Off Target But Hitting the Mark

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. Similar 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 32-year-old woman presented to the emergency department (ED) with 3 months of abdominal pain and 1 week of vomiting.

The differential diagnosis of abdominal pain is broad. This presentation could be caused by disorders of the gastrointestinal (GI), gynecologic, urinary, or, less likely, the neuromuscular systems. The presence of vomiting supports a GI cause. Pregnancy should be excluded in any woman of childbearing age presenting with abdominal pain.

Characteristics of the pain, including location, temporal characteristics, severity, and aggravating and alleviating factors, can narrow the differential diagnosis. The past medical history, including prior surgeries, menstrual, and obstetric history, is also critical.

Approximately 3 months prior to presentation, she reported a tick bite that had evolved into a circumferential targetoid rash. Her primary care provider performed serologic testing for Lyme disease, which was negative, and prescribed doxycycline, which she stopped after a week because of nausea and diffuse, achy, and constant abdominal pain. After initial improvement, symptoms recurred a week prior to presentation. The nausea was now associated with intractable vomiting and anorexia. She denied hematemesis or coffee ground emesis. Her abdominal pain intensified and radiated to her back. She lost 10 pounds over the past week. She denied headache, constipation, diarrhea, blood per rectum, melena, dysuria, vaginal discharge, or rash. She reported chills and temperatures up to 37.8°C at home.

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She had a history of migraine headaches for which she took ibuprofen occasionally but took no other prescription or over-the-counter medications. She had never smoked, consumed 2 alcoholic beverages a month, and denied illicit drug use. She lived with her boyfriend on a farm in Indiana where she raised chickens, rabbits, and ducks.

The patient dates the onset of nausea and abdominal pain to a course of doxycycline, presumably prescribed for early Lyme disease, which was stopped after only 1 week. GI side effects, including nausea, vomiting, and upper abdominal pain, are common with doxycycline and may account for the early symptoms. However, these symptoms typically resolve promptly with drug discontinuation. Doxycycline may rarely cause esophageal and gastric ulcers, which could explain her symptoms.

Fewer than half of patients with erythema migrans caused by Lyme disease are seropositive at presentation, as there has been insufficient time for antibodies to develop. Lyme disease typically affects the skin, joints, heart, and nervous system and only rarely affects the GI tract. Acute Lyme disease can cause intestinal pseudoobstruction, splenomegaly, and mild hepatitis. Although Lyme disease is unlikely to be the cause of the current symptoms, serologic testing should be repeated and should be positive if the patient now has early disseminated disease.

Patients with Lyme disease are occasionally coinfected with a second organism. *Ixodes scapularis*, the tick that transmits Lyme disease in the Northeast and Midwest, can be coinfected with *Babesia microti*, a red cell parasite. Babesiosis can persist for months and presents with fever, malaise, and many other nonspecific symptoms, including some that this patient has: anorexia, weight loss, abdominal pain, and vomiting.

The history of migraine and intractable vomiting suggests the possibility of cyclic vomiting syndrome. This syndrome is characterized by episodic bouts of vomiting lasting from hours to as long as a week. The vomiting is often accompanied by abdominal pain and occasionally headaches. Episodes are separated by asymptomatic periods that may last months. Cyclic vomiting syndrome can occur at any age but is more

common in children, those with a personal or family history of migraines, and heavy users of cannabis. At least 3 stereotypical episodes are required to make the diagnosis, so a history of prior similar symptoms should be explored.

The differential diagnosis of abdominal pain and vomiting should stay broad until a comprehensive physical exam and initial laboratory tests are performed. Volume status should be assessed by estimating jugular venous pressure and by obtaining supine and standing blood pressure measurements. The abdomen should be examined carefully, and the presence or absence of hepatomegaly, splenomegaly, masses, and ascites should be specifically noted. The presence of bradycardia, oligoarticular arthritis, or neuropathy could provide supporting evidence for Lyme disease. Pregnancy is less likely given the diffuse and persistent nature of the pain but should still be excluded.

On physical examination, she was distressed, writhing on the bed, and appearing comfortable only on her side with her knees flexed. Her temperature was 36.5°C, heart rate 83 beats per minute, respiratory rate 18 breaths per minute, blood pressure 143/77 mmHg, and oxygen saturation 94% while breathing ambient air. Her abdomen was diffusely tender, most markedly in the epigastrium. Abdominal rigidity, rebound tenderness, and costovertebral tenderness were absent. There was no rash; the previously reported targetoid skin lesion was no longer present. The remainder of the exam was normal.

Laboratory evaluation showed a white count of 7900/mm3, hemoglobin 14.3 gm/dL with normocytic indices, and a platelet count of 175,000/mm3. Sodium was 130 mmol/L, potassium was 3.1 mmol/L, bicarbonate 26 mmol/L, blood urea nitrogen 15 mg/dL, creatinine 0.6 mg/dL, and glucose 92 mg/dL. Serum calcium, aspartate aminotransferase, alanine aminotransferase, bilirubin, and lipase were normal. A urine pregnancy test was negative. Urine analysis was negative for nitrites and leukocyte esterase. Abdominal and pelvic computed tomography (CT) scan with intravenous (IV) contrast performed 3 days prior at an outside ED revealed a 3.4 centimeter left ovarian cyst. A subsequent transvaginal ultrasound was negative for cyst torsion and confirmed appropriate placement of an intrauterine device.

The absence of abdominal rigidity and rebound tenderness does not exclude peritonitis. A normal white blood cell count also does not reliably exclude serious intraabdominal pathology. However, the CT scan argues strongly against many common causes of abdominal pain, including appendicitis, diverticulitis, perforated ulcer, intestinal obstruction, and malignancy, assuming the symptoms have not changed since it was performed.

The patient's laboratory studies argue against biliary obstruction, pancreatitis, pregnancy, hypercalcemia, and ongoing urinary tract infection. Patients with functional gallbladder disorders may have normal laboratory and CT findings but typically have recurrent, biliary-colic-type pain. The low serum potassium, a high blood urea nitrogen to creatinine ratio, and a low serum sodium reflect her significant vomiting. The hyponatremia is consistent with the appropriate release of antidiuretic hormone (ADH) in the setting of volume depletion. She should receive isotonic fluids plus potassium in addition to symptomatic treatment of pain and nausea. Given the severity and duration of symptoms, an esophagogastroduodenoscopy (EGD) should be performed to exclude GI mucosal disease, including peptic ulcer disease and gastritis, which may not be evident on the CT scan.

Additional diagnoses should be considered at this point. This patient has exposure to chickens, ducks, rabbits, and ticks as well as reported chills and mild temperature elevation at home. Tularemia, which can be transmitted by tick bites or exposure to infected rabbits, can cause a prolonged illness. Some patients have abdominal pain, anorexia, nausea, and weight loss, although fever is usually more prominent. Tularemia is uncommon and most frequently seen in the south-central part of the United States but has been reported throughout the country. She should be queried regarding additional exposures, including well water to assess her risk for *Campylobacter* infection.

Opiate withdrawal can present with pain and vomiting, but she reports no opiate use and lacks other findings such pupillary dilation or piloerection. Given the prevalence of opiate abuse, however, a toxicology screen should be performed. Hypercalcemia and diabetic ketoacidosis as metabolic causes of abdominal pain have been ruled out by her laboratory values. If no other cause is identified, other metabolic etiologies like Addison disease, familial Mediterranean fever, or porphyria should be considered.

Cyclic vomiting syndrome should still be on the differential. It is a diagnosis of exclusion requiring a history of recurrent, stereotypical episodes, which should be explicitly explored.

The patient was admitted to a medical unit by the hospitalist service and received IV normal saline, parenteral potassium, and IV pantoprazole. She underwent an EGD that revealed minor erosions in the antrum of the stomach. Biopsies were obtained.

Seven hours after the endoscopy, the patient had a brief period of confusion followed by a generalized tonic-clonic seizure lasting 1 minute. A head CT without contrast was negative for any focal abnormality. Repeat laboratory evaluation revealed that serum sodium was 125 mmol/L, and serum glucose was 113 mg/dL. She was transferred to the progressive care unit and received IV levetiracetam.

The endoscopy excluded structural abnormalities of the stomach and duodenum. The patient now has an additional problem, seizure, which needs to be incorporated in the diagnostic reasoning.

Seizures can be caused by the rapid development of severe hyponatremia, with serum sodium levels usually less than 120 mmol/L. Seizures caused by hyponatremia are typically pre-

ceded by headache and lethargy, as the intracellular movement of excess water causes cerebral edema. Hyponatremia is unlikely to be the cause of her seizure but should nevertheless be evaluated with a urine sodium concentration and serum and urine osmolality. If she is euvolemic, the IV fluids should be stopped and her free water intake should be restricted to avoid worsening the hyponatremia, as it is potentially caused by the syndrome of inappropriate ADH (SIADH).

There are many other possible causes for new onset seizures in adults, including brain tumor, head trauma, alcohol withdrawal, medications, and central nervous system infection, including Lyme disease. Lyme serologies should be repeated.

In this patient, it is likely that the seizure is a manifestation of the same illness that is causing her vomiting and abdominal pain. Seizure is not a feature of cyclic vomiting syndrome in adults. It is also not a feature of tularemia, adrenal insufficiency, or opioid withdrawal.

Acute intermittent porphyria (AIP) can cause both abdominal and neurologic problems. Hyponatremia is common during acute attacks, caused by either the inappropriate release of ADH or the appropriate release of the hormone if there is fluid loss. AIP is a rare diagnosis but could explain the uncommon combination of abdominal pain, vomiting, seizure, and hyponatremia. A spot urine porphobilinogen test should be sent to assess for AIP.

Additional laboratory studies were sent. Serum osmolality was 269 mosm/kg with a corresponding urine osmolality of 699 mosm/kg. A random urine sodium was 145 mEq/L. Thyroid stimulating hormone and cosyntropin stimulating testing were normal. IgM and IgG antibodies to *Borrelia burgdorferi* were negative. Urine porphobilinogen was sent. An electroencephalogram did not reveal epileptiform discharges. Magnetic resonance imaging (MRI) of the brain was significant for T2/FLAIR hyperintensity in the cortex and subcortical white matter of the occipital lobes bilaterally. Hypertonic saline and fluid restriction were initiated.

The patient's labs are consistent with SIADH. Excessive ADH release because of volume depletion and consequent hyponatremia should have improved rapidly with the administration of saline. The high urine sodium suggests that she is now volume replete, while the high urine osmolality is consistent with the presence of excessive ADH in the absence of appropriate stimuli. In the context of normal thyroid and adrenal function, the hyponatremia is likely due to the SIADH.

Negative serologic testing for Lyme disease, 3 months after the onset of rash, excludes this diagnosis.

The MRI findings are consistent with posterior reversible encephalopathy syndrome (PRES), a clinicoradiographic syndrome of headache, altered mental status, seizure, and/or vision loss with associated white matter abnormalities of the posterior cerebral hemispheres. PRES has been reported with AIP as well as other disorders, most commonly hypertensive encephalopathy, eclampsia, and immunosuppressive drug use.

The patient's sodium improved with fluid restriction and the administration of hypertonic saline. There was no recurrence of seizure activity. Amlodipine was initiated for blood pressure readings as high as 156/106 mmHg. A hepatobiliary scan revealed a gallbladder ejection fraction of 13%. Biopsies from her endoscopy revealed nonspecific inflammation without the presence of *Helicobacter pylori*. The patient was discharged home 7 days after admission after stabilization of serum sodium, improvement in her abdominal pain, and tolerance of oral intake. A plan was made for outpatient cholecystectomy.

Many causes of abdominal pain have been excluded and the remaining diagnostic possibility, porphyria, is rare. The clinicians have revisited their differential and considered other causes of abdominal pain, including functional gallbladder disorders. However, chronic cholecystitis (or functional gallbladder disorder) is not this patient's primary problem. The diffuse, severe, and constant abdominal pain prior to admission is not typical of biliary pain, and many medical conditions and drugs, including amlodipine, can lead to a positive hepatobiliary scan. Chronic cholecystitis would not explain her seizure.

AIP remains at the top of the differential for this young woman. A urine porphobilinogen has been sent and must be followed up prior to any further workup or surgery.

One week after discharge, the patient's urine porphobilinogen resulted at 172.8 mCmol/ (upper limits of normal 8.8). Sequencing analysis for genes coding the enzymes involved in the synthetic pathway for heme were sent. Hydroxymethylbilane synthase, coproporphyrinogen oxidase, and protoporphyrinogen oxidase mutation assays were all normal. Despite the normal genetic assays, the diagnosis of AIP was made on the basis of the clinical presentation and elevated urine porphobilinogen. The patient was referred to a hematologist and initiated on oral glucose supplements and hematin infusions.

DISCUSSION

Although abdominal pain has a broad differential, the combination of abdominal pain and neurologic or psychiatric symptoms should suggest the possibility of porphyria, especially if symptoms are recurrent or unexplained. The porphyrias are a group of disorders caused by defects in the synthetic pathway of heme, leading to an overproduction and accumulation of precursors. Heme is a component of multiple proteins, including hemoglobin, myoglobin, and the cytochrome P450 enzymes. Although it is synthesized in all tissues, the bone marrow and liver are the organs most actively involved. The porphyrias can be classified according to the primary site of the overproduction and accumulation of heme precursors (liver vs bone marrow). Although there is overlap between the 2 groups, hepatic porphyrias often present with acute neurovisceral symptoms, while the erythropoietic porphyrias often cause cutaneous photosensitivity.[1]

AIP is the most common hepatic porphyria with a prevalence

of 1 in 20,000 in Caucasians of Western European descent.[1] AIP is caused by a defect in the gene that encodes porphobilinogen deaminase, leading to the accumulation of porphobilinogen.[1] The cardinal manifestation is an acute porphyric attack. While the precise mechanisms underlying the symptoms are unknown, the accumulating metabolites may be directly neurotoxic.[2] Attacks are precipitated by factors that induce heme synthesis, including caloric restriction, alcohol, and certain medications, particularly those that upregulate cyP450. The most commonly implicated drugs are anesthetics, antiepileptics, sulfonamides, rifampin, and estrogen and progesterone. Attacks can also be precipitated by changes in endogenous sex hormone levels, like the increase in progesterone seen in the luteal phase of the menstrual cycle, which may account for the higher incidence of symptomatic attacks in women.[3]

Acute attacks of AIP may have a wide variety of presentations; the disease was referred to as the "little imitator" in the early 20th century.[4] The most common symptom is acute, severe abdominal pain, which may mimic an acute abdomen. Because the pain is neuropathic rather than inflammatory, abdominal tenderness, rebound, fever, and leukocytosis are usually absent, as they were in this patient. Abdominal pain is often accompanied by neuropsychiatric symptoms, including sensory and motor neuropathy, anxiety, hallucinations, delirium, and altered level of consciousness. Seizure occurs in 20% of cases. Involvement of the autonomic nervous system causes tachycardia and new onset hypertension in the majority of patients as well as restlessness and tremor. Hyponatremia, mediated by the syndrome of inappropriate ADH secretion, occurs in nearly a third of patients.[5,6] MRI findings consistent with PRES have also been described in AIP.[7]

The diagnosis of AIP is often delayed; diagnosis later in the disease course is associated with a poorer prognosis.[8] Reported intervals between presentation and diagnosis range from several months to as long as 20 years.[9] Associating the use of medications, caloric restriction, or the menstrual cycle with the exacerbation of symptoms or darkening of urine can help prompt an earlier diagnosis.[6]

AIP can be diagnosed by detecting a greater than 5-fold elevation of urinary porphobilinogen excretion in conjunction with the typical symptoms of an acute attack.[5] Renal dysfunction causes urinary excretion of PBG to fall and serum levels to rise.[10] Serum PBG levels should therefore be sent when AIP is suspected in the setting of renal dysfunction. The primary role of genetic testing in a patient who has AIP confirmed clinically and biochemically is to assist in genetic counseling and to identify asymptomatic family members.[11] Genetic testing is not required to confirm the diagnosis and does not help prognosticate. It is unusual that a mutation was not detected in this case, as the current sensitivity of genetic testing is 97% to 100%.[11]

There are 4 principles of management of an acute porphyric attack. First, any precipitating factors such as medications should be stopped. Second, abdominal pain should be treated appropriately with opioids, if necessary. Third, if autonomic dysfunction is present, beta-blockers or clonidine should be given to treat hypertension.[5] Finally, glucose and/or hemin should be administered to downregulate aminolevulinic acid (ALA) synthase by negative feedback. Downregulation of ALA synthase decreases the accumulation of the neurotoxic porphyrin precursors ALA and PBG.5 For patients with mild symptoms, glucose alone (300-500 g/d) may be enough to abort the attack.[12] This can be achieved via a high-carbohydrate diet in those able to tolerate oral intake or via continuous infusions of dextrose containing fluids.[5] For more severe attacks with associated polyneuropathy, respiratory muscle weakness, or seizures, or for attacks that are not resolving, heme preparations dosed at 3 to 4 mg/kg/d for 3 to 4 days are indicated.[5]

The recent diagnosis of acute Lyme disease was a distractor in this presentation. In Lyme endemic areas, patients with erythema migrans are treated based on the clinical presentation rather than serologic testing.[13] Although this patient took only 1 week of doxycycline, testing during this hospitalization showed that she had either been cured early or had not had Lyme disease in the first place. There is no known association between Lyme disease and the porphyrias, and doxycycline is not a common precipitant of AIP attacks.[14] However, the GI side effects of doxycycline may have decreased caloric intake and ultimately provoked the patient's first attack of AIP. The clinicians in this case appropriately avoided the "target" but hit the mark by correctly diagnosing AIP.

KEY POINTS

- Consider AIP in patients with unexplained abdominal pain, especially when accompanied by neuropsychiatric symptoms and autonomic lability.
- Diagnose AIP by sending a urine PBG during a suspected acute attack.
- Treat AIP acutely by removing precipitants, treating abdominal pain, and initiating dextrose-containing fluids and hemin infusions to downregulate ALA synthase.

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References

1. Desnick RJ, Balwani M. The Porphyrias. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 19th Edition*. New York: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com.proxy.medlib.uits.iu.edu/content.aspx?bookid=1130&Sectionid=79754263. Accessed June 14, 2016.
2. Bissell DM, Lai JC, Meister RK, Blanc PD. Role of Delta-aminolevulinic Acid in the Symptoms of Acute Porphyria. *Am J Med*. 2015;128(3):313-317.
3. Bonkovsky HL, Guo JT, Hou W, Li T, Narang T, Thapar M. Porphyrin and Heme Metabolism and the Porphyrias. *Compr Physiol*. 2013;3(1):365-401.
4. Crimlisk HL. The little imitator--porphyria: a neuropsychiatric disorder. *J Neurol Neurosurg Psychiatry*. 1997;62(4):319-328.
5. Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. *Appl Clin Genet*. 2015;8:201-214.
6. Ventura P, Cappellini MD, Biolcati G, Guida CC, Rocchi E; Gruppo Italiano Porfiria (GrIP). A challenging diagnosis for potential fatal diseases: recommendations for diagnosing acute porphyrias. *Eur J Intern Med*. 2014;25(6):497-505.

7. Dagens A, Gilhooley MJ. Acute intermittent porphyria leading to posterior reversible encephalopathy syndrome (PRES): a rare cause of abdominal pain and seizures. *BMJ Case Rep*. 2016:bcr2016215350.
8. Pischik E, Bulyanitsa A, Kazakov V, Kauppinen R. Clinical features predictive of a poor prognosis in acute porphyria. *J Neurol*. 2004;251(12):1538-1541.
9. Sack GH. Acute intermittent porphyria. *JAMA*. 1990;264(10):1290-1293.
10. Sardh E, Andersson DEH, Henrichson A, Harper P. Porphyrin precursors and porphyrins in three patients with acute intermittent porphyria and end-stage renal disease under different therapy regimes. *Cell Mol Biol (Noisy-le-grand)*. 2009;55(1):66-71.
11. Whatley SD, Badminton MN. Role of genetic testing in the management of patients with inherited porphyria and their families. *Ann Clin Biochem*. 2013;50(3):204-216.
12. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med*. 2005;142(6):439-450.
13. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43(9):1089-1134.
14. American Porphyria Foundation. Drug database. http://www.porphyriafoundation.com/drug-database. Accessed July 21, 2017.