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Clinical Reasoning Case

A Diagnostic Deficiency

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A 29-year-old woman with no significant past medical history presented to the emergency department with diffuse abdominal pain. She has had several recurrent episodes in the past four months, and the episodes have been worsening in severity and frequency. This episode began abruptly while she was lying in bed at rest. It is colicky in nature, and very severe at peak intensity—rated as a "10 out of 10" pain. The pain is diffuse, poorly localized, and did not radiate. She noted a burning quality to the pain in more recent episodes and reports that these symptoms typically would worsen just prior to the onset of menstruation. Her abdominal pain was not associated with the ingestion of food and has been refractory to medications, such as antacids, proton pump inhibitors, and over-the-counter pain medications. On review of systems, she endorsed associated symptoms including nausea, dysphagia, urinary retention and constipation. Additionally, she reported a 30–40-pound unintentional weight loss over the past several months due to poor oral intake and difficulty swallowing. She denied any chest pain, shortness of breath, vomiting, hematuria, or signs of gastrointestinal bleeding (i.e. bloody diarrhea, melena, hematochezia).

A young woman with subacute to chronic, recurrent episodes of abdominal pain with concerning associated features—weight loss, dysphagia, and urinary retention— presents a broad diagnostic challenge. The colicky and episodic nature of the pain could suggest intermittent gastrointestinal luminal obstruction. The absence of prominent nausea and vomiting speaks against a proximal obstruction (i.e. gastric outlet, proximal small bowel); however, transient, partial distal small bowel or colonic obstruction are considerations. Transient biliary luminal obstruction (i.e. cholelithiasis) is also a possibility. Inflammatory bowel disease should be strongly considered; this is a common condition that often manifests in her age range and can be associated with a variety of extra-intestinal manifestations. The patient's worsening symptoms prior to menstruation raises suspicion for a hormonally influenced disorder, such as endometriosis.

The patient's profound unintentional weight loss increases the likelihood of a serious pathology; it is unclear if it is due to her dysphagia, a malabsorptive process, or increased metabolic demand. In isolation, dysphagia may be due to a primary disorder of the oropharynx or esophagus; however, in combination with urinary retention, neurologic etiologies should be considered. A thorough history must be taken, and gastrointestinal, gynecologic, neurologic, and psychiatric etiologies must all be considered. Given the patient's young age and lack of prior medical history, it is most likely that the patient has a single diagnosis that unifies all her symptoms.

Since the patient began having recurrent episodes of abdominal pain, she experienced two generalized tonic-clonic seizures, for which she was briefly prescribed levetiracetam by her neurologist. Her only medication is acetaminophen with codeine as needed for abdominal pain. Her surgical history included a cholecystectomy performed two years ago for cholelithiasis that developed after pregnancy and her family history was noncontributory. She worked as a dental hygienist and denied alcohol, tobacco, or recreational drug use.

Over the past four months, she presented to multiple hospitals with abdominal pain. An upper endoscopy was performed and showed no evidence of *Helicobacter pylori* infection, gastric/duodenal ulcers, or celiac disease. Multiple computed tomography (CT) scans of the abdomen and pelvis with intravenous contrast were only notable for moderate stool burden and mild proctitis. A colonoscopy was unrevealing aside from nonspecific colonic inflammation. She underwent an exploratory laparotomy three months prior during an episode of severe abdominal pain, which failed to identify an underlying pathology.

Prior diagnostic workup for gastrointestinal and gynecologic pathologies were mostly unremarkable and did not clearly explain the etiology of this patient's symptoms. While severe constipation could account for intermittent abdominal pain, it would not explain her other symptoms. Functional or factitious disorders may be considered, but her multisystem involvement with objective weight loss mandates further workup before considering them. When imaging and direct visualization (i.e. endoscopy, open laparotomy) are unremarkable in the workup of persistent abdominal pain, clinicians should consider "image negative" etiologies. These include intraluminal pathologies, metabolic disturbances, and toxidromes like irritable bowel syndrome, diabetic ketoacidosis, hypercalcemia, adrenal insufficiency, acute intermittent porphyria, opioid toxicity and withdrawal, anticholinergic toxicity, and lead poisoning. The patient's seizures are further evidence of a systemic pathology with a neurologic signature. Many of the metabolic disturbances noted above can either directly or indirectly cause seizures. A detailed neurologic examination should be performed and advanced neuroimaging considered.

On examination, her axillary temperature was 36.7°C, the blood pressure 137/89 mmHg, the pulse 140 beats per

minute, the respiratory rate 12 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. She appeared fatigued and in apparent pain. Her abdominal examination was notable for diffuse tenderness to palpation without guarding or rebound tenderness. Neurologic examination revealed 1/5 strength in her proximal upper and lower extremities, and 3/5 strength in her distal upper and lower extremities. Global areflexia and loss of proprioception in the toes was also noted. Her voice was hoarse. Cranial nerves 2 through 12 were intact and there was no fatigability on sustained upward gaze. She was alert and oriented. Cardiopulmonary and skin examination were normal.

On further questioning, she reported progressive bilateral leg weakness over the past month, ultimately requiring an assistive walking device for mobility. She also noted the development of vocal hoarseness and dysphagia during this period.

Tachycardia of this degree with or without hypotension should prompt the consideration of an arrhythmia and an electrocardiogram should be obtained. If sinus rhythm is detected, sepsis with impending shock and profound hypovolemia should be considered. Prompt intravenous hydration should be administered while evaluating for infectious or inflammatory causes. If tachycardia persists, autonomic instability and hyperadrenergic states including hyperthyroidism and pheochromocytoma could also be considered in the right clinical context. The patient's neurologic examination reveals diffuse proximal muscle weakness, global areflexia, and a loss of proprioception, which are concerning for a rapidly progressive polyneuropathy. While neuroimaging to rule out spinal cord and brain pathology would be appropriate, her examination is less consistent with a central neurologic process. Acute inflammatory demyelinating polyneuropathy, paraprotein related polyneuropathies, acute intermittent porphyria, and lead poisoning should be considered. Lumbar puncture with cerebral spinal fluid analysis and nerve conduction study with electromyography should be considered in consultation with neurology. While a myopathy would not be expected to cause a loss of proprioception, it could account for the other findings, and a serum creatinine kinase test should be sent. Finally, her development of hoarseness is concerning for vocal cord dysfunction. Given the supportive evidence for polyneuropathy, I would be concerned that whatever disease process is occurring involves the recurrent laryngeal nerve.

The patient's heart rate improved with intravenous fluids, though she continued to have intermittent tachycardia. The basic metabolic panel was normal other than a sodium of 126 mmol/L (normal range 135-145 mmol/L) and a potassium of 3.4 mEq/L (normal range 3.6-5.2 mEq/L). Liver chemistry tests were notable for an aspartate aminotransferase of 117 U/L (normal range 8-33 U/L) and an alanine aminotransferase of 259 U/L (normal range 7-45U/L). Alkaline phosphatase, total bilirubin, and albumin were within normal limits. Creatinine kinase was 14 U/L (normal range 22-200U/L). Thyroid stimulating hormone was 0.44 mIU/L (normal range 0.5-5mIU/L) and a morning cortisol was 15 mcg/dL. A complete blood count was normal. Repeat imaging, including computed tomography of the abdomen and pelvis with contrast and magnetic resonance enterography, showed extensive stool burden and no other notable findings. Magnetic resonance imaging of the brain and spine with and without gadolinium contrast were unremarkable. Evaluation of cerebral spinal fluid was unremarkable. Autoimmune markers including Antinuclear Antibody (ANA), Anti-Sjögren's syndrome type A (Ro) antibody (SSA) and Anti-Sjögren's syndrome type B (La) antibody (SSB), antitopoisomerase I antibody (SCL-70), and Anti-Neutrophil Cytoplasmic Antibody (ANCA) were negative. A heavy metal screen was negative. A nerve conduction study with electromyography revealed a sensorimotor axonal polyneuropathy. Laryngoscopy revealed unilateral vocal cord paralysis. During the hospitalization, the patient continued to have severe abdominal pain that was refractory to multimodal pain medications including high doses of opioids.

An extensive workup for this patient's abdominal pain has again returned unremarkable other than a large burden of stool. An aggressive bowel regimen should be started; however, constipation does not explain the full extent of her pain, nor does it account for her objective neurologic deficits. At this time, the patient could be described as having a progressive, widespread, neurologic process with abdominal pain, seizures, and a sensorimotor axonal polyneuropathy, without a clear signature of disease on advanced neuroimaging. Diabetes is a common cause of polyneuropathy, and diabetic ketoacidosis can present with severe abdominal pain and potentially seizures; however, this patient's blood sugar is normal and there is no acidemia. Certain vitamin deficiencies like B12 and thiamine deficiencies can cause polyneuropathy; however abdominal pain and seizures are not commonly associated. Cancer associated polyneuropathies, whether from a paraproteinemia or a paraneoplastic immune-mediated process, should be considered and may require specialized testing. The patient's age and lack of imaging findings make malignancy less likely, but do not exclude it. Urine and serum electrophoresis, immunofixation, and serum free light chain testing should be performed. Lead, arsenic, and thallium are heavy metals that can cause a rapidly progressive polyneuropathy and lead specifically is associated with episodic abdominal pain. However, a serum heavy metal screen was negative ruling out these etiologies. Another metabolic disturbance that is commonly associated with "image negative" abdominal pain and a progressive neurologic syndrome including seizures and polyneuropathy is acute intermittent porphyria (AIP). Hyponatremia and mild elevations in transaminases, both seen in this case, are also commonly noted in AIP. Testing for this disease entity should be sent.

A 24-hour urine porphobilinogen (PBG) was elevated at 176.5 µmol/L (normal <8 µmol/L). Given the results of this test and her clinical presentation, a diagnosis of acute intermittent porphyria was made. She was started on a high-carbohydrate diet and intravenous hemin (4 mg/kg/day). By the fourth dose of hemin, her abdominal pain and weakness began to improve, and by the sixth day of hospitaliza-

tion, her dysphagia and dysphonia also began to improve. Genetic testing confirmed a pathogenic mutation in the hydroxymethylbilane synthase (HMBS) gene. This gene codes for the HMBS enzyme, and its lack of function causes acute intermittent porphyria (AIP).

The patient's highly elevated 24-hour urine PBG in the context of her clinical presentation is diagnostic of acute intermittent porphyria. She was appropriately started on treatment and appears to be responding well post discharge*.*

Discussion

Acute intermittent porphyria (AIP) is a rare autosomal dominant disorder characterized by a deficiency of the enzyme porphobilinogen deaminase (PBG-D), which plays a critical role in the heme synthesis pathway. This enzymatic deficiency leads to the accumulation of neurotoxic heme precursors, particularly delta-aminolaevulinic acid (d-ALA) and porphobilinogen (PBG), which are primarily responsible for the clinical manifestations.[1-3]

Although genetically inherited, AIP exhibits variable penetrance, with only 10–20% of carriers experiencing symptomatic attacks. Most commonly, it affects young women of reproductive age (20's to 30's).[3] Triggers include hormonal fluctuations (particularly progesterone, which may explain why attacks are more commonly seen in women of reproductive age and are unusual before menarche and after menopause), fasting, physiologic stress, alcohol, tobacco, and other drugs that induce cytochrome P450 (i.e. antiepileptics, sulfonamides, anesthetics).[1-4] This patient had multiple identifiable triggers, including levetiracetam use, exposure to anesthetics during her diagnostic procedures, and her elevated progesterone levels in relation to her menstrual cycles.

Her case also illustrates the hallmark features of AIP: abdominal pain and neuropsychiatric symptoms. Severe abdominal pain due to ileus is usually the presenting feature, along with nausea, vomiting, and constipation. Neurological symptoms are also common, and include polyneuropathy, muscle weakness, and paresthesia. A symmetrical motor neuropathy with weakness beginning proximally in the upper limbs is typical, and it may rarely progress to result in incontinence, urinary retention, or dysphagia, as seen in this patient. Seizures occur in roughly 20% of acute attacks. In severe cases, it may even result in complete paralysis or respiratory failure so early diagnosis is critical.[1-4] Moreover, psychiatric disturbances often accompany acute attacks, and combined with the nonspecific nature of symptoms, many AIP cases can be easily misdiagnosed as psychosomatic disorders, functional disorders or drug-seeking behavior.

In addition to GI symptoms and neuropsychiatric abnormalities, acute flares commonly present with autonomic dysfunction, such as tachycardia and hypertension, as seen in this case.[1,3,4] Rare complications of attacks include rhabdomyolysis and cardiac arrhythmias, which may account for occasional reports of sudden death.[4] However, laboratory evaluation is usually normal apart from a minor elevation of liver-enzyme levels and a low serum sodium level. Hyponatremia (thought to be secondary to SIADH) is frequently observed, in up to 40% of AIP episodes.[4]

Finally, despite the name "porphyria" which implies purple-colored urine, freshly voided urine in AIP is typically colorless, as D-ALA and PBG are not pigmented. The urine will only darken over time with exposure to light and ambient temperature, as this requires the formation of pigments like porphobilin.[5] The literature does not provide a specific percentage of AIP patients who present with purple urine. However, it is noted as a relatively rare and nonspecific finding that should not be relied upon for diagnosis.

Urine PBG and ALA are elevated during acute attacks and confirm diagnosis.[6] Treatment involves IV hemin and carbohydrate loading to suppress hepatic ALA synthase. These measures resulted in rapid relief of this patient's symptoms, but in recurrent cases, prophylactic therapy with Givosiran, an RNAi that targets ALAS1 mRNA, can be considered.[7] Liver transplantation is a curative option in refractory cases.[8,9]

CONCLUSION

The diagnosis of AIP is often delayed or misattributed to psychosomatic disorders due to the rarity and nonspecific nature of symptoms. However, AIP should be considered in patients with unexplained abdominal pain and neuropsychiatric symptoms. While port-wine colored urine has been well associated with AIP, it is a relatively uncommon and nonspecific finding, which may be replaced with more commonly seen findings of dysautonomia, neuromuscular weakness, hyponatremia, and seizures. Early recognition of this disease can prevent unnecessary interventions, reduce morbidity, and allow for targeted therapy.

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