MAYO CLINIC

58-Year-Old Woman With Progressive Nausea and Fatigue

Kavel Visrodia, MD; Raina Shivashankar, MD; and Amy T. Wang, MD

See end of article for correct answers to questions.

Resident in Internal Medicine (K.V.) and Gastroenterology (R.S.), Mayo School of Graduate Medical Education, Mayo Clinic, Rochester, MN; Advisor to residents and Consultant in General Internal Medicine, Mayo Clinic, Rochester, MN (A.T.W.).

A 58-year-old woman presented to her primary care physician for unremitting nausea and fatigue of 6 months' duration. A review of systems yielded normal findings. She had no remarkable medical history, and her family history was notable for hypothyroidism. On physical examination, she was noted to be "tanned" and to have neck fullness. Thyroid function testing revealed an elevated thyrotropin (TSH) level (7.4 mIU/L; reference range, 0.3-5.0 mIU/L) and normal levels of triiodothyronine, thyroxine, and thyroperoxidase antibodies. Thyroid ultrasonography performed to evaluate neck fullness revealed changes characteristic of Hashimoto thyroiditis. Symptomatic primary hypothyroidism was diagnosed, and treatment with levothyroxine (50 μg/d) was initiated, after which her symptoms worsened. During follow-up with her primary care physician, an alternative cause for her symptoms was not identified.

One year later, she presented to our institution's emergency department with acutely worsening nausea, vomiting, fatigue, generalized weakness, light-headedness, and dry cough for 10 days. Review of her medical record was notable for a gradual and unintentional 5-kg weight loss over the preceding $1\frac{1}{2}$ years. Her vital signs were as follows: temperature, 36.3°C; blood pressure, 61/50 mm Hg; pulse rate, 60 beats/min; and respiratory rate, 24 breaths/min. Physical examination revealed mild distress, decreased skin turgor, dry mucous membranes, and hyperpigmentation of her face, neck, arms, and palmar creases. When asked about the hyperpigmentation, she recalled receiving compliments during the past year on her "year-round tan" as well as questions regarding whether she had "dye" on her palms that could not be washed off.

The results of the initial laboratory tests (reference ranges provided in brackets) were remarkable for normocytic anemia (hemoglobin, 9.9 g/dL [12.0-15.5 g/dL]), hyponatremia (sodium, 124 mmol/L [135-145 mmol/L]), hyperkalemia (potassium, 6.0 mmol/L [3.6-5.2 mmol/L]), and elevated creatinine level (1.2 mg/dL [0.6-1.1 mg/dL]). Her TSH level was 2.4 mIU/L while she was taking thyroxine replacement. Chest radiographic findings suggested an atypical pneumonia.

1. **Given these findings, which *one* of the following is the *most likely* etiology of this patient's symptoms?**
   a. Primary adrenal insufficiency
   b. Secondary adrenal insufficiency
   c. Hyporeninemic hypoaldosteronism
   d. Cushing syndrome
   e. Carcinoid syndrome

This patient has primary adrenal insufficiency, or Addison disease, and is presenting in adrenal crisis triggered by infection. Primary adrenal insufficiency is caused by damage to the adrenal cortex resulting in the loss of glucocorticoid and mineralocorticoid production. Unexplained hypotension is a frequent manifestation and multifactorial in etiology. Cortisol deficiency reduces cardiac output and vascular tone, while aldosterone deficiency reduces sodium reabsorption. In response to ensuing hypotension, vasopressin is secreted by the posterior pituitary gland and increases water retention resulting in hyponatremia, as seen in our patient and in 80% of patients at the time of diagnosis.[1] Hypokalemia secondary to aldosterone deficiency and reduced potassium excretion is present in 40% of patients. Other chronic symptoms include nausea, weakness, and fatigue. This patient also has hyperpigmentation due to loss of negative feedback from cortisol resulting in pituitary hypersecretion of corticotropin and downstream melanocyte stimulation. This does not occur in secondary adrenal insufficiency, where corticotropin is the primarily deficient hormone. Patients with hyporeninemic hypoaldosteronism can present with hyperkalemia but usually have volume expansion due to underlying renal insufficiency

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and would not have hyperpigmentation. Cushing syndrome results from exposure to excess glucocorticoids, leading to central obesity, hypertension, and abdominal striae. Carcinoid syndrome involves oversecretion of serotonin, most commonly producing symptoms of diarrhea and flushing.

The patient was admitted to the intensive care unit, and during the first 2 hours she received 8 L of fluid resuscitation with intravenous normal saline. A recheck of her vital signs revealed a blood pressure of 72/50 mm Hg and pulse rate of 76 beats/min, and she continued to be in mild distress. Results of random cortisol measurement remained pending.

2. Which *one* of the following should be administered to this patient at this time?

a. Hydrocortisone
b. Dexamethasone
c. Fludrocortisone
d. More fluids
e. Azithromycin

Adrenal crisis is a life-threatening emergency, and clinical suspicion alone warrants immediate administration of stress-dosed glucocorticoids, usually in the form of hydrocortisone or dexamethasone. Dexamethasone is preferred if the diagnosis of adrenal insufficiency has not yet been confirmed to reduce interference with cortisol assays that may later be necessary for diagnostic workup. Once the diagnosis is confirmed, hydrocortisone is the glucocorticoid of choice given its mineralocorticoid properties at doses over 50 mg.[1] Hydrocortisone is often chosen for long-term management of adrenal insufficiency because its shorter-acting nature can more closely mimic physiologic cortisol production, compared with longer-acting corticosteroids like prednisolone and dexamethasone, which result in increased exposure to corticosteroids over time. Although the pathophysiology underlying adrenal crisis may be more attributable to mineralocorticoid deficiency, immediate replacement with fludrocortisone is not effective due to its slow onset of sodium-retaining effects.[2] Aggressive fluid resuscitation (initial rates of 1 L/h with continuous cardiac monitoring[1]) and antibiotics to treat the underlying infection are important, but the patient continues to be in hypovolemic shock despite resuscitative attempts and will benefit the most from immediate treatment with glucocorticoids.

Due to availability, hydrocortisone (100 mg) was given intravenously. The patient was also given azithromycin (500 mg) intravenously with an additional 5 L of normal saline. Her blood pressure improved to 96/62 mm Hg, and she had rapid clinical improvement. She remained in the intensive care unit for cardiac monitoring and continued to improve after hydrocortisone was temporarily switched to dexamethasone in anticipation of further diagnostic testing. Her random cortisol level (drawn prior to receiving corticosteroids) returned low at 4.2 μg/dL (reference range, 7-25 μg/dL), consistent with adrenal insufficiency. The next day, she was stable for transfer to the internal medicine ward for continued care.

3. To confirm this patient's diagnosis, which *one* of the following would be the *most appropriate* next step?

a. Corticotropin measurement
b. Corticotropin stimulation test (also known as a cosyntropin stimulation test)
c. Insulin tolerance test
d. Metyrapone test
e. Corticotropin-releasing hormone stimulation test

This patient's random cortisol level of 4.2 μg/dL was very low, especially given her critical illness, a situation in which cortisol levels are expected to be elevated. This finding is highly suggestive of adrenal insufficiency, and an elevated corticotropin level would confirm the diagnosis of primary adrenal insufficiency. If the corticotropin level is normal or low or if the cortisol level is indeterminate, a corticotropin stimulation test is a safe and reliable test that can be used next to evaluate for adrenal insufficiency. It involves the measurement of serum cortisol before and 30 and 60 minutes after the administration of high-dose synthetic corticotropin (0.25 mg intravenously) to evaluate for an appropriate increase in cortisol levels. Failure to produce peak cortisol levels of greater than 18 μg/dL confirms primary adrenal insufficiency with an overall sensitivity and specificity of 96%.[1,2] If the results of corticotropin stimulation testing remain inconclusive *and* there is concern about secondary adrenal insufficiency,

an insulin tolerance test can be performed by administering intravenous insulin to induce hypoglycemia. In normal persons, this test should stress the hypothalamic-pituitary-adrenal axis and cause an appropriate increase in the plasma cortisol level. This test is contraindicated in patients with diabetes mellitus, cardiovascular disease, and/or a history of seizures. The metyrapone test was previously used for the diagnosis of secondary adrenal insufficiency but is no longer available for this purpose. Corticotropin-releasing hormone stimulation testing was previously used to help differentiate secondary adrenal insufficiency of hypothalamic and pituitary etiology, but it is no longer performed because these 2 conditions are treated in the same way.

The patient's corticotropin level was markedly elevated at 738 pg/mL (reference range, 10-60 pg/mL), confirming the diagnosis of primary adrenal insufficiency. Although it was not necessary to confirm the diagnosis, a corticotropin stimulation test was pursued and yielded findings consistent with primary adrenal insufficiency: baseline AM cortisol level, less than 1.0 μg/dL (related to recent glucocorticoid administration); cortisol level 30 and 60 minutes after corticotropin administration, 1.3 μg/dL and 1.7 μg/dL, respectively; and aldosterone, undetectable at less than 4.0 ng/dL.

4. Which *one* of the following is the *most likely* cause of this patient's disease?

a. Exogenous corticosteroid use
b. Pituitary tumor
c. Congenital adrenal hyperplasia
d. Tuberculosis
e. Autoimmune adrenalitis

With exogenous corticosteroid use and pituitary tumor, corticotropin levels would be expected to be low instead of high, like in this patient. The first presentation of adrenal insufficiency in congenital adrenal hyperplasia classically occurs in newborns rather than adults. When adrenal insufficiency was first characterized in 1855, tuberculous involvement of the adrenal glands was the most prevalent cause, and although it is now less common, tuberculosis still remains a major cause of adrenal insufficiency in the developing world.[3] In developed countries, however, autoimmune adrenalitis is the most common etiology of primary adrenal insufficiency and accounts for 80% to 90% of cases.[3] Our patient's personal and family history of autoimmune disease also make this etiology more likely. Antibodies to 21-hydroxylase can be detected in 80% of patients with recent-onset autoimmune adrenalitis.[3]

Abdominal computed tomography did not reveal evidence of adrenal hemorrhage, infiltration, or masses, and results of an extensive infectious disease work-up were unremarkable. The patient's 21-hydroxylase antibody level was elevated at 60 U/mL (reference range, <1.0 U/mL), confirming the diagnosis of autoimmune adrenalitis. She was evaluated by the endocrinology service for further management. By the time of dismissal, her glucocorticoid and mineralocorticoid replacement regimen had been titrated to: hydrocortisone (15 mg) and fludrocortisone (0.1 mg) in the morning and hydrocortisone (10 mg) in the afternoon. She received a medical alert bracelet and education regarding stress-related dose adjustment of glucocorticoids and an emergency injectable corticosteroid. Before discharge, her nausea had resolved.

5. In which *one* of the following situations is it *not necessary* for this patient's glucocorticoid dosage to be increased?

a. Long-distance travel
b. Pneumonia
c. Surgery
d. Impending sickness
e. Pregnancy

Long-distance travel does not typically warrant dosage adjustment, but any instance of medical stress, including infection (eg, pneumonia), surgery, or bodily trauma should prompt an increase in glucocorticoids to prevent adrenal crisis. This also applies to low-grade symptoms that may or may not evolve into actual sickness because the benefit of preventing a fatal crisis outweighs any potential adverse effects of temporary dose increases. During pregnancy, there is normally a gradual increase in cortisol-binding globulin and free cortisol; therefore, in patients with adrenal insufficiency, glucocorticoid replacement may need to be increased by 50% in the third trimester.[1]

The patient was followed up in the endocrinology clinic 3 months after discharge from the hospital and had complete resolution of her nausea, fatigue, anemia, and electrolyte

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abnormalities. She continued to have hyperpigmentation, although less marked than before. Her medications, including thyroxine, were not changed. Scenarios in which her glucocorticoids should be increased were reviewed, and she was scheduled for annual follow-up.

DISCUSSION

Primary adrenal insufficiency was first described by Thomas Addison as a disease characterized by wasting and hyperpigmentation.[3] It is caused by failure of the adrenal glands and their ability to produce glucocorticoids and mineralocorticoids. It is a relatively uncommon disease with a prevalence of 93 to 140 per million persons and an incidence of 4.7 to 6.2 per million per year in white populations, most commonly presenting in the fourth decade of life and affecting women more often than men.[3]

Clinically, primary adrenal insufficiency presents mainly with nonspecific symptoms of nausea, fatigue, and anorexia, and therefore it may remain unrecognized for months and even years. Half of patients with adrenal insufficiency experience symptoms for more than a year before diagnosis.[3] In a recent survey, more than 67% of patients with adrenal insufficiency reported seeking evaluation from 3 or more physicians before diagnosis, and 68% were initially misdiagnosed.[4] Delayed recognition leaves patients vulnerable to life-threatening adrenal crisis, which can occur when they are medically stressed and unable to mount a physiologic stress-related steroid response. Primary care physicians often have the first opportunity to detect underlying adrenal insufficiency and prevent such complications. This case highlights the importance of recognizing early symptoms of chronic adrenal insufficiency before adrenal crisis ensues.

Our patient initially presented to her primary care physician with several clues to her underlying disease that may have been overlooked in part because of premature closure. Premature closure occurs when a physician fails to seriously consider other possible diagnoses after an initial diagnosis is made. Once the elevated TSH was found, all of her symptoms were attributed to hypothyroidism, even when her symptoms worsened with thyroxine replacement. Although there is indeed an overlap of nonspecific symptoms between hypothyroidism and adrenal insufficiency, including fatigue and weakness, it should be stressed that symptoms of nausea and weight loss are quite atypical of hypothyroid disease. Given this patient's unremitting symptoms of nausea, a broader differential to further evaluate for common causes of nausea, including disorders of the gastrointestinal tract or medication adverse effects, could have been considered. If this work-up was unrevealing, less common etiologies of nausea, such as endocrine abnormalities like adrenal insufficiency, could have been explored, especially given various features in her presentation that might raise suspicion for this condition. A basic metabolic panel, which was not performed, may have revealed hyponatremia and/or hypokalemia and provided additional and early clues to the underlying diagnosis.

Hyperpigmentation also would not be expected with hypothyroidism and is actually a relatively specific finding for primary adrenal insufficiency. It can also be caused by drugs (busulfan, cyclophosphamide, zidovudine), systemic diseases (hemochromatosis, scleroderma), and ectopic corticotropin-producing tumors (small cell lung cancer).[2] Hyperpigmentation occurs in primary adrenal insufficiency because cortisol deficiency decreases negative feedback resulting in pituitary hypersecretion of corticotropin, which stimulates melanocyte receptors.[1] This is most marked in areas of skin exposed to friction, such as palmar creases, knuckles, scars, and oral mucosa, and is augmented by sun exposure.[1-3] Concordantly, our patient noted it to be most prominent in her palmar creases, elbows, and an old scar on her face.

Although our patient presented with an elevated TSH level and was found to have autoimmune hypothyroidism, it is worth noting that an isolated elevation in TSH in the absence of thyroid disease is not uncommon in patients with primary adrenal insufficiency. Cortisol physiologically suppresses TSH secretion by the anterior pituitary gland in healthy individuals, but this suppression is lost in patients with primary adrenal insufficiency and can result in elevated TSH levels of up to 10 mIU/L, with triiodothyronine and thyroxine levels often being normal or low.[5] These abnormalities can be expected to normalize after glucocorticoid replacement.[1,3,5] Ironically, our patient's symptoms worsened after thyroxine replacement,

perhaps because thyroxine accelerates cortisol clearance from the body and raises the basal metabolic rate, thereby increasing the body's need for cortisol and potentially exacerbating symptoms of cortisol deficiency.[3,5-8] In some cases, thyroxine replacement alone in patients misdiagnosed with hypothyroidism can precipitate adrenal crises,[6-8] but fortunately, this did not occur in our patient.

Coexistent autoimmune adrenal and thyroid disease is well recognized as autoimmune polyendocrine syndrome type 2, or Schmidt syndrome, as seen in our patient and in 60% to 70% of patients with autoimmune adrenalitis.[1] Coincident autoimmune diseases including type 1 diabetes mellitus, vitiligo, and pernicious anemia can be present in autoimmune polyendocrine syndrome type 2 as well.[1] The syndrome has a polygenic inheritance pattern and is strongly associated with HLA-DR3 and CTLA-4.[1] Although autoimmune thyroid disease is far more prevalent than autoimmune adrenalitis, this syndrome highlights the importance of maintaining a high index of suspicion for autoimmune adrenalitis in patients with preexisting autoimmune diseases who experience unusual symptoms.

Glucocorticoid replacement in primary adrenal insufficiency typically entails 15 to 25 mg of oral hydrocortisone divided into 2 to 3 doses to best mimic the diurnal release of cortisol. Physicians must monitor the patient's symptoms to find the lowest effective dose in an effort to reduce glucocorticoid excess and its undesired effects of weight gain, hyperglycemia, hypertension, and osteoporosis. Mineralocorticoid replacement is typically achieved with 0.05 to 0.2 mg/d of oral fludrocortisone and can be monitored most objectively using blood pressure, serum sodium and potassium concentrations, and plasma renin activity.

Crisis prevention training for patients and their families is crucial in reducing the risk of future life-threatening adrenal crisis. Many crises are the result of patients or physicians failing to initiate stress-related dosing; thus, patients should be instructed to double or triple their regimen until resolution of the intercurrent illness. Patients also should carry a medical information card, wear a medical alert bracelet (displaying "give corticosteroids" or "adrenal insufficiency") and have a hydrocortisone emergency self-injection kit available at all times. Once an adequate replacement regimen is in place, most patients lead normal lives, and the long-term survival of patients with primary adrenal insufficiency approaches that of the normal population.[9]

This case highlights the importance of avoiding premature closure especially when an initial diagnosis does not adequately explain the main presenting symptoms. Furthermore, this case underscores the importance of early recognition of primary adrenal insufficiency in preventing life-threatening adrenal crisis. The diagnosis is often challenging and delayed because of nonspecific symptoms, but more specific clues may be present when adequately explored. Early recognition can considerably improve a patient's quality of life.

Correspondence: Address to Amy T. Wang, MD, Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (wang.amy@mayo.edu).

REFERENCES

1. Arlt W. Disorders of the adrenal cortex. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012. http://accessmedicine.mhmedical.com/content.aspx?bookid=331&Sectionid=40727147. Accessed March 05, 2014.
2. Reddy P. Clinical approach to adrenal insufficiency in hospitalised patients. *Int J Clin Pract*. 2011;65(10):1059-1066.
3. Arlt W, Allolio B. Adrenal insufficiency. *Lancet*. 2003;361(9372):1881-1893.
4. Bleicken B, Hahner S, Ventz M, Quinkler M. Delayed diagnosis of adrenal insufficiency is common: a cross-sectional study in 216 patients. *Am J Med Sci*. 2010;339(6):525-531.
5. Arlt W. The approach to the adult with newly diagnosed adrenal insufficiency. *J Clin Endocrinol Metab*. 2009;94(4):1059-1067.
6. Graves L III, Klein RM, Walling AD. Addisonian crisis precipitated by thyroxine therapy: a complication of type 2 autoimmune polyglandular syndrome. *South Med J*. 2003;96(8):824-827.
7. Shaikh MG, Lewis P, Kirk JM. Thyroxine unmasks Addison's disease. *Acta Paediatr*. 2004;93(12):1663-1665.
8. Wang G, Cai C, Wu B. Thyroid hormones precipitate subclinical hypopituitarism resulted in adrenal crisis [letter]. *J Am Geriatr Soc*. 2010;58(12):2441-2442.
9. Li-Ng M, Kennedy L. Adrenal insufficiency. *J Surg Oncol*. 2012;106(5):595-599.

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