathy, migratory polyarthralgia, and fever with or without erythema nodosum.
- Diagnosis of sarcoidosis is made from a combination of symptoms, radiologic findings, evidence of noncaseating granulomas in involved organs and exclusion of other known causes of granulomatous inflammation.
- Standard treatment of sarcoidosis is prednisone 20-40 mg/day that is tapered every 4-12 weeks and follow-up with a rheumatologist or pulmonologist.
- If symptoms reoccur, maintenance therapy with prednisone 10-15 mg/day can be continued for 3-6 months.
- In cutaneous disease, topical high-potency steroids, methotrexate or hydroxychloroquine can be used.

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A Case of Cryptogenic Organizing Pneumonia Managed without a Diagnostic Biopsy

Kamal Amer, MD, McKensie Walker, BSc, and Vincent Yeung, MD

INTRODUCTION

Organizing pneumonia (OP) is a type of diffuse interstitial lung disease characterized by a specific histopathologic pattern of response to lung injury. When the etiology of the injury is unknown and in the absence of inflammatory or connective tissue disease, this entity is termed cryptogenic organizing pneumonia (COP) or primary organizing pneumonia (POP). Disease states in which the etiology of underlying injury is known is termed secondary organizing pneumonia (SOP). Causes of SOP include drug toxicity, chronic heart or renal failure, rheumatic disease, collagen vascular disease, infection, immunodeficiency, autoimmune disease, and interstitial lung disease.[1]

OP is characterized by the accumulation of inflammatory cells, fibroblasts, and myofibroblasts in the lumens of bronchioles and alveoli creating plugs of debris. This leads to alveolar epithelial injury, which is followed by leakage of plasma cells and the recruitment of fibroblasts and fibrin within the alveolar lumen. This accumulation of granulation tissue within the alveolar sacs extends into the alveolar ducts as well as the bronchioles causing symptom onset. The clinical presentation of OP is variable and involves nonspecific symptoms such as mild fever, cough, malaise, anorexia, weight loss, and progressive dyspnea.[2] Some reports describe wheezing and clubbing, but these symptoms occur in only 5% of cases. While "crackles" is the most common abnormal finding of OP on auscultation, 25% of reported cases present with a completely normal pulmonary exam.[3]

The decision to treat patients for OP depends on the clinician's ability to rule out other potentially reversible causes of dyspnea as well as the number of criteria met for this diagnosis of exclusion, based on histopathologic, radiographic, and clinical findings.[4] Diagnosis is made via biopsy; though surgical biopsy via thoracoscopy has remained the gold standard, trans-bronchial biopsy has recently gained prevalence.[5] We aim to present a suspected case of COP as an uncommon cause of interstitial lung disease.

CASE PRESENTATION

Our patient is a 75-year-old man with a past smoking history of 50 pack-years as well as a history of heart failure with preserved ejection fraction, hypertension, non-insulin dependent type 2 diabetes mellitus, obstructive sleep apnea, peripheral vascular disease, and gout who presented to the emergency department (ED) with one week of shortness of breath and dyspnea on exertion. He did not endorse any associated fevers, productive cough, sick contacts, weight loss, paroxysmal nocturnal dyspnea, or chest pain. He had stable orthopnea and lower extremity edema. On arrival to the ED, he was hypoxemic to 72% on room air and required 4 liters of oxygen via nasal cannula to maintain oxygen saturations above 90%. His chest x-ray demonstrated multifocal opacities with a left lung predominance that was distinct from prior imaging studies (Figure 1). He was started on a course of broad spectrum antibiotics (vancomycin and zosyn) without clinical improvement. His oxygen requirements increased and he was transitioned to 6 liters of oxygen via nasal cannula with a periodic need for continuous positive airway pressure (CPAP).

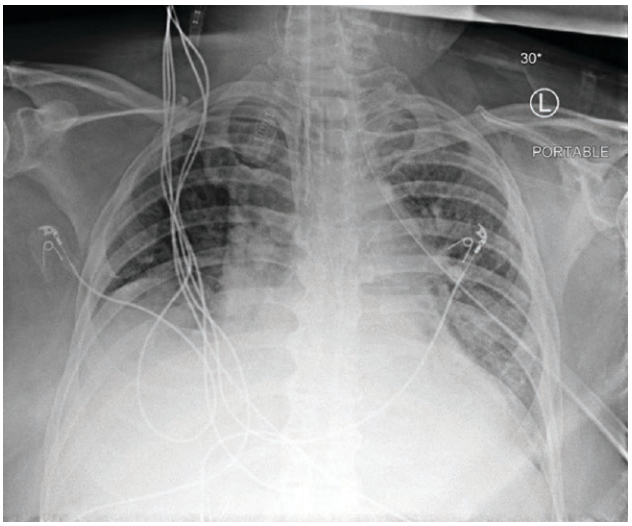
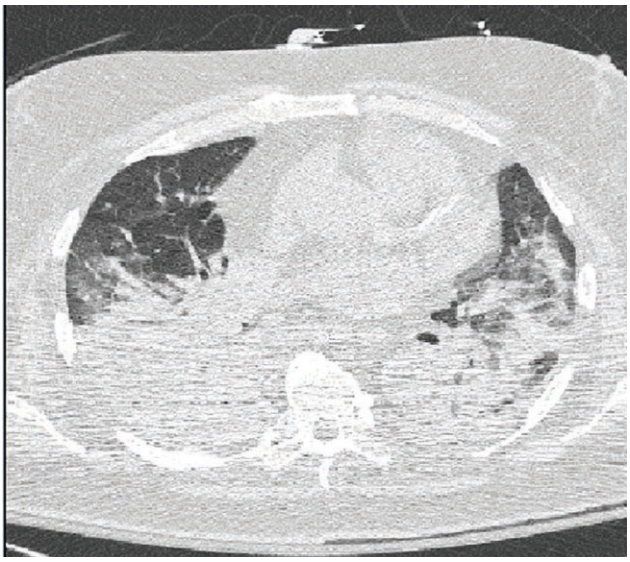


Figure 1. Chest x-ray upon presentation with multifocal opacities.

A computed tomography (CT) scan of his chest demonstrated diffuse patchy bilateral airspace opacities with lower lobes predominance as well as scattered ground-glass opacities concerning for multifocal pneumonia (Figure 2). He had a speech and swallow assessment to evaluate for aspiration, which was negative. Sputum cultures and blood cultures were negative. Urine streptococcal and legionella antigens, influenza and RSV viral swabs, as well as a MRSA swab were sent but failed to identify a pathogen for the



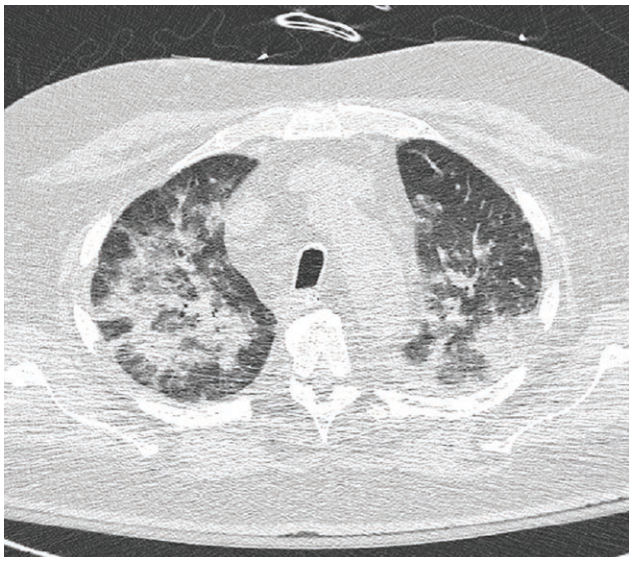


Figure 2. Computed tomography scan of the chest showing patchy bilateral airspace opacities, most predominant in the lower lobes, with associated scattered ground-glass opacities bilaterally.

patient's suspected pneumonia. He also underwent evaluation for autoimmune and connective tissue diseases that could have contributed to his presentation, with negative ANA, ANCA, anti-Scl 70, anti-dsDNA, and anti-Jo1 testing. He never presented with an elevated eosinophil count.

Prednisone was added to his empiric broad spectrum antibiotics given concern for possible organizing pneumonia based on his imaging findings with clinical improvement. By the third day of his admission, the oxygen saturations were consistently 98% on 2L nasal cannula. His antibiotics were de-escalated to moxifloxacin to complete a five-day course and he was started on a prolonged prednisone taper to empirically treat cryptogenic organizing pneumonia, as the patient declined surgical and trans-bronchial biopsy to confirm this suspicion. At the time of discharge, he was stable on room air at rest but required 1-2L of supplemental oxygen with ambulation and CPAP at night.

FOLLOW UP

The patient was followed closely at the outpatient pulmonary office. He was readmitted every couple of months after his initial presentation with shortness of breath and increased work of breathing that notably flared toward the end of his prednisone tapers and rapidly improved with intravenous steroids administered in the hospital. These admissions were attributed to COP flares though his diagnosis was never confirmed; an infectious workup as detailed during his initial admission were repeated at each subsequent admission and was similarly negative every time. The last time he was seen in the outpatient pulmonary office, he reported fevers at home with a newly-productive cough. His outpatient labs demonstrated a leukocytosis of 16.1 billion/L, although whether this was related to ongoing steroid use or underlying infection was uncertain. He was readmitted and started on stress-dose steroids as well as broad-spectrum antibiotics and anti-fungal therapy, as a repeat CT scan revealed a worsening of the diffuse airspace opacities seen on prior imaging studies concerning for superimposed infectious pneumonia. His sputum cultures at this interval grew yeast. He developed hypoxic respiratory failure, requiring intubation and tracheostomy, and septic shock complicated by disseminated intravascular coagulation and pulseless ventricular tachycardia resulting in his eventual death. The patient's family declined autopsy.

DISCUSSION

Treatment of COP has not been well evaluated in clinical trials and therefore is based upon clinical experience. Prednisone is the first-line treatment for COP due to its anti-inflammatory effects and 65-85% of patients respond to this therapy.[6] Relapses are common in up to 58% of cases and are associated with corticosteroid tapers.[7,8] For refractory or recurrent cases, Vaz et al. found macrolides to be effective at achieving remission after one year of treatment.[9] Cytotoxic and immunomodulating agents such as rituximab have also shown efficacy in treating refractory COP in preliminary case reports.[10] In patients where steroids are difficult to taper, azathioprine has been suggested as a steroid-sparing agent although evidence for this therapy is limited.[11] Cyclophosphamide has also been used in patients who fail to improve with glucocorticoids but data regarding its use is similarly sparse.[12]

About 33% of patients who are treated for less than one year with corticosteroids experience recurrence.[13] Studies have shown that relapse is associated with multiple factors such as gastroesophageal reflux disease, a decrease in functional vital capacity, a decrease in serum protein, and severity of illness at diagnosis.[2,14,15] Lazor et al. studied relapses in 48 cases and found that a delay in initial diagnosis was also associated with an increase in relapse.[8] Watanabe et al. found that the level of hypoxemia at time of diagnosis was the most important factor in predicting relapse.[7]

In this report, we described a patient with suspected COP based on clinical presentation and response to empiric prednisone with recurrence of presenting symptoms toward the end of prolonged steroid tapers. His negative infectious workup during each of his four hospital admissions and his negative evaluation for autoimmune and connective tissue diseases helped guide our clinical suspicion for COP even in the absence of a confirmatory biopsy. Our patient originally presented with recurrent episodes of presumed community-acquired pneumonia. The most common presentations of COP are nonspecific flu-like symptoms such as cough, fever, dyspnea, and malaise; most patients are thus started on antibiotic treatment but remain unresponsive to this therapy. As this case reflects, the diagnosis of COP is usually delayed and therefore a high index of suspicion is required to correctly and promptly address this disease.

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Amyotrophic Lateral Sclerosis Presenting as Chronic Cough

Marjorie Friedman, MD

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a debilitating, uniformly fatal disease. While it most commonly presents with limb weakness, patients may also present with neurocognitive, respiratory, or bulbar symptoms. Despite its poor prognosis, an early diagnosis can save patients from unnecessary and expensive testing, lead to interventions that improve quality of life, and give patients and family time for advanced planning.[1] This case highlights an unusual presentation of ALS.

CASE PRESENTATION

A 77-year-old male with a past medical history of coronary artery disease, three-vessel coronary artery bypass graft surgery, mild chronic obstructive pulmonary disease (COPD) and a 40 pack year cigarette smoking history presented with a chief complaint of cough which began in March 2016. His only other complaint was mild dyspnea on exertion. He was treated twice with oral steroids and antibiotics as an outpatient for COPD exacerbations without improvement. In August 2016, he saw a new pulmonologist for his persistent cough. The pulmonologist obtained a chest xray and pulmonary function tests (PFTs) (Table 1), and adjusted his medications. The chest xray showed a left hemidiaphragm elevation but was otherwise unremarkable. A follow up fluoroscopic sniff test showed no evidence of paradoxical motion.

He initially presented to the hospital in October 2016, and complained of coughing fits and progressive dyspnea on exertion. His cough was productive of yellow sputum and worse with lying flat. He also complained that his voice had a new nasal quality. He denied heartburn, dyspepsia, post nasal drip, lower extremity edema or chest pain. His vital signs were within normal limits and he appeared well. Cardiac exam was normal. He had scattered expiratory wheezes and no clubbing. Admission labs are listed in Table 2.

DIFFERENTIAL DIAGNOSIS

The patient's chief complaint was a chronic cough. The patient did have a history of smoking, a diagnosis of COPD, and ACE inhibitor use, all of which are commonly associated with cough. Excluding these risk factors, the most common causes of chronic cough are upper airway cough syndrome, asthma, and GERD.[2] However, the patient's abnormal PFTs provided a starting point for evaluating his symptoms.

The patient's PFTs were most notable for restrictive lung physiology: FEV1/FVC ratio was elevated, and TLC was markedly low. The 11% absolute change in his FEV1 with bronchodilator challenge suggested an element of obstruction as well (close to the cutoff of 12% generally used). However, given that the FEV1/FVC ratio was elevated and repeated treatments for COPD exacerbations did not relieve his symptoms, it was thought that his presentation was not entirely explained by COPD alone.

Table 1: PFTs from September 2016

	% Predicted	% Predicted: After bronchodilator challenge
FEV1/FVC	111%	110%
FEV1	52%	57%
TLC	45%	
RV	36%	
DLCO	68%	
DLCO/VA (corrects for alveolar volume)	133%	

Table 2: The Patient's Admission Labs

	Patient Result	Normal Value Range
WBC	9.7 B/L	4-11 B/L
Hgb	14.6 g/dL	14.0-17.0 g/dL
Platelets	193 B/L	140-400 B/L
Creatinine	1.3 mg/dL	0.7-1.4 mg/dL
Bicarbonate	21 mmol/L	24-32 mmol/L
Troponin T	< 0.01 ng/mL	< 0.01 ng/mL
proBNP	33 pg/mL	< 450 pg/mL
VBG pH	7.36	7.32-7.43
VBG CO2	59 mmHg	38-50 mmHg
Lactate	2.2 mmol/L	0.5-2.0 mmol/L
TSH	0.22 uIU/mL	0.3-5.0 uIU/mL
Free T4	1.1 ng/dL	0.7-1.7 ng/dL

The differential diagnosis for restrictive lung physiology includes interstitial lung disease (ILD), extrinsic disorders that cause chest wall compression such as kyphosis or obesity and neuromuscular disorders. The patient had no evidence of ILD on chest CT. The elevated DLCO/VA on PFTs implied no issues with diffusion of gases across the alveoli membrane which further argued against ILD. The patient was mildly obese with a body mass index of 33, but his habitus was not thought to be sufficient enough to cause extrinsic restriction to the degree seen on his PFTs. The differential diagnosis of neuromuscular disorders that cause restrictive lung disease can be divided into the following categories: spinal cord disease such as multiple sclerosis, motor neuron disease such as amyotrophic lateral sclerosis (ALS), neuromuscular junction disease such as myasthenia gravis and muscle disease such as polymyositis.

OUTCOME AND FOLLOW-UP

During his initial hospitalization, the patient received nebulizers and a course of steroids and moxifloxacin. Additional laboratory work to evaluate for neuromuscular disorders (arterial blood gas and creatine kinase) was unremarkable. Neurology was consulted but did not consider the patient's history and physical exam concerning for a neuromuscular disease. His symptoms improved and he was discharged.

A week later, he returned to the emergency room complaining of severe dyspnea, wheezing and a persistent cough that woke him from sleep. Although compliant with medications, he experienced little symptomatic relief. He was admitted to the hospital and underwent a transthoracic echo and CT of the sinuses both of which were unremarkable. His symptoms improved within one day and he was again discharged. The patient was referred to otolaryngology as an outpatient who started the patient on a trial of omeprazole for laryngospasm and tramadol for neurogenic cough.

In November 2016, the patient presented again. His symptoms had progressed to the point that he had to sleep upright in a chair and could not catch his breath after walking up a flight of stairs. His initial oxygen saturation was 80% on room air. He was again treated with nebulizers and antibiotics and admitted for further workup. After several days he was noted to have fasciculations of his hand muscles. An EMG was performed and results were consistent for ALS.

Before discharge, the patient was seen by palliative care for assistance with coping with his diagnosis and advanced care planning. He was discharged home on BiPAP which led to a profound improvement in his sleep, dyspnea, and cough. He continues to follow regularly with Jefferson pulmonology and neurology at the Jefferson Weinberg ALS Center and has only been admitted to the hospital once since the diagnosis was made.

DISCUSSION

The average time between onset of symptoms and diagnosis of ALS is 13-18 months.[1] The majority of ALS cases (70-80%) present initially with asymmetric limb weakness whereas respiratory symptoms are present in about 5% of patients and bulbar symptoms (such as hoarse voice and laryngospasm) are present in only about 20%.[3] Given the rarity of ALS (incidence of 2:100,000 in western countries), patients tend to undergo treatment of more common conditions prior to diagnosis of ALS as seen in our case.[3] Also, our patient did not have a classic presentation of ALS which added to the delay in his diagnosis.

In addition to providing a unique presentation of ALS, our patient's case highlights several important features of caring for patients with ALS. Non-invasive positive pressure ventilation (NIPPV) is an important tool that has been shown to improve quality of life and increase survival by an average of 15 months.[4] Advanced care planning is also crucial for patients diagnosed with ALS and should involve creation of a living will, appointing a power of attorney, and discussions regarding PEG and tracheostomy placement. Continued healthcare at a multidisciplinary center for ALS, which our patient receives, has been shown to lead to better outcomes.[1]

KEY POINTS

- Our patient presented with chronic cough and restrictive lung disease and after extensive workup was diagnosed with ALS.
- Bulbar and respiratory symptoms are uncommon initial presentations of ALS.
- Early diagnosis of ALS can allow for advanced care planning and help patients initiate treatment earlier which can lead to improved quality of life.

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Sharon Li, MD

Adverse Effects of Checkpoint Inhibitor Immunotherapy in Medical Oncology

Michael Brister, MD and Colin Thomas, MD

INTRODUCTION

The development of checkpoint inhibitor immunotherapy marks a significant innovation in the field of medical oncology over the past decade. Checkpoint inhibitors are antibody drugs that have demonstrated efficacy in treating a wide range of malignancies including advanced melanoma, non-small cell lung cancer, and Hodgkin lymphoma. These drugs antagonize cell-associated molecules responsible for immunologic down-regulation including programmed cell death receptor 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Curtailing the function of these intrinsic immunologic down-regulators enhances the body's own antitumor immune mechanisms. Despite the promise of these new therapies, a variety of immune-related adverse events (irAEs) have been described.[1,2] Utilization of immunologic checkpoint blockade is increasing in medical oncology, and the importance of understanding these new toxicities is evident. Here we discuss some of the most important adverse effects of checkpoint inhibitors and review the basic principles of managing these conditions. There is a lack of strong evidence guiding the optimal management of irAEs, but treatment algorithms exist based on clinical experience.

GASTROINTESTINAL TOXICITY

The most common gastrointestinal irAEs are diarrhea and colitis. Symptoms generally develop about 6-8 weeks after treatment initiation.[3] Whereas diarrhea is based on an increase in stool frequency or ostomy output compared to baseline, indicators of colitis include stools with blood or mucus, or the presence of abdominal pain and cramping. Enteritis involves symptoms similar to colitis, but anatomically the small bowel is affected. Esophagitis and gastritis have also been reported as irAEs, but are much less common. Gastrointestinal irAEs are more frequent in patients treated with CTLA-4 targeting therapy such as ipilimumab, compared with PD-L1 or PD-1 inhibitors such as Nivolumab.[4,5] In a study of patients with melanoma receiving ipilimumab monotherapy, 28% developed diarrhea and 8% developed colitis. Interestingly, 5% of patients developed severe (grade 3/4) colitis.[4,6] Gastrointestinal irAEs frequently reach grade 3/4 in severity, thus early recognition and appropriate management is important to reduce the risk of life-threatening complications such as bowel perforation.

Patients that develop diarrhea or abdominal pain while on checkpoint inhibitors should first be evaluated for infectious diarrhea including *C. difficile*. If infectious diarrhea can be excluded and symptoms persist or worsen, an adverse reaction to immunotherapy becomes more likely. However, it is difficult to make this distinction definitively and treatment is often empiric. The Common Terminology Criteria for Adverse Events (CTCAE) defines grade 1 diarrhea as an increase of fewer than four stools per day above baseline, and patients with grade 1 colitis are usually asymptomatic. These patients are treated symptomatically with loperamide or diphenoxylate and atropine, and immunotherapy may be resumed as scheduled with close monitoring and patient education. Grade 2 diarrhea is defined as four to six stools per day above baseline, and grade 2 colitis is defined by the presence of abdominal pain or bloody stools. For these patients, checkpoint inhibitor therapy should be stopped until symptoms improve to grade 1 with symptomatic management. However, if symptoms persist for more than 5 days, systemic corticosteroids should be begun at a dose of 0.5-1.0 mg/kg/day of intravenous (IV) methylprednisolone or the oral equivalent. In this case, colonoscopy or computed tomography (CT) evaluation is helpful to confirm the diagnosis. If symptoms worsen or do not improve within 3 days of steroid treatment, the diarrhea or colitis should be managed as grade 3/4 with 1.0-2.0 mg/kg/day of IV methylprednisolone, and the immunotherapy should be permanently discontinued. Steroids may only be tapered after symptoms improve to grade 1, and the taper should be performed slowly over at least 1 month. If symptoms do not improve to grade 1 and persist for more than 3 days despite higher steroid dosing, it is recommended to add infliximab to the treatment regimen, similar to the management of active inflammatory bowel disease (IBD).[7] Grade 3/4 diarrhea is defined as seven or more stools per day above baseline, and grade 3/4 colitis includes severe abdominal pain, sometimes with peritoneal signs. If intestinal perforation has occurred, infliximab use is contraindicated.

Patients with hepatotoxicity from checkpoint inhibitor therapy are usually asymptomatic and patients are diagnosed based on increased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or total bilirubin noted 8-12 weeks after immunotherapy initiation. Occasionally, mild symptoms are present including fatigue or fever, but death from fulminant hepatitis has also been reported.[8] Grade 2 hepatotoxicity is based on measurement of AST or ALT

2.5-5 times the upper limit of normal, or total bilirubin 1.5-3 times the upper limit of normal. Grade 3 or grade 4 hepatotoxicity is defined as AST or ALT greater than 5 times the upper limit of normal or total bilirubin greater than 3 times the upper limit of normal. In the CheckMate 067 phase III trial, both nivolumab monotherapy and ipilimumab monotherapy were associated with an 8% incidence of hepatotoxicity based on any grade of transaminase elevation, and grade 3/4 transaminase elevations occurred in 2% of both patient groups.[9] Patients receiving combination nivolumab plus ipilimumab had a much higher rate of transaminitis, with 33% of patients developing hepatic injury of any grade.

Management should include exclusion of other causes of hepatitis, including medication-induced hepatic injury or viral hepatitis. As with other irAEs, immunotherapy should be delayed if grade 2 toxicity is present. With grade 3 or 4 hepatotoxicity, immunotherapy should be discontinued indefinitely and steroids should be started at a dose of 1.0-2.0 mg/kg/day of IV methylprednisolone or oral equivalent. Mycophenolate mofetil may be added if there is no improvement within 3 days. Unlike treatment of severe immunotherapy-related diarrhea or colitis, grade 3/4 hepatotoxicity should not be treated with infliximab, as this drug has been independently implicated as a cause of medication-induced hepatotoxicity.

PNEUMONITIS

Pneumonitis is a potentially fatal complication of checkpoint inhibitor immunotherapy. This is a particularly important consideration in patients with compromised pulmonary reserve including those who have had radiation therapy, lung resection, or patients with a history of exposure to chemotherapies associated with pneumonitis such as bleomycin, docetaxel, or gemcitabine. In an early phase study of nivolumab monotherapy, deaths due to pneumonitis were reported in 2 patients with non-small cell lung cancer and 1 patient with colorectal cancer, in total representing 1% of patients in this study.[10] Pneumonitis caused by checkpoint inhibitors can be difficult to diagnose and the clinical manifestations are diverse. In one study, pneumonitis presented up to 19 months after initiation of checkpoint inhibitor therapy, with a median time to onset of about 3 months. However, one-third of patients were asymptomatic at the time of diagnosis and were identified based on radiologic findings alone, suggesting an even later median time to onset clinically.[11] When symptoms were present, patients presented with dyspnea, cough, fever, or chest pain.

Before diagnosing immunotherapy-related pneumonitis, more common etiologies of pulmonary symptoms must be excluded. Caution should be taken to rule out infection, often in association with an infectious disease consultation. Previously undiagnosed malignancy infiltrating the lungs must also be considered, and pulmonary consultation is advised when there is concern for grade 2 pneumonitis (mild to moderate new symptoms). CT imaging is helpful to guide diagnosis, and bronchoscopy or lung biopsy may also be warranted, but there are no radiographic or pathologic findings specific to pneumonitis caused by checkpoint inhibitor exposure.

Grade 1 toxicity involves radiographic changes only and requires repeat imaging every 3 weeks to assess if immunotherapy should be delayed. Grade 2 toxicity should be managed with 1.0 mg/kg/day of methylprednisolone or the oral equivalent, and doses of 2.0-4.0 mg/kg/day are recommended for grade 3 or higher toxicity. Prophylactic antibiotics for *Pneumocystis* pneumonia (PCP) should be added if the patient will require the equivalent of 20 mg of prednisone daily for greater than 4 weeks. If patients do not improve after 48 hours of steroid therapy, additional immunosuppression with infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil should also be considered. In a group of 43 patients receiving PD-1/PD-L1 inhibitor therapy who were diagnosed with immunotherapy-related pneumonitis, 86% improved with either corticosteroid administration or discontinuation of immunotherapy. Of the remaining 6 patients, 5 died from either infection or cancer progression.11 In a comparison of PD-1 inhibitors to PD-L1 inhibitors for the treatment of non-small cell lung cancer, PD-1 inhibitors were found to be more than twice as likely as PD-L1 inhibitors to cause pneumonitis (3.6% versus 1.3%).[12]

ENDOCRINOPATHIES

The endocrine system relies on finely tuned quantities of hormones controlling target organs, and the body is especially sensitive to altered levels of endocrine signaling. Unlike other organ systems adversely affected by immune checkpoint blockade, endocrine organ dysfunction from checkpoint inhibitors does not readily reverse with corticosteroids.[13] Life-long hormone supplementation is required in many patients with endocrine irAEs. In a phase 3 trial of patients receiving ipilimumab and nivolumab, more than 50% of patients who developed any grade of endocrine toxicity required long-term hormone supplementation. Even so, substantial improvement in symptoms was observed.[9]

Endocrinopathies can present a diagnostic challenge because patients develop non-specific complaints including fatigue, weakness, nausea, and abdominal pain. The anterior pituitary is critical for thyroid function, gonadal function, and adrenal activity. The most common endocrine irAEs are hypothyroidism, hyperthyroidism, and hypophysitis. In a study of patients receiving

ipilimumab for melanoma, 8% developed hypophysitis and 6% developed thyroiditis.[14] There is variability in the time to onset of endocrine-related adverse effects, with a trend towards later presentations compared with irAEs affecting other organ systems. In patients receiving ipilimumab, the median time to onset of hypophysitis was observed to be between 4-8 weeks after treatment initiation, but patients have been diagnosed with immunotherapy-related thyroiditis up to 3 years after treatment initiation, including long after checkpoint inhibitor therapy has been discontinued.[14,15]

Patients suspected to have endocrine irAEs should have laboratory testing of thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and cortisol. These tests should be repeated at regular intervals in patients diagnosed with endocrine irAEs. If there is concern for hypophysitis, the patient should undergo visual field testing and pituitary MRI should be considered to assist in confirming the diagnosis. Patients with hypophysitis who become symptomatic should be treated with 1.0-2.0 mg/kg/day of methylprednisolone or the oral equivalent. Immunotherapy treatments should be delayed and appropriate hormone replacement therapy should be started. If the complication is grade 4 (life-threatening), checkpoint inhibitor treatments must be permanently discontinued. Prophylactic antibiotics for PCP should be considered, and if symptoms improve, steroids may be tapered over a minimum of 1 month, but usually longer.

Thyroiditis secondary to checkpoint inhibitors often presents similarly to Hashimoto's thyroiditis with a period of clinical hyperthyroidism preceding a progressive transition towards hypothyroidism over several weeks. In cases of asymptomatic TSH elevation, immunotherapy may be continued; however, patients with a TSH that is less than half the lower limit of normal, or greater than 2 times the upper limit of normal, should have free T4 testing with each cycle of immunotherapy. If hypothyroidism is present, the patient should be started on levothyroxine, but in contrast to the treatment of most irAEs, it is unclear if steroids are helpful in the long-term management of symptomatic thyroiditis.

Less common endocrine irAEs include primary adrenal insufficiency and type 1 diabetes mellitus, which have each been observed in less than 1% of patients.[16,17] The development of adrenal crisis is a dangerous complication that must be differentiated from sepsis and immediately treated with intravenous corticosteroids. Immunotherapy-related endocrinopathies are variable in presentation, often permanent, and require careful consideration in patients exposed to checkpoint inhibitors presenting with vague systemic complaints.

CONCLUSION

Immunotherapy is becoming increasingly prevalent in medical oncology. Studies have indicated checkpoint inhibitors are better tolerated and associated with fewer adverse effects overall in comparison with standard chemotherapy,[18] but the toxicities associated with immunotherapy are often difficult to recognize and may affect several organ systems. The most important irAEs are diarrhea, colitis, hepatitis, pneumonitis, and endocrinopathies. The skin, however, is the most commonly involved organ, and the most frequently observed cutaneous toxicity is a mild pruritic maculopapular rash. Less common toxicities include myocarditis, encephalitis, uveitis, inflammatory arthritis, and kidney injury. The various toxicities associated with immunotherapy may present clinically as early as several weeks after checkpoint inhibitor initiation, or may not manifest for several years.

Management of suspected irAEs typically includes ruling out infectious causes of symptoms, delaying further immunotherapy, and initiating treatment with corticosteroids. Endocrinopathies related to checkpoint inhibitors are often irreversible and require indefinite hormone replacement therapy. There are no prospective trials guiding management of irAEs. Future studies should aim to identify subpopulations of patients most at risk for developing severe irAEs, and rigorous trials should evaluate optimal management of these toxicities. Clinicians from many specialties must be aware of the spectrum of immune-related toxicities associated with checkpoint inhibitors, as these medications are being used to treat an increasing number of cancer patients, and immunotherapy holds immense promise in the field of medical oncology.

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Sharon Li, MD

Sclerosing Mesenteritis: Clinical Presentation, Imaging Findings, and Treatment

Jennifer Nauheim, BSc and Rose Onyeali, MD

CASE PRESENTATION

A 67-year old male with a history of myocardial infarction status post percutaneous coronary intervention and stage IV bladder cancer status post radical cystoprostatectomy with ileal neobladder reconstruction and chemotherapy (cisplatin and gemcitabine) presented with progressive, severe epigastric and lower abdominal pain associated with nausea. The pain had intensified over the previous week and was associated with a recent fifteen pound weight loss in the setting of poor oral intake. He denied nausea or diarrhea.

His physical exam was notable for abdominal tympany and tenderness. His labs were notable for mild hyperkalemia (potassium 5.0 mmol/L), normal white blood cell count, lipase of 28 U/L, normal liver function tests, and positive 2+ leukocyte esterase and 1+ blood in his urine. Upper endoscopy showed a small Schatzki's ring in the distal third of the esophagus with small hiatal hernia and gastritis. On CT, there was thickened, indurated mesentery and a mesenteric mass (Figure 1) with abdominal lymphadenopathy and a new adrenal nodule.

EPIDEMIOLOGY & CLINICAL PRESENTATION

Sclerosing mesenteritis, also known as mesenteric panniculitis, is part of a spectrum of idiopathic primary inflammatory and fibrotic processes that affect the mesentery and is characterized by inflammation of mesenteric fat. Although its etiology is unclear, it has been associated with previous abdominal surgery, autoimmunity, paraneoplastic syndromes, ischemic injury, and infection. Sclerosing mesenteritis is also associated with a high prevalence of coexisting malignancies and future cancer development.[1] In a study evaluating 7620 patients presenting with a chief complaint of abdominal pain, the prevalence was 0.6%.[2]

The presentation of sclerosing mesenteritis is variable. In a series of 68 patients with sclerosing mesenteritis, 75% had abdominal pain, 26% had nausea/vomiting, 20% had anorexia and weight loss, and 20% had altered bowel habits.[3] In an 84-patient cohort, only 35% had abdominal pain, and 20% had an incidental abdominal mass on exam.[2] The duration of symptoms ranged from 24 hours to 2 years.[2]

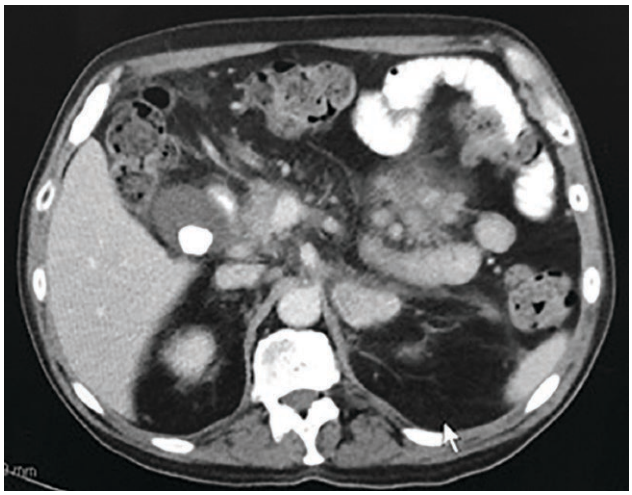

Figure 1. CT of the patient's abdomen showing a thickened, indurated mesentery.

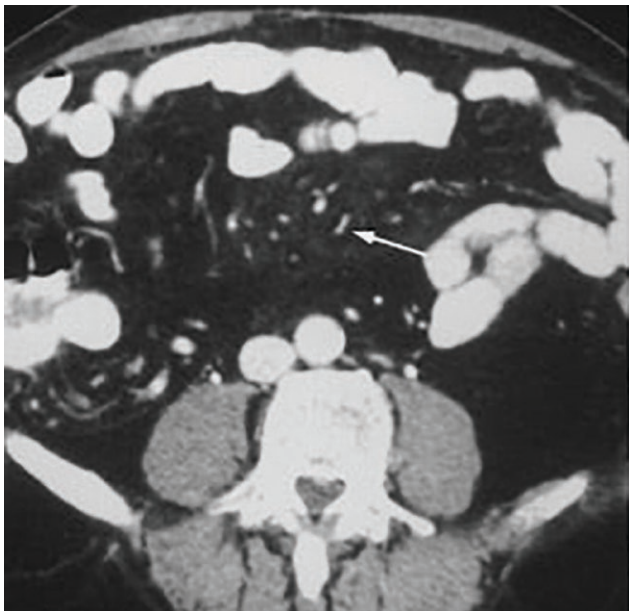

Figure 2. Fat ring sign (white arrow) seen on CT abdomen.

Up to 20% of patients with sclerosing mesenteritis develop complications, often intestinal obstruction from mass effect.[3] Other complications include mesenteric vascular occlusion, chylous ascites, and adverse effects from medications used to treat sclerosing mesenteritis.

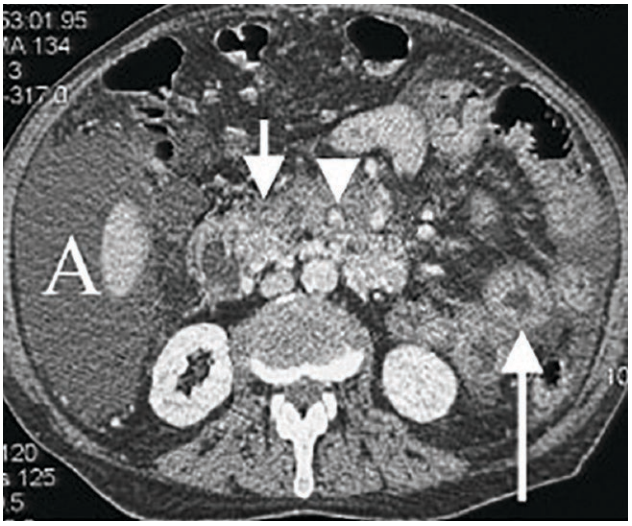

Figure 3. Tumor pseudocapsule (white arrow) seen on CT abdomen.

DIAGNOSIS

The diagnosis of sclerosing mesenteritis is made by histology and radiographic findings, with noninvasive imaging being preferred over surgical sampling. Dual phase computed tomography is the most sensitive imaging modality for detecting sclerosing mesenteritis.

Sclerosing mesenteritis typically presents on imaging as, in decreasing order of frequency, diffuse mesenteric thickening, a single mass with an average size of 10 cm, or multiple masses.[2] "Misty mesentery," haziness and stranding in the mesenteric fat, can be observed in sclerosing mesenteritis, but is not a specific imaging finding. The "fat ring sign," fat around mesenteric vessels spared from the changes of mesenteric panniculitis, is seen in 56-90% of cases (Figure 2). A tumoral pseudocapsule is ocassionally seen (Figure 3). These latter two findings are not seen in other mesenteric diseases such as lipoma, lymphoma, or liposarcoma.[4]

TREATMENT

The preferred first-line therapy for sclerosing mesenteritis includes glucocorticoids in combination with tamoxifen, although glucocorticoids alone or with colchicine/azathioprine may be beneficial.[5] Patients with greater inflammatory components respond best to these regimens. A response to hormonal therapy with tamoxifen and progesterone has been reported as well.[6] In refractory cases, thalidomide has been used.

OUTCOME & DISCUSSION

The patient was started on tamoxifen and steroids for his sclerosing mesenteritis, but a biopsy of the enlarged abdominal lymph nodes and the adrenal nodule demonstrated worsening metastatic malignancy. Medical oncology advised that the patient discontinue tamoxifen and taper the steroids because of a lack of improvement in his abdominal pain. The patient received a celiac nerve block as an outpatient without any complications.

The differential diagnosis of a patient presenting with abdominal pain is broad. The differential for this patient after imaging included idiopathic sclerosing mesenteritis in the setting of metastatic bladder cancer, constipation secondary to opioid pain medications, narcotic bowel syndrome, pancreatitis, and worsening metastatic disease. It is likely that this patient's abdominal pain was multifactorial: his initial CT of his abdomen showed evidence of sclerosing mesenteritis with abdominal lymphadenopathy and an adrenal mass that were found on biopsy to be metastatic foci.

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Syncope Diagnosed by Inducible Sustained Ventricular Tachycardia

Amit Vira, MD

INTRODUCTION

Syncope is a common complaint in the emergency department (ED), accounting for approximately 3% of all ED visits.[1] Although most causes of syncope are benign and self-limited, others are associated with significant morbidity and mortality.

CASE PRESENTATION

An 85-year-old male with a history of coronary artery disease status post prior coronary artery bypass grafting, moderate to severe aortic stenosis, hypertension, and stage IIIA chronic kidney disease presents to emergency room after abrupt onset of unwitnessed syncope. He reports exercising on an elliptical machine at home and falling on the floor. He denies any prodrome symptoms of chest discomfort, shortness of breath, palpitations, flushing, feeling cold or clammy, visual disturbances, nausea or vomiting. He believes the episode was brief and woke up within seconds feeling completely back to his baseline. He denies any confusion, bladder or bowel incontinence, or physical trauma immediately after the syncope. He reports waking up that morning feeling well, eating a normal breakfast and staying well-hydrated.

His medications include aspirin, atorvastatin, amlodipine, and rampiril. He has no known tobacco, alcohol, or illicit drug use.

Physical exam: Temperature 98.4 °F, Blood pressure 129/62, Heart rate 82, Respiratory rate 16, saturating 99% on ambient air. Orthostatic vitals were negative. Cardiac exam revealed a regular 3/6 mid-peaking systolic ejection murmur with preservation of S2 at the cardiac base. No jugular venous distention. Lungs were clear to auscultation and the abdomen exam was soft, non-tender, with normoactive bowel sounds. Extremities were warm with +2 equal peripheral pulses. Neurologic exam was non-focal with normal gait.

Laboratory Studies: Metabolic panel was significant for a creatinine of 1.4 mg/dL (at baseline) with the remainder of the electrolytes being normal. Complete blood count was significant for a hemoglobin level of 12.3 g/dL (at baseline). His serial cardiac enzymes were negative.

EKG showed normal sinus rhythm, normal QRS duration, corrected QT of 455 ms, incomplete right bundle branch and multiple premature ventricular complexes. An echocardiogram revealed low normal right and left ventricular function with inferoapical akinesis consistent with an old infarcted scar and moderate aortic stenosis with a mean gradient of 30 mmHg and valve area of 1.0 cm^2, which was unchanged from a prior echocardiogram. 24-hour telemetry revealed multiple premature ventricular complexes and short runs of non-sustained ventricular tachycardia (Figure 1).

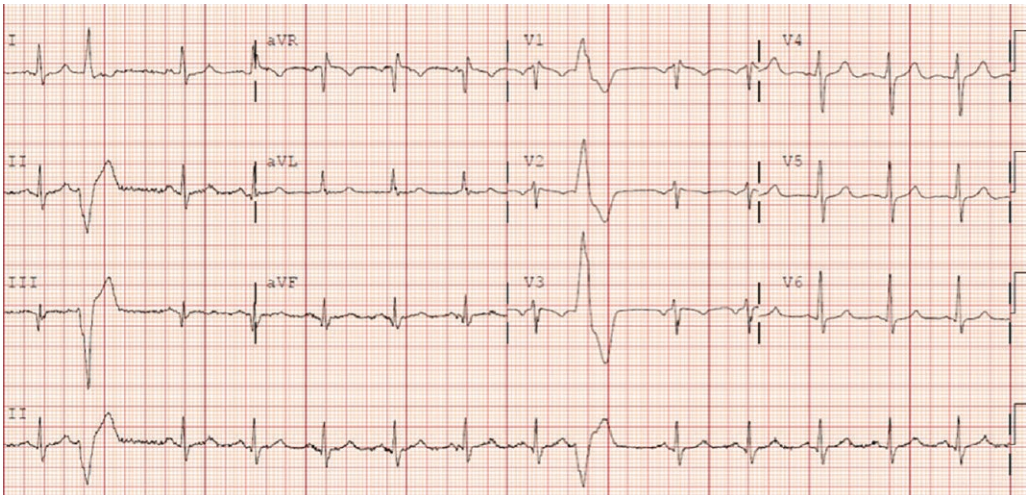

Figure 1. Patient's continuous cardiac monitoring revealed multiple premature ventricular complexes (seen on EKG) and short runs of non-sustained ventricular tachycardia.

OUTCOME

Given his abrupt exertional syncope during exercise without prodrome, cardiac syncope was suspected. EKG showed evidence of conduction disease and significant ventricular ectopy. His overall echocardiogram was unchanged from prior and showed focal scar. Given this constellation of signs and symptoms, a ventricular tachyarrhythmias was suspected as the cause. Electrophysiologic study was recommended and revealed an easily inducible sustained monomorphic ventricular tachycardia. The ventricular tachycardia showed a right bundle branch pattern with left superior axis morphology consistent with an inferoapical site with the likely origin being from the scar from his prior myocardial infarction as seen on echocardiogram. Given these findings, an implantable cardioverter defibrillator was recommended for secondary prevention.

DISCUSSION

Syncope or "true syncope" is the sudden and transient loss of consciousness and postural tone attributable to inadequate cerebral blood flow. In comparison, pre-syncope refers to near loss of consciousness and occurs more commonly than syncope. However, both syncope and pre-syncope should be considered in the same disease spectrum.

There are many causes for transient loss of consciousness (Table 1). Non-syncopal causes of transient loss of consciousness include seizure disorders, concussions, intoxications, metabolic disturbances, and conversion disorders. Distinguishing these conditions from true syncope is challenging, but it is crucial in order to determine appropriate management.

The differential diagnosis of true syncope is broad, and management focuses on treating the underlying cause. Below are the most common causes of syncope seen in emergency rooms.

1. Neurally mediated syncope is one of the most frequent etiologies of syncope and is often referred to as vasovagal syncope.[2] It is characterized by peripheral vasodilation and hypotension, along with bradycardia which is believed to be due an increase in parasympathetic tone and concomitant inhibition of sympathetic outflow.[3] The hypotension can lead to loss of consciousness if severe or pre-syncope if less severe. A wide variety of stimuli can trigger this reflex, the most common stimulus being orthostatic stress. Other triggers include prolonged standing, crowded places, or unpleasant sight, smell, or pain. Typically, one experiences nausea, lightheadedness, a feeling of warmth, and pallor before losing consciousness.

Table 1: Common Causes of Syncope

Neurally mediated
Vasovagal (emotional stress, pain, standing)
Orthostatic hypotension
Drug induced (alpha-blockers, vasodilators)
Hypovolemia (dehydration, blood loss)
Diabetic neuropathy
Parkinson's disease
Dementia
Aging
Cardiac arrhythmias
Supraventricular tachyarrhythmias
Ventricular tachyarrhythmias
Torsade de pointes
Sinus bradycardia
High-grade atrioventricular blocks
Pacemaker malfunction
Cardiac non-arrhythmias
Advanced cardiomyopathy
Aortic stenosis
Hypertrophic obstructive cardiomyopathy
Pulmonary embolism
Pulmonary stenosis
Pericardial tamponade
Acute myocardial infarction
Aortic dissection

Table 2: High Risk Criteria Requiring Prompt Hospitalization

Severe structural or coronary artery disease
Heart failure or previous myocardial infarction
Clinical or ECG features suggesting arrhythmic syncope
Exertional syncope
Palpitations preceding syncope
Family history of sudden cardiac death
Non-sustained ventricular tachycardia
Evidence of atrioventricular block
Bifascicular-block
Pre-excited QRS complex
Prolonged or short QT interval
Brugada pattern

2. Orthostatic hypotension is characterized by an inadequate physiologic response to postural changes in blood pressure that decreases cerebral perfusion. A wide variety of conditions can cause postural hypotension, with two major mechanisms including autonomic failure and volume depletion. Autonomic failure is further subdivided into intrinsic and extrinsic. Intrinsic causes include neurodegenerative diseases (ie Parkinson's dementia) or neuropathies (i.e. diabetes) while extrinsic causes include medications (i.e. alpha-blockers, phosphodiesterase inhibitors, or vasodilators).[4] In comparison, severe intravascular volume depletion (i.e. dehydration or blood loss) can lead to syncope due to functional failure of the system despite having normal functioning autonomic reflexes. Common symptoms of orthostatic hypotension include dizziness, lightheadedness, weakness, fatigue, or nausea.

3. Cardiac syncope is often the most concerning as it can occur without warning leading to major morbidity and mortality. It often occurs either with conduction system disease (i.e. brady- and tachyarrhythmias) or in the presence of structural abnormalities such as valvular disease or cardiomyopathies. Bradyarrhythmia can develop from natural pacemaker dysfunction or the development of heart block. Tachyarrythmias can be subdivided into either supraventricular or ventricular in origin. Supraventricular tachycardia usually causes palpitations but rarely causes syncope. In contrast, ventricular tachyarrythmias often cause syncope. Valvular heart disease, particularly aortic stenosis, can lead to syncope which most often occurs during exertion.

Typically, in older adults, cardiac syncope is often seen in patients with preexisting cardiovascular or structural heart disease and is often sudden without any prodrome. Common symptoms include palpitations, chest pain, and shortness of breath.

After a syncopal episode, the essential next step is to establish the etiology. For nearly all patients, the initial evaluation for syncope should include obtaining a comprehensive history, complete physical examination, and review of an electrocardiogram (ECG). A transthoracic echocardiogram is useful to evaluate for the presence and severity of structural heart disease if structural heart disease status is uncertain, after completion of a history, physical examination, and ECG. Additional diagnostic evaluation, if indicated, should be individualized based upon the suspected etiology of syncope.

Wherever the initial syncope evaluation leads, one must determine whether the affected individual needs in-hospital care for further evaluation and/or initiation of treatment. The primary factor determining whether the patient with presumed syncope should be hospitalized is the individual's immediate mortality risk. Patients can be classified as high risk (requiring admission), intermediate risk (admission is case-by-case), and low risk (can be outpatient). See table 2 for risk stratification.[5] In all cases, arrangements for prompt outpatient care is essential.

KEY POINTS

Have a high degree of suspicion for cardiac syncope when a patient presents with syncope without prodomal symptoms. A comprehensive history, complete physical examination, and review of an ECG is essential. High risk patients as identified by a history of preexisting cardiovascular disease or structural heart disease or baseline abnormal ECG should be hospitalized for further evaluation and treatment.

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White Paper: Improving Handoff Culture in Intensive Care Unit to Floor Handoffs

Grant Turner, MD, Kristin Lohr, MD, Andrew Brown, MD, Allison Greco, MD, and Rebecca Jaffe, MD

ABSTRACT

The frequency of handoffs between providers has increased since the 2011 Accreditation Council for Graduate Medical Education (ACGME) work hour restrictions, generating concerns over the quality of these handoffs and their impact on patient safety. At Thomas Jefferson University Hospital (TJUH), the 2016 Safety Culture Survey revealed that across all specialties, many residents felt that "things fall through the cracks" when transferring patients from one unit to another. The interdepartmental Housestaff Quality and Safety Leadership Council (HQSLC) at TJUH sought to improve handoffs at our institution and identified two areas of focus: (1) standardizing the language of handoffs with a commonly accepted handoff technique (IPASS), and (2) standardizing the process of handoffs from the ICU to the floor. Qualitatively, resident comfort with handoffs improved with no adverse impact on time to patient movement between units. This project demonstrated the difficulty of changing the handoff culture at an institution, establishing lasting change via a new EMR system, and training housestaff of a new handoff method. Future directions include monitoring compliance with the new standardized handoff curriculum, and determining whether these efforts and interventions translate to improved patient safety at our institution.

BACKGROUND

The frequency of handoffs between providers has increased following the implementation of the ACGME work hour restrictions. In this context, properly structured and timed handoffs are essential to patient safety now more than ever.[1] Despite this, studies have shown that errors in communication of code status, medication allergies, and changes to plan of care are common; errors which can lead to adverse outcomes to patients.[2] Improving the quality of handoffs between providers is a growing priority in an effort to reduce medical errors. In alignment with these goals, the standardized handoff curriculum known as I-PASS, a mnemonic for "illness severity, patient summary, action list, situation awareness, and synthesis by receiver" has been validated in single-center and then multi-center trials which showed a reduction in medical error rate by 23% and the rate of preventable adverse events by 30%.[3,4]

At TJUH, the 2016 Agency for Healthcare Research and Quality Hospital Survey on Patient Safety Culture (AHRQ HSOPS) was administered to 869 house staff. Of 639 respondents, only 43% viewed handoffs and transitions favorably across all specialties. 37% of residents felt that "things fall through the cracks" when transferring patients from one unit to another. The ACGME's Clinical Learning Environment Review (CLER) committee regularly reviews the culture of handoffs at training programs and had also identified this as an area for improvement in their 2015 report to TJUH, specifically identifying ICU to floor handoffs as an area of weakness.

In this context, the HQSLC, a group comprised of 30 house staff from 15 departments which seeks to strategically impact key quality and safety issues across the institution, chose to focus their annual project on improving transitions of care at TJUH. This interdepartmental working group identified the following root causes affecting the safety of handoffs and transitions of care at TJUH: 1) lack of standardization in handoff content and transfer process, (2) variation in handoff training curricula between training programs, and (3) failure of the former electronic health record to reinforce best practices or ideal processes. To target these root causes, a specific focus was put on standardizing house staff handoff practice using the ICU to floor transfer as a prototype, as well as standardizing the content of handoffs used by house staff across the institution through implementation of the IPASS handoff curriculum.

INTERVENTION

An ideal handoff should be safe, timely, effective, efficient, equitable and patient-centered (STEEEP).[5] With this in mind, we proposed the following 4-tiered model to implement change to the current house staff training and practice of handoffs at TJUH:

1. **Build Momentum:** Identify department-based champions, to include a resident and faculty member dyad.

2. **Standardize Curricula:** Create a training module for use in Jefferson GME programs, based on the framework described by the I-PASS study group, and incorporating both didactics and simulation exercises facilitated by resident peers.

3. **Assess Proficiency:** Develop a framework to assess learner mastery and provide longitudinal feedback regarding performance.

4. **Reinforce Compliance:** Best practices should be made easy to follow through intentional process design, health IT, innovative team structures, and feedback to frontline providers.

In order to support step 1 of the model, a faculty member in every core GME training program was selected to participate in TeamSTEPPS Master Training.

Evaluation of the existing workflow for ICU to floor handoffs at TJUH identified barriers to safe transfers, as well as existing processes that could be harnessed to reinforce high reliability and safe communication. A high degree of variation in the ICU to floor transfer process was found in the following areas: (1) timing of the handoff, (2) incorporation of best practice of using both a verbal and written handoff, and (3) use of closed loop communication between sending and receiving teams.

The workgroup determined an ideal workflow for a safe ICU to floor transfer should include: (1) bedside evaluation by the ICU team and documentation of this in the medical record prior to transfer, followed by (2) a verbal and written handoff between sending and receiving residents, and finally (3) review of patient orders and placement of an order (physician staff information) signifying that a handoff had occurred and identifying the new primary team. To improve compliance with this new process, a new hard stop was created in the transfer process restricting a patient from moving to the new unit until the order review and handoff was completed by house staff. Residents staffing the ICU as well as nursing and physician leadership in the ICU were educated on the intervention and process change prior to its implementation. Residents were surveyed at the end of each month of the pilot to determine barriers to behavior change.

To evaluate compliance with the process change, chart review was done to determine frequency of the bedside evaluation and ensure the order for team staff information change was placed by a member of the receiving team. Data from the patient flow management center on time from assignment of floor bed to transfer out of the ICU was also analyzed to evaluate effects on total transfer time.

RESULTS

Prior to the process intervention, zero patients had a bedside evaluation prior to leaving the ICU. After implementation of the new process, 13.6% of patients transferred out of the ICU had a bedside evaluation completed and documented in the medical record by the ICU team prior to transfer. Debriefing with house staff in the ICU revealed barriers to compliance with this process. First, it was felt that too much time was required to complete the bedside evaluation, and that this detracted from the residents' ability to care for other critically ill patients or be present on rounds. Additionally, many transfers occurred overnight when the covering resident was less familiar with the patient's plan of care, and staffing ratios are reduced which exacerbated the time burden of this process.

At the beginning of the new structure, zero patients had their staff information changed by the receiving team. Following implementation of this process change, 50% of patients had the updated physician staff information order placed by the receiving team, signifying that the floor team had received a verbal and written handoff prior to the patient leaving the ICU. Analysis of patient flow data before and after the pilot demonstrated no significant difference in time to move a patient once a bed had been assigned.

DISCUSSION & SYSTEMATIC BARRIERS TO IMPROVEMENT

Handoffs are a critical component of quality care of the hospitalized patient, and require constant vigilance to maintain high quality given their increasing frequency. At our institution, handoffs from one unit to another within the hospital were identified on many levels to be an area needing improvement, and the HQSLC set out to demonstrate that standardization of the content and process of handoffs is crucial to improving the safety of our patients.

Although our pilot for a new transfer workflow resulted in only a modest behavior change in practice, it stimulated significant dialogue around handoff practice and culture. We believe this housestaff driven discussion helped to make safe handoffs an institutional priority. With this project occurring just prior to a transition to a new electronic medical record, our results informed the creation of a new electronic documentation workflow for patient flow from the ICU to the floor affecting lasting culture change at our institution.

With the proven validity of IPASS as a standardized method for effective handoffs, we were able to demonstrate to GME leadership at our institution the necessity to provide this training to all house staff. As a result, all incoming interns in 2017 were trained in IPASS using a curriculum that was developed with abbreviated IPASS materials specific to our hospital system.

We were met with several large barriers implementing the ICU to floor handoff change. The extensive heterogeneity of handoffs in practice seemed to be the greatest barrier to improvement. Handoffs and transitions of care are by nature heterogeneous. Different providers require different subsets of information and have different priorities when giving and receiving handoffs. However, best practices have been described and the creation of a shared mental model, where all providers have the same expectation of content and process of a good handoff, is crucial to excellent patient care.

Conceptually, handoffs can either be viewed as black and white ("Patient is mine, and now he's yours"), or they may acknowledge a "grey period" of shared responsibility. Structures, such as closed units, and stressful working conditions reinforce a black/white mindset, and opportunities for collaboration to meet the patient's needs may be missed.

In addition, we found that leadership buy-in for improvement in handoff culture varied across departments and units. We found that driving change from below in this area is difficult without a mandate and support from faculty and senior house staff. Buy-in needs to be achieved at all levels of interprofessional practice, departmental and educational leadership, and hospital administration. Unfortunately, lack of support for process change can arise from various concerns, such as pressures to meet benchmarks for time to patient transfer, at the expense of good quality handoffs. In reality, the need for rapid and efficient transitions in care should make the role of clear, effective and standardized communication that much more vital.

Finally, a broad push for handoff education across the institution will help to create a common language and vocabulary for effective communication and higher quality handoffs. Training incoming and junior staff appears to be the most feasible approach to encourage and reinforce behavior change from the ground up, as was completed at our institution. To ensure continued lasting success in handoff safety initiatives at TJUH, the HQSLC has continued to disseminate IPASS education to senior residents across all GME training programs, with a total of nine programs trained to date. In order to evaluate the quality of handoffs, including the appropriate use of the IPASS format, HQSLC members are currently participating in formal interdisciplinary handoff observations involving real time, direct feedback. Further research efforts are necessary to continue to evaluate the effect of standardized handoff training in improving the perception of handoff safety at TJUH and its role in improving patient safety.

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Sharon Li, MD

The Opioid Epidemic – Addressing Provider Roles and Responsibilities

Anita Modi, MD, Debbie Chen, MD, Neha Bansal Etherington, MD, Brianna Shinn, MD, and Colin Thomas, MD

PANELISTS

Abigail Kay, MD
Assistant Dean of Academic Affairs and Undergraduate Medical Education, and Assistant Professor in the Department of Psychiatry and Human Behavior

Brooke Worster, MD
Assistant Professor of Palliative Care in the Department of Family and Community Medicine

Rachel Nash, MD
Chief Resident in the Department of Internal Medicine

Jill Zavodnick, MD
Hospitalist at Thomas Jefferson University Hospital

Ms. Kate Siddiqi
Social worker at Thomas Jefferson University Hospital

Ms. Meghan Morley
Lead Patient Navigator at the Center of Excellence at the Narcotic Addiction Rehabilitation Program (NARP) in the Division of Substance Abuse

INTRODUCTION

Colin: This year marks the 19th volume of Jefferson's annual publication spearheaded by Internal Medicine residents and supported by its fellows. Our Editorial Board includes Neha, Debbie, Anita, Brianna, and myself. Our mission is to further medical knowledge by sharing each other's observations and studies both through our publication, which you can find online, as well as through annual discussion at Grand Rounds.

This year, we've chosen to focus on our roles as providers in the midst of the National Opioid Epidemic. The National Institute on Drug Abuse has reported that the number of opioid-related overdose deaths from both illegal and prescription opioids has risen in our state over the last 15 years. This information is available for each state online. While addiction has been a nationwide issue for centuries, provider practices and societal attitudes in relation to opioids has greatly varied. We'll introduce you to our panelists, giving a very brief overview of the history of opioid use in our country, then turning the discussion over to them.

Today, we have Dr. Abigail Kay, Assistant Dean of Academic Affairs and Undergraduate Medical Education and Assistant Professor in the Department of Psychiatry and Human Behavior. Ms. Meghan Morley is the Lead Patient Navigator at the Center of Excellence at the Narcotic Addiction Rehabilitation Program (NARP) in the Division of Substance Abuse. Dr. Rachel Nash is a current Chief Resident in the Department of Internal Medicine. Ms. Kate Siddiqi is a social worker at Jefferson. Dr. Brooke Worster is an Assistant Professor of Palliative Care in the Department of Family and Community Medicine. Dr. Jill Zavodnick is a hospitalist at Jefferson. Drs. Kay, Nash, and Zavodnick and Ms. Morley are members of Jefferson's Opioid Task Force, established in the fall of 2017 to provide structure, focus, and direction to Jefferson's response to the current Opioid Crisis. No one involved with these Grand Rounds has any relevant disclosures.

Brianna: First we're going to go over some definitions so we can all be on the same page as we move forward in our discussion. "Opiate" is a term used to describe any drug derived from actual opium. "Opioid" was a term initially used to describe synthetic or semi-synthetic versions of opiates but has now come to encompass any agent which binds to opioid receptors in the CNS and GI tract, including natural, synthetic, and semi-synthetic drugs. The body produces natural, endogenous opioids such as endorphins which are unable to independently cause respiratory depression or adequate pain relief in extreme circumstances. Opium alkaloids include morphine and codeine; semi-synthetic opioids resemble the structure of opiates and include heroin, oxycodone, and buprenorphine; and fully synthetic opioids which don't resemble the structure of opiates at all include methadone.

Prescription and illegal opioids can lead to patterns of tolerance, dependence, and addiction with chronic use. We'll go over those three terms as well. Tolerance suggests that a person require higher and/or more frequent doses of drug to achieve desired effects such as pain control. Dependence implies that one's neurons only function normally in the presence of drug and thus that its absence results in withdrawal symptoms. Addiction refers to compulsive or uncontrollable drug-seeking behavior despite harmful consequences—either at work, in relationships, with one's health, or with the law.

Colin: The Smithsonian published an article just last week called "How Advertising Shaped the First Opioid Epidemic, and What It Can Teach Us About the Second." It sets the stage in the 1800s, when physicians and manufacturers who recognized the effectiveness of morphine as a painkiller began incorporating it into many drugs. There was no Food and Drug Administration (FDA) to regulate safe and standardized production yet, so medicines were sold without a full listing of their active ingredients and often without need for a doctor's prescription. Cocaine and alcohol were also common additives to popular medications then.

Morphine was heralded as a cure-all, recommended by physicians at the time for everything from wounds obtained by soldiers during the Civil War to the menstrual cramps and teething pains of their wives and children. Use of IV and oral formulations of opioids was ubiquitous and most patients who sought prescriptions were of respectable social backgrounds. Once doctors and journalists began to take note of the addictive nature of these medications, the Pure Food and Drug Act was created in 1906 and eventually gave rise to the FDA.

Brianna: Now I'm going to walk us through a timeline of opioid development, which stretches back to the 1800s all the way to today. This timeline is interesting because it clearly demonstrates the swinging pendulum in regards to the support and criticism surrounding the use of opioids. We'll start way back in the 1800s when morphine was first isolated from plant. Merck began marketing it in the 1820s in a pill form. Codeine was first isolated in the 1830s and used for cough. Then the syringe was invented in 1850s and you can see morphine really came into use in its IV form during the Civil War in the 1860s. Then, in the 1870s, heroin was invented and marketed as a safer drug. You'll see this theme as we go forward—the realization that a certain opioid or type of opioid was addictive, government intervention, then the production and marketing of a "safer drug." Next, as awareness of opioid addiction grew in the 1900s, the act giving rise to the FDA was established. This reduced the use of morphine both as prescribed and over-the-counter medications, but doctors were instead encouraged to employ "less addictive" painkillers such as oxycodone and methadone in subsequent years.

In the 1970s, pharmaceutical companies which had previously limited their marketing to physicians also began redirecting their advertising to consumers directly which contributed to a nationwide clamor for these semi-synthetic and thus reportedly safer agents. When the addictive nature of these agents were subsequently elucidated, the War on Drugs was declared and the "Just Say No" campaign launched. Just a decade later, the Drug Enforcement Agency was also established at this time. Extended-release versions of morphine, oxycodone, and fentanyl were later released for chronic non-cancer pain and again purported to be less addictive. Educational programs funded by pharmaceutical companies and supported by such institutions as the American Pain Society (APS) designated pain as "the fifth vital sign" as recently as the 2000s and prescription opioid use peaked in 2010 with 82 prescriptions for every 100 persons. This takes us to present day; with the rise of opioid-related ED visits for nonfatal overdoses as well as actual deaths, the pendulum has swung back in the direction of discouraging opioid use and the establishment of the Prescription Drug Monitoring Program (PDMP).

TRANSCRIPT

Colin: In the last couple years, President Trump has declared the Opioid Crisis a national epidemic and public health emergency, vowing to dedicate $13 billion to new resources for addiction treatment, physician education on appropriate prescribing, and prosecution of drug traffickers. Most recently, the CDC has released an annual surveillance report of drug-related risks and outcomes for 2017, reflecting on the previous year. We'll leave up these statistics as we begin our conversation with our panelists, centered on our role as providers in the midst of the Opioid Crisis. To begin, I think it would be nice to just go down the line and explain your role and experience taking care of patients in the Opioid Crisis.

Dr. Kay: I'm Dr. Abby Kay and from 2005-2015, I was the Medical Director of NARP. When I became the Dean, I switched to being a regular, everyday doctor there and I teach both locally and nationally about how to use medically-assisted treatment options and how to treat addiction in general.

Dr. Worster: Hi, I'm Dr. Brooke Worster and I live in the palliative care world so I sort of straddle this interesting bifurcation of opioids in that we employ them often in end-of-life care. I also live in the world of cancer pain management and, I'm happy to report, cancer survivorship which entails a lot of substance abuse disorders which are often iatrogenically created. I'm a part of the Task Force here and deal with a lot of substance abuse disorders, opioid abuse disorders, but have to maintain some availability because they aren't all bad.

Dr. Nash: I'm Rachel Nash, I live in the resident world and am one of our current chiefs. I became interested in this topic mainly out of frustration, being on Green medicine and being a night Medical Admitting Resident and feeling like I was taking care of the same patients over and over again that struggled with opioid use disorder. As a result of that, I did additional training in addiction medicine in Boston and have been involved in the Task Force ever since, focusing on resident education and increasing the use of the PDMP and familiarity with suboxone on campus here.

Dr. Zavodnick: I'm Jill Zavodnick, I'm one of the hospitalists here which makes me a very frequent inpatient prescriber and occasional short-term outpatient prescriber of opioids. I've seen lots of the medical complications of addiction as well as the medical consequences of our inability to treat pain very well, so that's part of what got me interested in this issue—the consequences of hospitalized addicted patients with withdrawal symptoms that we're not great at managing which makes us not great at managing their other medical problems. My goal is to help inpatient providers figure out what to do with people who are suffering from withdrawal when they are in the hospital partially to facilitate their medical care and then figure out how we can use our inpatient visits as a way to help get people more engaged and linked into recovery.

Ms. Morley: Hi everyone, I'm Meghan Morley, the Lead Patient Navigator at the Center of Excellence for the Department of Psychiatry in the Division of Substance Abuse. I'm a professional counselor and started at NARP as a therapist doing substance abuse counseling there for methadone maintenance patients. The Center of Excellence is a grant that was given to the university from Governor Tom Wolf to help connect people with treatment through warm handoffs, and most of my efforts are focused at Methodist Hospital but also at Main Campus. I also work with offices that prescribe suboxone to help people connect with counseling services, so I'm happy to be here today to talk about our service and how we can provide you with support in connecting your patients with treatment.

Ms. Siddiqi: I'm Kate Siddiqi and I'm an inpatient social worker and have been here for 14 years as of today itself. We have a large number of patients as you've all mentioned who have cycled back through, and it's very frustrating but we've had success from Meghan and the Center of Excellence connecting people to the outside. There are barriers that we're slowly trying to whittle away at, but they are institutional and outside of our system, so it's a group process to work through those together.

Colin: Thank you. What Brianna and I will do is ask a few questions before punting it to the audience to ask some questions too. Our first question is, How has increased awareness of the opioid epidemic changed your practice of prescribing opioids and counseling patients on their appropriate use.

Dr. Nash: In the inpatient world, the pendulum has swung from using opioids to really try other alternatives before going to opioids for pain management. Most providers are more aware of the risks and benefits of using opioids. What's astounding is that the more I read about chronic opioid use, the more confused I've become. I do worry about the limits that are being proposed on the number of morphine equivalents providers can prescribe, leaving a patient population that are like pain refugees in a way. I think we really need to evaluate prescribing patterns of physicians as a whole at our institution, which we're beginning to do, and identify variations in practice habits. This is much like the tenets of quality and safety—where you evaluate your performance, see where your outliers are, and address them. Our Opioid Task Force looked at surgical data, habits of surgeons who were prescribing narcotics after routine procedures such as cholecystectomy. We called patients a few days after discharge and found that 60% of these patients' narcotics were not being used. That's a real area of us to evaluate our prescribing habits, what patients really need, and reduce the number of opioids in the system that may theoretically decrease diversion. That's certainly a way that some patients become addicted. So I would say that the pendulum is swinging and prescribers are aware of risks, but still work needs to be done in evaluating variations in prescribing patterns.

Dr. Worster: Personally, I have changed my prescribing practices significantly; I live in the outpatient world. I probably prescribe opioids nearly every single day. I take care of patients with cancer, I take care of patients who are dying. But I think there's a couple of things that have really meaningfully contributed to the conversation that I'm having a lot more with patients. One of them is the PDMP and I'm so frustrated that Pennsylvania was one of the last adopters of this nationwide—and for a while we couldn't actually query New Jersey or Delaware, so you had a partial picture but not even the whole picture. Finally, that's in place and I think that is something that is just best practice; everyone that we give a medication to, we should be looking. The other thing is that public awareness. I think public understanding of the crisis has people coming into my office saying, "I'm scared of opioids." I just left a patient today who is 70 years old and has metastatic prostate cancer who basically became non-ambulatory because he had such bad bony pain but didn't want to take opioids because he was scared of becoming addicted. So as the pendulum swung so far one way, with pain being the fifth vital sign and us saying "Everyone needs opioids," I also do caution that we can't throw the baby out with the bathwater here. There is some goodness to this, and I think the best change that could be happening out of all of this in terms of prescribing patterns is that it really becomes an informed conversation between the patient and the provider. We have to understand what is driving patients who are either taking the medication or not, how to take it safely, and how to get rid of it if they're not taking it. Eighty percent of the opioids people take are outside of one physician prescribing them, so we're missing the boat in connecting the dots between "What pill am I going to write for you today?" and what happens beyond that setting.

Dr. Nash: I think two things the audience should be aware of is that there is now a Take-Back box in Jefferon's apothecary, open the same hours as that pharmacy, where you can bring back your medications. You can tell your patients that the box is available now. I also just got off the phone with Dr. Jeff Riggio who wanted me to inform you that the PDMP is going to be integrated into Epic very soon. You'll be able to press Care Everywhere and see the PDMP data if you are registered. This is another reason Dr. Zavodnick and I are really pressing house staff to become registered with PDMP because of its value.

Dr. Kay: One comment I want to make—and, yes, there are exceptions, but in general—for every patient that I've admitted to the Methadone Clinic who has said, "I had no addiction until I got the Percocet for this surgery," that hasn't been the case. The problem is, there are things that are addictions that we don't consider addictions; when they were 12 they were smoking a pack a day of cigarettes or using alcohol heavily or using marijuana on a regular basis. We sort of throw those out the window. My feeling is that these are really important things to pick up on and think about, I think the history is the piece we're often missing. I'm not saying that if a patient has that history, it puts them at risk for future addiction. It's not that you wouldn't give them opioids if necessary, but you might have a different conversation with them. The thing that drives me crazy is that I'll come see one of the methadone patients at the hospital and when I look at the H&P, it'll say "One pack a day of cigarettes, three glasses of wine occasionally." By definition, they're on methadone; they have a significant addiction history with opioids and there's nothing documented. I see a great tobacco and alcohol history but that really isn't a surrogate for an addiction history. I think we have to be much more thoughtful about the history.

Dr. Zavodnick: I think Dr. Kay made a really good point about naming the problem, and that's a big change that I've seen since I was a resident here not terribly long ago. I thought that when I was a resident our notes would sometimes inaccurately document the problem, like "IVDA" or IV Drug Abuse which would be listed in the social history but nowhere else. We'd have Night Float getting calls in the middle of the night and who would tell us, "They're always asking for this or that," but no one was actually naming a diagnosis for them. What I'm seeing more and more is that when we're documenting or talking to the patient or talking to the team, "Opioid Use Disorder" or "Opioid Addiction" is actually a part of the problem list and is something we create a plan to address. Our conversations with patients include what we can do about symptom management and what we can expect about pain needs during the admission. What we need to get better as providers in the Opioid Crisis is to start treating opioid use disorder as a diagnosis and as a problem instead of as some background issue that's really only going to be handled by the intern taking pages overnight.

Colin: We've already touched on this a little bit, but what differences have you noticed in patient attitudes towards opioids since the opioid epidemic was declared a national priority?

Dr. Worster: We jokingly say that I'm either begging someone to take a milligram of morphine or I'm begging them to stop taking 7,000 milligrams of morphine. That's certainly an exaggeration, but I think patient attitudes have diverged very broadly because of this crisis. Some of them have this awareness and are scared—and I think we should all have some healthy fear of opioids—but there are other patients who say, "I don't care what you tell me, this is the only thing that works for me and I'm going to take it and be damned if you're going to take it away from me." Patients are nervous about it because it's in the news and everyone's talking about it, and all of a sudden, even the process of getting pain medications is changing. You can't go to the ED and walk away with 30 days of a prescription anymore. I find that it is a more emotionally-charged patient that I see when I'm talking about opioids, one way or the other. It's becoming more of a difficult conversation and I think it's becoming really important that we all participate in with these patients. It should be something that is noted on the problem list and something we talk about with them directly—not as shaming, not something that gets marginalized, but something that is a part of how we best take care of them.

Colin: How does your management differ for patients with acute care needs as compared to patients admitted on chronic opioid therapy?

Dr. Zavodnick: I have a very low threshold for calling the Acute Pain Service. I do remember being taught in medical school about how likely we are to underdose patients with opioid dependence and that's something I worry a lot about with increased awareness; as we swing the pendulum potentially too far in the other direction and find ourselves policing people with chronic pain, deciding whether their pain is legitimate—"Well, let's not given them IV," "Let's make sure that they have an outpatient prescriber so I'm not the one prescribing it." I can see a lot of fear from providers as well. I have a low threshold to ask for help in treating acute on chronic pain because I don't know how well I'm going to be able to treat pain with the medications I have without causing respiratory depression and so I think about ketamine early. These patients need more aggressive treatment, not less.

Dr. Nash: It's almost easier inpatient, because your patient is monitored. You don't want something bad to happen to your patient, but when he or she is on a monitored unit, it's easier to make adjustments to treat acute on

chronic pain. My thinking about some of these patients has changed; I've come to realize that patients on long-acting opioids need that medication almost to feel normal and function as their normal selves.

Dr. Zavodnick: I've also seen the lines between acute and chronic pain blur; when I see a diagnosis of "Acute on Chronic Pain," I'm not sure when we have acute pain and when we have inadequately managed chronic pain. I think it's great that we've become more aware of the risks of narcotics but there are also people who want, expect, and maybe need these medications who aren't able to access them. In the same way I sometimes have difficulty transitioning heroin users to the outpatient world, I sometimes have difficulty transitioning chronic pain patients to the outpatient world because they're started on narcotics for chronic pain in the hospital and I'm not able to find anyone willing to follow them.

Dr. Kay: I just want to make a few quick comments: The first is to remember that the goal for patients on methadone maintenance is to get them on a blocking dose such that if they used any opioids, they would not get high off of them but would still get pain management. They can get opioids, the important thing is to make sure they don't feel as though it is "stirring up" their addiction, to ask the question. The other thing is that when managing patients' acute or chronic pain, I like to think of it as a pie and explain to them, "I can't give you one pie, but I can give you eight different slices of different pies to make up a whole pie." It's not going to be that one medicine takes care of everything, pain management involves a multimodal approach. I also want them on standing NSAIDs because that will greatly reduce their opioid needs.

Dr. Worster: I think that's a great point and emphasizes the need for education about what pain is. The pathophysiology of pain is very different depending on whether you're talking about inflammatory pain or neuropathic pain or visceral pain. I didn't get that education and I think that's crucial. If you're trying to treat neuropathic pain with opioids and the patient's requiring more and more, no kidding—neuropathic pain isn't really responsive to opioids based on the pathophysiology. There's a reason why, with inflammatory pain, you get more bang for your buck using NSAIDs as opposed to opioids.

Dr. Kay: One more take-away is to ask, "What's the patient's goal with the medication?" One of my NARP patients was going for a root canal and I suggested he take 600 milligrams of ibuprofen before the lidocaine wore off. He told me, "I don't mind the pain, I want to not care about the pain." The opioid would have done that while the NSAID would not have had that effect. Sometimes patients take opioids to knock them out, help them sleep. It's always worth asking what the patient's goal is with the medication.

Brianna: Kate and Meghan, would you be willing to talk with us about the community resources available to get our patients plugged in?

Ms. Morley: Sure, I have information up here about our team and we're working to get ourselves listed as an official Consult in Epic. As far as Jefferson goes, we do have two methadone clinics, the Family Center for pregnant and parenting woman as well as NARP for everyone else. My team doesn't just refer to Jefferson resources. When patients are admitted to either Jefferson Main Campus or Methodist, I come in and really lead with motivational interviewing. Something that I have the luxury of is time and I know that not everybody has that. Social work sure doesn't, you don't as providers. I understand that. I can spend 20-30 minutes just having a conversation with patients about their use and life and traumas before I even say the word "treatment," and I think that having the time to build that relationship is really important to getting people to that motivational place where they are open to discussion.

Once patients have decided that they are ready for treatment, we work in tandem with Social Work to refer them to appropriate programs—be it methadone, suboxone, vivitrol (medication-assisted therapies), or even if they want to go into counseling, we can facilitate those warm hand-offs and make sure that there's no gap in care. The day that they're being discharged from the hospital or the following day, they're being admitted to whatever program we have decided to send them to. We can also link them to outpatient providers that aren't in the "clinic world" or the "substance abuse world" as a lot of patients who are professional aren't going to be able to engage in those programs because there are often group or individual therapy sessions that run during the day that a working individual isn't going to be able to attend. We're able to have conversations with people about what their life looks like and what program makes the most sense for them. One of the biggest barriers for us is when a patient doesn't have a urine drug screen (UDS). A patient can't be admitted to any type of medication-assisted program without a urine drug screen that's positive for an opioid. That's something we've been preaching and pushing because the lack of a UDS stops people from being admitted to the program they chose that next day. Basically without telling them to, we know and they know they're going to have to go out and use before being admitted to these programs. There are other barriers to these programs like identification and it's something to keep in mind when prescribing medication-assisted therapies as an inpatient—you need to think about the other documents that are necessary to continue these therapies as an outpatient. These are the sorts of issues that my team deals with and we want to be known! Someone once told me that we're the best-kept secret

and Jefferson and we really don't want to be. We're trying to get our name out there as a resource for you.

Dr. Kay: You make a very good point about there being three types of opioids—natural, semi-synthetic, and synthetic. Each has a different urine drug screen, you have to specifically test for methadone and buprenorphine. If I use heroin today and you just test me for methadone, I'm going to come up negative and vise-versa.

Ms. Siddiqi: To reinforce what Meghan said, we absolutely need the UDS. Without it, I can refer until the cows come home and nothing will happen. The other barrier, as she mentioned, is the lack of ID. Some clinics are becoming more receptive to expired ID or are getting copies from previous treatment centers, but not everywhere. Today I actually called my colleagues at an agency named BHSI which helps the uninsured get insurance and, in the interim, guarantee payment to a clinic so we can get someone directly in from discharge here who is uninsured. They have remained very strict about identification, so if there's no photo ID, our ability to refer to them at the moment is limited. I've had some arguments with physicians who prescribe methadone as an inpatient to keep people in the hospital to receive the rest of their medical care. On the other hand, starting someone that we cannot comfortably get into ongoing care after discharge raises some other ethical issues as well, because no one will prescribe methadone to someone who is out in the community but not connected. Another dilemma that we have as an inpatient related to patients who are on methadone and need IV antibiotics or wound care for an extended period of time. We are kind of up the creek as there are only two facilities in area that accept these patients as inpatients; one is Kensington Hospital, the other is Valley Forge. Kensington is in a position now where they can cherry-pick and only accepts patients on Medicaid-HMO (not state Medicaid). Valley Forge is difficult to get into. If you have a patient on state Medicare, we're kind of screwed also. Medicare seems to have a bizarre notion that older people no longer have substance abuse issues and that's something that really needs to be addressed as a society. It's really criminal, in some respects, that there is no ongoing access for these patients.

Dr. Kay: Even if you're not entirely sure the patient will be followed up as an outpatient, I'd still put someone who addicted to opioids and is agreeable on methadone because if you don't, you run into two problems. First, if someone just had a heart attack, having them in withdrawal is really not safe cardiac-wise, with their pulse racing and blood pressure up. The other issue is that they're at high risk of leaving against medical advice. To get them the proper care and for medical safety, my feeling is you should be putting them on methadone.

QUESTIONS

Dr. Emily Stewart: What's the highest we can safely do that and then discharge them if they don't intend to quit?

Dr. Kay: There is no magic number. When I first started here, I was obsessed with the practice that everyone who was started on methadone in the hospital had to be tapered off before discharge. Since then I've discovered that the taper doesn't really matter and the way that I think about it now reflects something I've picked up from a colleague of mine—which is to say that they were using before they came in, unfortunately as much as I'd like to get everyone into treatment, not everyone is ready and the reality is that some people are going to leave the hospital and use again. Another thing to remember is that often patients' friends will bring them things into the hospital. So there is no magic number, but there are, of course, safety issues with higher and higher doses of methadone. We could have a whole separate Grand Rounds about inpatient management of methadone.

Dr. Zavodnick: This is about to get much, much easier. The treatment subcommittee has been working on a guideline for inpatient management of patients in withdrawal. There are a couple different pathways, including one for patients interested in seeking medication-assistant therapy in the long-term and for whom you'll need to consider outpatient care up front. The Center of Excellence is really great at this, thank you for bringing to the forefront these new resources for our patients and making the bridges to outpatient care stronger and stronger. We've included in the guidelines some tips for the providers overnight, because Psychiatry and Social Work is all well and good in the morning but we want to interns on Night Float to have support in caring for patients' withdrawal symptoms overnight and at least begin to have a conversation with the patient about whether he or she would be open to methadone or suboxone long-term which could then be started as an inpatient. We'll have guidelines about how to start these medications, how to titrate them, when to call Psychiatry. Not every patient who comes in is going to be interested in engaging in treatment and we're still going to have guidelines for robust symptom management with clonidine and Zofran, for example. Just because some patients might not be interested in methadone doesn't mean we don't want to treat their withdrawal. I think we as front-line generalist providers are going to get a little more support in making these decisions for our patients and saying, "Here are the things we offer for withdrawal management, which of these do you want to try?" and "I'm here to partner with you on this inpatient stay and we're going to call the Center for Excellence to figure out an outpatient plan, too." I think guided inpatient management of withdrawal and warm hand-offs to outpatient resources make up the gold standard that we should all be reaching for with our patients.

Dr. Sarah Rosenberg: As a healthcare system, I can't help but feel like we're completely blowing this in a way that's baffling to me. It seems as though politicians and the laypeople are blaming doctors for the Opioid Crisis but do you have any tips on how to repair our therapeutic relationships with patients?

Dr. Worster: What goes hand-in-hand with that are conversations with patients that are like, "I want it"/"No, you can't have it"—this bargaining. I tell people all the time, "I'm fine with you being angry at me. That's okay, I can take that. I need you to hear that all I care about at the end of the day is providing you with care that is safe." Because that's the first thing we all signed up for here, to do no harm. I think with empathy, you can communicate that with a patient. We can say that it's fine for patients to feel angry, sad, or frustrated. We hold those emotions for them. But we need to have realistic one-on-one conversations with patients about safety, I think that's where repairing those therapeutic relationships start. I think most patients will partner with you if you provide a safe, non-judgmental space. I think it's a small minority that will see you as the cause of the problem or stay angry with you because you're not giving them anything at all.

Dr. Rebecca Jaffe: I'd like to commend that approach because I think what I've seen over the last five years is a discomfort about what's happening and an unwillingness to engage in that partnership. You'll see people saying, "Well, I can't prescribe that for you," or "My clinic won't prescribe opioids," and that's very different from a harm-reduction strategy where you might say, "This is the current state of where we are, this is where we plan to go long-term, what are the steps to get there?" Talk about the different things that we can do with patients to improve safety and build partnership.

Dr. Kay: I have a ton of experience with this on the benzo front and have often approached patients with terrible anxiety by saying, "I don't think this plan that we've had is working for your anxiety. The Xanax isn't cutting it, we need to do better. Let's come up with another plan."

Dr. Suchit Bhutani: I know the emergency room (ER) is a place of first-exposure for many patients. There are some centers in New Jersey which have advertised "Opioid-Free ERs," is that something that we've considered or could be changing here?

Dr. Worster: If you look at this on a larger level, the number of total ER opioid prescriptions over the last few years have gone down. Now, it defaults to a 72-hour prescription instead of seven or 10 days. I don't see how you can provide great, individualized care to people by making blanket statements. That's like saying, "Listen, I just don't do antibiotics, so we will never give you antibiotics." We also can't just stop providing good medical care. Our ER providers are very engaged in this problem. If they see my name in the PDMP, they'll give me a call and I'm happy to have that conversation with someone. That's what we really need to do, to increase our communication about this problem.

A Missed Date

Timothy Kuchera, MD

"You're a DOCTOR, NOT a CLERK," bellowed my attending as I blinked with bloodshot, sunken eyes. "So use your BRAIN like a DOCTOR!" It was February of my intern year. At this point, I was exhausted and emotionally drained. I had minimal contact with friends and family and lost all ability to converse with those outside of medicine. My favorite hobbies now included repleting daily potassium and ensuring that my patients had regular bowel movements. Honestly, I got so good by the end of the year that just by walking down the hallway, my patients would experience a rectocolic reflex and a symphony of call bells would fill the air. It was music to my ears. It was during this unique and trying time in my life that I met a patient named Mary.

Mary's admission was abrupt and unexpected. She was 69 years old and had been otherwise healthy until she presented with two weeks of fevers and fatigue. On admission, she was found to be pancytopenic, and a bone marrow biopsy was performed. Shortly thereafter, Mary was diagnosed with Hemophagocytic Lymphohistiocytosis, also known as HLH, in addition to a very rare T-cell lymphoma. HLH is an aggressive and life-threatening syndrome of excessive immune activation. A diagnosis with HLH can drastically cut life expectancy. Mary's dual diagnoses of HLH with T-cell Lymphoma reduced her life expectancy to one to two months. Despite the overwhelming odds, like any family struck with this sudden news, Mary and her family were hopeful that prompt treatment would alter the course of her illness and reach a cure.

In spite of her grave prognosis, I was struck by the life and energy that Mary exuded. Even at the age of 69 with multiple organ failure, she would greet me every morning with an energetic, "GOOD MORNING, BABY!" She constantly joked with the nurses, residents and attending physicians. She was a favorite patient among staff. Everyone was pulling for her. One morning out of the blue, Mary asked me where I was taking her on our first date. Completely caught off guard I sputtered, "Well, where do you want to go?" "I don't know!" She shot back, "But if it ain't somewhere nice, you and me are through!" When my attending heard about this, she stated that Mary had the worst case of steroid-induced psychosis she had ever seen...

It seemed Mary's spirit could not be extinguished. Diagnosed with HLH? Bring it on. Lymphoma? Whatever. GI bleed? Flirt with the GI fellow. One morning, a rapid response was called for syncope. By the time I arrived, she recovered and was cracking jokes with the residents and nursing staff. In even the most desperate of times, she maintained her enthusiasm and lightheartedness.

Unfortunately, this story ends the way you probably expected. One morning, Mary was transferred to the ICU for emergent dialysis. From there on, her clinical course took a precipitous turn. The HLH, lymphoma, GI bleed, UTI, pneumonia, liver failure, and kidney failure compounded, and Mary and her family decided that they had enough. For four weeks, Mary was poked, prodded, biopsied, imaged, dialyzed, and filled with cytotoxic chemicals. A mutual decision was made to pursue comfort measures and have Mary spend her final days in the company of her family. Coincidentally, this decision came on the final day of my oncology rotation. I had not seen Mary since her transfer to the ICU and when I stepped into her room I barely recognized her. The previously raucous, animated, jubilant Mary now lay cachectic and motionless in her hospital bed. I stumbled over my words as I filled the silence with superficial conversation. I began to experience overwhelming feelings of loss and despair as I realized our time was short. I missed the energetic person I had come to know and care for one month prior. If I could just see her laugh, I thought, maybe everything would be okay. I asked, "Mary, where are we going on our date?" What I hoped for was a quip. What I hoped was for Mary to spring back to life. Instead, I got something much different. She slowly shifted her gaze to mine, pointed at the sky and whispered, "In Heaven." I attempted to collect myself and managed to choke out, "Well you better pick somewhere good!" "Don't worry," she said. "I'll have plenty of time."

Despite our efforts, Mary passed away on April 9th, 2017. I am grateful for Mary. Her love and passion for life were infectious and I am very fortunate to not only have met her but to care for her as her doctor. Caring for Mary was a privilege and truthfully reminded me of my humanity. Doctors and nurses have all experienced that medicine can be a draining and potentially jading profession. My hope is that my colleagues have the opportunity to experience rejuvenating and heartwarming people in their practice like Mary; both in the patients they treat and the people they work with.