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62-Year-Old Man With Persistent Postoperative Nausea and Vomiting

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See end of article for correct answers to questions.

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A 62-year-old man with a history of type 2 diabetes mellitus, hypogonadotropic hypogonadism (diagnosed 6 months before presentation), stage 3 chronic kidney disease, and coronary artery disease was admitted to the hospital for treatment of mitral valve endocarditis. Broad-spectrum antibiotics, including vancomycin and rifampin, were initiated, and in addition, he underwent mitral valve replacement because of vegetations causing severe valvular stenosis. On hospital admission and initiation of broad-spectrum antibiotics, progressive nausea, vomiting, fatigue, and anorexia developed. These symptoms persisted for up to 15 days postoperatively. The symptoms were constant and not necessarily postprandial. He also had fevers and chills, but these symptoms resolved with antibiotic therapy. He reported no abdominal pain and had no history of abdominal surgery. His bowel movements remained regular. The patient had no symptoms of gastroesophageal reflux, headaches, or vertigo. His diabetes was recently diagnosed and was controlled with diet. His symptoms continued despite maximum doses of antiemetics. He had not had similar symptoms before the current episode.

Vital signs on evaluation included a temperature of 37.1°C, heart rate of 65 beats/min, blood pressure of 138/73 mm Hg, and oxygen saturation of 96% while breathing room air. On physical examination, the patient was cachexic and had generalized nonfocal weakness. His body mass index was 19 kg/m^2. His abdomen was soft, nondistended, and nontender, and normal bowel sounds were present. He had no rashes or lower extremity edema.

1. At this time, which *one* of the following is the *best* step in evaluation of this patient's symptoms of nausea and vomiting?

a. Computed tomography of the abdomen and pelvis
b. Abdominal radiography
c. Laboratory testing
d. Review of the medication administration history
e. Upper endoscopy

Imaging studies, such as computed tomography of the abdomen and pelvis and abdominal radiography, and laboratory testing are only helpful once a thorough history is obtained. A careful review of medication administration history is imperative in evaluating patients with nausea and vomiting to guide appropriate test selection and interpretation and to avoid unnecessary cost and radiation exposure associated with testing in cases in which culprit medications can be identified. Upper endoscopy is an invasive procedure and can be considered if the history suggests that it would have diagnostic or therapeutic value. In general, a comprehensive history and physical examination helps to identify most causes of acute nausea and vomiting.[1]

Many medications are associated with nausea and vomiting. Most commonly, however, one should look for opioid analgesics, nonsteroidal anti-inflammatory drugs, antibiotics, antiarrhythmics, and anticonvulsants.[2] In the outpatient setting, the physician should ask about illicit drug use because cannabinoids have been recognized as an important cause of cyclic nausea and vomiting.[3]

Review of our patient's medications was notable for vancomycin and rifampin, which had been initiated several days before symptom onset. He was not taking any analgesics including opioids or nonsteroidal anti-inflammatory drugs.

Laboratory testing revealed the following (reference ranges provided parenthetically): leukocytes, 8.5 × 10^9/L (3.5-10.5 × 10^9/L); creatinine, 3.5 mg/dL, which was at baseline for the patient (0.8-1.3 mg/dL); serum urea nitrogen, 33 mg/dL (8-24 mg/dL); sodium, 131 mmol/L (135-145 mmol/L); potassium, 5.2 mmol/L (3.5-5.0 mmol/L), which was higher than the patient's baseline (<4.5 mmol/L);

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bicarbonate, 25 mmol/L (22-29 mmol/L); fasting glucose, 64 mg/dL (70-140 mg/dL); alkaline phosphatase, 55 U/L (45-115 U/L); aspartate aminotransferase, 21 U/L (8-48 U/L); alanine aminotransferase, 10 U/L (7-55 U/L); total bilirubin, 0.8 mg/dL (1.2 mg/dL); direct bilirubin, 0.6 mg/dL (0.0-0.3 mg/dL); and thyrotropin, 1.9 U/mL (0.3-5.0 mIU/L).

2. On the basis of the clinical presentation, physical examination findings, and laboratory results, which *one* of the following is the *most likely* cause of the patient's symptoms?

a. Acute gastroenteritis
b. Adrenal insufficiency (AI)
c. Cholecystitis
d. Small-bowel obstruction
e. Gastric outlet obstruction

Acute gastroenteritis is unlikely in our patient because of the absence of diarrhea and systemic symptoms and the prolonged symptom duration.[4] At this point, the most likely etiology of the patient's symptoms is AI. This diagnosis is supported by symptoms of nausea, vomiting, anorexia, and hypoglycemia and classic electrolyte findings of hyponatremia and hyperkalemia. Cholecystitis is less likely in the absence of leukocytosis, fevers, and abdominal pain or tenderness on examination. Small-bowel obstruction is an important cause of nausea and vomiting. However, any form of intestinal obstruction or pseudo-obstruction is highly unlikely in this patient because of the lack of abdominal pain or changes in bowel habits.

Because of the high suspicion for AI, a morning cortisol measurement was obtained. The value was low at 3.6 μg/dL (7-25 μg/dL).

3. Which *one* of the following is the *best* step in evaluating the patient's AI at this time?

a. Corticotropin-releasing hormone (CRH) test
b. Aldosterone and renin measurements
c. Corticotropin measurement
d. Magnetic resonance imaging (MRI) of the brain
e. Prolactin measurement

Corticotropin-releasing hormone is released from the hypothalamus. Testing CRH involves measuring the corticotropin response following CRH administration, which can help distinguish secondary from tertiary AI.[5] This test is expensive and cumbersome to perform and is not needed at this time because primary AI has not been ruled out. Aldosterone levels are expected to be low in patients with primary AI, with resultant elevation in renin levels. Both tests can be considered once primary AI is confirmed to assess associated mineralocorticoid deficiency. Measuring the corticotropin level simultaneously with the cortisol level is the best step at this time in order to distinguish primary from secondary AI.[6] Elevation of the corticotropin level to more than 100 pg/mL would confirm primary AI.[7] Brain MRI can be performed to assess for the presence of a pituitary mass as a cause of secondary AI. At this point, however, secondary AI should be confirmed before imaging or prolactin level measurement.

The patient's corticotropin level was 58 pg/mL (10-60 pg/mL). A corticotropin stimulation test performed to confirm the diagnosis yielded a normal response to corticotropin with an increase of cortisol levels to 19 μg/dL and 22 μg/dL at 30 and 60 minutes, respectively.

4. In view of these test results, which *one* of the following is the *most likely* cause of the patient's AI?

a. Autoimmune adrenalitis
b. Adrenal hemorrhage
c. Bilateral adrenal metastasis
d. Sepsis
e. Medication

Our patient's laboratory test results (low morning cortisol level) are consistent with AI. His corticotropin stimulation test resulted in a normal cortisol response, ruling out primary AI. Autoimmune adrenalitis, adrenal hemorrhage, and bilateral adrenal metastasis are all unlikely because they cause primary AI. With normal vital signs and white blood cell count, the patient does not have clinical signs of sepsis.

Therefore, medication-induced AI is the correct diagnosis, with rifampin the most likely culprit. Rifampin is thought to induce hepatic enzymes responsible for peripheral metabolism of corticosteroids, resulting in

decreased circulating cortisol levels.[8,9] This process would explain our patient's low morning cortisol level and appropriate corticotropin stimulation response. His simultaneously obtained corticotropin level was inappropriately in the normal range, raising suspicion for decreased pituitary reserve. Rifampin can precipitate AI in the setting of decreased pituitary or adrenal reserve. As noted previously, our patient has a history of hypogonadotropic hypogonadism, which suggests probable decreased pituitary reserve. The hypogonadotropic hypogonadism had been diagnosed at another institution 6 months before the current presentation, presumably due to an adenoma. At that time, MRI revealed soft tissue along the lateral left sella medial to the adjacent traversing right internal carotid artery, signaling and enhancing similar to the adjacent pituitary gland. The patient's cortisol level was normal at that time (17 μg/dL).

We continued the rifampin for treatment of the patient's endocarditis but also initiated hydrocortisone replacement, 20 mg of hydrocortisone twice daily. He returned for a follow-up visit to assess his response to hydrocortisone.

5. Which *one* of the following would be the *best* indicator of our patient's response to treatment with hydrocortisone?

a. Clinical signs and symptoms
b. Morning serum cortisol level
c. Serum cortisol day curves
d. Corticotropin stimulation test
e. Urinary free cortisol level

Monitoring the response to hydrocortisone treatment is best achieved by assessing clinical signs and symptoms. Obtaining a morning serum cortisol measurement is helpful in screening for AI. However, it is not routinely used to monitor the response to exogenous corticosteroid replacement. Serum cortisol day curves have been shown to be of limited value compared with clinical signs and symptoms.[10] Although a corticotropin stimulation test, as used in our patient, can be helpful to confirm the diagnosis of AI and for distinguishing between primary and secondary deficiencies, it has no role in monitoring response to corticosteroid replacement. Urinary free cortisol is not an accurate measurement of the adequacy of corticosteroid replacement because it is affected by administration of the drug in a single dose vs divided doses.

The patient's symptoms improved dramatically within 48 hours of initiation of hydrocortisone therapy. He was able to tolerate oral intake, and his weight continued to increase on follow-up. He completed his course of antibiotics and is in the process of tapering off the hydrocortisone.

DISCUSSION

Adrenal insufficiency can be acute or chronic. Acute AI or adrenal crisis usually manifests primarily as shock because the major hormonal deficiency is due to mineralocorticoid rather than glucocorticoid. Chronic AI, however, has a more insidious onset, with nonspecific symptoms making its diagnosis challenging. Adrenal insufficiency is also classified as primary or secondary. Primary AI involves a defect in corticosteroid production in the adrenal glands. Primary AI is thought to affect up to 140 people per million worldwide.[11] Conversely, secondary AI results from a deficiency of corticotropin. Secondary AI is thought to have a higher prevalence of up to 280 persons per million.[11]

The underlying causes of AI are vast. Sudden withdrawal of exogenous corticosteroid is one of the most common causes of AI. Exogenous glucocorticoids cause suppression of the hypothalamic-pituitary-adrenal axis. Hypothalamic-pituitary-adrenal suppression can occur as early as 3 weeks after initiation of moderate-dose exogenous corticosteroid therapy. Therefore, rapid withdrawal of exogenous corticosteroids can lead to AI. Common causes of primary AI include but are not limited to autoimmune adrenalitis, tuberculosis, AIDS, and related opportunistic infections.[6] Panhypopituitarism is the most common cause of secondary AI.[11]

Clinical manifestations of chronic AI include nonspecific symptoms such as anorexia, weight loss, fatigue, and generalized weakness.[6] Other gastrointestinal manifestations of chronic AI include nausea and vomiting. Certain laboratory derangements might serve as helpful clues to the presence of underlying AI. These factors include hyponatremia and hyperkalemia (which may be mild) and occur mainly due to mineralocorticoid deficiency. Hyponatremia is reported to occur

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in up to 90% of patients with AI. Certain symptoms and findings are more likely to be associated with primary rather than secondary or tertiary AI. These symptoms include hyperpigmentation, most commonly in the palmar creases and in the buccal mucosa, gastrointestinal symptoms, and hyperkalemia.[12] Notably, hyperpigmentation is not present in either secondary or tertiary AI due to the lack of corticotropin production. Conversely, hypoglycemia is more likely to be present in secondary AI.[12]

It is important to recognize medications that may contribute to AI. These include, but are not limited to, antifungal agents such as ketoconazole and fluconazole, phenytoin, and etomidate, in addition to rifampin as in our case. These medications are less likely to cause AI in patients with an intact hypothalamic-pituitary-adrenal axis but are more likely to cause clinically overt AI in patients with limited pituitary or hypothalamic reserve. Notably, our patient had development of AI while receiving rifampin in the setting of probable decreased pituitary reserve due to his history of hypogonadotropic hypogonadism. After hospital discharge, he will undergo a thorough evaluation including MRI of the brain and hormonal testing of pituitary function.

Successful management of AI involves identification and treatment of the underlying cause in addition to appropriate glucocorticoid replacement. Therapy is monitored through improvement in clinical signs and symptoms.

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CORRECT ANSWERS: 1. d. 2. b. 3. c. 4. e. 5. a