Diagnosis by Treatment

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient’s case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

This icon represents the patient’s case. Each paragraph that follows represents the discussant’s thoughts.

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A 46-year-old Mexican woman with acquired immune deficiency syndrome (AIDS), admitted for 6 months of diarrhea and failure to thrive, developed acute shortness of breath following colonoscopy. She reported dyspnea in the recumbent position, associated with a nonproductive cough, which improved with elevation of the head of the bed. She denied chest pain, palpitations, lightheadedness, hemoptysis, abdominal pain, nausea, and fever.

The approach to acute shortness of breath in hospitalized patients should include evaluation for life-threatening cardiopulmonary processes. The patient should be assessed for cardiopulmonary process, including myocardial infarction, pulmonary embolism, aortic dissection, congestive heart failure, unstable arrhythmias, cardiac tamponade, and pneumothorax. The presence of orthopnea does suggest pulmonary congestion and a cardiac process. Given the timing of her symptoms, there is also concern for complications related to the colonoscopy, including aspiration pneumonitis, bronchospasms due to ethylene glycol, and methemoglobinemia from benzocaine used during the procedure.

The patient had been admitted the prior day for 6 months of diarrhea, weight loss, and failure to thrive. On admission, she was afebrile with a blood pressure of 110/50 mmHg and a pulse of 110 beats per minute; electrocardiogram (EKG) at the time revealed normal sinus rhythm. Her oxygen saturation was 100% on ambient air, and she had no complaints of cough, fevers, or dyspnea.

On admission, a peripherally inserted central catheter (PICC) was placed and total parenteral nutrition (TPN) was initiated. A gastroenterology consult was obtained, and colonoscopy was recommended to evaluate the cause of her chronic diarrhea. Overnight, the patient was started on polyethylene glycol electrolyte solution, with nothing else by mouth, and initiation of intravenous intravenous normal saline at 50 ml/hr in addition to her TPN. The patient expressed difficulty completing the colonoscopy preparation, but her preparation was acceptable to proceed with the procedure. She denied fever, chills, abdominal pain, and respiratory symptoms. She was taken down to endoscopy where she underwent conscious sedation, followed by an uneventful colonoscopy with mucosal biopsies. She subsequently was transported back to her hospital room in the supine position and almost immediately began to complain of mild shortness of breath. No aspiration event was witnessed following her procedure and transport.

Considering the patient’s chronic diarrhea, there may be a unifying cause of both the gastrointestinal (GI) and pulmonary symptoms. Possibilities include infectious causes (Toxoplasma gondii and Trypanosoma cruzi), infiltrative diseases (amyloidosis), and metabolic processes (hyperthyroidism). More specifically, T. cruzi can cause dilated cardiomyopathy, with subsequent congestive heart failure and associated pulmonary symptoms; furthermore, it can lead to a dilated colon with abnormal bowel movements. Opportunistic infections, including Microsporidia, Cryptosporidium, Mycobacterium avium complex (MAC), and cytomegalovirus (CMV) should be considered. MAC and CMV can present with non-bloody diarrhea and evolve into respiratory illnesses. Lastly, human immunodeficiency virus (HIV) is known to involve multiple organ systems, including the heart and gastrointestinal tract. History of prior cardiac or pulmonary disease, CD4 count and viral load, use of antiretroviral and prophylactic medications, and recent travel should be obtained.

Thirteen years previously, the patient was diagnosed with HIV, and subsequently developed AIDS with thrush and uncomplicated CMV viremia. At that time, highly active antiretroviral therapy (HAART) was initiated, but she was intolerant of her medications and received therapy intermittently. Her past medical history included multiple fractures secondary to osteoporosis. She denied any history of respiratory or cardiac symptoms. The patient was born in rural Mexico and immigrated to the United States 20 years prior. Her last visit to Mexico occurred 2 months prior to admission, and 4 months following the development of chronic diarrhea. Previously, she worked as a housekeeper and was not aware of any toxic exposures during cleaning. She denied a history of alcohol or recreational drug use. Despite her generalized weakness, her baseline functional status included performing all activities of daily living without symptoms.

Over the prior 6 months, the patient had developed diffuse watery diarrhea, associated with a 20-pound weight loss. Stool evaluation, 1 week prior, was negative for...
Clostridium difficile, Microsporidia, Isospora, Cryptosporidium, Escherichia coli, Campylobacter, and ova and parasites. Her CD4 count was 8 cells per cubic millimeter.

The low CD4 count predisposes the patient to all opportunistic infections. Considering the history of CMV viremia, there is likelihood of reactivation with viremia and colitis, leading to chronic diarrhea and pneumonia. Disseminated MAC infection is also a consideration and would account for wasting, diarrhea, and dyspnea. However, it is important to note that the acute onset of dyspnea is atypical for CMV and MAC infections.

On physical exam, she was a thin woman with temporal wasting, in mild respiratory distress. Her temperature was 37.3°C, blood pressure 133/55 mmHg, heart rate 140 beats/min, respiratory rate 22 breaths/min, and oxygen saturation 89% on room air. Her oropharynx was clear and without acral cyanosis. Use of accessory muscles for breathing was noted. The trachea was midline and no lymphadenopathy or thyromegaly were present. Her jugular venous pulse was normal. Cardiac exam revealed tachycardia with a new S4 gallop. A prominent apical impulse was noted. No murmurs or rubs were appreciated. There was no pulsus paradoxus. Her radial, femoral, and dorsalis pedis pulses were 2+ without delay. Her lung exam revealed inspiratory crackles involving the lower one-third of both lungs. The lower extremities revealed 2+ pitting edema to the knees. The rest of her exam, including her neurologic evaluation, was unremarkable.

These clinical findings are consistent with left-sided heart failure, concerning for ischemic injury or structural disorders of the heart. It is possible that the patient has had progressive heart failure, which is now unmasked by the volume received with TPN and endoscopy. If the heart failure has been longstanding, one has to consider potential non-ischemic causes of cardiomyopathy, including infectious etiologies such as HIV, Epstein-Barr virus (EBV), coxsackie virus, CMV, Toxoplasma gondii, and Trypanosoma cruzi; alcohol-associated; and pericardial disease with Mycobacterium tuberculosis (MTB). Toxoplasma should be evaluated if the patient has exposure to cats. Considering her country of origin and travel history, risk factors for trypanosomiasis and MTB should be assessed.

At this point, the patient’s respiratory failure should be aggressively addressed. Supplemental oxygen should be administered. She should be evaluated for acute coronary syndrome with an EKG and serial cardiac enzymes. A chest x-ray should be obtained to grossly evaluate for pulmonary, pericardial, and aortic illnesses. Brain natriuretic peptide (BNP) levels should also be sent. Considering the evidence of volume overload and her HIV status, liver function tests, serum electrolytes, and urinalysis should be sent to exclude liver and renal involvement.

The patient was placed on 2 liters of oxygen by nasal cannula with resolution of her symptoms and improvement in her oxygen saturation to 95%. An EKG demonstrated sinus tachycardia, without evidence of ischemia. Metabolic panel revealed sodium 134 mmol/L; potassium 4.3 mmol/L; chloride 105 mmol/L; bicarbonate 16 mmol/L; creatinine 0.6 mg/dL, and liver function tests were within normal limits. Her troponin level was within the normal range for a negative value, and BNP was 823 pg/ml (normal <100). The complete blood count demonstrated leukopenia and anemia (hemoglobin 9.8 g/dL), which were unchanged from admission. Urinalysis was negative. A portable chest x-ray demonstrated vascular congestion and mild pulmonary edema, without evidence of pneumothorax or pleural effusion.

The significantly elevated BNP and pulmonary vascular congestion seen on chest x-ray confirm the clinical diagnosis of heart failure. However, the negative troponin and unremarkable EKG suggest a non-ischemic cause for her symptoms. An echocardiogram should be obtained with specific emphasis on the presence of valve regurgitation, pericardial effusion, and ventricular/atrial thickening consistent with infiltrative disorders. Thyroid stimulating hormone (TSH) and serologies for infectious agents, including, T. cruzi, HIV, CMV, and Toxoplasmosis gondii, should also be sent. The patient should receive intravenous loop diuretics to improve her cardiac dynamics and pulmonary edema.

Intravenous furosemide was administered. Her symptoms improved and oxygen saturation on room air was 92%. An echocardiogram revealed global hypokinesis with left ventricular ejection fraction (LVEF) of 35% to 40%. There was no evidence of an underlying valvular or infiltrative process. TSH was normal. T. cruzi antibodies were sent.

The echocardiogram did not reveal an underlying structural heart abnormality. Infiltrative cardiomyopathies do not typically demonstrate global hypokinesis on echocardiogram, particularly without evidence of ventricular wall thickening or increased echogenicity, that can be seen in amyloid and sarcoid cardiomyopathies. Therefore, infiltrative cardiomyopathy is unlikely to be a cause of this patient’s heart failure. The rapid improvement of her symptoms with furosemide decreases the likelihood of infectious causes for her acute decompensation. In reviewing the patient’s history, she had developed severe chronic diarrhea associated with poor oral intake and a 20-pound weight loss prior to hospitalization. These symptoms, along with a history of osteoporosis at an early age without traditional risk factors, indicate a state of severe malnutrition, placing her at risk for thiamine deficiency. Checking the thiamine level would be appropriate.

Considering the patient’s long history of malnutrition and negative infectious and ischemic evaluation, she was empirically treated for wet beriberi with thiamine supplementation through her TPN. A serum thiamine B1 was obtained prior to supplementation. A vitamin D 25OH level was also sent, which was 15 ng/mL (normal >30 ng/mL), further suggesting malnutrition.

The patient continued to improve and furosemide was discontinued. Her initial serum thiamine level was 49 nmol/L (reference range: 70-180 nmol/L). A repeat echocardiogram 5 days later revealed resolution of her systolic dysfunction and regional wall motion abnormality. The LVEF improved to 60%. Her colonoscopy biopsies revealed evidence of HIV enteropathy and CMV inclusion bodies. Her CMV viral load was 1223 genomes/mL. The T. cruzi antibodies were negative. She was restarted on HAART and ganciclovir. She continued to have diarrhea and was discharged home with TPN. Her serum thiamine level at discharge was 123 nmol/L.
Heart failure due to thiamine deficiency, or wet beriberi, was diagnosed considering the rapid clinical improvement in cardiac function after initiating thiamine therapy. While HIV cardiomyopathy could have contributed to heart failure in this patient, it is unlikely to improve so significantly over such a brief period of time.

DISCUSSION

Beriberi is a disease caused by severe thiamine deficiency. In fact, thiamine, also known as vitamin B1, was first named “the anti-beriberi factor” in 1926. However, the earliest descriptions of beriberi can be found in Chinese medical texts dating back to 2697 BC.1 Beriberi is most commonly seen in descriptions of beriberi can be found in Chinese medical texts. However, the earliest intestinal absorption such as post-bariatric surgery patients.2

In 1985, the first case of beriberi as a complication of TPN without vitamin supplementation was reported.3 Subsequent cases of Wernicke’s encephalopathy and beriberi have been noted in patients with gastrointestinal diseases and malabsorption on chronic TPN. More recently, thiamine deficiency has also been recognized in patients on long-term diuretic therapy, as diuretics increase urinary excretion of this water-soluble vitamin.4,5 Since there is limited tissue storage of thiamine and its biologic half-life is 10 to 20 days, high-risk patients can develop thiamine deficiency within 4 weeks of initiation of diuretic therapy.5

Beriberi is classically divided into 2 types: wet, characterized by congestive heart failure, and dry, manifested as a symmetric peripheral neuropathy with both sensory and motor impairments.7 These 2 types of beriberi can coexist in the same patient; however, it is unclear why both types occur in some patients and not in others. Wet beriberi, also known as beriberi cardiomyopathy, typically presents as high-output heart failure secondary to vasodilation, with a compensatory increase in blood volume and tachycardia.8 This state eventually leads to myocardial injury with systolic dysfunction and development of a low-output state.8 Patients experience hypotension, lactic acidosis, and eventually fulminant vascular collapse. Although minor EKG changes such as sinus tachycardia, low-voltage ventricular complexes, QT prolongation, and biphasic or inverted T waves are not uncommon in beriberi cardiomyopathy, major EKG changes, such as ST segment elevations and tall or deeply inverted T waves, are rare. Similarly, troponin elevation in beriberi cardiomyopathy is uncommon, but has been described.6

The pathogenesis of heart failure in beriberi is multifactorial. Thiamine is required for glucose to enter the Krebs cycle for aerobic metabolism, serving as a catalyst in the conversion of pyruvate to acetyl-CoA. Without thiamine, anaerobic metabolism occurs, leading to the development of lactic acidosis and cellular malfunction. In fact, severe metabolic acidosis with serum pH values as low as 6.70 have been reported in cases of fulminant beriberi (although it is unclear if the lactic acidosis is mostly from anaerobic metabolism or from the low-output state ultimately caused by thiamine deficiency).3

Laboratory diagnosis of thiamine deficiency, based on measurements of thiamine stores and metabolites, is often fraught with error and therefore unreliable. Serum pyruvate and lactate levels are commonly measured, and while elevated levels may be sensitive for thiamine deficiency, they are nonspecific. Measurement of whole blood thiamine is easy and the test is widely available; however, a low blood thiamine concentration is not always a sensitive indicator of deficiency since less than 1% of total body thiamine is found in whole blood.9 Additionally, this value may also be artificially elevated by thiamine intake immediately preceding the measurement. Urinary thiamine excretion has been proposed as a more accurate measurement, but this laboratory test is also problematic since urinary thiamine excretion reflects dietary intake more than total body stores.9 Erythrocyte transketolase activity (ETKA) is a functional enzyme test in which transketolase uses thiamine pyrophosphate as a catalyst. This may be a more reliable measurement since red blood cells are among the first cells to be affected by thiamine depletion.9 Although a low ETKA level often indicates thiamine deficiency, this test is influenced by the hemoglobin concentration, and it is not widely available. Thus, the diagnosis of wet beriberi is usually made on the basis of rapid response to thiamine replacement.

Similar to the patient discussed, the clinical improvement in wet beriberi occurs within hours of treatment. There is an initial elevation in blood pressure and resolution of acidosis, followed by decrease in heart rate and normalization of cardiac output. Overall cardiac function improves within 24 to 48 hours after treatment, and return to a normal hemodynamic condition often occurs within 2 weeks of the start of treatment.10

There are no well-established guidelines for the treatment of patients with beriberi, but general recommendations are an initial loading dose of intravenous thiamine 100 to 500 mg followed by 25 to 100 mg orally for 7 to 14 days.11 Thereafter, the daily thiamine requirement can be calculated based upon total caloric intake. The current recommendations in the United States are 0.5 mg of thiamine per 1000 kcal.12 However, one must consider whether a patient has impaired intestinal absorption or increased urinary losses when determining an appropriate maintenance dose.

Chronic malnutrition can lead to significant morbidity and mortality. Prior to admission, this patient already exhibited signs of severe malnutrition with a history of multiple pathologic fractures and diagnosis of osteoporosis. Considering her age and lack of risk factors for bone disease, osteoporosis suggests vitamin D deficiency. In this patient with chronic diarrhea caused by CMV, it is unlikely that a selective absorptive deficiency would occur. When the common causes of acute heart failure following volume challenge were excluded, the diagnosis of thiamine deficiency became more likely. Fortunately, an empiric trial of intravenous thiamine resulted in “diagnosis by treatment” and improvement of her cardiac function.
KEY TEACHING POINTS

1. Hospitalists should consider vitamin B₁ deficiency in patients with chronic illness and malnutrition.
2. Diagnosis of wet beriberi based on laboratory values can be challenging and, therefore, high clinical suspicion should prompt immediate treatment with thiamine.
3. Congestive heart failure due to thiamine deficiency can be reversed with thiamine replacement.

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References