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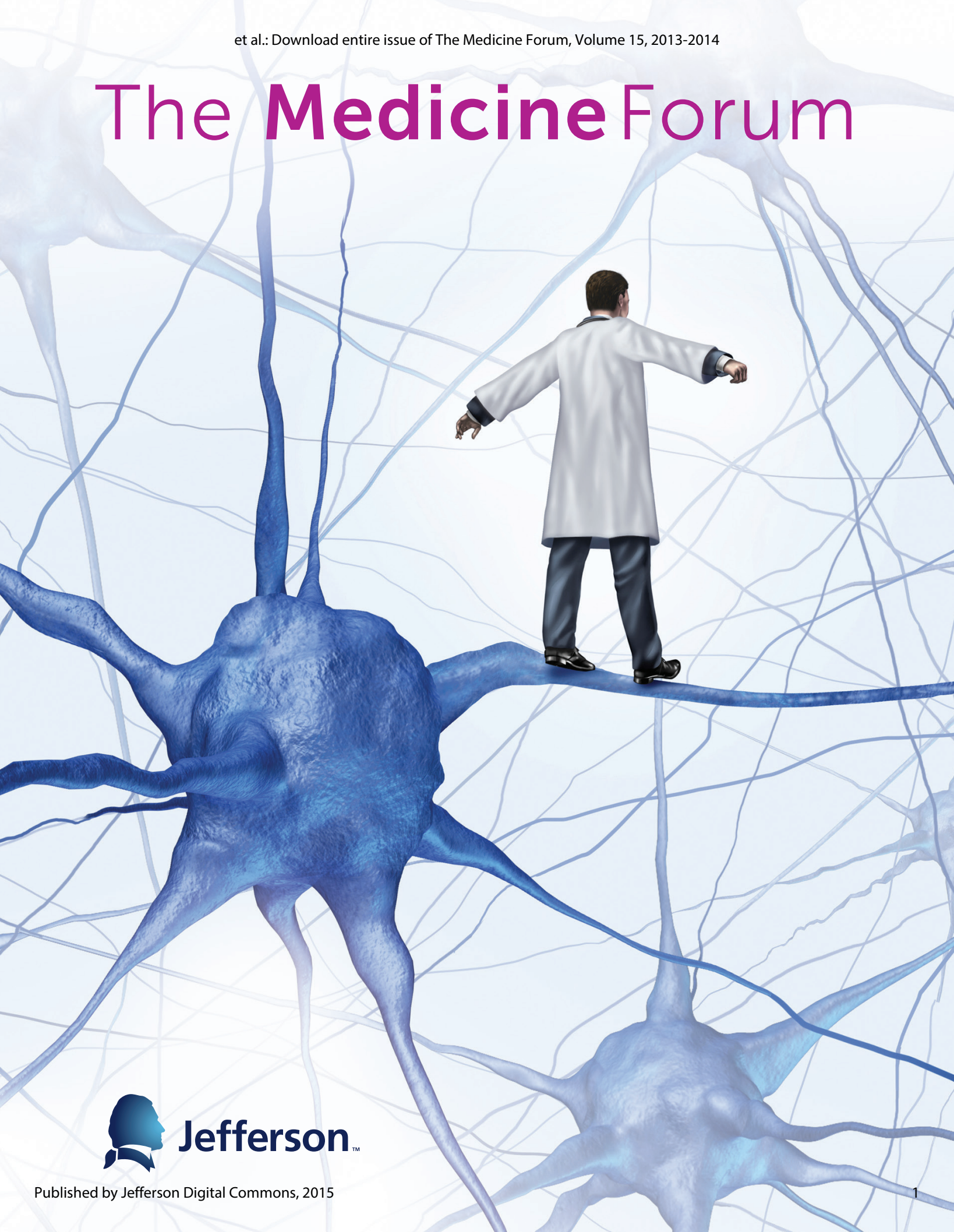

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FROM THE DESK OF THE RESIDENCY PROGRAM DIRECTOR

Welcome to the Forum!

We have experienced another wonderful year in the Jefferson Internal Medicine Residency Program! Our program continues to attract the best and brightest medical students who over three years become outstanding clinicians, accomplished researchers and compassionate physicians. Residency training is increasingly complex, with competing demands compressing their work into fewer hours. I am consistently impressed with the camaraderie among our housestaff—they not only take care of patients, but they take care of each other. It is something that sets our program apart from others and is something of which I am incredibly proud.

Like every year, this year has come with changes. Besides being one of the worst winters on record in Philadelphia and having a hospital that was often bursting at the seams with patients, the Next Accreditation System from the ACGME was implemented. This has shifted the way residency programs are accredited and prompted us to overhaul our evaluation system for residents. Our patient safety and quality improvement curriculum began this year with great success and the housestaff have embraced it. We have already seen results from improvement cycles and engagement into systems changes resulting in delivery of better care to our patients. Our residents know this hospital inside and out and are in a great position to be the leaders we need in quality improvement and patient safety at Jefferson.

Our residents have put together yet another outstanding journal showcasing their academic interests and humanistic talents. I hope you will enjoy reading it!

Gretchen Diemer, MD, FACP
Assistant Professor of Medicine
Program Director

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FROM THE EDITORS

We are proud to publish the 15th issue of The Medicine Forum. Since its inception, this journal has provided a medium for medical students and housestaff to share their scholarly pursuits and clinical experiences with the Jefferson community. It has served as a platform both for those pursuing careers in academic medicine as well as those wishing to share their personal experiences with a larger audience. This year we are introducing a new section called Clinical Images which will showcase interesting physical exam findings and radiographic images accompanied by brief patient vignettes. We have been fortunate to have received numerous fascinating case reports, review articles, and clinical images, as well as one narrative essay for this year's edition. Additionally, we are very proud to present original photography, artwork, and illustrations by Internal Medicine housestaff throughout this edition. We appreciate the efforts of all those involved in the publication of The Medicine Forum, particularly those individuals who have donated funds to allow for this journal's publication, the editorial staff, Jefferson Creative Services, and the Internal Medicine Department.

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Sustained Achromobacter Xylosoxidans Bacteremia in a Patient with Adenocarcinoma of the Colon

Matt Enriquez, MS IV, Andi Favini MS IV, Kevin Curl, MD

INTRODUCTION

Achromobacter xylosoxidans is a rare cause of bacteremia; however patients with underlying illness, especially malignancies, are at increased risk of infection. Antibiotic therapy against this pathogen can be difficult owing to its inherent resistance to multiple common antibiotics.

CASE PRESENTATION

A 69-year-old male with adenocarcinoma of the colon status post right hemicolectomy and chemotherapy presented with fever and fatigue 10 days following endoscopic retrograde cholangio-pancreatography (ERCP) with biliary stent placement for new liver metastases. The patient had undergone partial hemicolectomy and had completed 12 cycles of adjuvant FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin) at the time of initial diagnosis. Two years following the completion of chemotherapy, the patient was found to have obstructive jaundice and new liver metastases on CT scan. He underwent an ERCP procedure with biliary stenting for palliation and was discharged home.

Ten days following the procedure, the patient presented with complaints of fever to 102◦F and fatigue. Vital signs revealed a fever of 101.3◦F but were otherwise unremarkable. Physical examination revealed improvement of his jaundice, normal cardiopulmonary examination, and right upper quadrant tenderness. Despite four days of vancomycin and piperacillin-tazobactam, the patient continued to be febrile to 102.5◦F.

DIFFERENTIAL DIAGNOSIS

The medical team remained concerned about infectious etiologies, including cholangitis, bacteremia, and endocarditis. Non-infectious causes of his fever were

Table 1. Antibiotic sensitivities (represented as percent susceptible) of Achromobacter xylosoxidans in several case reports and the current patient's susceptibilities.

Antibiotic	Turel O, et al. (34 isolates)	Glupczynski Y, et al. (37 isolates)	Current Patient
Antibiotic			
Trimethoprim-Sulfamethoxazole	100	67	Unknown
Meropenem	100	100	Susceptible
Piperacillin-Tazobactam	91	91	Resistant
Ciprofloxacin	82	0	Susceptible
Ceftazidime	82	81	Resistant
Cefepime	15	0	Unknown
Gentamicin	0	0	Intermediate

*Turel O, et al. isolates were from a neonatal intensive care unit in Turkey, while Glupczynski, et al. isolates were from a single hospital in Belgium.

also considered, such as post-ERCP pancreatitis, deep venous thrombosis, and malignancy-related fever.

OUTCOME AND FOLLOW-UP

Routine laboratory studies were unremarkable, including serum amylase and lipase. Right upper quadrant ultrasound and CT scan of the abdomen and pelvis did not show any visible infectious source. Transthoracic echocardiogram was not consistent with endocarditis. Lower extremity Dopplers were negative, and while upper extremity Dopplers revealed no deep venous thrombosis, they did show a right cephalic vein clot. Blood cultures drawn on admission were found to be positive for gram-negative bacilli on hospital day three. Subsequent blood cultures drawn after the initiation of broad-spectrum antibiotics were also positive for gram-negative bacilli. Prior to speciation, the Infectious Disease team recommended discontinuing vancomycin and switching the piperacillin-tazobactam to meropenem. On hospital day number seven, the patient became afebrile and blood culture speciation revealed *Achromobacter xylosoxidans* with sensitivities listed in Table 1. Blood cultures drawn after the adjustment of antibiotic therapy to meropenem remained negative. It was believed that the patient had a transient bacteremia of *Achromobacter xylosoxidans* related to the ERCP that had seeded his cephalic vein thrombus, leading to persistent bacteremia. Based on culture sensitivities, the patient's antibiotics were changed to oral ciprofloxacin to complete a four week course of antibiotics. He was also started on prophylactic enoxaparin for his cephalic vein thrombus and was discharged home.

DISCUSSION

Bacteremia due to *A. xylosoxidans* remains rare, yet patients with underlying illness, particularly malignancies, are at increased risk of infection. Other predisposing conditions include cardiovascular disease, renal failure, and immune suppression.[1] Though *A. xylosoxidans* is not a typical component of endogenous human flora, it is known to inhabit aqueous environments with common sources including contaminated water and IV fluids, intravenous catheters, humidification fluids, and instrumentation utilized during surgical interventions.[1]

Common symptoms of *A. xylosoxidans* bacteremia include fever, fatigue, and persistence of symptoms despite broad-spectrum antibiotic therapy. A unique symptom to this presentation was right upper quadrant abdominal pain consistent with a gastrointestinal source of infection secondary to the patient's prior ERCP. Aside from gastrointestinal infections, other common sources of infection include catheter-associated infections and pneumonia.[1]

As *A. xylosoxidans* bacteremia is often associated with specific predisposing conditions and sources of infection, early identification of risk factors for infection remains a crucial component of diagnosis. Initial diagnostic tests to determine if the bacteremia is due to *A. xylosoxidans* include repeating blood cultures which may demonstrate sustained gram-negative rod bacteremia. Another useful part of the diagnostic work-up includes identifying the original source of the patient's bacteremia in addition to ongoing site of infection. In this case, ultrasound served to localize a right cephalic vein clot as the probable ongoing site of infection; this clot had likely been seeded by a gastrointestinal source around the time of the ERCP procedure.

Choosing antibiotic therapy to treat *A. xylosoxidans* bacteremia proves challenging because of its inherent resistance to multiple antibiotics in addition to its ability to harbor and horizontally transfer resistance genes (Table 1). A proposed transfer mechanism for *A. xylosoxidans* has been shown to potentially involve integrons, R plasmids, and insertion sequences.[2-4]

A. xylosoxidans remains an important emerging cause of nosocomial and community-acquired infections because of its resistance to multiple antibiotics. Although individual patterns vary, most strains of A. xylosoxidans are resistant to aminoglycosides and quinolones.[2] The majority of isolates have demonstrated susceptibility to tazobactam, imipenem and meropenem, but as demonstrated in Table 1, this patient harbored a strain that was also resistant to piperacillin-tazobactam. Aggressive measures to sterilize hospital solutions and equipment, as well as to enforce policies to prevent antibiotic misuse, should be employed to prevent future cases of *Achromobacter xylosoxidans* bacteremia and to quell the propagation of drug resistance in this pathogen.

KEY POINTS

This case serves as a reminder to consider A. xylosoxidans when treating patients with underlying illnesses, particularly malignancies, who have persistent gram-negative bacteremia despite therapy with common broad-spectrum antibiotics.

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"En Route to Whistler Along the Sea to Sky Highway, British Colombia"
photograph by Andrew Zabolotsky, MD

An Uncommon Presentation of Amyloidosis

Brandon Kujawski, MS III, Drew Johnson, MS III, Kushan Radadia, MS IV, Eric Feduska, MD, Robert Ford, MD, Guldeep Uppal, MD, Mariam Kabir, MD,PhD, John Stewart, MD

INTRODUCTION

AL amyloidosis is a rare disease, with only 1200-3200 new cases in the US per year.[1] Two-thirds of patients are male; presentation typically occurs after age fifty.[1,2,3] Amyloid can involve the kidneys (74%), heart (60-90%), liver (27%), peripheral nervous system (22%), and carpal tunnel (20%).[3] We describe an atypical presentation of AL amyloidosis and highlight the importance of recognizing this disease in patients with systemic signs.

CASE PRESENTATION

A 60 year old Caucasian male was transferred from an outside hospital with four months of progressive lower extremity burning pain and weakness, unintentional 34-pound weight loss, fatigue, subjective fevers, night sweats and intermittent blood in his stool. Review of systems was otherwise negative. Medical, surgical, and family history were unremarkable; he took no medications. Social history was notable for heavy alcohol use until four months prior to admission.

At the outside hospital, the patient had undergone a thorough workup for his GI bleeding, which included an MRI of his abdomen, esophagogastroduodenoscopy, and colonoscopy. Hepatomegaly was noted on the abdominal MRI, and several internal hemorrhoids were seen on the colonoscopy.

Vital signs were within normal limits. Physical exam was notable for cachexia, hepatomegaly, and 3-out-of-5 strength in the upper and lower extremities. The remainder of the exam was normal.

Laboratory evaluation showed a hemoglobin of 8.0 g/dL (normal range = 14-17 g/dL) with a normal mean corpuscular volume, ferritin of 997 ng/mL (normal range = 50-150 ng/mL), iron of 29 mcg/dL (normal range = 55-160 mcg/dL), and total iron binding capacity of 176 mcg/dL (normal range = 250-400 mcg/dL),

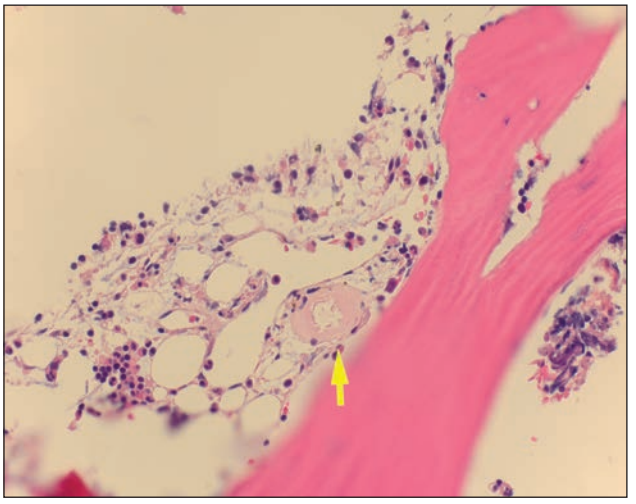

Figure 1. Bone marrow biopsy showing a vessel with deposition of pink amorphous material in the wall (Hematoxoylin & Eosin, original magnification 400X). There was no evidence of a neurogenic process or malignancy.

indicating anemia of chronic disease. White blood cell count was 9.0 x10^9/L (normal range = 4-11 x10^9/L) with a normal differential. Platelet count was 1167 x10^9/L (normal range = 140-400 x10^9/L). Blood smear showed Howell-Jolly bodies and thrombocytosis with reactive platelets. His electrolytes and creatinine clearance were normal. Prothrombin time (PT) was elevated at 36.9 sec (normal range = 9.4-12.4 sec), and this did not correct with Vitamin K (oral or subcutaneous). His partial thromboplastin time (PTT) was high at 51 sec (normal range = 28-38 sec). Both PT and PTT corrected with mixing studies indicating a factor deficiency.

Hepatic panel revealed an alkaline phosphatase of 563 IU/L (normal range = 25-150 IU/L). He was negative for HIV, Hepatitis B and C, and syphilis. Serum protein electrophoresis (SPEP) showed hypogammaglobulinemia with an abundance of lambda light chains; urine protein electrophoresis (UPEP) showed a free lambda level of 12.26 mg/dL (normal range = 0.02-0.67 mg/

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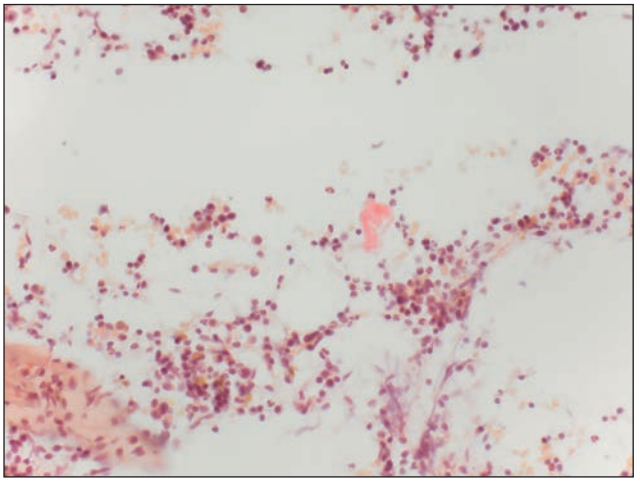
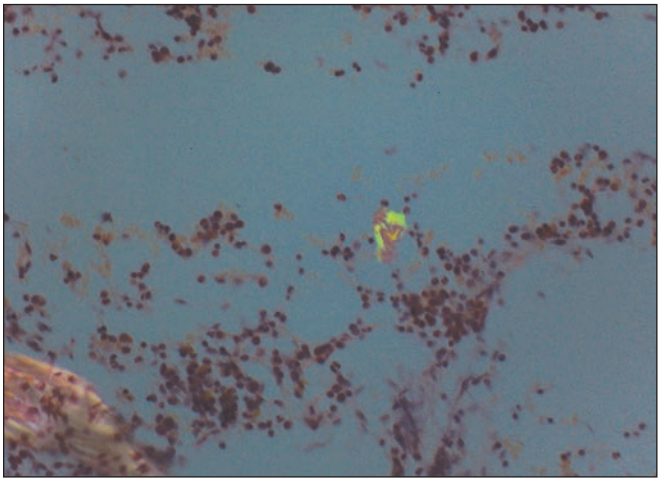

Figure 2 & 3. Bone marrow biopsy showing Congo Red staining (Figure 2) and apple green birefringence in the vessel wall under polarized light (Figure 3) (Congo Red stain, original magnification 200X).

dL) indicating a likely plasma cell dyscrasia with lambda overproduction. Pro-B-type natriuretic peptide (pro-BNP) was 3936 pg/mL (normal range = <100 pg/mL).

CT scans of the thorax, abdomen, and pelvis were unremarkable except for an enlarged liver. His bone scan and skeletal survey were negative for lytic lesions. Electrocardiogram showed normal sinus rhythm with intraventricular conduction delay, first-degree AV block, and low voltage throughout. A trans-thoracic echocardiogram showed an ejection fraction of 60% with impaired relaxation of the left ventricle. There was no speckled pattern in the myocytes and no restrictive cardiomyopathy.

DIFFERENTIAL DIAGNOSIS

Our differential diagnosis included myelofibrosis, essential thrombocytosis, and reactive thrombocytosis from a systemic disease such as inflammatory bowel disease or amyloidosis. Although multiple myeloma was also a concern, the absence of lytic lesions, hypercalcemia and renal failure essentially ruled it out.[4,5] Given the patient's presentation and laboratory abnormalities, Hematology was consulted.

The patient was negative for the JAK2V617F mutation, making myelofibrosis or essential thrombocytosis unlikely.[6] Given the presence of a monoclonal protein on SPEP and UPEP, factor X deficiency (5%), and the presence of immunoglobulin light chains in the serum and urine, a systemic fibril deposition disease such as amyloidosis was most likely. Bone marrow biopsy was performed, which showed an infiltrate of monoclonal lambda positive plasma cells (5%) on immunohistochemical staining, with deposition of amyloid fibers in blood vessels (Figure 1). Congo red stain showed apple-green birefringence under polarized light (Figures 2-3). This led to the diagnosis of light chain amyloidosis.

OUTCOME AND FOLLOW-UP

The patient was discharged to a subacute rehabilitation facility with plan to follow-up with a hematologist/oncologist within one week of discharge. No treatment plans were made during his hospital stay due to his level of deconditioning. Since his gastrointestinal bleeding was minimal, intermittent, and he never required blood transfusion, his factor deficiency did not require correction.

DISCUSSION

Amyloidosis is caused by the abnormal deposition of amyloid protein in a single or multiple organs. Sixty different types of amyloid protein have been identified so far, and thirty-six have been connected with deposition disease.[7,8] For example, AA amyloidosis is caused by the deposition of an acute phase reactant protein in various organs. This acute phase reactant is usually generated in the setting of inflammatory disease (inflammatory bowel disease, rheumatoid arthritis, etc) or chronic infection (tuberculosis, chronic osteomyelitis, etc).[9] AL

amyloidosis, on the other hand, is due to deposition of protein derived from immunoglobulin light chain fragments. It is a plasma cell dyscrasia that can occur alone or with multiple myeloma, Waldenstrom's macroglobulinemia, or non-Hodgkin's lymphoma.[2]

The diagnostic criteria for AL amyloidosis include the presence of an amyloid-related systemic syndrome, positive amyloid staining by Congo red in any tissue, evidence that the amyloid is light-chain related, and evidence of a monoclonal plasma cell proliferative disorder.[2] Although the most definitive proof of light chain amyloid is by mass spectrometry of a biopsy sample, immunohistochemical staining of the sample can also be used for diagnosis.[10] Our patient met all of the above criteria, as follows. He had evidence of liver involvement, cardiac involvement (low voltages, first degree AV block), and likely peripheral neuropathy. There was evidence of amyloid by Congo red staining. Immunohistochemical staining of his bone marrow showed plasma cells with lambda light chain predominance. In addition, he had excessive lambda light chains in his serum and urine, indicating monoclonal plasma cell proliferation. We did not send a sample for mass spectrometry.

AL amyloidosis with liver involvement has several interesting features. A review of patients with AL amyloidosis analyzed a total of 98 patients with hepatic involvement.[11] Among these, 71% had weight loss and hepatomegaly; our patient had both of these. Laboratory studies showed alkaline phosphatase elevations in 86% of patients; AST/ALT were only elevated in 37% of patients. Our patient only had an alkaline phosphatase elevation. Amyloidosis also led to functional hyposplenism with reactive thrombocytosis in ~28% of patients. A classic hematologic finding in these patients on peripheral blood smear was the presence of Howell-Jolly bodies, as were seen on our patient's blood smear.

A unique finding in our patient was the prolonged PT with associated gastrointestinal bleeding, which was found to be secondary to factor X deficiency. A study looking at acquired factor X deficiency in patients with AL amyloidosis, found that 32/368 (8.7%) had factor X deficiencies.[12] Another study of 337 patients done by Mumford et al[10] found that 172/337 had prolonged PT, PTT, or thrombin time. Cutaneous bleeding occurred in 60/337 (18%), and gastrointestinal bleeding occurred in 16/337 (5%).[10]

Treatment choices for AL amyloidosis include melphalan or cyclophosphamide in conjunction with dexamethasone.[13] Stem cell transplant (SCT) is offered to patients who fit the criteria, which include age <70, troponin <0.06, pro-BNP <5000, creatinine clearance >30, NYHA Class I or II heart failure, no more than two organs involved, no large pleural effusion, and no hypoxia.[13]

The prognosis of patients with AL amyloidosis is poor. Without treatment, the median survival is 13 months.[13,14] An Italian study of 705 AL amyloidosis patients who underwent treatment showed a median survival of 46 months. A UK study of 600 patients with treatment showed a median survival of 2-3 years.[15,16]

KEY POINTS

We present a patient with amyloid deposition disease, discuss criteria for the diagnosis of AL amyloidosis, and demonstrate how our patient met these criteria. In addition, we point out that although AL amyloidosis most commonly involves the kidney and the heart, there is a less common pattern that affects the liver and causes hepatomegaly, coagulopathy and bleeding. It is important to recognize this pattern and provide timely treatment. In addition, we stress that although there are treatment options available for AL amyloidosis, the prognosis, even with treatment, is poor.

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"T-Rex in the City of Brotherly Love"
photograph by Andrew Zabolotsky, MD

A Case of Bilhemia: A Rare Complication of Transjugular Intraheptic Portosytemic Shunt

Michael Zhang, MS III, Michael A. Valentino, MD, PhD

INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is a common procedure used to alleviate the secondary effects of portal hypertension including uncontrolled variceal bleeding, refractory ascites, and hepatic pleural effusion (hydrothorax). There are several well-known complications of TIPS, including portosystemic encephalopathy, hemolytic anemia, hepatic ischemia, and stent thrombosis.[1] In this case report we present a rare but serious complication of TIPS – bilhemia - in which bile escapes into the bloodstream through a fistula between the biliary tree and the hepatic venous system.

CASE PRESENTATION

A 56 year-old female with cirrhosis due to chronic hepatitis C presented to the hospital for a scheduled esophagogastroduodenoscopy (EGD) for evaluation and banding of esophageal varices. During the procedure, a large varix ruptured, requiring the patient to undergo an emergent TIPS procedure to control the hemorrhage.

A TIPS was attempted using a 10mm x 10mm Viatorr covered stent. In the operative report, the interventional radiologist noted that multiple unsuccessful attempts were made accessing the right portal vein, requiring repeated repositioning of the cannula. Ultimately, a successful bridge was created between the right hepatic vein and central portal vein, which reduced the portosystemic gradient from 14 mmHg to 3 mmHg. The patient was stabilized hemodynamically with a transfusion of seven units of packed red blood cells and was admitted to the medical intensive care unit (MICU).

Three days following the procedure the patient became jaundiced. Her laboratory profile at that time showed that her total and direct bilirubin levels had increased almost 10-fold, while her transaminases and INR remained stable (Table 1). An abdominal ultrasound was performed to evaluate the stent, which was found to be patent. There was also no evidence of biliary obstruction/dilatation on ultrasound. Over the course of her hospital stay, the patient's bilirubin continued to rise (Figure 1) while her alkaline phosphatase, transaminases, and INR remained stable (Figures 2-3). The continual rise in bilirubin prompted an abdominal CT, which showed a patent TIPS and no evidence of hepatic ischemia or biliary duct dilatation.

DIFFERENTIAL DIAGNOSIS

Elevated direct bilirubin levels are typically a sign of hepatocellular or biliary injury/obstruction. After undergoing TIPS placement, the shunting of blood from the portal vein to the systemic circulation can occasionally lead to hepatic ischemia.[1] Clinically, this

Table 1. Liver function tests pre-TIPS and three days post-TIPS.

Antibiotic	Pre-TIPS (normal range)	3 Days Post-TIPS
Total bilirubin (mg/dL)	1.4 (0.1-0.9)	12.2
Direct bilirubin (mg/dL)	0.6 (0.0-0.3)	9.1
Alkaline phosphatase (U/L)	58 (25-120)	90
AST (U/L)	144 (7-42)	139
ALT (U/L)	37 (1-45)	57
INR	1.66 (0.79-1.21)	1.15

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presents as worsening right upper quadrant abdominal pain, hepatic encephalopathy, elevated aspartate transaminase (AST) and alanine transaminase (ALT) levels as well as an elevated serum bilirubin.[1-2] However, the patient had an isolated hyperbilirubinemia, without transaminase elevation or worsening synthetic liver function. In addition, she had no abdominal pain and demonstrated no signs of encephalopathy. Therefore it was determined that hepatic ischemia was an unlikely diagnosis. To that same effect, worsening cirrhosis was equally unlikely as the patient demonstrated neither deterioration in her synthetic liver function nor any clinical signs of decompensated cirrhosis such as ascites or encephalopathy. Moreover, worsening cirrhosis post-TIPS is typically associated with TIPS thrombosis or stenosis, and both the ultrasound and CT scan showed a patent TIPS.[3]

Biliary tree stricture or blockage is another condition that can lead to hyperbilirubinemia. Again, we considered this unlikely due to the patient's isolated hyperbilirubinemia, normal alkaline phosphatase level, as well as a lack of bile duct dilatation on ultrasound and CT scan.

Bilhemia is a rare condition which presents with sudden jaundice and a rapid elevation in direct bilirubin without evidence of hepatocellular injury or biliary obstruction.[3] It was determined that this was the likely diagnosis given the patient's rapidly rising bilirubin levels in the setting of otherwise unchanged liver function tests and no evidence of obstruction on imaging. Furthermore, the biliary-venous fistula could be explained by the difficulty encountered in cannulating the portal vein during the TIPS procedure.

OUTCOME AND FOLLOW-UP

Fifteen days after the TIPS procedure, an ERCP was performed to evaluate for evidence of a biliary-venous fistula. The cholangiogram did not show evidence of a fistula or bile duct dilatation. However, a common bile duct stent was placed and sphincterotomy was performed in an attempt to lower the biliary pressure in order to reduce the flow of bile through a potentially unseen fistula. Despite this procedure, the patient's bilirubin continued to rise, and a venogram was performed to visualize and occlude the biliary-venous fistula. The venogram was also unremarkable, and it was determined that the only

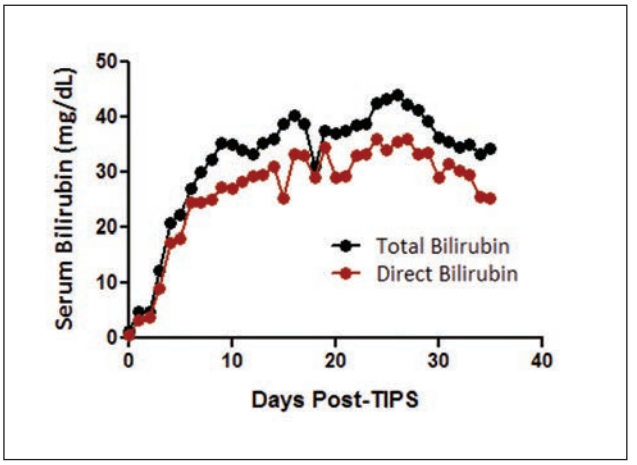

Figure 1. Total and direct serum bilirubin levels post-TIPS

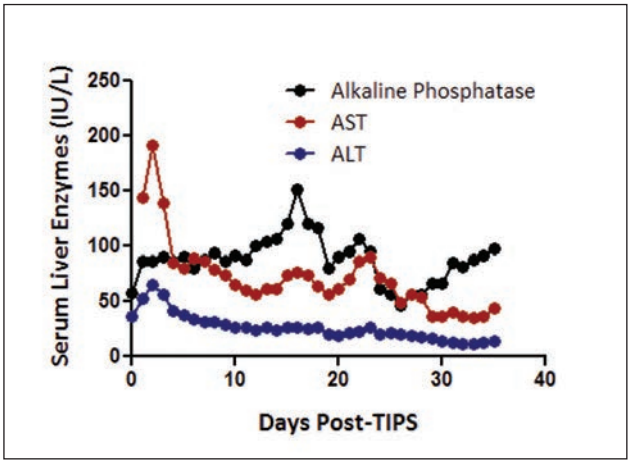

Figure 2: Serum alkaline phosphatase and hepatic transaminases post-TIPS

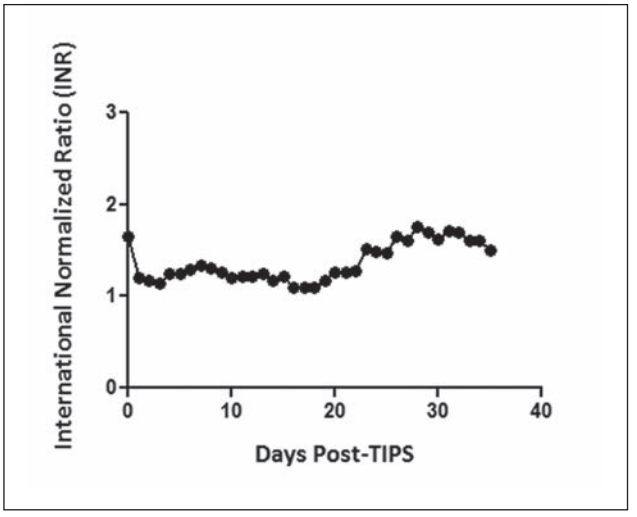

Figure 3: INR post-TIPS

viable way to reverse the bilhemia was through liver transplantation.

During her hospital course, the patient developed a resistant Klebsiella bacteremia. Even with appropriate treatment, she remained persistently bacteremic, likely due to seeding of her TIPS. She developed sepsis complicated by renal failure and was transferred back to the MICU. Unfortunately, the patient's infection precluded her from undergoing liver transplantation and, after multiple discussions with the patient and her family, she was ultimately discharged home with hospice care.

DISCUSSION

Bilhemia is a condition characterized by a rapid rise in total and direct serum bilirubin without other signs of hepatic dysfunction or biliary obstruction.[4] It is typically a consequence of hepatic trauma, though it has been known to occur as a complication of TIPS procedures.[5] The pathophysiology relates to a pressure gradient between the common bile duct (mean pressure = 12-14 mmHg) and the hepatic vein (mean pressure = 7 mmHg) which results in the direct flow of bile into the hepatic vein.[4, 6] This is in contrast to a fistulous communication between the higher pressure portal venous system and the biliary tree which typically results in hemobilia (flow of blood into the biliary system).

One consequence of bilhemia is fat embolism from the passage of large amounts of undissolved bile into the systemic circulation.[6-7] Bacteremia is another consequence and is thought to be caused by the bilious contamination of the systemic circulation with enteric flora.[8-10]

Treatments for bilhemia aim to decompress the biliary system, commonly with biliary stenting and sphincterotomy.[6-8] Other case studies have shown that percutaneous biliary drainage, endoscopic nasobiliary drainage, and venous balloon occlusion are also viable options with liver transplantation being the only definitive treatment for bilhemia.[4-5,7-8] In the absence of treatment, spontaneous closure of the biliary-venous fistula within three weeks has been observed.[7]

The patient's sudden jaundice and rapid rise in bilirubin three days after TIPS matches the clinical presentation of other cases reports of TIPS-induced bilhemia. In this case, biliary stenting and sphincterotomy was unsuccessful in managing the condition. Liver transplantation was determined to be the only option for treatment; however the patient's persistent bacteremia eliminated the possibility of transplant.

KEY POINTS

Bilhemia is a rare complication of TIPS which should be suspected in post-TIPS patients with a rapid rise in serum bilirubin without other signs of hepatic dysfunction. The formation of a biliary-venous fistula can lead to thrombo-embolism and bacteremia. Decompression of the biliary tree should be attempted, and liver transplantation should be prioritized as this condition is fatal in ~50% of cases.[6]

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Congenital Absence of the Pericardium

Lillian C. Man, MD, Jaehee Kim MD, Rakesh Gupta, MD

INTRODUCTION

Congenital absence of the pericardium (CAP) is an uncommon finding previously recognized only post-mortem or during surgery. However, its incidence has been on the rise with the use of multiple contemporary imaging techniques. CAP can present with paroxysmal, left-sided chest pain and should be considered in the differential diagnosis of atypical causes of chest pain. We present the case of a 50-year-old male who presented with chest pressure, symptoms of heart failure, and was found to be in atrial fibrillation in whom partial absence of the left pericardium was diagnosed.

CASE PRESENTATION

A 50 year-old African-American male presented to the Emergency Department with a chief complaint of shortness of breath (SOB) and worsening dyspnea on exertion for one week. He described worsening SOB when lying on his left side, as well as palpitations, orthopnea, and non-radiating, left-sided chest pressure. On physical exam, the patient was tachycardic with an irregularly irregular heart rate, crackles in the lower lobes, trace bilateral lower extremity edema, and a non-palpable apical impulse. Laboratory studies were significant for a pro-B-type natriuretic peptide (pro-BNP) level of 2830 pg/mL (normal range = <100 pg/mL) and negative troponins. Electrocardiogram (ECG) showed a ventricular rate of 146 beats per minute, irregularly irregular rhythm, right axis deviation, and poor R-wave progression. Chest x-ray (CXR) (Figure 1) revealed cardiomegaly and a diminished right heart border. Subsequent echocardiogram showed severe mitral regurgitation and moderate tricuspid regurgitation. Of note, it also showed the heart shifted posteriorly in the apical window, suspicious for congenital absence of pericardium. CT scan confirmed the diagnosis of partial absence of the left pericardium.

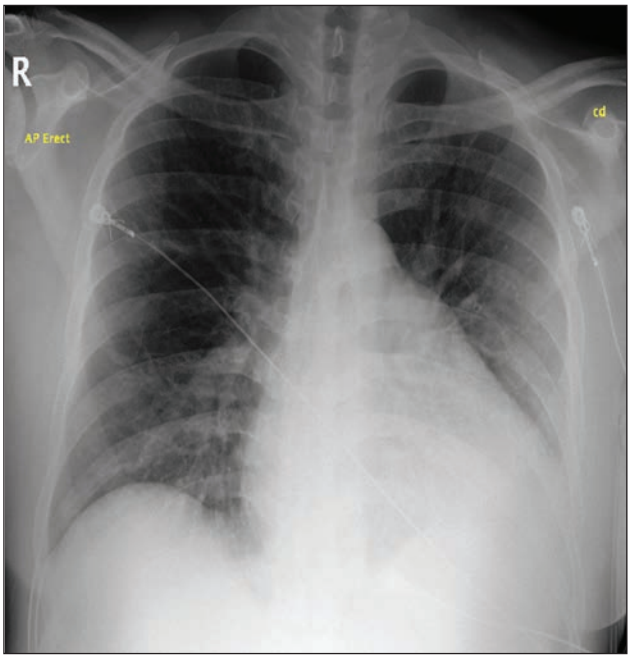

Figure 1: Admission chest X-ray

DISCUSSION

Congenital absence of the pericardium is a rare entity formerly recognized only at autopsy or during surgery[1], with about 400 reported cases in the literature. Up to 70-80% of pericardial defects involve the left side and are due to premature atrophy of the left common cardinal vein during embryologic development.[2] About one-third of all cases of CAP are described in association with other cardiac defects, such as patent ductus arteriosus, mitral stenosis, and tetralogy of Fallot.[3,4]

The clinical presentation of symptomatic patients tends to be non-specific. Patients with partial CAP may have dyspnea and trepopnea, or the presence of dyspnea when the lying on one side, which our patient had.[4] A number of case reports also described patients who presented with left-sided chest pain of varying quality,

such as stabbing, throbbing, postural, or exertional.[3,5] In other case reports, patients have reported the sensation of a "shifting heart". Since the pericardium provides structural support for the heart, its complete or partial absence allows the cardiac apex to move posteriorly or laterally, leading to a significantly displaced or non-palpable apical impulse,[3,4,6] which our patient had. Interestingly, patients with complete absence of the pericardium tend to be asymptomatic.

ECG findings may show right-axis deviation, right bundle branch block, and poor R-wave progression.[2] These findings are related to the posterior displacement of the left ventricle, allowing the right heart to become more prominent anteriorly. CXR can show levoposition in which the heart is shifted laterally and into the left chest, leading to an absent right heart border. The left cardiac border may be straightened and elongated, known as the "Snoopy sign." Echocardiogram may show what appears to be a dilated right ventricle due to its anterior location and abnormal interventricular septal motion.[5,7,8] CT or cardiac MRI are the best diagnostic tools for pericardial absence, with cardiac MRI being the gold standard.[7]

Management depends on the size of the pericardial defect and presence or absence of symptoms. Patients with a partial pericardial absence are at risk for entrapment of the heart through the defect. This can lead to strangulation of the atria, appendages, and ventricles, causing sudden death in the most severe cases.[7,9,10] Patients without such significant complications can still experience bothersome, sharp, left-sided chest pain. Surgical pericardioplasty is usually reserved for symptomatic patients or those with partial defects in which herniation is an imminent risk.[2] On the other hand, patients with a large or complete pericardial defect can usually be safely observed because of a lower risk of herniation and incarceration of cardiac structures.

KEY POINTS

Although CAP is usually an incidental finding, awareness of it is important for a number of reasons. Patients with partial defects may experience disabling, left-sided chest pain without obvious cause. In the most severe cases, the atria, appendages, or ventricles may herniate through the pericardial defect, leading to sudden death. Given that CAP has a nonspecific clinical presentation but the potential for severe complications, maintaining a high index of suspicion is important in diagnosing and managing this condition in symptomatic patients.

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Recurrent Cryptococcosis in a Human Immunodeficiency Virus-negative Patient

Lillian C. Man, MD

Acknowledgements: Dr. Jeffrey B. Baliff, Jefferson University Department of Pathology

INTRODUCTION

Idiopathic CD4+ lymphocytopenia (ICL) is a rare disorder that can predispose otherwise immunocompetent individuals to life-threatening opportunistic infections. We present a case of a human immunodeficiency virus (HIV)-negative patient with ICL who presented with recurrent cryptococcosis.

CASE PRESENTATION

A 39-year-old Caucasian, HIV-negative male with a past medical history of stroke 13 years prior to admission and an episode of cryptococcal meningitis 18 months prior to admission presented to the hospital with generalized weakness for 7 days. The patient had a 10 pack-year smoking history and no significant environmental or occupational exposures. On admission, vital signs were significant for a temperature of 101.1◦F, a heart rate of 117 beats per minute, and a blood pressure 93/75 mm Hg. Physical exam was remarkable for an ill-appearing male with dry mucous membranes and tachycardia.

Initial laboratory studies were significant for a white blood count of 3.14 cells/μL (normal range = 4.5-11 cells/μL), hemoglobin of 8.7 g/dL (normal range = 13.5-17.5 g/dL), and creatinine of 5.2 mg/dL (normal range = 0.6-1.2 mg/dL). Blood cultures were positive for *Cryptococcus neoformans*. Subsequent laboratory studies revealed a serum cryptococcal antigen titer of 1:256 and a CD4+ count of 227 cells/μL (normal range = 410-1590 cells/μL). The CD4+ count was 98 cells/μL when the patient was diagnosed with cryptococcal meningitis 18 months prior. Enzyme-linked immunosorbent assays for HIV were negative. Anti-nuclear antibody titer was 1:80 and anti-double stranded DNA, anti-Smith, anti-SSA, anti-SSB , and anti-ribonucleoprotein antibodies were negative. Lumbar puncture (LP) showed a normal opening pressure and was negative for cryptococcal infection.

Chest X-ray revealed a right pleural mass. Subsequent CT of the thorax revealed a 6.3 x 3.3 cm pleural-based mass in the right upper lobe of the lung (Figure 1). Due to suspicion for a pulmonary malignancy, a Technetium bone scan was performed and found increased uptake in the right femur and left humerus. X-ray of the right femur showed well-circumscribed lytic lesions in the mid-femoral diaphysis (Figure 2). CT-guided biopsy of the pleural mass and the femur lesion revealed narrow-based, budding yeast that stained Gomori methenamine silver (Figure 3a) and a capsule that stained red with mucicarmine (Figure 3b), consistent with a diagnosis of cryptococcosis.

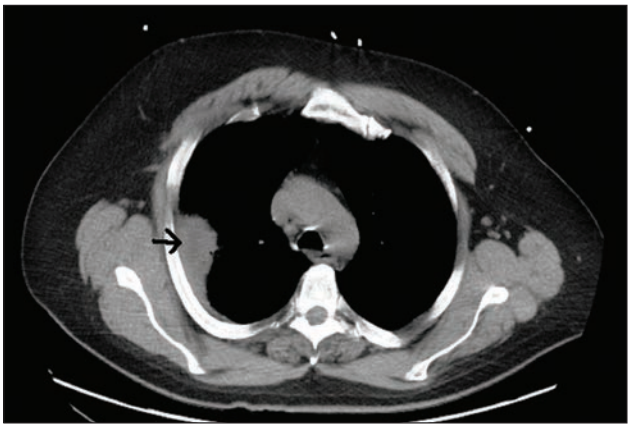

Figure 1: CT thorax without contrast showing a right pleural mass (arrow).

OUTCOME AND FOLLOW-UP

The patient was treated with a four-week course of liposomal amphotericin B and flucytosine and then discharged on fluconazole. He was also recommended to follow up at the National Institutes of Health (NIH) for further work-up of ICL as the predisposing etiology of his recurrent cryptococcosis.

Two months after discharge, the patient was hospitalized at an outside hospital for muscle pain and

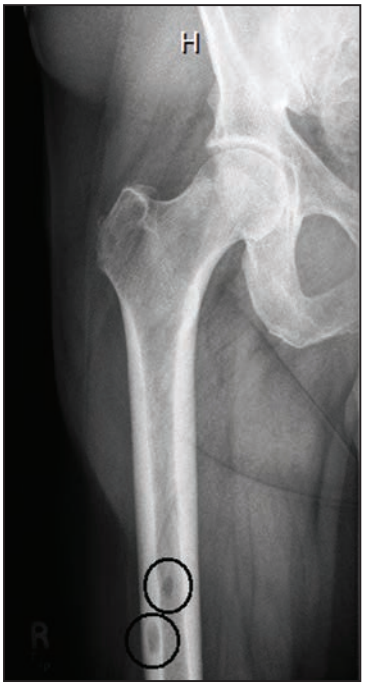

Figure 2: X-ray of right femur. Lytic lesions are shown (circled).

was still undergoing evaluation. He had not followed up at the NIH yet and was still on fluconazole therapy.

DISCUSSION

ICL is a rare disorder first defined by the US Centers for Disease and Control in 1992 as a CD4+ count <300 cells/mm^3 or a CD4+ cell count < 20% of total T-cells on two occasions and no serologic evidence of HIV infection.[1] The pathogenesis of ICL remains unclear. Researchers suggest a multifactorial etiology from diminished T-cell precursors, increased CD4+ lymphocyte apoptosis, and genetic factors.[2,3] There is also an association between autoimmune diseases and ICL, most commonly Sjogren's. However the mechanism by which autoimmunity contributes to ICL's pathogenesis is ill-defined.[2] Some reports suggest IL-2 therapy may increase CD4+ counts as well as decrease susceptibility to opportunistic infections, but currently there are no clear strategies to increase CD4+ lymphocytes.[3]

The most important differential diagnosis for ICL is HIV infection. ICL typically becomes apparent through the manifestation of opportunistic infections, the most prevalent of which are cryptococcosis, mycobacteriosis, and herpes zoster.[4] Disseminated cryptococcosis

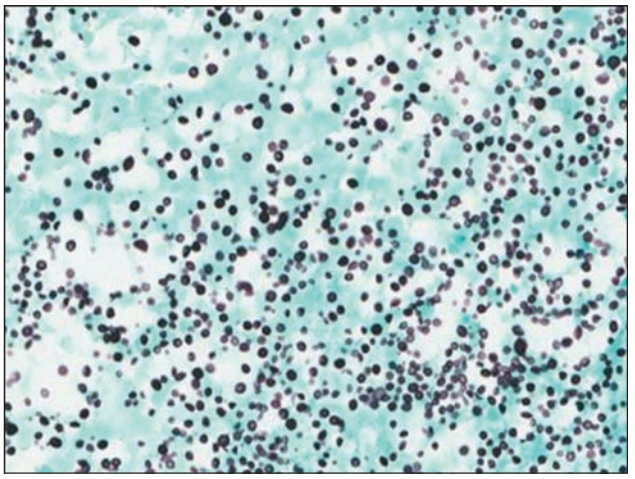

Figure 3a: Gomori methenamine silver (GMS) of the pleural mass biopsy showing innumerable darkly stained yeast.

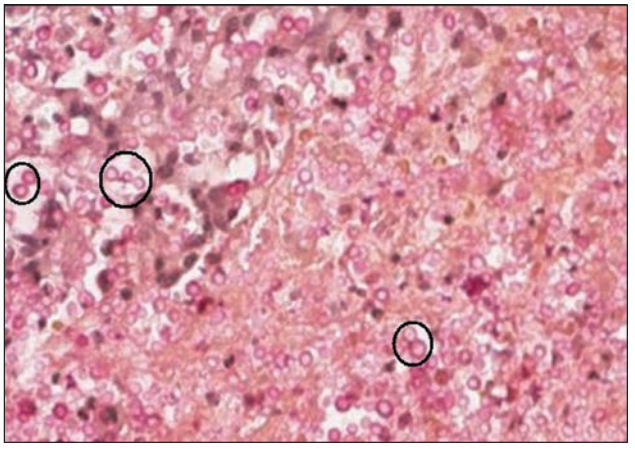

Figure 3b: Mucicarmine stain of the pleural mass biopsy. Multiple budding yeast are shown (circled).

can affect multiple organ systems including the adrenal glands, prostate, and bones and may be mistaken for malignancy with metastasis,[5] as was the case with our patient. Given that meningitis is the most common presenting illness in patients with cryptococcosis, LP is essential even in the absence of neurological symptoms.[6,7] Untreated cryptococcal meningitis carries a high mortality rate and can lead to cranial nerve palsies, hearing loss, and blindness.[8]

According to the current Infectious Diseases Society of America guidelines, non-HIV patients with disseminated cryptococcosis should be treated with a four-week course of amphotericin B and flucytosine for induction therapy followed by maintenance therapy with fluconazole for 6-12 months.[7] However, the recommen-

dations for non-HIV patients with cryptococcosis are often based on studies of HIV-infected patients. Given that our patient presented with recurrent cryptococcosis in the presence of ICL, it was thought that he should be maintained on fluconazole indefinitely.

KEY POINTS

In summary, ICL patients can present with an array of opportunistic infections even in the absence of HIV. The pathogenesis of ICL remains unclear, and guidelines on the treatment of ICL patients with opportunistic infections are largely based on studies of HIV-infected patients. Cryptococcosis is one of the most common opportunistic pathogens that infect ICL patients. Patients with cryptococcosis should have an LP even in the absence of neurologic symptoms due to the high morbidity and mortality of untreated cryptococcal meningitis.

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"Chichen-Itza"
photograph by Michael Valentino

A Case of Dengue Hemorrhagic Fever and the Use of Supportive Therapy

Aishah Ali, MD, Emily Sutton, MD

INTRODUCTION

Dengue fever is a mosquito-bound viral illness that occurs in tropical climates. It is endemic in 110 countries.[1] Fifty to three hundred and ninety million people are infected worldwide every year,[2] leading to ~25,000 deaths.[3] It is often an asymptomatic self-limited illness, which can present with myalgias, arthralgias, and hemorrhagic manifestations such as petechiae. In a fraction of cases, dengue fever can proceed to dengue hemorrhagic fever (DHF), which can be life threatening causing thrombocytopenia, bleeding and increased vascular permeability. Dengue shock syndrome (DSS) can then ensue, if hypotension occurs, and is fatal in >10% of patients.[4]

Here we present a case of Dengue fever, which proceeded to DHF and finally DSS. Our case demonstrates the supportive nature of treatment and how catastrophic severe dengue fever can be.

CASE PRESENTATION

A 64 year-old Pakistani female with a history of diabetes mellitus presented to her local hospital with severe body aches and malaise three days after returning from a two month long trip to Pakistan. During her stay, several family members had a self-limited febrile illness and one was diagnosed with dengue fever. On admission she was found to be febrile and thrombocytopenic, raising concern for dengue fever. She rapidly deteriorated with acute renal failure, acute liver failure (Table 1), new onset seizures, and required intubation and mechanical ventilation. She was then transferred to Thomas Jefferson University Hospital where she was emergently started on molecular adsorbent recycling system (MARS) therapy and continuous veno-venous hemodialysis (CVVHD).

Table 1. Labs on Admisssion

Lab Parameter	Value (normal range)	Lab Parameter	Value (normal range)
AST	11035 IU/L (7 – 35)	Sodium	138 mmol/L (135-146)
ALT	1925 IU/L (1 – 30)	Potassium	3.3 mmol/L (3.5 – 5)
Total Bilirubin	6.5 → 14.7 mg/dL (0.1 – 0.9)	Chloride	84 mmol/L (89 – 109)
Direct Bilirubin	5.3 → 13.2 mg/dL (0.0 – 0.3)	Bicarbonate	13 mmol/L (24 – 32)
Alkaline phosphatase	230 → 239 IU/L (25 – 120)	BUN	22 mg/dL (7 – 26)
GGT	254 IU/L (5 – 55)	Creatinine	2.3 mg/dL (0.7 – 1.4)
LDH	8490 IU/L (105 – 333)	Glucose	179 mg/dL (70 – 100)
Lactate	27.6 mmol/L (0.5 – 2.2)	Anion Gap	13 mmol/L (4 – 16)
PT	25.9 seconds (8.6 – 13.0)	WBC	6.7 B/L (4 – 11)
INR	2.44 sec (0.79 – 1.21)	Bands	30 % (0 – 9)
PTT	39 sec (28 - 38)	Hemoglobin	8.4 g/dL (12.5 – 15)
Fibrinogen	180 mg/dL (203 - 451)	Hematocrit	25.5 % (36 – 46)
D dimer	2661 ng/mL (<331)	Platelets	33 B/L (140 – 400)

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DIFFERENTIAL DIAGNOSIS

The patient's recent history of travel suggested an infectious etiology, particularly dengue as it is endemic in Pakistan. In addition, history obtained provided evidence of a local outbreak. Furthermore, her timeline of fevers and thrombocytopenia 3-7 days after her return supported the diagnosis of DHF. The incubation period for dengue is typically 3-14 days.[5] Congo fever was also considered but was less likely as it isn't commonly seen in the area she visited in Pakistan. As her hospital course progressed and she became more thrombocytopenic with increasing evidence of severe vascular permeability (Figure 1), the diagnosis of DHF became more apparent. In addition, her serum dengue IgG and IgM were reported positive several days after admission.

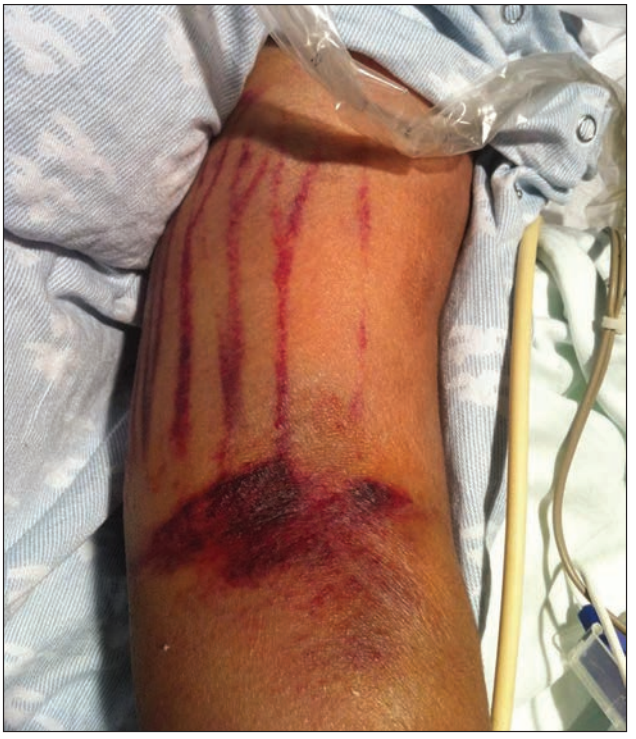

Figure 1. The tourniquet test also known as the capillary-fragility test. Seen in areas of pressure, such as tourniquets or blood pressure cuffs.

OUTCOME AND FOLLOW-UP

Although her aminotransferase levels improved rapidly on MARS (Table 2), the patient's hospital course was complicated by seizures and a new large ischemic stroke in the left medial temporal region. After one week of MARS therapy with no improvement in her mental status, she underwent a transjugular liver biopsy that showed 50-75% necrosis of liver parenchyma. Given her poor prognosis secondary to severe dengue infection, as well as the aforementioned stroke, she was deemed unsuitable for liver transplant. Post-ischemic stroke she did not have focal deficits, but it was difficult to fully neurologically assess her because of unresponsiveness. She was maintained on MARS/CVVHD for one more week with the hope that longer therapy would improve her outcome. Her hospital course was complicated by tracheobronchitis and septic shock requiring multiple vasopressors. As she still had no sign of neurologic recovery, the family decided to withdraw life support.

Table 2: Lab Values Pre and Post Therapy

Lab	Pre-supportive Therapy (normal range)	Post-supportive therapy (normal range)
AST	10705 IU/L (7 – 35)	101 IU/L (7 – 35)
ALT	1924 IU/L (1 – 30)	73 IU/L (1 – 30)
Total Bilirubin	6.5 mg/dL (0.1 – 0.9)	14.7 mg/dL (0.1 – 0.9)
Direct Bilirubin	5.3 mg/dL (0.0 – 0.3)	13.2 mg/dL (0.0 – 0.3)
Lactate	24.8 mmol/L (0.5 – 2.2)	7.2 mmol/L (0.5 – 2.2)
Creatinine	2.3 mg/dL (0.7 – 1.4)	0.8 mg/dL (0.7 – 1.4)

Pre-support therapy: before MARS and CVVHD were initiated
Post-supportive therapy: after MARS and CVVHD were initiated

DISCUSSION

Dengue fever is caused by the dengue virus, which is carried by several species of the mosquito in the genus Aedes. Classic dengue fever is a self-limited febrile illness that may last up to one week. However, it can become more severe and proceed to the hemorrhagic form where profound increases in vascular permeability can lead to shock and possibly multi-organ failure. The mechanism behind the vascular permeability is unknown but is thought to be secondary to the overwhelming inflammatory response to the virus.[6]

The treatment for dengue is entirely supportive, consisting of aggressive fluid resuscitation. MARS and CVVHD therapy may also be used for life threatening sequelae with potential improvement of acute liver failure, acute kidney failure, and disseminated intravascular coagulation.[5]

There is little evidence regarding the use of MARS in the setting of dengue fever. One case report demonstrated rapid improvement in a patient with dengue-associated hepatic encephalopathy and fulminant hepatic failure after treatment with MARS and CVVHD.[7] The patient's transaminitis rapidly corrected with MARS, with associated resolution of hepatic encepathopathy. The length of MARS with concurrent CVVHD in this case was three days. In our patient, MARS therapy corrected the transaminitis but did not affect her mental status. It was also surprising that her bilirubin levels remained elevated despite MARS which usually removes albumin-based substances such as bilirubin and bile acids.[8] It was unclear if her altered mental status was secondary to hepatic encephalopathy, stroke, uremia, or infection.

In hindsight, MARS may not have been indicated in this patient for an additional week after no clinical improvement in the first few days. There are no clear guidelines on the use of MARS or hemodialysis in a patient with acute liver failure. In one study evaluating the improvement in mental status in patients with acute liver failure and encephalopathy who were placed on hemodialysis, 61.5% had either total (43.6%) or partial (17.9%) regaining of consciousness.[9] Comparisons have been made between MARS in combination with continuous veno-venous hemodiafiltration (CVVHDF), CVVHDF alone, and single-pass albumin dialysis (SPAD).[7] All three forms are similar because they remove some type of waste product from the circulation. SPAD uses a standard renal replacement machine with an albumin dialysate solution and no additional recirculation pump, whereas MARS uses standard dialysis solution, an albumin solution, and an additional recirculation pump. MARS and SPAD were both efficient *in vitro* at removing albumin-bound substances, such as bilirubin; SPAD was actually superior to MARS in removing bile acid waste. Both SPAD and CVVHDF were better than MARS in taking out water-soluble solutes such as ammonia. The most notable difference was that SPAD cost significantly less than MARS; for a seven-hour session, SPAD cost $810 whereas MARS cost $2641. In our patient, MARS was an expensive treatment to continue without any proven correlation between prolonged length of use and improvement in mortality. Cost-effectiveness must be taken into consideration when alternate therapies are available for fractions of the cost.

As an adjuvant therapy for her fulminant hepatic failure, our patient also received eight days of N-acetylcysteine (NAC). NAC has been shown to be beneficial in patients when liver transplant is not available for non-acetaminophen associated acute liver failure. In a retrospective analysis of eight patients with dengue-associated acute liver failure, NAC was shown to be beneficial in early stages of liver failure but not in advanced stages.[10] The patient in this analysis had a maximum length of NAC use of 72 hours. No analysis exists comparing MARS versus NAC, or using both treatments, for improved outcomes in acute liver failure.

KEY POINTS

The treatment for dengue hemorrhagic fever is entirely supportive. Guidelines for the length of MARS treatment in dengue patients in fulminant hepatic failure needs to be further evaluated, as MARS is an expensive treatment only available at a few tertiary level centers.

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"Serenity on Howe Sound, British Columbia"
photograph by Andrew Zabolotsky

A Speedy Recovery with Medical Management in a Patient with Emphysematous Gastritis

Tanvi Khurana, MD

INTRODUCTION

Emphysematous gastritis is a rare and serious condition characterized by evidence of intramural air and inflammation of the gastric wall as well as systemic toxicity. It is generally caused by local infection by gas-forming organisms through a mucosal defect or via hematogenous spread from a distant focus.[1] Since emphysematous gastritis has a fulminant course with a mortality rate of 60%, prompt recognition as well as early treatment are crucial.[2] Here, we present a case of a 65 year-old male who presented with abdominal pain and had CT findings consistent with emphysematous gastritis. He was treated with antibiotics and had a swift recovery.

CASE PRESENTATION

A 65-year-old Caucasian man with past medical history of insulin-dependent diabetes, hypertension, hyperlipidemia, coronary artery disease (with history of three myocardial infarctions and stent placements), and peptic ulcer disease presented to Thomas Jefferson University Hospital with two weeks of loose stools and two days of nausea, vomiting and diffuse abdominal pain. In the emergency room, the patient had a temperature of 96.8◦F, heart rate of 99 beats per minute, blood pressure of 95/58 mmHg, respiratory rate of 22 breaths per minute, and oxygen saturation of 96% on 3L of oxygen. His cardiac and respiratory exams were unremarkable. His abdominal exam was notable for hypoactive bowel sounds and pain with deep palpation. He was tympanic to percussion. He did not have peritoneal signs. Labs were significant for a white blood cell count of 11.3 B/L (normal range = 4-11 B/L) and lactate of 1.0 mmol/L (normal range = 0.5-2.2 mmol/L) on presentation, which was repeated 6 hours later and found to have increased to 2.5 mmol/L. He underwent a CT scan of the abdomen which revealed a distended stomach with foci of intramural air, with air extending into the portal venous system (Figure 1). Soon after presentation,

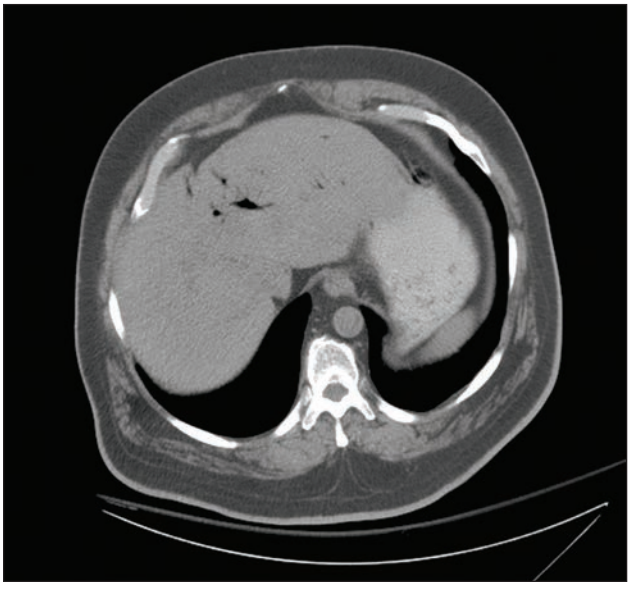

Figure 1. CT scan of the abdomen demonstrating air in the portal venous system as well as in the gastric wall.

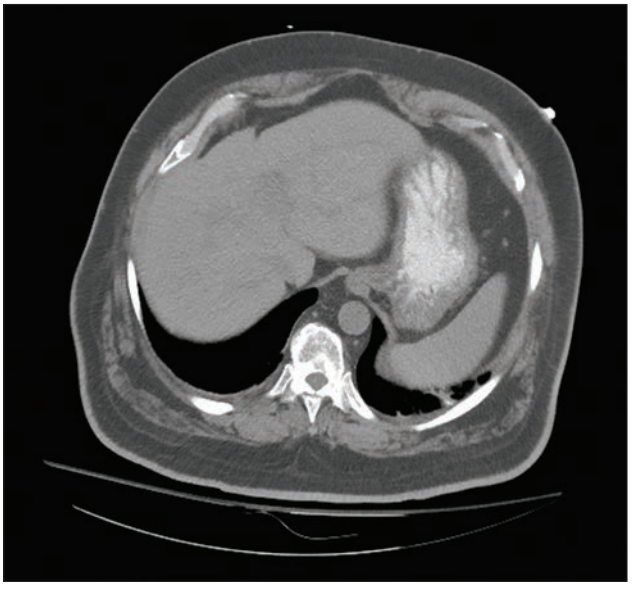

Figure 2. CT scan of the abdomen demonstrating resolution of all air on day 2 of hospitalization

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the patient became hypotensive to a systolic blood pressure of 85 mmHg and was resuscitated with 3L normal saline. He was sent to the intensive care unit where he received an additional 2L normal saline. His blood pressure responded appropriately. Surgery was consulted regarding the intramural air found on CT scan. However, since the patient did not have an acute abdomen, they deemed that he would not need emergent surgery. It was also decided that an esophagogastroduodenoscopy (EGD) would be too high risk given the increased risk of perforation. He was medically managed with antibiotics and supportive care. He was allowed nothing-by-mouth, pan- cultured, and started on a pantoprazole infusion and broad spectrum antibiotics (vancomycin, aztreonam, and metronidazole.

DIFFERENTIAL DIAGNOSIS

The significance of radiographic findings showing intramural air within the gastric wall is based entirely on the clinical situation. Intramural air in a patient who recently underwent instrumentation of their gastrointestinal tract significantly differs from intramural air found in an ill, septic patient. The differential for intramural air within the gastric wall includes emphysematous gastritis, as in our case report, versus cystic pneumatosis versus gastric emphysema.

OUTCOME AND FOLLOW UP

By day 2 of hospitalization, our patient had clinically improved with less abdominal pain and no further vomiting. Blood cultures were negative. A repeat CT scan showed resolution of gas in the stomach wall and portal venous system but showed new wall thickening of the proximal ascending colon (Figure 2). It was thought that the patient had bowel ischemia as a result of the emphysematous gastritis. By day 3 of hospitalization, our patient was restarted on a diet, which he tolerated well. He finished a 10-day course of antibiotics and had complete resolution of all his symptoms. He was discharged home with outpatient gastroenterology follow-up.

DISCUSSION

Emphysematous gastritis is described as gas in the lining of the stomach wall by gas-producing organisms caused by local spread of the organisms through the mucosa or by hematogenous dissemination from a distant focus.[3,5] Emphysematous gastritis was first described in 1889 by Frankel who believed it was caused from an infection where a prior insult to the mucosal barrier had occurred, either by corrosives, alcohol abuse, gastric ulcers, abdominal surgery, malignancy or gastroenteritis.[4,5] Gas within the GI tract occurs most often in the descending and sigmoid colons, while the stomach is the least common hollow organ for intramural air to occur due to the acidic environment.

Common organisms involved in emphysematous gastritis include *Enterobacter* species, *Pseudomonas aeruginosa*, *Candida albicans*, *Staphylococcus aureus, Streptococci,* and *Escherichia coli*. Patients usually present with gastrointestinal signs and symptoms with abdominal pain, distension, bloating, diarrhea, nausea and vomiting.[2,3,6] Diagnosis is usually based on the clinical history, a physical exam suggestive of an acute abdomen and imaging showing gas in the gastric wall and portal venous system, with CT scan being the most sensitive imaging modality.[3] Characteristic findings include cystic pockets or streaks of air within the gastric wall with thickened mucosal folds, pneumoperitoneum, portal venous gas and occasionally pneumatosis intestinalis.[2,6]

Unlike gastric emphysema, which is defined as gas in the stomach lining with no associated infection and has an excellent prognosis with medical management, emphysematous gastritis is rare and has a high mortality rate. Surgery should be avoided during the acute phase in the absence of bowel perforation due to the friability of the mucosa. It is important to treat patients based on their clinical condition and to initiate antibiotics early as mortality rates are as high as 75%.[1] Thus, early recognition of the illness, application of broad-spectrum antibiotics and meticulous supportive care are regarded as key therapeutic measures.[7]

KEY POINTS

Emphysematous gastritis is described as gas in the lining of the stomach wall caused by gas-producing organisms. It can be caused by an infection where a prior insult to the mucosal barrier has occurred, either by corrosives, alcohol abuse, gastric ulcers, abdominal surgery, malignancy or gastroenteritis. Diagnosis is usually made based on the clinical picture, a physical exam suggestive of an acute abdomen, and imaging showing gas in the gastric wall and portal venous system.

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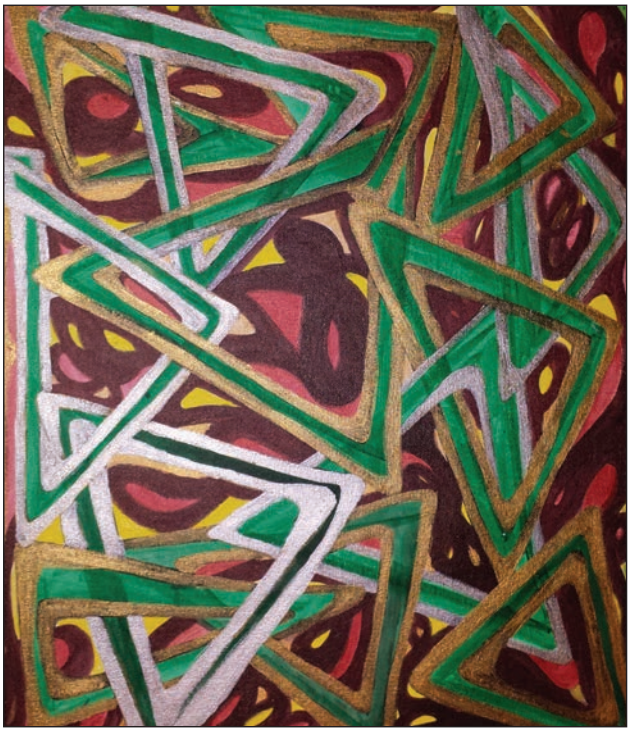
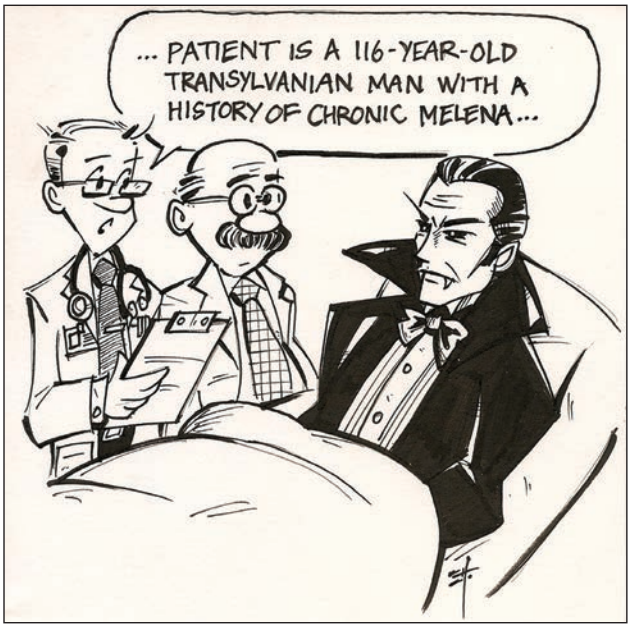
"Formless"

artwork by Mariam Kabir, MD



"Untitled"

cartoon by Eugene Han, MD, Isaac Matthias, MD



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A Case of Fibrosing Mediastinitis

Esther Molnar, MD

INTRODUCTION

Fibrosing mediastinitis (FM) is a rare disease of slowly progressive fibrosis that encases major mediastinal structures. Complications include obstruction of mediastinal vasculature, including main pulmonary arteries, which may lead to life-threatening hemodynamic compromise. In North America, the disease is usually a sequela of histoplasmosis. Because Histoplasma capsulatum (H. capsulatum) is found in the Ohio River Valley, physicians in Pennsylvania must be able to recognize and diagnose the disease.

CASE PRESENTATION

The patient is a 59 year-old female who was seen for follow-up in April 2013. She originally presented to the outpatient office in 2008 with chronic chest pain and shortness of breath. At that time her chest pain was constant, stabbing, non-pleuritic, located over the right anterior chest wall with radiation to the back, and was relieved with narcotic pain medications. She also had dyspnea on exertion. She described these symptoms as having been present for two years and noted that they had been getting progressively worse. On review of symptoms, she also noted light headedness with standing, occasional palpitations, and a dry cough. She denied weight loss, fevers, chills, hemoptysis, or lower extremity edema.

Her past medical history was significant for a pulmonary embolism at the age of 18, treated with warfarin, multiple episodes of pneumonia from 1999 to 2007, and a diagnosis of superior vena cava (SVC) syndrome in 2008. Her social history was significant for a 10 pack year history of cigarette smoking. Her family history was significant for her father with myocardial infarction at age 50.

On her most recent physical exam her vitals were temperature 99.1°F, blood pressure 110/82 mm Hg, pulse

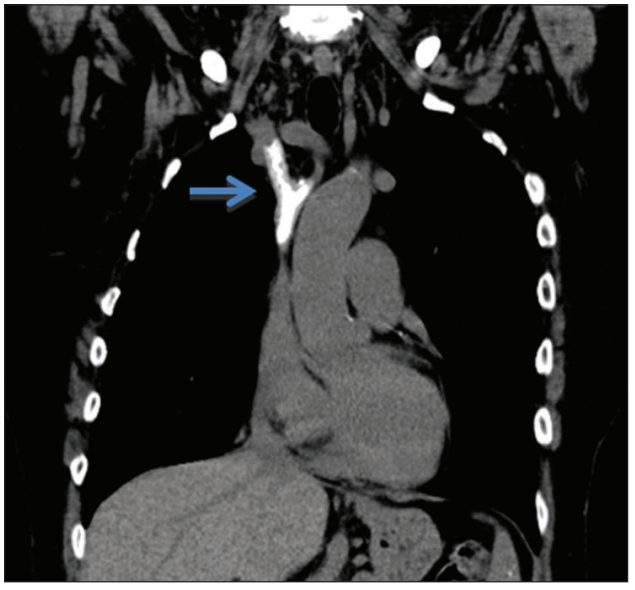

Figure 1: SVC occlusion with dense calcification suggestive of chronic inflammatory or post-radiation etiology

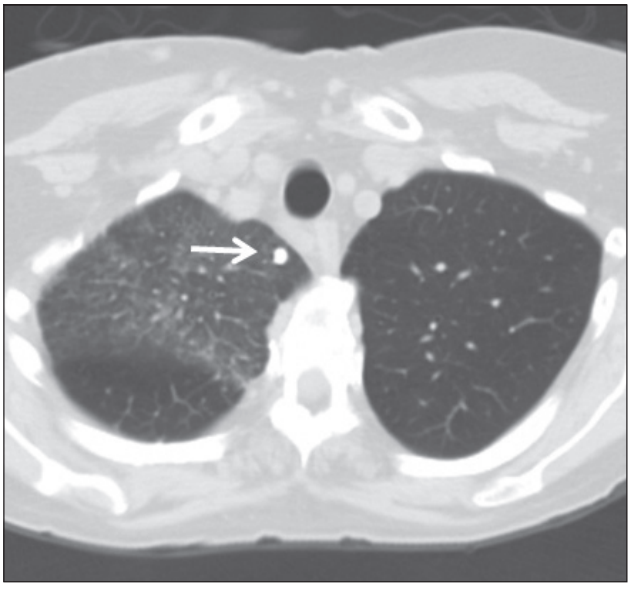

Figure 2. Calcified granuloma. Ground glass opacity of right upper lung. Loss of volume of right upper lung

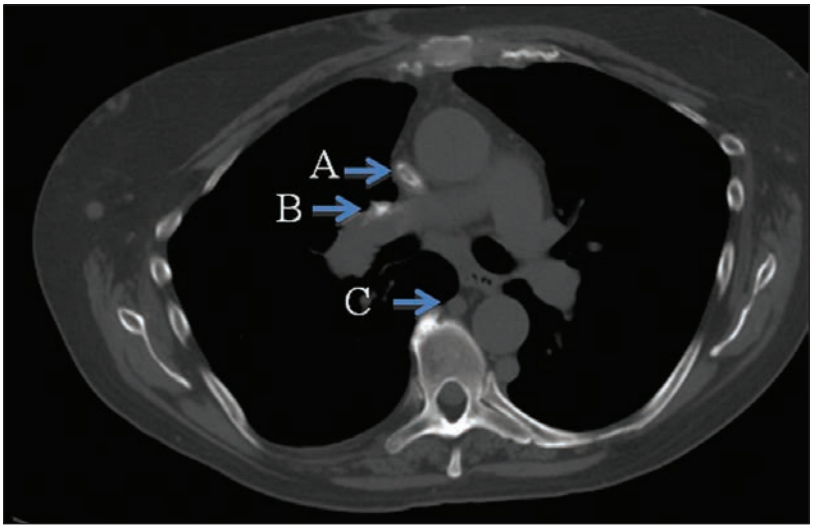

Figure 3: A. Narrow SVC B. Calcified mediastinal lymph node C. Dilated azygous vein.

of 72 beats per minute, and oxygen saturation of 97% on room air. She was without cervical lymphadenopathy and lacked neck or face swelling. Her lungs were clear to auscultation, and auscultation of her heart revealed regular rate and rhythm and normal heart sounds with no murmurs, rubs or gallops. There was no cyanosis, clubbing or edema of the extremities. Her skin exam was notable for prominent veins of the upper chest wall and dilated tortuous abdominal wall veins.

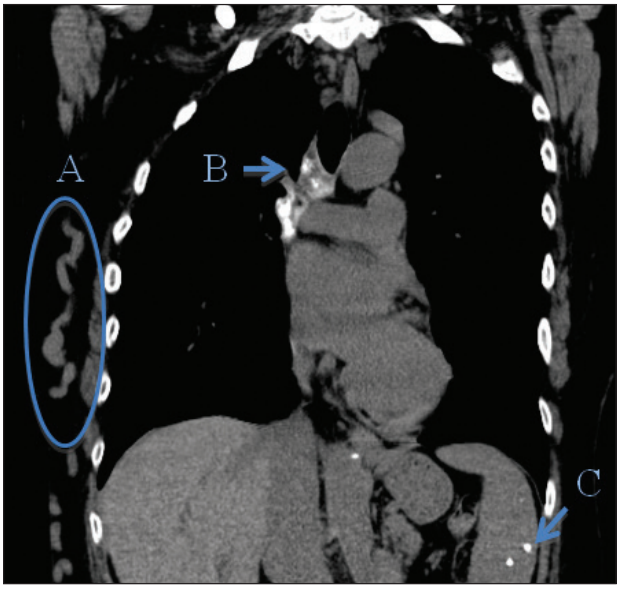

Figure 4: A. Dilated chest wall collaterals. B. Calcified SVC and hilar lymph node. C. Splenic calcifications.

SVC syndrome was diagnosed in 2008 when she presented to her primary care provider with left neck swelling. CT of her neck at the time showed a heterogeneous density in the left external jugular vein which was thought to be a thrombus; however, upper and lower extremity Dopplers were negative for acute thrombus. Further evaluation with CT of her chest with contrast showed SVC occlusion with dense calcification, suggestive of chronic inflammatory or post-radiation etiology (Figure 1). The patient, however, denied any history of radiation exposure or central vein catheterization. Interestingly, the CT of the chest also showed a chronic calcified occlusion of the right upper lung (RUL) pulmonary artery. She also had RUL ground-glass opacities with a calcified granuloma (Figure 2), and calcified mediastinal and hilar nodes, prominent venous collateral formation in the chest wall and mediastinum, and calcifications of her spleen (Figures 3,4).

DIFFERENTIAL DIAGNOSIS

Bronchoscopy performed to further evaluate her abnormal CT findings in her lungs was largely unrevealing. Tissue biopsy was negative for malignancy and sputum stained negative for acid-fast-bacilli (AFB). Fungal, AFB and respiratory viral cultures were also negative. Rheumatologic workup, including antinuclear antibody (ANA), perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic-ANCA (c-ANCA), and rheumatoid factor (RF) were negative.

Given the CT imaging which showed calcified mediastinal lymph nodes and calcified occlusions of the SVC and RUL pulmonary artery, as well as thick fibrotic tissue in the mediastinum, the patient was diagnosed with fibrosing mediastinitis (FM). FM is a radiologic diagnosis. Etiologies in North America include histoplasmosis (82%), idiopathic (18%), and Mycobacterium tuberculosis or other mycoses.[1]

OUTCOME AND FOLLOW-UP

The patient is followed annually for her fibrosing mediastinitis. The latest CT thorax performed in 2012 showed ground-glass opacities and loss of volume in the RUL with traction bronchiectasis. She also had new narrowing of the right superior pulmonary vein in addition to the chronic occlusion of the RUL pulmonary artery. Her imaging also showed dilated azygous and hemiazygous veins and extensive anterior chest wall venous collaterals that have increased in diameter over the last three years.

DISCUSSION

Fibrosing mediastinitis (FM) is a chronic form of mediastinitis that is characterized by invasive fibrosis that compresses and encases mediastinal structures, including lymph nodes, central vessels, and airways. FM is diagnosed by radiological findings of calcifications of hilar and mediastinal lymph nodes and evidence of fibrotic tissue within the mediastinum. While the pathophysiology of fibrosing mediastinitis is poorly understood, it is believed that most cases in North America are due to Histoplasma capsulatum.[1] About 80% of patients with FM present with radiographic or serologic evidence of Histoplasmosis infection or exposure.[2] Rare case reports have also described fibrosing mediastinitis secondary to tuberculosis and other fungal infections, including blastomycosis, coccidiomycosis and aspergillosis.[3] In about 18% of patients, no infectious cause is identified and the etiology is thus labeled as idiopathic. Other conditions that mimic the radiological findings of FM include sarcoidosis, mesothelioma, idiopathic retroperitoneal fibrosis, and radiation-associated mediastinal fibrosis.

The most likely etiology of this patient's FM is histoplasmosis, as she presented with radiological evidence of prior histoplasmosis infection, including the characteristic mediastinal granuloma and splenic calcifications. She is also from an area endemic to H. capsulatum. It is likely that her FM was secondary to histoplasmosis even in spite of her urine antigen testing for histoplasmosis being negative, as only ~10% of patients with chronic lesions have positive antigen testing, and patients with chronic forms of histoplasmosis such as FM generally do not have positive urine antigen testing.[1] The urine antigen testing is most useful in acute pulmonary histoplasmosis with large inoculum or disseminated histoplasmosis.

H. capsulatum is endemic to the Ohio and Mississippi River Valleys with several microfoci in Mid-Atlantic States, Africa, Southeast Asia, and Europe. The dimorphic fungus exists as a mold in the soil and as a yeast at 37°C. Nitrogen-rich soil from bird and bat excrement enhances the growth of H. capsulatum. The mold is easily aerosolized and inhaled. Once in the lungs it is phagocytized by macrophages.[4] The severity of illness depends on the amount of inoculum and host immune response. Over 80% of young adults from the Ohio and Mississippi River Valleys have been exposed, as evidenced by positive skin antigen testing. In most cases, patients have no symptoms or a very mild pneumonia-like illness that resolves on its own within four weeks. Acute exposure to a large amount of inoculum or severe immunosuppression can result in severe pneumonitis and respiratory failure.[5]

While most symptomatic infections with H. capsulatum have acute pulmonary manifestations, ~1% of patients have extra-pulmonary manifestations, including pericarditis, rheumatologic syndromes (arteritis, erythema nodosum), mediastinal lymphadenitis, progressive disseminated histoplasmosis, and mediastinal fibrosis.[5]

Mediastinal fibrosis is a rare complication of Histoplasma infection, and it is not known why <1% of patients exposed to the mold develop FM.[6] One widely accepted hypothesis for the pathophysiology includes leakage of fungal antigen from the infected lymph nodes in the mediastinal space resulting in a delayed hypersensitivity reaction.[7] Another hypothesis proposes that rupture of a caseous lymph node from a primary infection invokes an inflammatory reaction and subsequent fibrosis.[2] Fibrosing mediastinitis is also thought to be an abnormality of collagen production and organization, akin to idiopathic retroperitoneal fibrosis and on the spectrum of IgG4-related disease.[8] Genetic host factors may play a role as there is a slight predominance of women with the disease.[4]

During this chronic disease process, excess collagen production entraps mediastinal structures and causes subsequent symptomatology. Most patients present with nonspecific symptoms of chest pain, cough and dyspnea. Only ~20% of patients progress to severe occlusion of great vessels or airways.[5] Obstruction of pulmonary arteries often results in symptoms of right

heart failure. Airway obstruction will cause recurrent episodes of bronchitis or pneumonia in addition to wheezing, cough and dyspnea. Some patients will have difficulty swallowing secondary to posterior extension of the fibrosis entrapping the esophagus.[2] The extent of invasion and obstruction is best visualized with CT imaging and angiography, although MRI has also been used.[4]

There is no known treatment for fibrosing mediastinitis. No controlled trials of medical or surgical therapy have been conducted. Antifungal or anti-inflammatory treatment with corticosteroids is not indicated as this is a disease primarily of enhanced collagen deposition.[5] Placement of intravascular stents has been helpful in patients with vascular stenosis for symptomatic management. In one report, percutaneous stenting in pulmonary arteries or SVC showed effective short-term and mid-term success in improving vascular patency of six study patients; however, in-stent re-stenosis was a frequent complication and progressive fibrosis remained a clinical problem.[7] Thankfully, many patients have a self-limited course of fibrosis. In a retrospective study of 80 patients, most patients had a survival similar to age-matched controls.[3]

In our patient, her symptomatology can be directly related to FM. Her lightheadedness on standing is likely from poor filling pressures of her right atrium from chronic SVC occlusion. She also has pulmonary vein and pulmonary artery stenosis, contributing to her dyspnea and easy fatigability. Her recurrent pneumonias are also likely explained by airway obstruction. Significant physical exam finding of large superficial veins are evidence that her body is compensating for the fibrotic and obstructive process in her thorax by forming collateral blood flow. Evidence of collateral blood flow is also evident in CT imaging showing enlarged azygous and hemiazygous veins (Figure 3). Her radiographic imaging strongly points to histoplasmosis as the etiology of her FM. At the time of this case report's authoring, she did not show hemodynamic compromise requiring intravascular stenting; although, this is a therapeutic option to consider in the future if her disease progresses. She is currently being treated with narcotics and gabapentin for pain control.

KEY POINTS

In summary, fibrosing mediastinitis is a rare disease and a rare complication of histoplasmosis. The majority of adults in the Ohio River Valley have fungal exposure; however, only a small number of people with prior Histoplasma infection develop FM. Most patients with FM have a self-limited course of fibrosis, however some progress to fatal occlusion of great vessels.

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HIV Screening: A Review of Nationally Recommended Guidelines and Specific Instances in which HIV Screening is Often Overlooked

Anusha Ganesh, MD

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), one in five human immunodeficiency virus (HIV)-infected individuals are currently living without knowledge of their diagnosis.[1] In 2006, the cost of a rapid HIV test with pre/post-test HIV counseling was anywhere between 48-64 US dollars (USD). The majority of the cost incurred was for HIV counseling, with the cost of the rapid HIV test being between 8-25 USD.[2] Research looking at the cost-effectiveness of HIV screening shows that it is more cost-effective than routine screening for breast cancer with mammography yearly or even routine screening for diabetes mellitus with a one-time fasting blood glucose.[3] With the cost of testing reasonably low and prevalence of undiagnosed infection high, why are our rates of HIV screening not maximized?

CASE PRESENTATION

The following is an example of a patient who would have benefitted from HIV screening as per national guidelines. Ms. C is a 48-year-old female who presented at her gynecologist's office for a routine examination and PAP smear. The patient had never been offered HIV screening in the past. She had a positive HIV test at that visit and was sent to the Infectious Disease clinic for follow-up care. Ms. C denied any active symptoms. Her past medical and surgical history included syphilis, treated with a short course of penicillin G, lower back pain, depression, hypothyroidism, gastroesophageal reflux disease (GERD), asthma, tubal ligation, and lipomectomy. She has had multiple Emergency Department (ED) visits in the last three years for various unrelated complaints. Yearly mammograms had been performed for health maintenance and were all within normal limits. She denied history of tuberculosis, pneumonia, or other opportunistic infections. Her social history was positive for a history of non-intravenous drug use in the past and tobacco abuse. She had no recent travel and no current HIV risks or exposures. She has been married for twenty years and stated that she was sexually active and monogamous with her husband. Her vital signs were within normal limits, and there were no abnormalities noted on physical exam.

Based on national guidelines, her positive HIV enzyme immunoassay (EIA) screen was followed by a confirmatory HIV Western Blot.[4] Her baseline HIV viral load was 1090 copies/mL, and her CD4 count was 230 cells/μL. Although this patient had been treated in the ED numerous times, she remained compliant with health maintenance and had surgical procedures. However, she had never been screened for HIV. Screening for HIV at any of these points in time may have led to earlier diagnosis and treatment.

Broad screening is important, as earlier treatment of HIV has been studied compared to deferred treatment and has been shown to increase survival.[5] A study compared the risk of death in patients who were started on anti-retrovirals at a higher vs. lower CD4 counts. Those started with the higher CD4 count had improved outcomes with a reduction in number of deaths. Studies have also shown that the risk of transmission of HIV is directly related to viral load, which can be treated if addressed sooner.[6] The patients who are generally screened are "high risk" patients, such as people who engage in sex without protection, sharing of drug-use equipment, occupational hazards, men who have sex with men, and youths.[7]

This paper will review the current HIV screening guidelines from multiple national organizations (Table 1), which emphasize the importance of screening those individuals who are not necessarily "high risk".

Table 1: HIV Screening Recommendations		
Organization	Screening recommendations	Notes
CDC[15]	anyone ages 13-64 regardless of risk high risk patients annually all pregnant women repeat in third trimester for all high risk pregnant women infants exposed in utero victims of sexual assault	opt out method: allow patient to decline preventative counseling for HIV not required written consent not required
United States Preventative Services Task Force (USPSTF)[16]	anyone ages 15-6 younger adolescents and older adults who are at risk all pregnant women, including those who present in labor	
American College of Physicians (ACP)[17]	all patients once, more often for those "at risk"	"at risk": shared injection drug use, blood transfusion between 1978-1985, unprotected sex with multiple partners, having an STD
American Academy of HIV Medicine (AAHIVM)[18]	all adults over 15 all adults over 65 (aren't these the same thing?	opt out testing
American College of Gynecology (ACOG)[19]	all women between 19 and 64 women with risk factors outside that age range	opt out testing

DISCUSSION

Inpatient

In 2010, a study was conducted at the Veterans Affair Hospital in Washington, D.C. which looked at the percentage of patients accepting routine HIV screening in the hospital. Until 2010, only those patients who were considered "high risk" were tested. The testing rate increased from 4.25% (high risk only) in previous years to 23.8% (all patients offered screening) during this trial.[8] A similar study performed in New York City in 2005 showed that, of the patients who were asked to participate in HIV testing, there was not a significantly higher percentage who carried traditional risk factors for HIV. The study supported routine, voluntary testing for HIV, as it diagnosed patients who were not identified in the risk-based testing.[9] The CDC studied physician-referred HIV testing rates compared to HIV testing rates when a "Voluntary HIV Counseling and Testing" (VCT) program was implemented, allowing all patients to be queried about HIV testing. This program tripled the number of patients being tested for HIV daily.[10] All these studies validate the argument that, if offered routinely, the utilization of inpatient HIV screening would rise significantly, capturing those who may not be routinely followed in a primary care setting.

The Emergency Department has been cited by the CDC as an important location in which patients of a lower socioeconomic status have their first interaction with a physician. The CDC has recommended in its 2001 guidelines that ED-based HIV testing and counseling should be more widely implemented.[11] In one study, targeted screening was studied in a Midwestern, urban teaching hospital to determine the cost-benefit and higher true positive rate of testing of high-risk patients in the ED versus opt-out testing for all patients. The study deemed that, with a wider testing population, more positive tests were identified with a proportional increase in tests offered. There was no benefit to targeted screening, as it did not have a proportionately higher number of positive test results when compared to the large screening group.[12]

The Elderly

It is becoming increasingly important to address HIV screening in the elderly population who are often not considered candidates for testing, as safe sexual practices are not always comfortably discussed in this population.[13] Among all patients with HIV infection, 37% are now over the age of fifty. It is estimated that this number will increase to 50% by the year 2015.[13] Patients who are diagnosed at a later age will be more likely to experience increased morbidity and mortality and a higher risk of opportunistic infections.[13] The main risk factor for HIV acquisition in the elderly is heterosexual intercourse.[13] The reasons for missed opportunities for HIV screening in this population include lack of knowledge of HIV in older patients, underestimating the risk of contracting HIV, and the social stigma associated with HIV.[13]

Low Risk Factor Population

In 2006, the Institute of Medicine (IOM) studied offers of HIV screening to patients in the state of Virginia. IOM discovered that primary care physicians, although aware of the guidelines, were more hesitant to implement screening in all patients because they weren't comfortable treating patients who had a positive test result.[14] HIV testing also required more staffing and education to providers in the clinic. Further complicating this was the difficult conversation with individuals, such as our patient, who are not considered to be "high risk".[14] Nonetheless, the evidence shows that even in low risk populations, it is vital for primary care providers to address the importance of a one-time HIV screening to ensure the patient's health and safety.

KEY POINTS

The three main categories of patients who are often missed for HIV testing include patients in the acute care setting, elderly individuals, and the low-risk population. They should all be offered opt-out testing by their primary physician or hospitalist, as per national guidelines. It is a low-cost test, with an extremely high benefit value. All major national health organizations are recommending that physicians offer one time HIV screening in all patients regardless of age, gender, or perceived risk status.

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"Japanese Maple, Longwood Gardens"
photograph by Andrew Zabolotsky, MD

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Fever in a Man with HIV: An Unusual Case of an Immune System Gone Wrong

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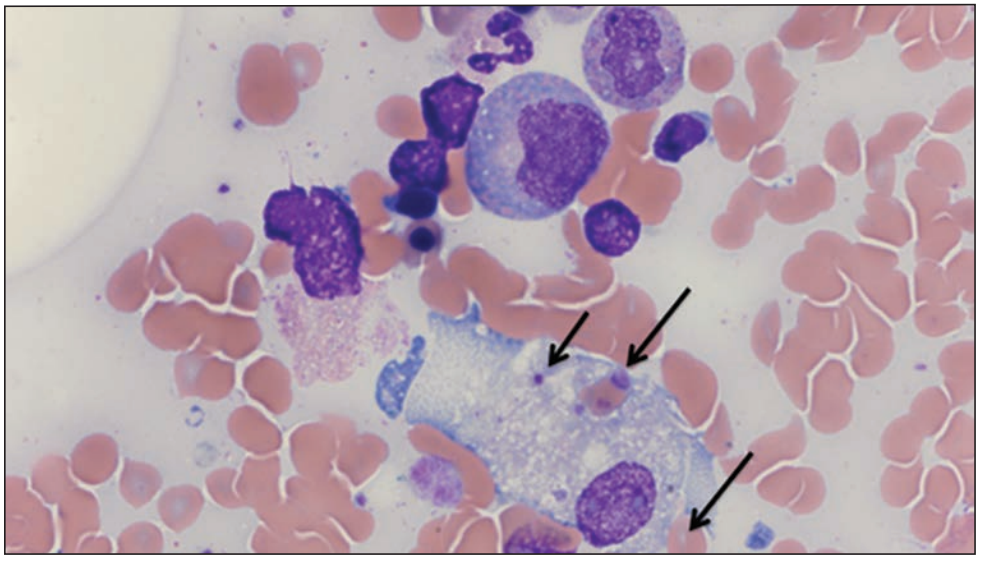

Figure 1: The patient's bone marrow biopsy demonstrating hemophagocytosis of platelets (short arrow) and erythrocytes (long arrows).

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of immune dysregulation that is often recognized as secondary to an underlying immune activating state, such as malignancy, rheumatologic disorders, and infections. This case highlights an association between HLH and human immunodeficiency virus (HIV) infection. Although HLH is a rare complication of HIV, it presents a difficult challenge for treatment. Without treatment, HLH is invariably fatal, but the consequence of the immunosuppressive treatment regimen in the setting of an underlying opportunistic infection can also have fatal outcomes.

CASE PRESENTATION

A 38 year-old man with a history of HIV infection with a CD4 lymphocyte count of 2 cells/mm^3 presented with fevers two weeks after starting antiretroviral therapy (ART). His initial extensive infectious workup was negative, including cryptococcal antigen in the serum and cerebrospinal fluid. His liver enzymes then began to rise, prompting concern for drug toxicity. At this time, ART and trimethoprim/sulfamethoxazole were discontinued, but he continued to have high-grade fevers as well as hypotension, pancytopenia and hypofibrinogenemia and was transferred to the medical intensive care unit (MICU). On admission to the MICU, he was febrile with a temperature of 103.6°F, hypotensive with a blood pressure of 78/37 mmHg, tachycardic with a heart rate of 127 beats per minute, tachypneic with a respiratory rate of 26 breaths per minute, and had an oxygen saturation of 97% on room air. On exam, he was thin, in moderate distress, and lethargic. He had no thrush or nuchal rigidity. He had cervical lymphadenopathy and hyperpigmented maculopapular rashes on his lower extremities; otherwise his exam was unremarkable.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included opportunistic infections given his CD4 count of 2 cells/mm^3, immune reconstitution inflammatory syndrome (IRIS) given his

Table 1: Diagnostic Criteria for HLH3
Diagnosis of HLH requires Molecular diagnosis consistent with HLH -OR- Fulfillment of 5 of the 8 criteria listed below:
1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages Hemoglobin < 9 g/dL Platelets < 100 x 10^3/mL Neutrophils < 1 x 10^3/mL)
4. Hypertriglyceridemia (fasting > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL
8. Elevated sCD25 (α-chain of sIL-2 receptor)

recent initiation of ART, drug reaction or toxicity, and hemophagocytic lymphohistiocytosis (HLH). Further laboratory studies revealed an elevated ferritin level of 83,987 ng/mL (normal range = 30-400), which was highly suspicious for HLH. The diagnosis was confirmed with a bone marrow biopsy revealing hemophagocytosis (Figure 1) as well as an elevated interleukin 2 receptor (IL2R) level of 9020 pg/mL (normal range = 0-1033).

OUTCOME AND FOLLOW-UP

The patient was treated with intravenous immunoglobulin, high dose dexamethasone, and anakinra, an IL1R inhibitor, resulting in cessation of his fevers, resolution of his respiratory distress, and improvement in his cell lines. He was transferred back to the floors with plans to restart ART. As no underlying infection had been found, his HLH was thought to be secondary to his HIV infection. However, three days later, he became acutely short of breath and hypotensive and was found to have *Cryptococcus neoformans* fungemia, although his initial blood and cerebrospinal fluid fungal studies were negative. He was transferred back to the MICU, initiated on intravenous amphotericin B/flucytosine, and ART was discontinued. However, he continued to decompensate rapidly and expired from septic shock and acute pulmonary edema later that day.

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is a severe and rapidly progressive disorder of immune activation and dysregulation that can occur as a familial disorder or, as is becoming increasingly recognized, secondary to a variety of underlying conditions. Secondary HLH occurs after strong immunologic activation, such as with severe infection, immunodeficiency, or underlying malignancy. In the past, HLH was also sometimes referred to as hemophagocytic syndrome. Another disorder on the spectrum of this disease state includes macrophage activation syndrome, which is a form of HLH associated with rheumatologic diseases.[1] Although the immune cells in HLH are functionally normal, it is thought to be the result of proliferation of activated T cells that go on to activate macrophages, as well as the lack of appropriate apoptosis of immunogenic cells. As these overly active macrophages and histiocytes proliferate and run rampant, they phagocytize other cells, including erythrocytes, leukocytes, and platelets, leading to the clinical symptoms. This highly stimulated immune system results in life-threatening cytokine storm and inflammatory reactions.[1,2]

As the clinical entity of HLH is a syndrome, it has features that can be seen in other clinical states, but it is the combination of findings that make the diagnosis likely. The diagnostic criteria for HLH include fever, splenomegaly, cytopenia of at least 2 of 3 cell lines, elevated ferritin, hypofibrinogenemia and/or hypertriglyceridemia, elevated CD 25 (IL-2 receptor), low or absent natural killer (NK) cells, and hemophagocytosis seen in the bone marrow, liver, spleen, or lymph nodes. Five of these eight criteria must be met in order to establish the diagnosis (Table 1).[3] Notably, the criteria only require a ferritin level >500 ng/mL, but a level >10,000 ng/mL is thought to be highly suspicious for HLH, with a specificity of 96%.[4] The ferritin level upon diagnosis has also been found to have prognostic value, and its decline correlates with response to treatment. The soluble IL-2 receptor was found to be a more sensitive marker than ferritin with a sensitivity of 93% and also carries prognostic implications.[5]

Without therapy, HLH is uniformly fatal. Treatment includes supportive care, immunomodulatory therapy, and treatment of any underlying condition. For the familial form of HLH, the treatment backbone is an induction phase involving chemotherapy, typically etoposide, combined with immunotherapy, such as cyclosporine A and steroids. This is followed by a continuation phase that is to be maintained until stem cell transplant is available, as transplant is the only curative treatment for familial HLH. The treatment for secondary HLH is not as well defined as it can vary based on the associated disease. For underlying malignancies, the treatment approach is often similar to the familial form, with chemotherapy and immunotherapy. For the secondary forms associated with immunodeficiency or rheumatologic causes, the approach relies more heavily on immunomodulators, such as the IL-1 receptor antagonist anakinra.[2]

In the context of HIV, HLH has been reported to occur secondary to opportunistic infections, as well as from HIV infection itself, both during the acute seroconversion phase and the profoundly immunosuppressed state.[6,7] Given the non-specific clinical manifestations of HLH and the otherwise heightened concern for opportunistic infections, one must have a high clinical suspicion for recognizing this disease in the setting of HIV. Treating HLH in the setting of severe immunosuppression from HIV presents a difficult challenge, as with this patient. As induction treatment for HLH requires high dose steroids and IV immunoglobulin to quell the life-threatening inflammatory response, underlying opportunistic infections may prove to be fatal if they go unrecognized. There are no current guidelines on antibiotic use in HIV patients with confirmed HLH, and it may be of value to treat these patients empirically for opportunistic infections in the setting of critical illness.

KEY POINTS

Patients presenting with a clinical picture of fever and highly elevated inflammatory markers should raise the suspicion for hemophagocytic lymphohistiocytosis (HLH). Five of the eight criteria must be met for the diagnosis, but a ferritin level >10,000 ng/mL is highly suspicious. HLH is fatal without treatment, but immunomodulatory therapy directed at HLH may be perilous in the setting of underlying infection. Currently, there are no guidelines on empiric antibiotic use for patients with HIV and HLH, but one must be vigilant in searching for underlying infections given the risk of the immunosuppressive regimen required to treat HLH in the setting of HIV.

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Interventricular Septum Rupture in the Catheterization Laboratory

Xing Zhang, MD, Loheetha Ragupathi, MD

INTRODUCTION

This is a case of acute ventricular septal defect (VSD) that was diagnosed while a patient with an acute ST-elevation myocardial infarction (STEMI) was being treated in the cardiac catheterization laboratory. Post-MI VSD is a well-recognized complication of STEMI, and this case was particularly interesting given the circumstances of its diagnosis.

CASE PRESENTATION

A 75 year-old female with a history of well-controlled hypertension presented with 3 days of substernal chest pain radiating down her left arm. The pain was severe, unremitting, associated with shortness of breath, nausea, vomiting, and was not relieved by simethicone or by changes in position. The patient had a blood pressure of 165/92 mmHg, heart rate of 104 beats per minute, and physical examination was unremarkable. The initial electrocardiogram (ECG) showed 1mm ST elevations in the inferior leads (Figure 1). ECGs taken 1 hour later showed an increase in the inferior ST elevations to 2-3mm, and troponin T was elevated to 2.36ng/mL (normal range = <0.01ng/mL) (Figure 2). Echocardiogram showed inferior and inferoseptal akinesis as well as decreased left ventricular systolic function with an ejection fraction of 30%.

The patient was admitted for STEMI, given a full dose aspirin and atorvastatin, started on eptifibatide infusion, unfractionated heparin infusion, and taken for cardiac catheterization. At this time, her blood pressure remained elevated, so she was started on a nitroglycerin infusion. Subsequently, she became profoundly hypotensive, and the nitroglycerin infusion was discontinued. Coronary angiography showed right dominant coronary circulation with total thrombotic occlusion of the distal right coronary artery (RCA) and severe multivessel disease. Balloon angioplasty of the RCA was performed, with the plan to proceed with definitive coronary artery bypass graft surgery within 24-72 hours. Due to persistent hypotension, an intra-aortic balloon pump was placed with good diastolic augmentation.

DIFFERENTIAL DIAGNOSIS

At this point, the differential diagnosis for the patient's decompensation included cardiogenic shock secondary to left or right heart failure, rhythm disturbances such as complete heart block, and mechanical complications. The three main mechanical complications to consider in the setting of acute hypotension with an acute myocardial infarction include papillary muscle rupture causing acute mitral regurgitation, ventricular free wall rupture, and ventricular septal defect.

During this event, the patient did not demonstrate any new heart block on ECG monitoring. Thus, mechanical causes of her acute hypotension were investigated. Contrast ventriculography has the benefit of evaluating left ventricular function as well as illustrating possible free wall rupture, acute mitral regurgitation, or any new VSD. In this case, contrast ventriculography was performed revealing a large ventriculoseptal defect (VSD) in the inferoseptal wall (Figure 3).

Post-procedure transthoracic echocardiogram confirmed inferoseptal VSD and found a contiguous partial myocardial tear of the inferior wall with pseudoaneurysm (Figure 4). Given the high mortality of VSD and impending rupture of the inferior free wall, the patient was taken for operative cardiac repair.

OUTCOME AND FOLLOW-UP

In the case of this patient, the initial plan during her cardiac catheterization was to revascularize her culprit lesion (the RCA) and then ultimately pursue bypass surgery given her multivessel disease. However, after

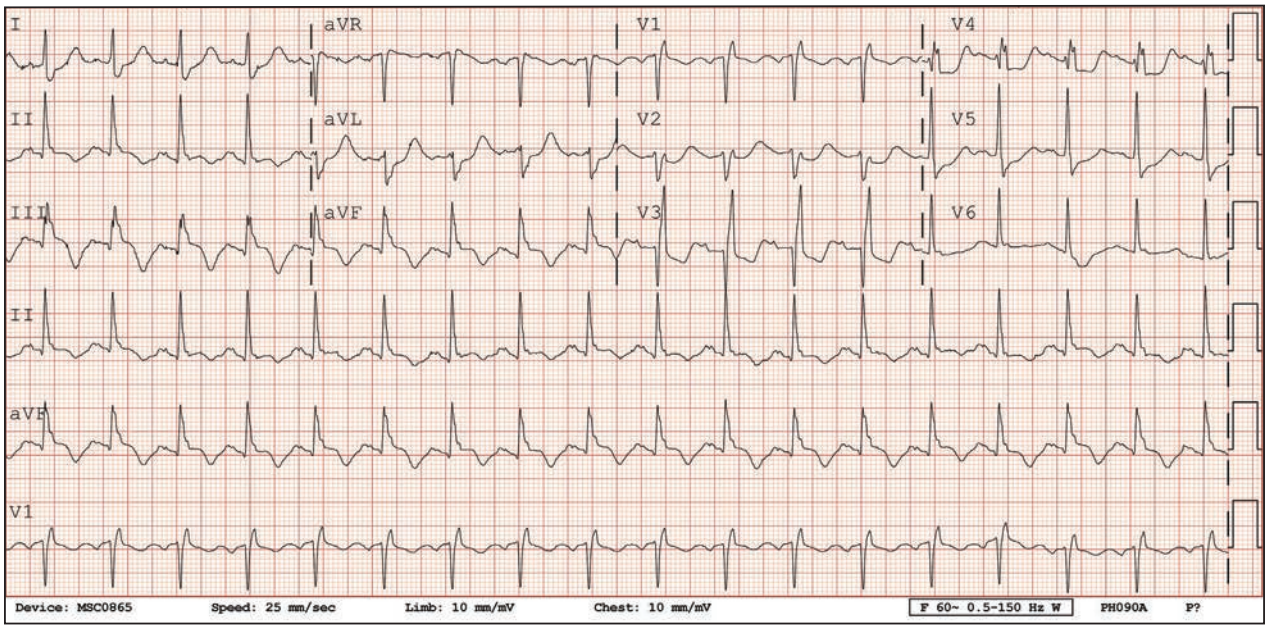

Figure 1: Initial ECG showing 1mm ST elevations in inferior leads

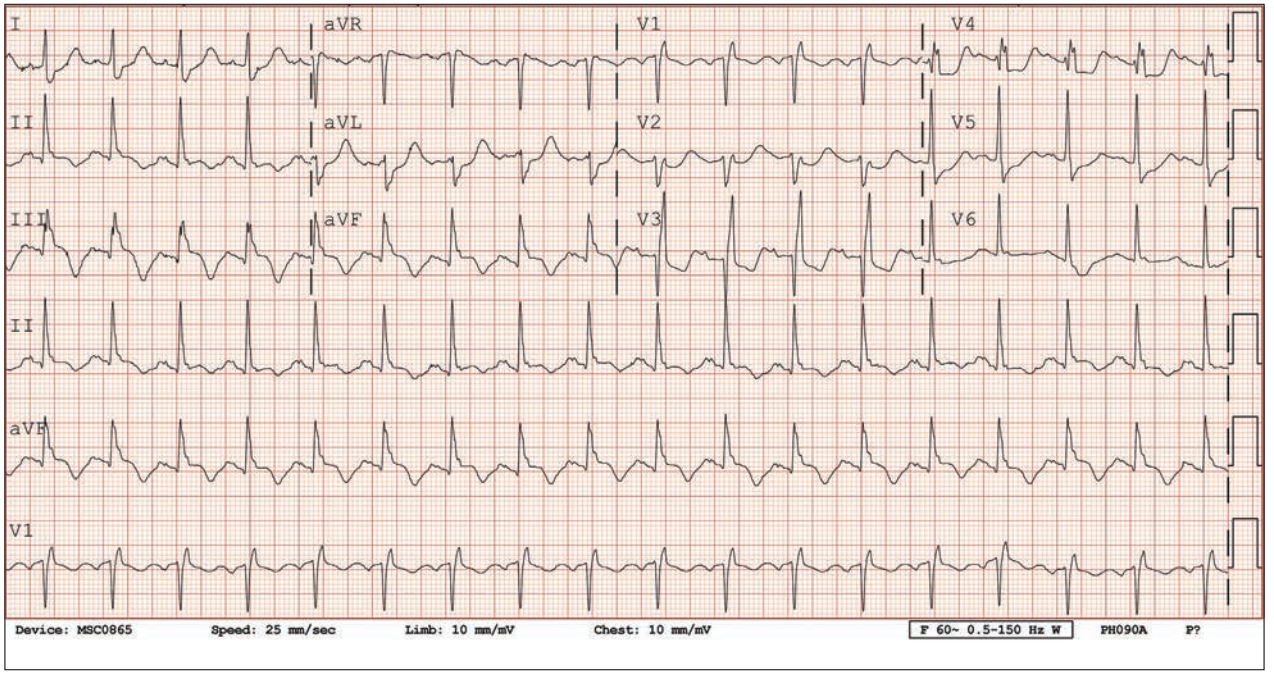

Figure 2: ECG taken 1 hour after presentation showing increase in inferior ST elevations to 2-3mm

her VSD was diagnosed, she had a balloon pump placed and she was taken emergently to the OR with successful repair of her defect. Unfortunately, after her procedure, she required significant vasopressor and inotropic support. She also developed and remained in complete heart block. After a week of aggressive medical therapy, her family ultimately elected to withdraw care.

DISCUSSION

While ventricular septal rupture is a well described complication of acute myocardial infarction, this case is relatively unique in that the diagnosis was made in the cardiac catheterization laboratory with the aid of contrast ventriculography. The incidence of VSD has decreased significantly after the advent of reperfusion therapy, from 2% of cases of infarction to as low as 0.2% described in the GUSTO trial.[1] However, it remains a problem with very high morbidity and mortality, especially in the setting of cardiogenic shock, as in this patient. It remains uniformly fatal without surgical intervention. This case helps highlight the importance of early and immediate recognition of VSD in facilitating emergency surgical repair. It also illustrates the importance of keeping VSD in the differential of acute hypotension during management of an acute myocardial infarction in the cardiac catheterization laboratory and the use of contrast ventriculography in making the diagnosis.

Ventricular septal rupture tends to occur 3 to 5 days after a myocardial infarction; however, cases have been described as recent as within 24 hours of an MI. Notably, this patient's initial MI was most likely 3 days prior to presentation to the ER. Risk factors include single vessel disease of the left anterior descending artery, advanced age, female sex, myocardial damage, massive MI, and poor septal collateral circulation.[2] In particular, patients with a "wrap-around" left anterior descending (LAD) appear to have an elevated risk. In the majority of individuals, the inferior third of the interventricular septum is supplied by the RCA; however, in some individuals the LAD extends beyond the apex, wrapping around to supply the inferior septum. Thus, these patients tend to have a higher risk of septal rupture in the setting of a STEMI, and ECG changes often show both anterior and inferior ST elevations.[3]

Patients present with hemodynamic compromise caused by biventricular failure, as well as a new harsh, holosystolic murmur heard best at the lower left and right sternal borders.[4] Patients may also have a palpable thrill and a hyperdynamic precordium. Among patients who are not reperfused, such as this patient, septal rupture is often associated with persistent ST elevation for greater than 72 hours.[5]

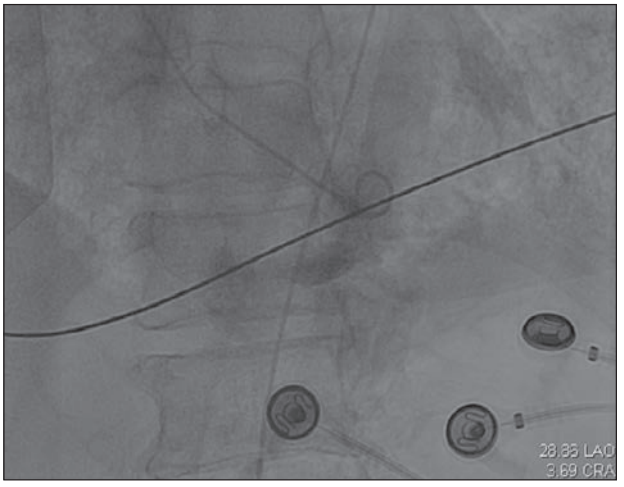

Figure 3: Contrast ventriculography showing a defect in the inferior wall of the left ventricle.

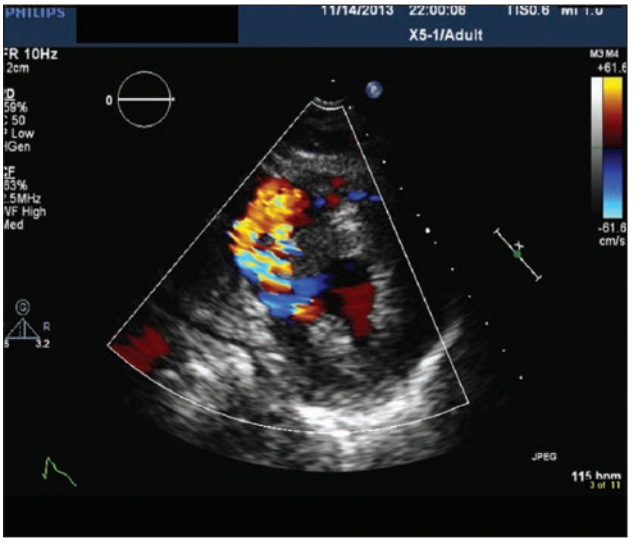

Figure 4: Parasternal short axis view with Doppler showing flow through the inferoseptal wall consistent with ventricular septal rupture

Diagnosis can be made in several ways. The gold standard remains insertion of a pulmonary artery balloon catheter which demonstrates a significant left to right shunt. Giant pulmonary capillary pressure V-waves may also occur secondary to volume overload and reduced atrial and ventricular compliance.[6] Two dimensional transthoracic echocardiogram can also visualize the defect directly. This ability is significantly enhanced with the use of color Doppler imaging, and one study

demonstrated that adding color Doppler improved the visualization of the VSD from 40% to 100%.[7] While left ventriculography can also be used to document the presence of the shunt, as in our patient, it tends to be unnecessary. However, with our patient presenting with acute cardiogenic shock while undergoing cardiac catheterization, it proved invaluable.

In patients presenting with frank cardiogenic shock, emergent surgery is required to prevent imminent death. Acute medical management involves afterload reduction with vasodilators and intraaortic balloon pump, which decreases the left to right shunt. Inotropic agents may also be used to increase cardiac output. Notably, several studies have also demonstrated that full revascularization of patients during operative repair of their VSD with bypass surgery also improves long term mortality.[8,9] Novel approaches are also being used, such as percutaneous closure in patients with contraindications to bypass surgery. However, long-term study outcomes of this procedure are currently unavailable.

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"The Amalfi Coast"
photograph by Michael Valentino

Anomalous Left Main Coronary Artery Originating from the Right Sinus of Valsalva

Silpa Yalamanchili, MS IV, Kevin M Curl, MD

INTRODUCTION

An anomalous left main coronary artery is a rarely seen clinical entity, particularly when it arises from the right sinus of Valsalva. This case report highlights this uncommon finding and how it affects the care of a patient with significant coronary artery disease.

CASE PRESENTATION

A 66 year-old male with a history of hypertension, hyperlipidemia, and type II diabetes presented with progressive exertional mid-epigastric and mid-chest discomfort. The patient stated that he had been feeling this "heaviness" with various activities and occasionally at rest for the past nine months. When it occurred with activity, the pain was generally relieved by rest within several minutes. His medications on presentation included insulin glargine, glyburide, metformin, simvastatin, pioglitazone, and lisinopril. Vital signs at the time of presentation included a temperature of 98.2°F, heart rate of 82 beats per minute, and blood pressure of 130/70 mmHg in both arms.

Laboratory investigation showed a total cholesterol of 178 mg/dL (normal range = 150-250), high-density lipoprotein (HDL) cholesterol of 42 mg/dL, low-density lipoprotein (LDL) cholesterol of 111 mg/dL, triglycerides of 123 mg/dL, and hemoglobin A1C of 7.9% (normal range = <5.7%). Pharmacologic nuclear stress testing revealed a severe, medium sized defect in the inferolateral wall that was predominately reversible. Thus, the patient underwent a cardiac catheterization which revealed an anomalous left main (LM) coronary artery arising from the right sinus of Valsalva separately from the origin of the right coronary artery (RCA). The distal left anterior descending artery (LAD) had a total occlusion, while the RCA had several areas of 70% stenosis. A subsequent coronary CT scan displayed an anomalous left coronary artery coursing anterior to the pulmonary artery (Figures 1, 2). The CT scan also showed moderate to high grade RCA stenosis in the mid to distal area of the vessel, as well as high-grade stenoses in the small-sized LAD and left circumflex arteries.

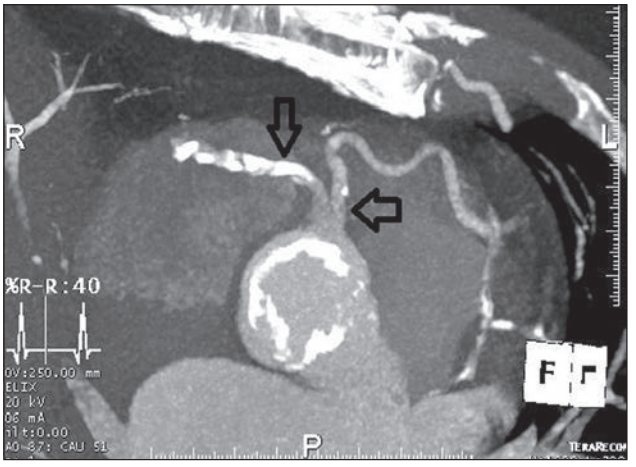

Figure 1. Coronary CT scan showing the separate origins of both the RCA (vertical arrow) and LM (horizontal arrow) from the right sinus of Valsalva.

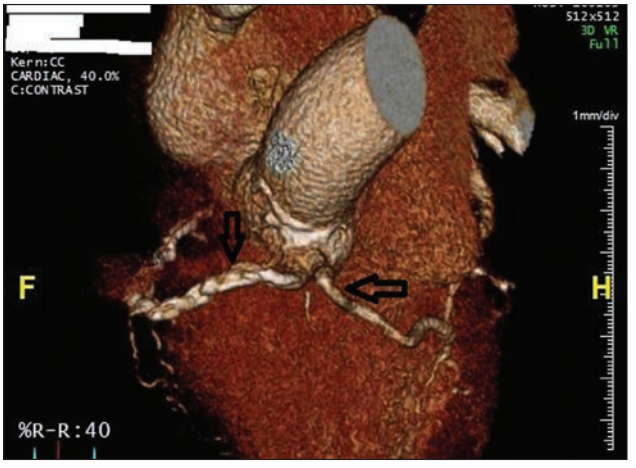

Figure 2. 3D coronary CT scan reconstruction again demonstrating dual origins of the RCA (vertical arrow) and LM (horizontal arrow) from the right sinus of Valsalva.

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OUTCOME AND FOLLOW-UP

This management of this patient is currently being discussed by a multidisciplinary team including his primary care provider, clinical cardiologist, interventional cardiologist and a cardiothoracic surgeon. It is felt that his anomalous coronary artery was an incidental finding and his uncontrolled medical co-morbidities have led to significant obstructive coronary disease causing his symptoms. Thus, aggressive medical management has been implemented while the patient's long term options are being reviewed, with a significant focus on tighter diabetic and lipid control.

DISCUSSION

An aberrant left main coronary artery originating from the right sinus of Valsalva is an extremely rare occurrence, with an incidence of 0.06% to 0.19% by angiographic study.[1] In such cases, the anomalous LM is classified into one of four categories based on its course in relation to the aorta and pulmonary trunk: (1) posterior or retroaortic; passing behind the aortic root, (2) interarterial or preaortic; passing between the aorta and pulmonary trunk, (3) anterior or prepulmonic; passing in front of the pulmonary trunk, or (4) septal or subpulmonic; passing within the interventricular septum, beneath the pulmonary trunk.[2] Of the four courses, an anomalous LM with septal course is the most common, while an anterior LM course is the least common.

While an anomalous LM with interarterial course is associated with myocardial ischemia or sudden cardiac death in young individuals,[1] an aberrant LM with an anterior, posterior, or septal course is generally considered benign.[3] Clinically significant symptoms associated with an anterior course are uncommon, but have been reported in two cases.[4] The most common symptoms of this variant include angina pectoris and myocardial ischemia in the absence of coronary artery disease.

Diagnostic evaluation of asymptomatic patients in which an anomalous LM is suspected is currently indicated only for those at highest risk of sudden cardiac death: young athletes and military personnel. In patients who present symptomatically, CT angiography is able to detect coronary anomalies nearly as effectively as coronary angiography.[5]

Symptomatic patients or young athletes with anomalous LM typically warrant surgical intervention, either by local repair of the anomalous segment or by coronary artery bypass and graft (CABG).[5] Other treatment options in these patients include medical management with beta blockers or coronary angioplasty with stent deployment.

KEY POINTS

Anomalous left main coronary arteries, although rare, can complicate the care of patients with clinically significant obstructive coronary artery disease.

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A Rare Case of Tumor Lysis Syndrome

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INTRODUCTION

Tumor lysis syndrome (TLS) is a metabolic disturbance caused by the destruction of rapidly dividing cancer cells following administration of cytotoxic chemotherapy. The subsequent release of intracellular material results in hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.[1] The clinical presentation of TLS, including acute kidney injury, results from these electrolyte abnormalities and can be life-threatening.[2] Here we present the second reported case of TLS in a woman with endometrial cancer.

CASE PRESENTATION

A 63 year old woman with newly-diagnosed endometrial cancer (International Federation of Gynecology and Obstetrics, FIGO, stage IVB) who received her first dose of carboplatin and paclitaxel four days earlier presented to the emergency room with shortness of breath and lower extremity swelling. Her physical examination was significant for a heart rate of 132 beats per minute and a respiratory rate of 26 breaths per minute. She was noted to have a harsh systolic murmur loudest at the right second intercostal space and a mildly distended abdomen. Chest radiography was unremarkable. A ventilation perfusion scan was negative for pulmonary embolism. Her labs at time of admission (Table 1) were consistent with tumor lysis syndrome. Based on the Cairo-Bishop criteria (described below), the diagnosis of tumor lysis syndrome was made.

OUTCOME AND FOLLOWUP

The patient received vigorous intravenous hydration with normal saline solution and treatment with intravenous rasburicase. After two doses of rasburicase her labs began to normalize (Table 1), and her symptoms dissipated. On the day of discharge all lab abnormalities had resolved, and the patient was discharged in stable condition.

Table 1. Laboratory Values

Lab Parameter (normal range at TJU)	Pre- chemotherapy	Admission	2 days after rasburicase
Serum potassium (3.5-5.0 mmol/L)	4.4	5.5	4.5
BUN (7-27 mg/dL)	14	68	65
Serum creatinine (0.7-1.4 mg/dL)	0.8	2.4	1.9
Serum phosphate (2.4-4.5 mg/dL)	n/a*	6.1	4.3
Serum calcium (8.5-10.5 mg/dL)	n/a*	8.3	8.3
Serum Urate (2.5-6.0 mg/dL)	n/a*	15	5.1

*values were not measured

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Table 2. Clinical Characteristics of Patients at High Risk for Tumor Lysis Syndrome
Tumors with a high proliferation rate and sensitivity to cytotoxic agents
Large tumor masses
Renal insufficiency and obstructive uropathy
Elevated serum lactate dehydrogenase or uric acid level
Dehydration

TABLE 3. Cairo-Bishop definition of laboratory tumor lysis syndrome in adults. Diagnosis requires two or more of the following abnormalities observed within three days before to seven days after initiation of chemotherapy:	
Uric acid	Greater than or equal to 8.00 mg/dL or 25% increase from baseline
Potassium	Greater than or equal to 6.00 mmol/L or 25% increase from baseline
Phosphorous	Greater than or equal to 4.5 mg/dL or 25% increase from baseline
Calcium	Less than or equal to 7.0 mg/dL or 25% decrease from baseline

Table 4. Cairo-Bishop definition of clinical tumor lysis syndrome in adults. Diagnosis requires meeting criteria of laboratory tumor lysis syndrome plus one or more of the following not directly or probably attributable to a therapeutic agent:	
1	Creatinine greater than 1.5 times upper limit of normal (our ULN = 1.4 mg/dL)
2	Cardiac arrhythmia/sudden death
3	Seizure

DISCUSSION

TLS is a rare but serious complication of cytotoxic chemotherapy. Malignancies with the highest risk of TLS are those with both high proliferative rates and tumor burden, particularly hematologic malignancies.[3] Solid tumors have a much lower incidence of TLS. A literature review found the highest incidence of TLS in small-cell carcinoma and breast carcinoma, with a few reported cases each in neuroblastoma, germ cell tumors, melanoma, and others.[4] While a few cases of TLS have been reported in association with gynecologic cancers,[5,6] there has been only one reported case associated with endometrial cancer. In this case from 2010, a 60 year old woman with recurrent FIGO stage IIB endometrial cancer developed TLS four days after receiving carboplatin and paclitaxel. The patient required hemodialysis and expired despite aggressive management.[7]

While TLS remains a rare complication of chemotherapy in patients with solid tumors, the clinical characteristics of patients at high risk for TLS should be recognized (Table 2).[8] In 2004, Cairo and Bishop proposed a system for diagnosing and classifying tumor lysis syndrome.

Table 3 describes the laboratory definition of TLS, and Table 4 describes the clinical definition of TLS. Acute kidney injury in TLS results from the release of nucleic acids from lysed tumor cells, which are degraded by xanthine oxidase to hypoxanthine, xanthine, and uric acid.[9] In the acidic environment that often occurs as a result of volume depletion, uric acid solubility decreases[10] and crystallization occurs in the distal tubules and collecting ducts. This crystallization obstructs the tubular lumen and leads to inflammation.[11] Uric acid may also contribute to acute kidney injury by crystal-independent mechanisms, due to its vasoconstrictive, anti-angiogenic, pro-inflammatory, and pro-oxidative properties.[12] The other features of clinical tumor lysis syndrome - tetany, cardiac arrhythmias, and seizures – also result from the metabolic derangements that occur when cancer cells are lysed by cytotoxic chemotherapy.[13] The patient described here did not exhibit these manifestations.

The treatment of tumor lysis syndrome is mainly supportive and includes cardiac and electrolyte monitoring, correction of electrolyte abnormalities, intravenous fluids (isotonic saline solution at 2500-3000 mL/m^2/24 hours), and renal replacement therapy if indicated.[14] Urinary alkalinization is controversial. The patient described here received four liters of normal saline and two doses of rasburicase. Rasburicase decreases uric acid levels by catalyzing the conversion of uric acid to allantoin, which is more soluble in urine.[15] This is in contrast to allopurinol, a prophylactic medication, which competitively blocks xanthine oxidase, preventing the conversion of purines to uric acid.[16,17] Once TLS is diagnosed, rasburicase is the appropriate therapy to eliminate the excess uric acid.[13]

KEY POINTS

Successful management and treatment of TLS is highly dependent on the prompt identification of clinical and laboratory characteristics, signs, and symptoms of patients at risk. The initiation of prophylactic measures, especially hydration and administration of allopurinol, and the early recognition and treatment of metabolic abnormalities using rasburicase can prevent the severe and life-threatening complications associated with TLS.

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Recurrent Unilateral Pleural Effusion from Constrictive Pericarditis of Unknown Etiology Requiring Pericardiectomy

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INTRODUCTION

Constrictive pericarditis is an uncommon cause of unilateral pleural effusion. In patient's who have repeated thoracenteses with no obvious cause for the pleural effusion, constrictive pericarditis should be considered. Right and left heart catheterization is used to diagnosis constrictive pericarditis by measuring filling pressures of the heart.

CASE REPORT

A 52-year-old man with a history of hepatitis C, hepatocellular carcinoma (HCC), status post liver transplant in July 2013, chronic kidney disease, gastroesophageal reflux disease and hypothyroidism presented with increasing dyspnea with minimal exertion and was found to have recurrent pleural effusion. Patient had been worked up as an outpatient for recurrent pleural effusion but no etiology had been found. Prior thoracentesis on three different occasions within a month had yielded exudative fluid with no evidence of malignant cells. The effusions re-accumulated within one week on each occasion. The patient had previously been treated with diuretics without resolution of his recurrent pleural effusion. With worsening of his renal function, diuretics had recently been discontinued. The patient denied shortness of breath at rest, cough and chest pain as well as fevers and chills. He also denied orthopnea and paroxysmal nocturnal dyspnea. Medications included tacrolimus, levothyroxine, omeprazole and a daily multivitamin. The patient has a history of prior alcohol abuse and prior tobacco use (10 pack years).

The patient's vital signs were significant for mild tachypnea (20 respirations per minute) with normal oxygen saturation. He initially appeared healthy and in no acute distress. He had jugular venous distention. Pulmonary exam was clear on the left with decreased breath sounds in the right mid- and lower-lung fields. There was mild, bilateral lower extremity pitting edema.

The patient's renal function was at his baseline (creatinine = 1.8 mg/dL, normal range 0.7 – 1.4). Complete blood count identified leukopenia, mild normocytic anemia, and thrombocytopenia. The patient's labs identified elevated pro-brain natriuretic peptide (2511 pg/mL, normal range <125 pg/ml) and normal hepatic function panel except mildly elevated total bilirubin (1.3 mg/dL, normal range 0.1 - 0.9 mg/dl). Chest X-ray in the Emergency Department identified a large right pleural effusion, increased from a study one week prior and associated right basilar atelectasis as well as a small left pleural effusion and background pulmonary edema. The patient was admitted and work-up for recurrent unilateral pleural effusion was initiated.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for an exudative unilateral effusion includes infectious etiologies, including tuberculosis and parapneumonic effusion. Additionally, there was concern for a malignant effusion secondary to the patient's history of HCC.

HOSPITAL COURSE

The patient's shortness of breath worsened over the first few days of hospital stay. He became more volume overloaded, with 2+ pitting edema in lower extremities and increasing ascites. He had a therapeutic thoracentesis every other day for three total occasions with a liter of pleural fluid removed each time. Pleural fluid labs showed an alkaline pH (7.63, normal 7.6 – 7.64), slightly elevated glucose (114 mg/dL, normal 75-100 mg/dl), elevated lactate dehydrogenase (LDH) of 115 IU/L (normal LDH is <50% of plasma), and increased

protein (3.5 g/dL). Serum LDH was 155 IU/L, yielding a pleural to serum LDH ratio of 0.7, consistent with an exudative pleural effusion. Cytology was negative for malignancy on each occasion.

The patient was scheduled for video-assisted thoracic surgery (VATS) for pleural biopsy and chest tube placement for continuous drainage of the pleural effusion. On pre-operative assessment, the cardiologist recommended a right heart catheterization (RCH) to evaluate pulmonary artery pressures. The RCH was significant for elevated right atrial, right ventricular, and pulmonary capillary wedge pressures. A left heart catheterization (LHC) was then planned to further evaluate the etiology of the patient's elevated right-sided pressures. Differential included left heart failure, constrictive pericarditis and restrictive cardiomyopathy. The LHC demonstrated elevated left ventricular end diastolic pressures with normal cardiac output. Hemodynamic respiratory alteration was inconclusive in distinguishing constrictive pericarditis from restrictive cardiomyopathy. An echocardiogram showed abnormal interventricular septal motion ("septal bounce"), findings consistent with both constrictive pericarditis and restrictive cardiomyopathy. The echocardiogram also showed mild pericardial thickening, making constrictive pericarditis the more likely diagnosis. Pericardiectomy, was discussed with the patient. The patient planned to be discharged and obtain a second opinion on treatment options.

Prior to planned discharge, the patient's status abruptly worsened with the development of ascites, progressive renal failure, and increasing shortness of breath requiring every other day thoracenteses. VATS at this time did not seem necessary as it would not treat the underlying condition. Because of the patient's clinical deterioration, pericardiectomy was pursued. The patient tolerated the procedure without complications. Right heart filling pressures decreased almost immediately after the procedure. The patient's renal function improved back to baseline and his right-sided pleural effusion did not re-accumulate. The patient was ambulatory on discharge. Final pathology of the pericardium showed chronic inflammation and fibrosis, consistent with constrictive pericarditis.

DISCUSSION

The majority of cases of constrictive pericarditis are idiopathic or viral in etiology, followed by post-cardiac surgery and post-mediastinal irradiation.[1] Most of the patients present with symptoms of chronic heart failure. Only a minority of patients present with recurrent pleural effusion, and those who do typically have a bilateral, transudative effusion.[2] That our patient had an unilateral, exudative pleural effusion was a red herring and caused significant diagnostic delay.

Postero-anterior chest x-ray is the initial diagnostic test of choice for evaluation of suspected pleural effusion and can identify as little as 200 mL of pleural fluid. Bilateral pleural effusion in a clinical setting suggestive of transudative effusion rarely require fluid analysis and can typically be treated by appropriately treating the underlying cause. Most common causes of transudative pleural effusion are increased hydrostatic pressure secondary to cardiomyopathy or liver cirrhosis. Less common causes include hypoalbuminemia, nephrotic syndrome, hypothyroidism, and mitral stenosis. The most common causes of exudative pleural effusions, on the other hand, are tuberculosis, malignancy, and parapneumonic effusion. Less common causes include pulmonary embolism, rheumatoid arthritis, pancreatitis, and post-myocardial infarction. Drugs and fungal infections are rare causes.

Our patient's abnormal right and left heart catheterization established diastolic heart failure as the cause of his pleural effusion, but the etiology of his heart failure was uncertain. Our differential included constrictive pericarditis vs. restrictive cardiomyopathy. Historically, clinically distinguishing these two entities has posed a significant challenge. Two-dimensional and Doppler echocardiography, pericardial visualization with CT scan or MRI and cardiac catheterization may be useful, but the diagnosis may remain equivocal after these tests in some patients.[3] Both cause diastolic heart failure with abnormal ventricular filling pressures. Typical hemodynamic measures during cardiac catheterization include early rapid filling and equalization of end-diastolic pressures in all four cardiac chambers, but these may also be present in patients with restrictive cardiomyopathy. Some authors have suggested that assessing dynamic respiratory changes that can be observed in patients with constrictive pericarditis during

cardiac catheterization may help distinguish these patients.[4] Definitive diagnosis requires pericardial or endomyocardial biopsy.

Despite the difficulty, clinically distinguishing constrictive pericarditis and restrictive cardiomyopathy is crucial, as their treatment differs greatly. Removing the fibrotic pericardium encasing the normal myocardium, a procedure known as "pericardial stripping" or pericardiectomy, treats constrictive pericarditis. With restrictive cardiomyopathy, however, the myocardium itself is impeding normal diastolic filling, and, thus, treatment is heart transplant.

Diagnostic uncertainty was a challenge for our patient. Our patient initially had a normal echocardiogram, but as his disease worsened his echocardiogram displayed a picture consistent with constrictive physiology, including mild thickening of pericardium and abnormal interventricular septal motion ("septal bounce"). Hemodynamic studies were inconclusive and the patient's abrupt clinical decline forced us to proceed with pericardiectomy based on clinical suspicion. Prior to pericardiectomy, our patient was warned that were pericardiectomy unsuccessful, indicating either myocardial atrophy due to prolonged constriction or a true diagnosis of restrictive cardiomyopathy, he would require a heart transplant.

Complete pericardiectomy remains the treatment of choice for constrictive pericarditis, as compared to partial pericardiectomy, and has been associated with lower peri-operative mortality and improved long-term survival. Like our patient, most patients with constrictive pericarditis have significant clinical improvement following pericardiectomy. The peri-operative mortality rate of pericardiectomy is 6%, most frequently secondary to low-output cardiac failure. Independent risk factors for increased risk of late mortality include increased age, higher pre-operative New York Heart Association (NYHA) class (class III and IV) and prior mediastinal irradiation. Myocardial atrophy after prolonged constriction can cause residual heart failure post-operatively despite successful pericardiectomy.[5]

KEY POINTS

Constrictive pericarditis is an infrequent cause of unilateral pleural effusion. This case was notable because etiology of his unilateral pleural effusion was unclear and his clinical status deteriorated quickly while the workup of his effusion was being completed. Constrictive pericarditis and restrictive cardiomyopathy must be on the differential when the etiology of pleural effusion is unclear. Imaging can suggest constrictive pericarditis; however, cardiac catheterization can further evaluate the patient's hemodynamics and strengthen the diagnosis.[5] Definitive diagnosis is made with pericardial biopsy. The treatment for constrictive pericarditis is total or partial pericardiectomy.

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An Unusual Atrial Mass: A Case Study

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BACKGROUND

This case highlights the evolution of a broad differential diagnosis when presented with a rare and diagnostically enigmatic clinical finding.

CASE PRESENTATION

A 43-year-old Puerto Rican male with a history of homelessness, intravenous drug abuse, and incarceration presented following an episode of syncope. His past medical history was notable for a recent diagnosis of granulomatous nephritis, thought to be secondary to isolated renal sarcoidosis. He had been treated with high dose prednisone and subsequently initiated on hemodialysis. On presentation, he complained of rigors, shortness of breath, cough, abdominal pain and coffee-ground emesis. On initial examination, the patient was ill-appearing, febrile, tachypneic and tachycardic. He was awake and oriented with no focal neurological deficits.

His sepsis evaluation included computed axial tomography (CT) scans of his chest, abdomen and pelvis. Imaging was notable for para-aortic lymphadenopathy, diffuse micro-nodular densities throughout the lungs, hilar and mediastinal lymphadenopathy, and advanced xanthogranulomatous pyelonephritis with extensive calcification of the right kidney. His blood and urine cultures grew a resistant strain of *Escherichia coli* and he was initiated on broad antibiotic coverage, delivered via a central venous catheter. Further evaluation for endocarditis included both transthoracic (TTE) and transesophageal (TEE) echocardiograms, which identified a well-demarcated, heterogeneous right atrial (RA) density measuring 1.7 x 1.6 cm. He was initiated on full anticoagulation for this presumed catheter-associated right atrial thrombus. A head CT demonstrated an abnormal 1.2 x 3.6 cm lobular hyper-density in the right frontal lobe with surrounding edema, and multiple dispersed punctate calcified hyper-densities.

Soon after presentation, the patient developed seizures and acute respiratory failure, necessitating intubation. His chest x-ray demonstrated progression of innumerable bilateral pulmonary micro-nodular densities. He underwent bronchoscopy, and pathology was notable for acute fibrinous and organizing pneumonia. Initial concentrated sputum smears were negative for acid-fast bacilli (AFB). He was, however, initiated on empiric anti-tuberculosis quadruple pharmacotherapy (RIPE) given his exposure risk, chronic immunocompromised state, and concern for miliary tuberculosis. He was eventually weaned from the ventilator and was extubated. Subsequently, a right-sided percutaneous nephrostomy tube was placed to relieve his obstructing xanthogranulomatous pyelonephritis. Cultures from the nephrostomy tube were notable for the growth of Mycobacterium Tuberculosis Complex (MTB), as were cultures from his bronchoscopy, confirming disseminated MTB. His original sputum cultures later grew MTB 19 days after collection.

Several weeks into his hospital stay, a lower gastrointestinal bleed prompted the discontinuation of his anticoagulation, necessitating re-evaluation of the right atrial mass. TTE revealed an expanded (4.2 x 3.3 cm) multi-lobulated, heterogeneous echo-dense RA mass extending towards the inferior vena cava/RA junction with new focal areas of brightness suggesting calcification. Hemodynamic assessment including orthostatics and central venous pressure estimation were normal. Although airborne precautions precluded endoscopic evaluation of the gastrointestinal hemorrhage, the imminent risk of the growing atrial mass prompted reinstitution of anticoagulation, which he was able to tolerate.

In the setting of disseminated MTB infection, the patient's chronic steroids were slowly tapered. However, he quickly developed a new facial droop, unilateral weakness and altered mental status. It was

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thought that his neurological change was secondary to tuberculous cerebritis. He was quickly re-initiated on high dose prednisone, and his mental status improved. He later developed recurrent polymicrobial bacteremia from his pyelonephritis and required a prolonged course of antibiotics. Nephrectomy was deemed to be prohibitively high risk in the setting of his multiple comorbid conditions.

As his infections were appropriately managed, a multidisciplinary approach in concert with cardiology, infectious diseases, radiology and interventional radiology was undertaken to further elucidate the etiology of his undifferentiated atrial mass. Given his multiple co-morbidities, poor functional status and chronic immunosuppression, invasive diagnostics were deferred, and it was decided that he would be continued on empiric anticoagulation in combination with RIPE therapy for both thrombus and atrial tuberculoma.

DIFFERENTIAL DIAGNOSIS

The patient presented with a previous pathological diagnosis of renal-limited sarcoidosis and had been treated with several months of high-dose corticosteroids. He then developed persistent fevers, neurological deficits, miliary pulmonary infiltrates, calcified cerebral hyper-densities, presumed enteritis, xanthogranulomatous pyelonephritis, and an atrial mass. Initially, a diagnosis of systemic sarcoidosis remained high on the differential. Given the patient's immunocompromised state, polymicrobial infections, and progression of systemic manifestations on corticosteroids, also included in the initial differential diagnosis were lymphoproliferative disorders, neoplasms, and infections (including disseminated tuberculosis).

An intra-cardiac mass is an uncommon finding that carries a broad differential diagnosis, including thrombus, vegetative endocarditis, myxoma, myosarcoma, rhabdomyosarcoma, infiltrative lymphoma, secondary deposits and cardiac tuberculoma.

OUTCOME AND FOLLOW-UP

Following institution of RIPE therapy for disseminated tuberculosis, targeted antimicrobials for bacteremia, steroids for tuberculous cerebritis and empiric anticoagulation for his atrial mass, the patient's clinical status improved. He has remained hemodynamically stable, precluding the need for surgical intervention of his atrial mass. He will require monthly monitoring with TTE, a prolonged course of RIPE, and long-term anticoagulation for management of his disseminated tuberculosis and undifferentiated right atrial mass.

DISCUSSION

The constellation of findings presented in this case represent a broad differential diagnosis, including systemic sarcoidosis, lymphoproliferative disorders, and infections.[1] Sarcoidosis and lymphoproliferative disorders are known to involve the lungs, kidneys, central nervous system, gastrointestinal tract and reticuloendothelial system. However, the isolation of MTB from two separate sources in an immunocompromised patient at high risk for previous MTB exposure makes the diagnosis of primary or reactivation disseminated tuberculosis most likely.[1-3] With strong clinical, microbiological and radiographic evidence supporting a diagnosis of disseminated tuberculosis, the immediate institution of RIPE and rapid identification and management of potential end-organ complications is paramount. [3]

Less than 1.5% of all MTB infections disseminate lymphohematogenously. Most often the lungs are affected, but, after lymphadenopathy, the next most common manifestations of non-pulmonary tuberculosis include gastrointestinal and hepatic (80%), genitourinary (27%), and meningeal (20%).[1,4,5] Infiltration of the myocardium is uncommon, and the documented incidence of intra-cardiac tuberculoma is rare, with a majority of cases diagnosed at autopsy.[6]

The few reported cases of cardiac tuberculoma diagnosed in vivo describe single or multiple well-circumscribed, heterogeneous masses often occupying the right atrial free wall.[6-9] Echocardiography is often used to characterize size, location and echogenicity. Magnetic Resonance Imaging is able to provide more detail, but often fails to distinguish tuberculoma from thrombus and myxoma.[7] Percutaneous biopsy under echocardiographic guidance provides a means of sampling the mass. However, identification of characteristic histopathological findings lacks sensitivity, and most reports indicate unacceptable yields for identification of MTB following Ziehl-Neelsen staining.[6,7,9] A confirmatory diagnosis requires invasive removal of the mass for

gross histopathological diagnosis.[7] Few studies have demonstrated successful reduction in size, and even complete resolution of cardiac tuberculomas following appropriate anti-tuberculosis pharmacotherapy alone.[6,8] Surgical intervention is indicated if the mass results in clinically significant hemodynamic compromise, or if diagnosis remains unclear after pharmacotherapy has failed to demonstrate improvement by imaging.[6,8,9]

Given the patient's encouraging response to anti-tuberculosis pharmacotherapy and anticoagulation, as well as persistently stable hemodynamics, further diagnostics of the right atrial mass were deferred. The risk of interventional diagnostics were thought to outweigh any benefits, given that the treatment plan of combining anticoagulation with RIPE therapy would remain unchanged.

KEY POINTS

Cardiac tuberculomas are a rare complication of disseminated MTB infection and should be considered in the differential diagnosis of an intra-cardiac mass in a patient with proven MTB. With strong clinical and radiographic evidence, and without hemodynamic compromise, invasive diagnostics may be deferred in favor of empiric medical management.

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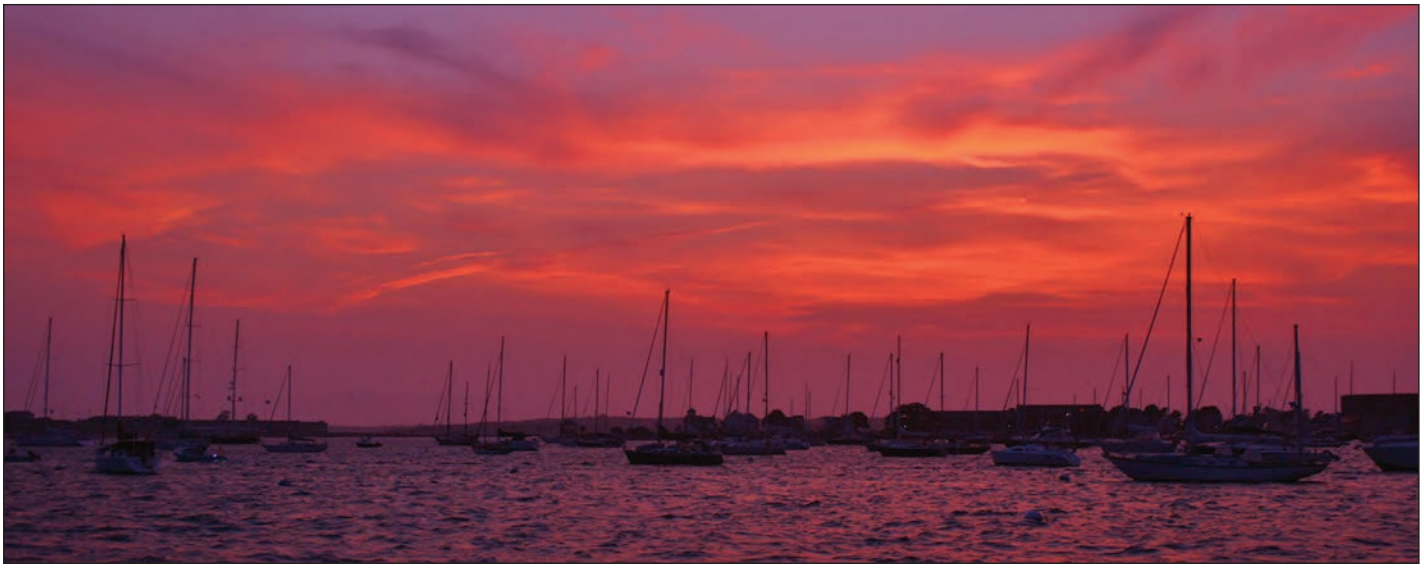
"Sunset over Naraganssett Bay, Rhode Island"
photograph by Andrew Zabolotsky, MD



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A Case of Complete Heart Block Secondary to ANCA-Associated Vasculitis

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INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides are systemic autoimmune diseases that often present as non-specific prodromal symptoms such as fever, fatigue, headache, and weight loss.[1] With modern treatment, the disease has changed from being universally fatal to being treatable. It can have a chronic relapsing and remitting course. Therefore, early diagnosis is necessary.[2,3]

CASE PRESENTATION

A 53-year-old male with a past medical history of chronic sinusitis and some epistaxis needing multiple courses of antibiotics and steroids, was admitted after being diagnosed with high-grade heart block at another institution. He was found to have a heart rate of 26 and was given a temporary pacemaker prior to the transfer. Subsequently, a dual-chamber pacemaker was placed. An echocardiogram showed mild aortic stenosis and regurgitation with right ventricular enlargement and an ejection fraction of 65%. No etiology was found for the heart block and work up was negative for medications, electrolytes, ischemia, significant structural heart disease or lyme disease. Pacer placement was without any complications. The patient was discharged home and did well for 10 days and then returned again to the emergency room with complaints of dry cough, chest pain, progressive shortness of breath, fatigue, and fever to 101.2 degrees Fahrenheit. He reported a fifteen pound weight loss over the past month. His family history was noncontributory. He worked as an auto mechanic and reported former cocaine use over 20 years ago. He had no history of tuberculosis exposure and was up to date on his screening colonoscopy.

Physical exam findings included mildly congested bilateral nares with some postnasal thick secretions. On careful examination, he had "saddle nose" anatomy that he claimed to have noticed just months prior to presentation. Auscultation of his lungs revealed crackles diffusely and posterior left lung base egophony but no wheezes. The lung findings were new as compared to the recent admission for heart block. There was nothing significant on the basic laboratory tests. Chest x-ray and CT scan on admission revealed diffuse bilateral airspace opacities and nodule consolidation with mediastinal and right hilar adenopathy. These findings were suspicious for multifocal pneumonia with a separate infectious inflammatory process.

DIFFERENTIAL DIAGNOSIS

On initial presentation the differential diagnosis ranged from infectious to autoimmune to malignant pathology. There was initial concern for tuberculosis, pneumonia or malignancy.

HOSPITAL COURSE

Blood, urine and sputum cultures didn't identify any bacterial or fungal infectious etiology. AFB stains were negative. He underwent bronchoscopy to better evaluate the lung process and biopsy was performed revealing mild interstitial pneumonitis and intraalveolar red blood cells. Further in the course, patient developed acute kidney injury with a baseline creatinine of 0.9 mg/dl that peaked at 2.0 mg/dl. He had no evidence of oliguria or dysuria. Based on his constellation of signs and symptoms, he underwent a work-up for vasculitides. This included pertinent negatives for the following lab studies: HIV screening, hepatitis serologies, anti-nuclear antibody (ANA), double stranded DNA (dsDNA), reduced complement levels, basement membrane antibody, anti-Ro/anti-La antibodies, and quantiferon assay. ANCA screen came back positive for p-ANCA (antimyeloperoxidase). A kidney biopsy revealed interstitial granulomatous inflammation with pauci-immune staining that was consistent with p-ANCA related glomerulonephritis. He was started on high-dose pulse steroids and cyclophosphamide.

DISCUSSION

This patient's prodromal flu-like symptoms of fever, fatigue, and weight loss were classic for the initial vasculitis presentation.[1,4] His history of chronic sinusitis and epistaxis that was best relieved by steroids was also an indication of vasculitic disease.[5] The lung biopsy showing hemorrhagic alveolar infiltrate and kidney biopsy showing glomerulonephritis were most consistent with granulomatosis with polyangiitis (GPA). However, no granulomatous vasculitis or pulmonary capillaritis were seen in his lung biopsy. Large observational studies have shown that rhinology, pulmonary, and renal are the systems most commonly affected in this spectrum of diseases.[6] This patient presented with heart block prior to the typical vasculitic symptoms. As no clear cut etiology was found for his heat block, there was a high suspicion for vasculitic origin of his heart block. On our review of literature, we found small number of case reports that reported first degree to complete heart block in patient's with GPA and other vasculitides.

ANCA-associated vasculitis is a subset of small-vessel vasculitis and includes GPA, eosinophilic granulomatosis with polyangiitis (EPGA), and microscopic polyangiitis (MPA). It is usually found in older adults but is reported in all ages.[5] GPA specifically shows granulomatous inflammation of the respiratory tract and abnormal urinary sediment. MPA shows no granuloma formation. EPGA shows characteristic rhinitis, asthma, and eosinophilia.[7]

Cardiac complications of GPA are thought to be rare. While involvement of heart has been reported to be around 30% at autopsy in known GPA, clinical cardiac involvement is low.[8] A recent report indicated evidence of cardiac involvement in 8% to 16% at the time of diagnosis and upto 25% during the course of the disease. 9 The predominant cardiological involvement has been pericarditis (effusion), coronary arteritis and myocarditis (left ventricular dysfunction) on pathology.[10] Valvuvar and conduction defects have been rarely described in the past. More recently, there have been increasing number of reports of conduction disease defects as well as valvular abnormalities associated with GPA. GPA can have pathological involvement of aortic or mitral valve, causing valvulitis leading to regurgitation as predominant valve dysfunction.[9] GPA has also been associated with bundle branch blocks to all grades of heart block. These are thought to be from granulomatous inflammation involving the AV node or the bundle of his.[11] We believe that our patient's heart block was associated with GPA. The close time between the two diagnosis, as well as similar sequence of events like diagnosis of heart block first and then diagnosis of GPA in some other case reports substantiate our association. Heart block has been reversible with treatment of GPA with immunosuppression in some literature.[12-14]

The approach to treatment of ANCA associated vasculitis can be divided into two categories: mild disease and moderate to severe disease. For mild disease, with no evidence of glomerulonephritis or organ-threatening disease, a regimen of glucocorticoids in combination with rituximab or methotrexate should be started. If the disease is refractory to methotrexate treatment the patient should have a trial of cyclophosphamide. Moderate to severe disease demonstrates organ damage and has a less defined recommendation for treatment. Overall, literature supports either a cyclophosphamide or rituximab-based regimen in combination with glucocorticoids.[3] Prophylaxis against opportunistic infections during induction immunosuppression is also suggested. Our patient's heart block resolved before starting steroids, so it was likely a temporary block.

KEY POINTS

ANCA-associated vasculitis can initially present with prodromal flu-like symptoms and signs of inflammation. Thought not very common, ANCA-associated vasculitis can be associated with cardiac valvulopathy and conduction abnormalities. Patients presenting with heart block and recent history of or current symptoms of inflammatory or infectious disease, should be screened for GPA and vasculitides in addition to lyme disease and viral myocarditis work up. If caught early, heart block due to vasculitis is potentially reversible and can save a patient from unnecessary procedures. The management consists of immunosuppression with steroids and other agents.

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"Sunset at the Jersey Shore"
photograph by Michael Valentino, MD, PhD

Hepatitis C Therapy: Serendipitous Successes

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INTRODUCTION

Hepatitis C virus (HCV) infection is a growing epidemic worldwide, with about 170 million cases reported by 2011.[1] New therapies have been introduced to the market, but the prior mainstay of therapy involves pegylated interferon-alpha (IFN) along with ribavirin (RBV).[2] Treatment with the first generation direct-acting antiviral agent-containing regimens consisted of at least 24 weeks of therapy, with the goal of sustained viral response (SVR) – no detectable virus 24 weeks after treatment is completed. We report two cases in which therapy was terminated early due to the developed of severe infection, yet the patients still achieved SVR.

CASE REPORT

Case 1

A 54 year old woman with a benign meningioma, who had recently had the tumor resected, was found to have abnormal liver function tests. Subsequent testing revealed she had chronic HCV infection, genotype 3a, with a baseline viral load of $1.57x10^6$ IU/mL. There were no signs of chronic liver disease on exam, and an ultrasound of her abdomen revealed normal liver echogenicity without cirrhosis or hepatocellular carcinoma. 24 weeks of IFN and RBV was planned. After 4 weeks of treatment, she had no detectable virus (rapid virologic response). Although she tolerated the therapy, after 5 weeks of initiation, the patient developed a wound infection at the bifrontal craniotomy surgical site requiring a re-operation. The treatment was terminated and no further treatment plans were made with an IFN-based regimen. 24 weeks after early termination of treatment, at just 5 weeks, the patient had SVR and was feeling well.

Case 2

A 63 year old man with history of melanoma and thyroid goiter, presented for retreatment of genotype 1 HCV with cirrhosis after relapsing to a prior 48-week course of IFN and RBV, two years earlier. He was Child-Pugh class A and had no evidence of liver decompensation on examination. His baseline HCV RNA was $1.50x10^6$ IU/mL. He started treatment with IFN, RBV and telaprevir. He experienced side effects of therapy including anorectal burning, constipation, fatigue, and anemia requiring erythropoetin injections. He also achieved rapid virologic response at one month into therapy. Three months into therapy, the patient developed an abscess in the right axilla, which required surgical drainage and an indwelling drain. Antiviral therapy was terminated at that time. 64 weeks after termination of treatment, the patient remains in SVR with no complaints.

DISCUSSION

HCV infection is a leading cause of chronic liver disease worldwide.[3] While many patients with HCV may have a normal life expectancy, about 30% progress to end-stage liver disease, with the complications of cirrhosis and hepatocellular carcinoma.[1] Due to this threat of severe disease, much focus on developing effective therapies has occurred over the past ten years.[2] The mainstay of therapy has been IFN, which is used synergistically with RBV, likely through multiple mechanisms of action.[2] IFN is thought to inhibit HCV replication by inducing IFN-stimulated host genes that have antiviral functions. It also induces viral clearance, along with displaying biochemical and histological benefits.[4] This combination has been used in chronic HCV infection with rates of SVR estimated to be 31-67% depending on the HCV genotype, the dosage of IFN and RBV, and the duration of therapy[4]. Newer agents have recently been introduced, some of which act directly on viral targets, and others target host proteins essential to replication. The most commonly used agents from 2011-2013 were telaprevir and boceprevir, which are inhibitors of the N3/4A protease. A newer once daily protease inhibitor, simeprevir, and the first HCV polymerase inhibitor, sofosbuvir, are also now available in the US and more

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than 15 agents are expected to be approved in the next four years. Future treatment looks to be IFN-free for most patients.

Response to HCV therapy has traditionally been monitored by measuring quantitative HCV RNA by a sensitive assay at weeks 4, 12, and 24 followed by 4 to 12 week intervals, at the end of treatment, and at 24 weeks after stopping treatment rather than by a clinical endpoint. The goal of therapy is to obtain SVR, which is defined as the absence of HCV RNA from serum at 24 weeks following discontinuation of therapy.[5] The achievement of SVR depends on HCV genotype, the interferon lambda 28B region in the host, and the early viral kinetics of treatment.[1] How quickly the virus is eliminated correlates with the rate of SVR [6], which is measured by rapid virologic response (RVR), defined as undetectable HCV RNA at week 4 of treatment. Patients who achieve an RVR may be able to shorten the duration of treatment but only 15-20% of persons with HCV genotype 1 infection and 66% with HCV genotype 2 and 3 infections achieve an RVR.[7] In our cases, both patients achieved RVR, predicting that their shorter courses may have been enough to achieve SVR.

While IFN and RBV have proven to be an effective combination in the treatment of HCV, they are associated with an often poorly tolerated side effect profile, leading to early termination of therapy in some patients. The most common adverse events include fatigue, headache, fevers, injection site reaction in greater than half of the patients, along with psychiatric side effects in 22-31% of patients.[5,8] Lab abnormalities are common, with neutropenia being a frequent indicator for IFN dose reduction or discontinuation.[1,5] Despite discontinuation of IFN being common in clinical practice for this reason, it has been shown that IFN-induced neutropenia does not necessarily predict the incidence of serious infection.[5,9] In our cases, IFN is likely implicated in increasing the patients' risk of infection

Typically early termination of therapy results in reduced efficacy of treatment, measured by rates of SVR. To achieve full efficacy, patients are expected to undergo greater than 80% of prescribed duration of treatment.[10] Patients who discontinued treatment prematurely had an SVR rate of 12% compared with 65% of those who continued treatment despite dose reduction.[11] Minimizing the duration of treatment has been investigated, due to the cost of therapy and side effect profile. In a study performed by Yu et al, it was found that SVR might be achieved for patients receiving a short treatment course of 8-16 weeks with IFN and RBV in genotype-2 patients with a RVR at week 4. It was also shown that a treatment duration of less than 20 weeks is likely inadequate for genotype-1 patients, before the advent of direct-acting antiviral agents.[4] It is unusual, as in our case, that SVR would be obtained in such a short treatment period. It raises the question as to whether concomitant severe infection while on IFN-based therapy may somehow enhance treatment success – a question that has not been thoroughly addressed in the literature to date. With the advent of new IFN-free therapies with shorter treatment durations and improved side effect profiles, including combinations of protease, NS5A, and polymerase inhibitors, with or without RBV, being evaluated and introduced to the market,[2] the study of early termination may not be relevant much longer, but remains an interesting medical curiosity.

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"Summer Love"
photograph by Michael Valentino

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A Case of Septic Portal Vein Thrombosis (Pylephlebitis)

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INTRODUCTION

Pylephlebitis, defined as suppurative thrombosis of the portal vein often associated with bacteremia, is a rare and serious complication of intra-abdominal infections. Prior to antibiotics, the mortality rate of this disease approached 100%.1 The veins adjacent to the infection are the first to be involved, with later spread to the portal vein and possibly the mesenteric and splenic veins.[2-3] Extension into the mesenteric veins can lead to bowel necrosis and increased morbidity and mortality.[2-4]

CASE PRESENTATION

A 63-year old male with a history of hypertension presented to the emergency department with one week of progressively worsening malaise, chills, severe fatigue, and right upper quadrant abdominal pain. He was tachycardic with a heart rate of 120 and hypotensive to 70/30 mm Hg. Exam revealed a mildly distended abdomen with tenderness to palpation in the right upper quadrant and right lower quadrant. Laboratory studies were significant for a leukocytosis with bandemia and an elevation of the total bilirubin and alkaline phosphatase. Abdominal CT scan showed mucosal thickening involving the rectosigmoid colon. Nodular rounded lesions containing bubbles of air, concerning for multiple abscesses, ran the length of the recto-sigmoid colon and extended into the mesentery. A thrombus was noted in the main portal vein and superior mesenteric vein. There was heterogeneity in the left hepatic lobe consistent with multiple hepatic abscesses. Of note, the patient had a recent colonoscopy showing multiple sigmoid diverticulae. He was started on broad-spectrum antibiotics with vancomycin and piperacillin-tazobactam. He briefly required vasopressor support. A heparin drip was also started to manage the portal vein and superior mesenteric vein thrombosis. Blood cultures eventually grew group C streptococcus, and vancomycin was discontinued per the susceptibility pattern. The patient was treated in the hospital for 14 days and was discharged on oral amoxicillin-clavulanic acid for 14 additional days. During his stay, the patient was bridged to warfarin with a goal INR of 2-3.

DIFFERENTIAL DIAGNOSIS

Upon presentation, the patient met severe sepsis criteria and the focus was on resuscitation. The initial radiology report was misinterpreted as concerning for sigmoid cancer with hepatic metastasis, though the portal vein thrombosis was correctly identified upon re-examination with the staff radiologist.

OUTCOME AND FOLLOW-UP

Despite the initial delay in diagnosis, the patient was still treated appropriately given his presentation. Surgery was consulted; however, since there were multiple small abscesses and no single large area to drain, it was decided to repeat imaging after two weeks of antibiotic treatment. On the repeat CT, the abscesses had resolved, but the portal vein thrombosis persisted. The patient showed great improvement over his hospital course, and was doing well at his one month follow-up with his primary care doctor. He was treated with warfarin for a six month course.

DISCUSSION

The most common presentation of pylephlebitis is fever and abdominal pain.[4] Laboratory abnormalities generally include leukocytosis with a left shift and elevations in alkaline phosphatase[5,6] Our patient fit these criteria.

Infections such as appendicitis and diverticulitis are the most frequent predisposing conditions to pylephlebitis, though other intra-abdominal infections have also been implicated [1,7]

Blood cultures are positive in 23-88% of patients.[1-4] When positive, organisms are usually bowel flora with

Bacteroides fragilis and *Escherichia coli* being the most common.[2-4] This patient grew group C streptococcus, which is somewhat less common, and his source was diverticulitis. The diagnosis depends on identifying an abdominal source of infection with an accompanying portal vein thrombus[8-11] CT is most useful in both respects.[5,8,9] Much of the increase in incidence of this disease can likely be attributed to the more prevalent use of CT.[8-12]

Once a diagnosis is made, the patient should be started on parenteral antibiotics, usually a third generation cephalosporin, a fluoroquinoline plus metronidazole, an extended spectrum penicillin or carbapenem for four to six weeks.[1,13] Once clinical improvement is observed, the patient can be transitioned to oral antibiotics. Usually, the recommended oral regimen is metronidazole plus a flurorquinolone;[13] however, under the guidance of an infectious disease specialist and the culture sensitivities, this patient was discharged on amoxicillin-clavulanic acid. Sometimes the infectious source may need drainage, but otherwise surgical intervention is not indicated for this condition.[14] There is no substantial evidence based medicine on the use of anticoagulation.[1,3,13]

Limited data shows that anticoagulation may have a role in the case of mesenteric vein thrombosis to prevent bowel ischemia.[15] Since this patient had SMV thrombosis, the decision was made to anticoagulate. While there is little data to support the use of anticoagulation, these are situations in which it could potentially decrease morbitity and mortality on a case-by case basis.

KEY POINTS

The mortality of pylephlebitis is estimated to be 11-32%.[1,3,5] Prompt diagnosis and treatment are necessary for a good outcome. This diagnosis should be considered in all patients with abdominal pain and fever who are found on CT to have an intra-abdominal infection with a portal vein thrombus. Draw blood cultures and treat with antibiotics for 4-6 weeks.[9]

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A Case of Fanconi's Syndrome in a Patient with HIV

Mariam Kabir MD, PhD, Christopher Miller MD, Rakesh Gulati, MD, MRCP, William R. Short MD, MPH

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue reverse transcriptase inhibitor (NtRTI), which blocks reverse transcriptase, an enzyme found in HIV. Since its approval for use in HIV by the FDA in 2001, it has contributed to effective treatment in numerous patients. The most common side effects include nausea, vomiting, diarrhea, asthenia, abdominal pain and hepatotoxicity. A less common side effect is nephrotoxicity leading to Fanconi's syndrome. Here is an interesting case of Fanconi's Syndrome caused by Tenofovir.

CASE

A 50-year-old Caucasian female with a past medical history of HIV and Hepatitis C presented to the Emergency Department with hypokalemia and acute renal failure. She had been diagnosed with HIV in 2003 and was being managed on co-formulated Truvada (Emtracitabine/Tenofovir) and Efavirenz since 2008. She was previously on Lamivudine/Zidovudine and Efavirenz, which were discontinued due to side effects. Over the past month, the patient was noted to have hypokalemia and worsening serum creatinine (sCr), which was being treated with potassium supplements and avoidance of NSAIDs. On presentation she denied any diuretic use, nausea, vomiting, diarrhea, weakness, fatigue, paralysis, palpitations, syncope, lightheadedness or chest pain.

The patient's HIV was under good control (last CD4 count of 1400 cells/mm3 and viral load undetectable at <20 copies/ml), and her viral load for hepatitis C was negligible (HCV RNA quantitative real time PCR <43 IU/ml). She did not have any history of seizure disorder, refractory migraine or use of drugs such as zonisamide or carbonic anhydrase inhibitors. Pertinent medications included Truvada 1 Tablet every 48 hours and Efavirenz 600 mg at bedtime. She had no drug allergies. Social history was only positive for 1 pack per day of cigarette use for many years.

On physical exam the patient was afebrile and her vital signs were stable. She appeared to be in no apparent distress. She was alert and oriented to time, place and self. She did not have any scleral icterus or thrush in her throat. She had moist mucous membranes. Her pulmonary, cardiovascular, abdominal and neurological exams were normal. She did not have any costrovertebral angle tenderness. She also had no pedal edema.

Her laboratory data were as follows: sodium 135 mmol/L (normal 135-146mmol/L), potassium 1.9 mmol/L (normal 3.5-5mmol/L), chloride 97 mmol/L (89-109 mmol/L), bicarbonate 22 mmol/L (24-32 mmol/L), BUN 20 mg/dL (normal 7-26 mg/dL), creatinine1.7 mg/dL (0.7-1.4 mg/dL), anion gap 16 mmol/L (4-16 mmol/L), magnesium 1.9 mEq/L (1.3-2.1 mEq/L), phosphate 2 mg/dL (2.4-4.5 mg/dL)(low). Urinalysis showed yellow urine with a pH of 7.0, 1+ Glucose, 1+ protein, urine potassium 13 mmol/L, urine osmolality 211 mmol/L, serum osmolality 293 mmol/L. Serum creatinine and potassium in 2008 were 0.8 mg/dL and 3.6 mmol/L respectively, and 1mg/dL and 3.5 mmol/L six months ago. Renal ultrasound showed mildly echogenic kidneys suggesting renal parenchymal disease.

DIFFERENTIAL DIAGNOSIS AND HOSPITAL COURSE

Given her glycosuria, proteinuria, hypophosphatemia in addition to hypokalemia and acute renal failure, a diagnosis of renal tubular acidosis type 2 and Fanconi's Syndrome was made. The etiology of this was thought to be her Tenofovir use (part of the Truvada combo); she had been receiving this for the past 5 years. Based on our consulting nephrologists recommendations, her Truvada was discontinued, her potassium was repleted with both intravenous and oral supplements, and her

renal function improved with intravenous hydration. At the time of discharge her Creatinine was 1.1 mg/dL and her potassium was 2.8 mmol/L. She was discharged with oral potassium supplementation and appropriate follow up with her infectious disease doctor.

DISCUSSION

Tenofovir is available in combination with Emtricitabine in a product with the brand name Truvada. It is also available in a single tablet regimen, Atripla, which contains Tenofovir, Emtricitabine and Efavirenz. Tenofovir is the only NtRTI approved for use in HIV.[1] It is also approved for the treatment of chronic hepatitis B and as pre-exposure prophylaxis against HIV infection.[1]

Tenofovir has been deemed a suitable NtRTI secondary to less adverse effects on blood lipids and less mitochondiral toxicity. It was also found to have less renal toxicity in early randomized clinical trials.[2] Although initially there were concerns given Tenofovir's molecular/structural similarity to other nucleotide analogs Adefovir and Cidofovir, which cause proximal tubulopathy by decreasing mitochondrial DNA replication (inhibits mtDNA polymerase), it was found that mtDNA depletion was negligible with Tenofovir.[3] However in other studies, Tenofovir has been shown to be nephrotoxic to proximal tubular cells.[4] The discrepancy is thought to be secondary to the strict inclusion and exclusion criteria applied in the clinical trials.[4]

Nephrotoxicity from Tenofovir can result in proximal tubular dysfunction with normal renal function, or with acute or chronic renal failure. The renal failure can happen months to years after starting the drug. The major renal biopsy finding is proximal tubular injury, ranging from mild and localized to diffuse and severe. This is associated with varying degrees of chronic tubulointerstitial scarring (i.e., tubular atrophy and interstitial fibrosis).[5]

The proximal tubulopathy results in Fanconi's syndrome, either partial or complete.[6] Complete Fanconi's syndrome consists of renal tubular acidosis, glycosuria with hypophosphatemia, aminoaciduria, hypouricemia and tubular proteinuria. Renal function decline may follow tubular dysfunction.[7] B2-microglobinuira is prevalent. [8] Patients may have osteomalacia secondary to phosphate wasting and calcitriol deficiency, since calcitriol is absorbed in the mitochondria of proximal tubules.[7,9] Our patient in the above-mentioned case had most of these findings.

The incidence and prevalence of Tenofovir toxicity is varied. A study conducted in 2006 by a Spanish medical group found that 22% of tenofovir-treated patients had tubular dysfunction as opposed to 12% of naive HIV patients and 6% of HAART-treated patients. A retrospective study of HIV-infected patients on Tenofovir identified 1% whose sCr increased.[10]

Thus, in order to manage patients with HIV on Tenofovir, one must be able to figure out who is at risk of nephrotoxicity. Postmarketing clinical data analysis showed that advanced age, low body weight, higher serum creatinine levels before starting Tenofovir treatment, comorbidities (diabetes, hypertension, HCV coinfection), concomitant nephrotoxic medications, advanced HIV infection (low CD4 counts, AIDS), and male sex were risk factors for Tenofovir-induced GFR reduction.[2,10,11]

FUTURE DIRECTIONS

Tenofovir alafenamide (TAF) is a pro-drug of Tenofovir and is currently in Phase III clinical trials.[12] Compared to Tenofovir, TAF has increased HIV-1 activity, increased intracellular Tenofovir diphosphate levels by 7 fold, decreased circulating plasma Tenofovir levels by 90%, which results in lower levels of Tenofovir in kidney and bone tissue. This decrease will hopefully cause less renal toxicity as well as decreased bone mineral toxicity. In a recent phase 2 randomized, placebo-controlled trial, treatment naive HIV-1 infected individuals were randomized 2:1 to receive Elvitegravir/Cobicistat/Emtricitabine/TAF or Elvitegravir/Cobicistat/Emtricitabine/Tenofovir. In the 24 week analysis, those receiving the compound with TAF had high levels of virologic suppression as well as a significantly smaller increase in serum creatinine and smaller decreases in bone mineral density of the hip and spine.

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KEY POINTS

Tenofovir is a widely used antiretroviral therapy, which, unfortunately, can cause RTA type 2 and renal failure.

Although our patient had to stop an effective antiretroviral medication secondary to its side-effect of RTA type 2 Fanconi's syndrome, she may still be able to use it in the near future if TAF gets approved.

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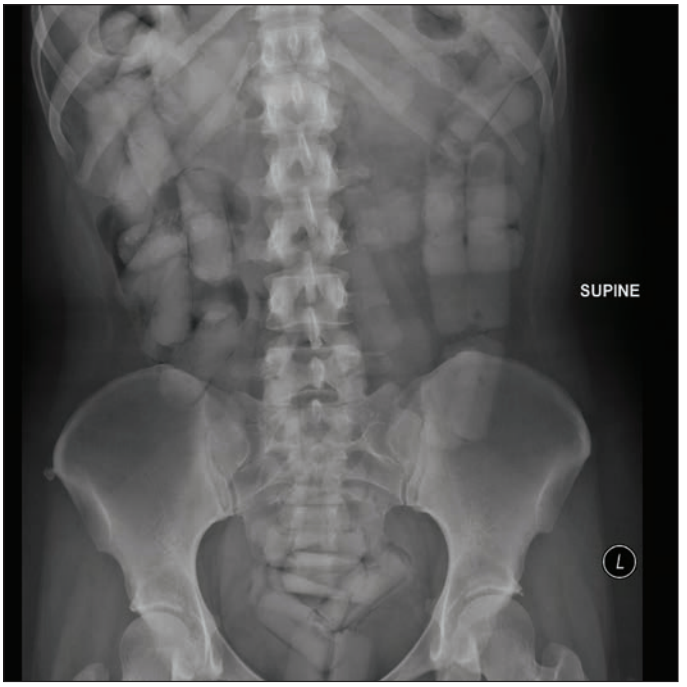
"Opposites Attract, Cape May, NJ"
photograph by Andrew Zabolotsky)

A Case of Body Packing: Internal Smuggling of Illicit Drugs

Michael A. Valentino, MD, PhD

The patient is a 27-year old Hispanic female who was brought to the ER from the airport by the Drug Enforcement Agency (DEA) on suspicion of "body packing" (illicit drug smuggling via ingestion). An abdominal X-ray (Figures 1a,b) was obtained in the ER which showed multiple radiopaque foreign bodies which were uniform in size measuring 5 cm x 2 cm throughout her colon. The patient then admitted to ingesting numerous heroin pellets. She subsequently had a CT Abdomen/Pelvis performed (Figure 2) which again showed numerous tubular radiopaque foreign bodies throughout the gastro-intestinal tract. She was admitted to the medical intensive care unit (MICU) under police escort. She was treated with oral laxatives to accelerate passage of the pellets, and she was monitored for signs of opiate intoxication due to pellet rupture. Surgery was consulted in the event of pellet rupture and resultant drug toxicity uncontrolled with pharmacologic therapy as well other potential complications including intestinal obstruction and/or perforation. She had serial abdominal x-rays performed to monitor for passage of all of the heroin pellets. All heroin pellets were collected by the DEA as evidence. During her hospitalization, the patient was able to pass all of the heroin pellets without any adverse events and was discharged into police custody.



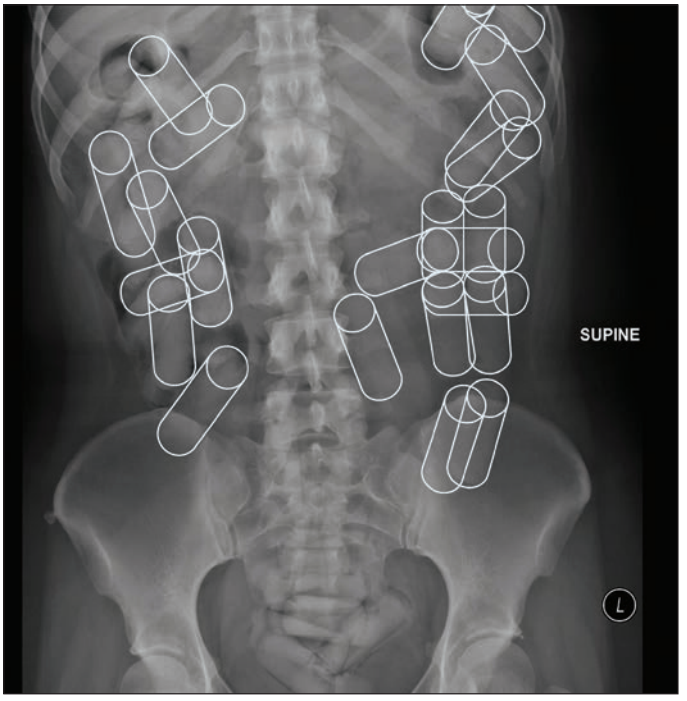


Figure 1. (a) Admission abdominal X-ray. (b) Admission abdominal X-ray with pellets highlighted.

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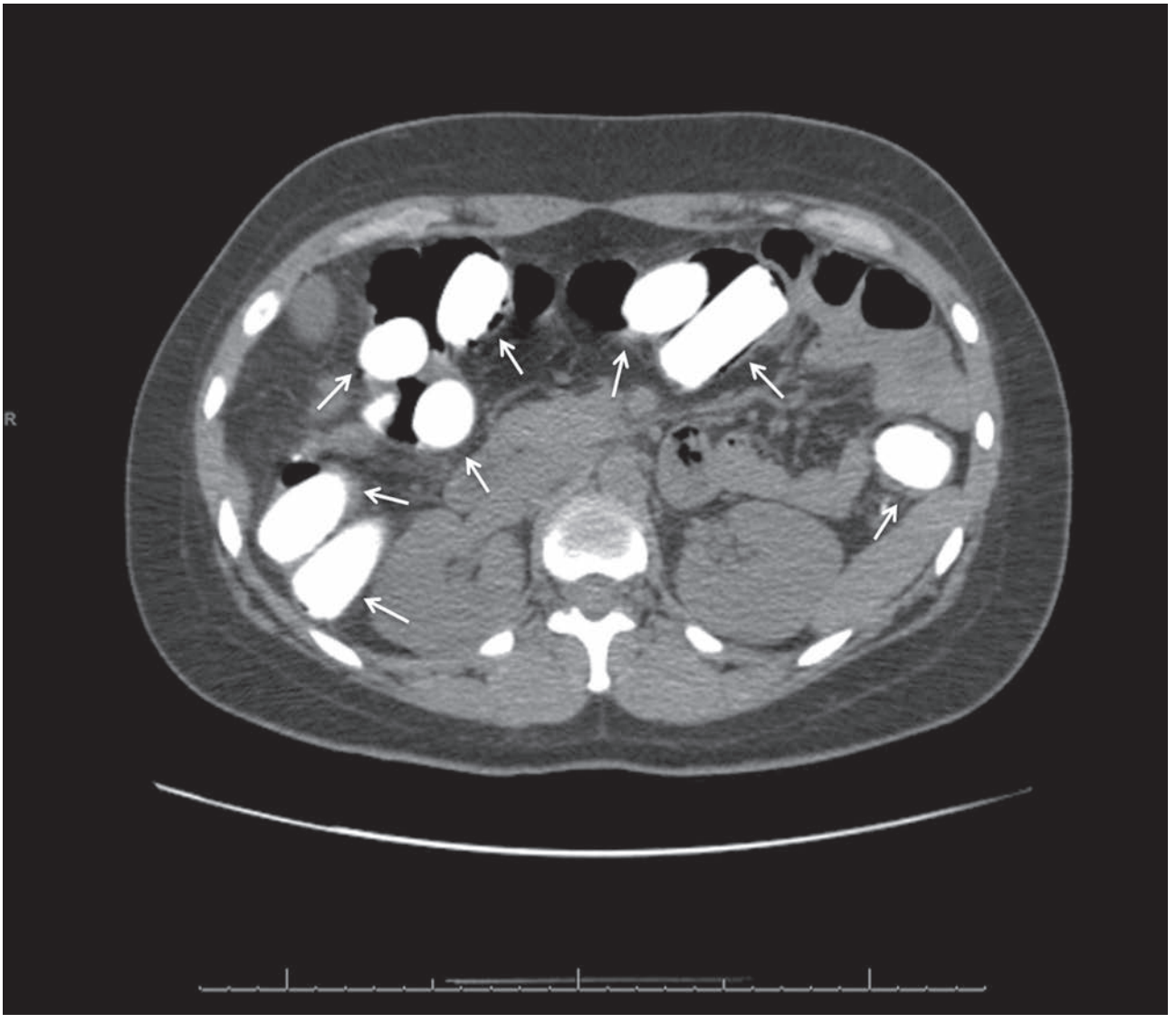

Figure 2. Admission CT Abdomen/Pelvis

Technique for Safe Placement of a Dobhoff Tube without a Cortrak® Machine

Jon Chao, MD, Jennifer Alloo Hong, MD

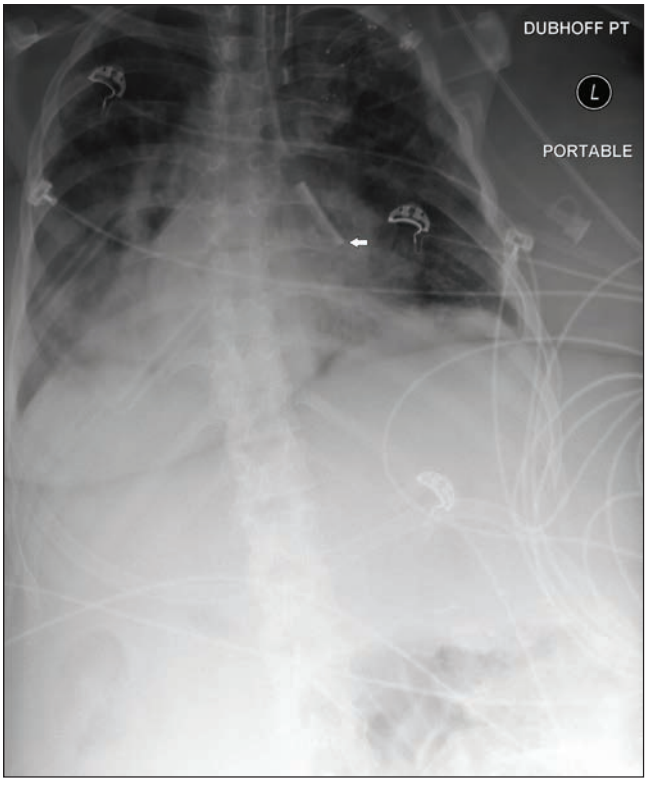

Figure 1: Dobhoff in left mainstem bronchus

A 58 year old female with a history of end stage renal disease on hemodialysis, insulin dependent diabetes mellitus, ischemic cardiomyopathy, and adrenal insufficiency, presented from home with altered mental status and hypotension. She developed refractory hypotension requiring vasopressors and was admitted to the medical ICU for management of septic shock due to bacterial peritonitis. She was intubated and had an oro-gastric tube placed for enteral nutrition. However, significantly elevated gastric residuals developed secondary to delayed gastric emptying. We decided to place a post-pyloric Dobhoff tube as an alternative gastric access to continue enteral feeding. Since a Cortrak machine (an electromagnetic-guided enteral access system) was unavailable, we used a two-step approach with a portable chest x-ray to assess accurate and safe placement.

We followed the two-step bedside approach that was first described in 1989.[1] First, we advanced the tube to 30 centimeters and took a chest x-ray. As seen in Figure 1, the tip of the Dobhoff tube is in the left mainstem bronchus. If we had continued to advance the tube, we would have risked causing a pneumothorax. The tube was removed and re-advanced. Figure 2 shows the tube well positioned in the esophagus. Finally, the Dobhoff tube is completely advanced. Figure 3 shows the tip of the tube beyond the pylorus.

In patients suffering from critical illness who require intubation, enteral feeding is preferred. However, some patients develop high gastric residuals limiting feeding via oro- or naso-gastric tube. A post pyloric Dobhoff tube is an excellent alternative, although it can carry a serious risk of pneumothorax if placed blindly. When a Cortrak machine is not available, a two step technique using a chest x-ray to confirm placement in the esophagus and then through the pylorus is an effective way to prevent serious complications.[2,3]

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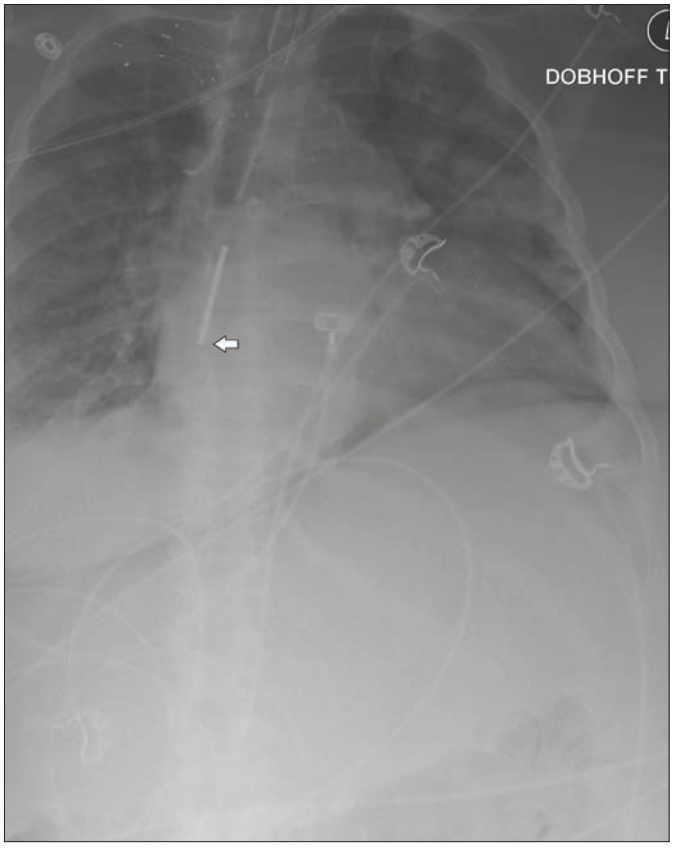

Figure 2: Dobhoff in the esophagus

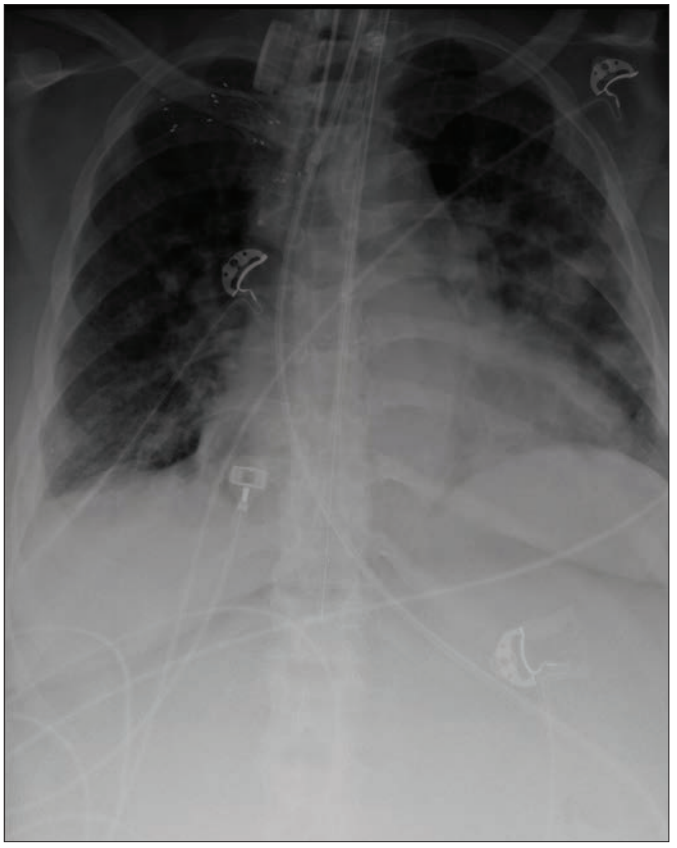

Figure 3: Dobhoff in post pyloric region

TB, or not TB?

Michael A. Valentino, MD, PhD

The patient is a 43-year-old African American male with a past medical history of hypertension, hyperlipidemia, and chronic low back pain who presented to the ER for worsening dyspnea and a 30-lb weight loss over the past 3 months. He also reported a nonproductive cough over this period of time as well as an eruption of small ~1cm flesh-colored nodules on his extremities and trunk. He denied any fevers, chills, or night sweats. In the ER, he had a chest x-ray performed (**Figure 1**) which showed diffuse centrilobular nodules visualized throughout the lung fields in a miliary pattern. He subsequently had a CT Thorax (**Figure 2**) performed which showed innumerable miliary nodules and extensive mediastinal and hilar lymphadenopathy. There was suspicion for miliary tuberculosis (TB), and the patient was admitted and placed on airborne precautions. He was also found to be hypercalcemic with calcium of 11.9 mg/dL (normal range 8.5-10.2 mg/dL) on admission, which improved with IV fluids.

The patient was incarcerated over 10 years ago but had no other risk factors for tuberculosis: no travel to endemic areas, no history of homelessness, no substance abuse, and no known exposure to an individual with TB. Consultation by Infectious Disease, Pulmonary, and Dermatology was requested. The differential diagnosis included: TB, disseminated fungal infection, and sarcoidosis. A Quantiferon TB Gold test and three daily acid-fast bacilli sputum cultures were negative. He also had negative tests for cryptococcal antigen, histoplasma antigen, and blastomyces antibody. He did, however, have an elevated serum level of angiotensin-converting enzyme at 440 U/L (normal range 9-67 U/L). Dermatologist biopsied one of the patient's cutaneous nodules, and the pathology revealed sarcoidal granulomatous dermatitis. Thus, the patient was diagnosed with disseminated sarcoidosis and initiated on steroids. The patient's hypercalcemia was also due to sarcoidosis, as he had a low intact parathyroid hormone level and an elevated calcitriol level consistent with hypercalcemia of granulomatous disease. With treatment with steroids, the patient's dyspnea improved. He was discharged on oral prednisone and recommended to follow-up with Pulmonary.

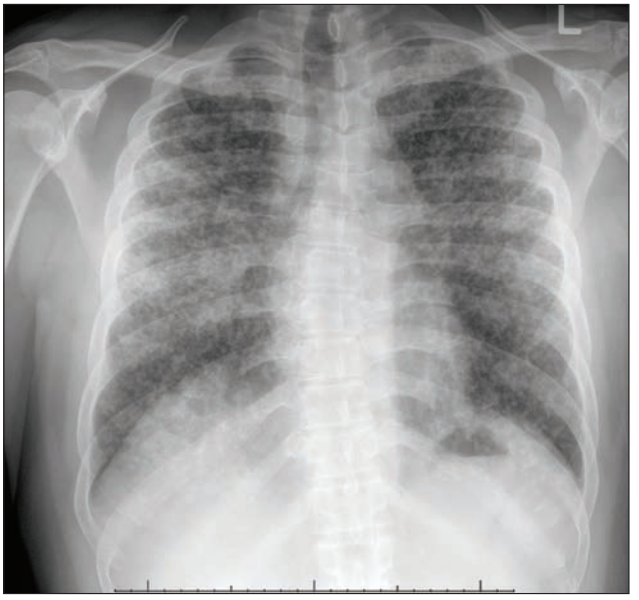

Figure 1: Admission chest X-ray

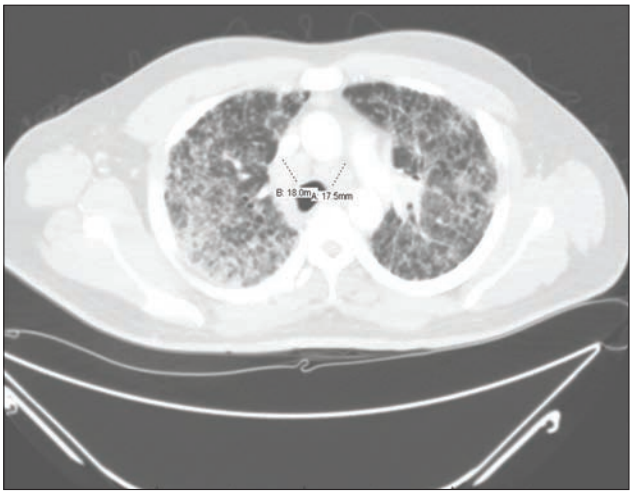

Figure 2: Admission CT Thorax.

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Pyoderma Gangrenosum Associated with Acute Myelogenous Leukemia

Lekha Mikkilineni MD, Aishah Ali MD

A 20-year-old man presented with a non-healing ulcer on the dorsum of the left foot that initially appeared after the patient fell and hit his left foot on the edge of a door. An ulcer had formed and grown in size over the past several weeks after repeated physical insults and despite home wound care, as seen in Figure 1. Additionally, the patient had a non-healing ulcer inferior to his left knee. He had a notable past medical history of acute myelogenous leukemia (AML) in remission after a haploidentical stem cell transplant, uncontrolled diabetes type 1, and graft-versus-host disease of the skin. Both wounds showed no signs of osteomyelitis or cellulitis on MRI.

The patient's ulcers most closely resembled pyoderma gangrenosum (PG), and his history was consistent with the pathergy associated with this disease. Pathergy is defined as the evidence of new skin lesions arising at sites of intradermal trauma due to an inflammatory response mediated largely by neutrophils.[1] Pathergy is also seen in bowel associated dermatosis-arthritis syndrome, Behcet's disease, and rheumatoid arthritis. PG occurs most frequently in the lower extremities and can be divided into five subgroups: classic, bullous, pustular, vegetative, and peristomal types.[2] Lesions usually start as tender nodules, plaques, or sterile pustules that become larger with trauma and debridement. Over several days to a week, the lesion often enlarges into a sharply demarcated ulcer with violaceous borders and a zone of erythema. PG lesions are extremely painful. They are thought to arise from loss of innate immune regulation and altered neutrophil chemotaxis.[2] AML is the most common hematologic malignancy that underlies PG, with the bullous subtype of PG being the predominant type found in these cases. PG lesion development foreshadows a poor prognosis in AML, and its presence in myelodysplastic syndromes may herald a malignant transformation.[1] Chronic and atypical cases have a higher association with underlying AML and myelodysplastic syndromes than typical cases.

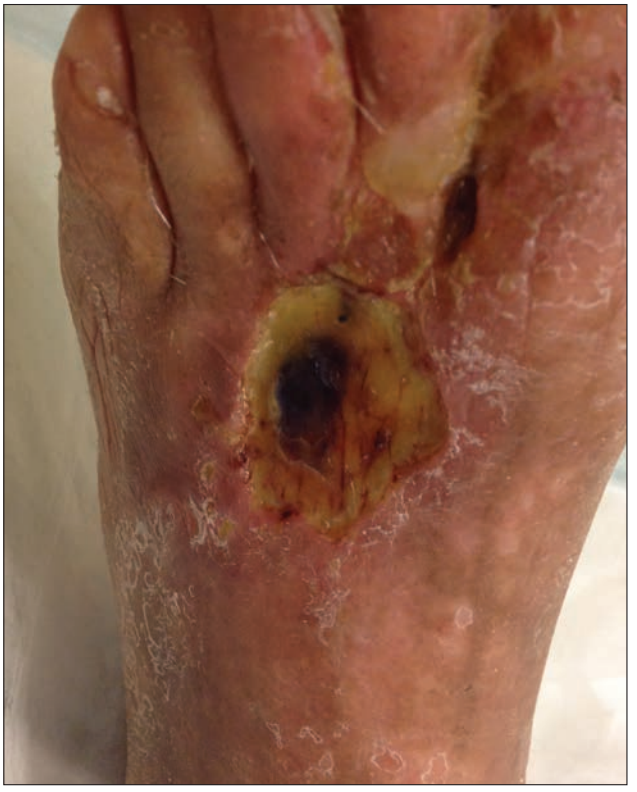

Figure 1: Pyoderma gangrenosum of left foot

PG is treated with anti-inflammatory agents such as steroids and tumor necrosis factor-alpha inhibitors. If PG appears as a dermatologic manifestation of a systemic disease, treating the systemic disease is necessary.[3]

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Swyer-James-McLeod Syndrome

Esther Molnar, MD, Arun Matthew, MD

Admission chest x-ray of an 81 year-old man admitted to the hospital for atrial fibrillation with rapid ventricular response is shown in Figure 1. The chest x-ray shows a unilateral hyperlucent lung, with paucity of peripheral vessels and decreased lung volume. Differential diagnosis for unilateral hyperlucent lung includes Swyer-James-McLeod syndrome (SJMS), centrilobular emphysema, allergic bronchopulmonary aspergillosis, congenital lobar over inflation, bronchial atresia and congenital interruption of pulmonary artery.[1] High resolution CT imaging confirmed the diagnosis of SJMS in this patient.

SJMS is a manifestation of post-infectious obliterative bronchiolitis. SJMS was first described in 1953 as a unilateral hyperlucent, hypovascular lung with a small ipsilateral hilum. Bronchiectasis, bronchial wall thickening and small pulmonary arteries are commonly associated findings. SJMS is thought to occur from severe post-infectious bronchiolitis occurring at less than eight years of age. The damage to the airways in early childhood impairs normal development of the alveolar ducts and leads to diminished arterial flow and hypoplastic pulmonary vasculature. Terminal air sacs distal to areas of bronchiolar obstruction become hyperinflated and alveoli are overdistended, adding to resistance of blood flow and giving the appearance of radiographic hyperlucency. The most common etiology of this phenomenon is adenovirus infection, but other infectious causes include paramyxovirus, Bordetella pertussis, mycobacterium tuberculosis, mycoplasma pneumoniae, influenza A or respiratory syncytial virus infections. The prevalence of SJMS has been reported as less than 0.01% in the general population.[2,3]

To make the diagnosis of SJMS, available modalities include ventilation-perfusion scintigraphy (V/Q scan) and CT imaging. V/Q scanning supports the diagnosis with matched ventilation/perfusion defects.[4] High resolution CT (HRCT) during forced expiration is useful in demonstrating air trapping. The appearance of the lung on HRCT expiration with mosaic pattern attenuation and lack of change in volume with expiration is essential in making the diagnosis. HRCT is also useful in ruling out other potential causes of unilateral hyperlucent lung, such as bronchial atresia.[5,6]

SJMS is most commonly diagnosed by the fourth decade of life, usually as an incidental finding. Symptoms tend to be widely varied, ranging from completely asymptomatic patients to those with wheezing, coughing, hemoptysis, dyspnea on exertion, and recurrent bronchopulmonary infections. Management of SJMS includes early treatment of infections and influenza and pneumococcal vaccination. Bronchodilators may be helpful to patients demonstrating obstructive defects on spirometry. For severe cases with recurrent bronchopulmonary infections, lobectomy or pneumonectomy is helpful.[2]

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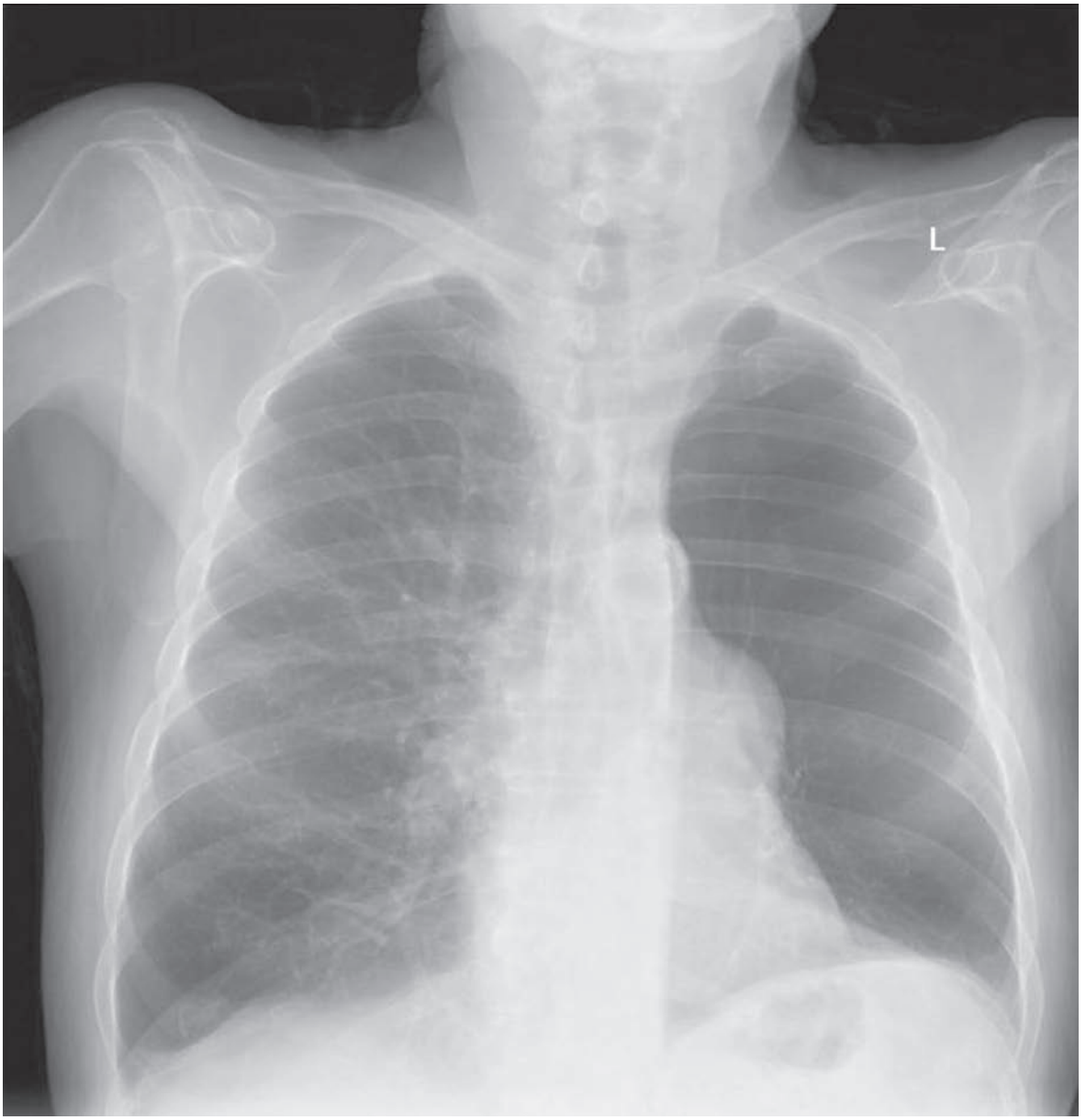

Figure 1: Admission chest X-ray

Stay

Jennifer Alloo Hong, MD

As an intern, I thought of myself as the member of the team who gets the things done. I took pride in prioritizing my long list of tasks and efficiently working through each item. I spent most of my time at the computer, on the phone, in front of the chart, or in a consultant's office. My time with patients was so limited that I grew more comfortable thinking about their medical problems away from their bedside.

At the end of my intern year, one of my patients in the cardio-vascular intensive care unit, developed atrial fibrillation with a rapid ventricular rate, during morning pre-rounds. Thankfully, my resident was there to help me think through what to do, since I was nervous about evaluating tachyarrhythmias. We started the treatment and I walked away to review the labs and telemetry. My resident called out, "Where is Jennifer? She should stay and see this." I walked back to the room with some hesitation as I was worried there was something wrong. Indeed, we had to adjust our treatment, and with the change I stayed to watch the response. Throughout the experience, the patient laid quietly looking to us for reassurance, which we gave as we quickly titrated his medication, and controlled his tachycardia. In this moment at the bedside, after I had pulled myself away from the gripping rhythm of completing tasks for rounds, I realized the necessity of seeing the impact of my treatment as it was happening. Beyond this, I experienced the power of staying with my patient to reassure him. I realized that he relied on me and that he needed me to be there with him.

It is shocking when one moment seems to change your life forever. I have been there when a patient receives a new diagnosis and in that moment his life is completely different. Similarly, there have been moments when my patient's experience redefines how I act as a physician.

This past summer I took care of a middle aged gentleman at the peak of his life who had a devastating bladder cancer. In addition to our medical therapy he required multiple urologic procedures to lighten the burden the tumor had on his body. After one of these procedures he grew delirious and combative. I arrived at the bedside and starting working through my differential diagnosis. His wife was grasping his hand while desperately trying to reorient his wandering mind. I thought to myself, "Ok, let me work through my mnemonic GO TIMES: glucose, oxygen, toxins, infection, metabolic causes, endocrine causes, and stroke or seizure." At the end of my work up I was left with a medication reaction from benzodiazepines and hypoxia. I remained at his bedside throughout the work up and explained what I was thinking and doing to his wife who worked with me to keep reorienting him. When I left late that evening he was calm, still mildly confused, but better. We were all feeling better and calmer.

After a long three weeks of treatment it was finally time for him to leave the hospital. At the end of our last conversation, he asked me if he could give me a hug. His wife smiled, and I said, "Sure." He hugged me and said, "You saved me."

I didn't save him from his cancer. He died just one month later. Since I wasn't able to save his life, it was hard for me to understand why he would say such powerful words to me. I had stayed close by his bedside when he needed help with his pain, delirium or anxiety. As I eased his suffering, he grew to trust me and rely on me. I felt like I was solving small problems by staying with him to make sure his pain, anxiety, and delirium were treated well. These problems seemed insignificant, even trivial, in the shadow of his cancer. In the end they weren't insignificant at all.

It is sometimes easy to forget that my routine work up of common problems can have a profound effect on my patient. Whether I realize it or not, I can change a life by staying by the bedside to see how my patient responds to what I prescribe or to just talk about what is happening in his body that's out of his control. In the process of the struggle with disease my patient changes me into a deeply caring physician with the power to save a life in ways big and small.

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