A 64-year-old man presented to the emergency department with progressive altered mental status of 1 week’s duration. He was also experiencing nausea, vomiting, diarrhea, and upper respiratory tract symptoms. His medical history was notable for coronary artery disease treated with drug-eluting stent, aspirin, and atorvastatin, hypertension treated with carvedilol, psoriatic arthritis treated with adalimumab, type 2 diabetes mellitus treated with insulin, meningioma treated with resection, inferior vena cava thrombus treated with apixaban, and renal cell carcinoma treated with ipilimumab and nivolumab. The patient had recently undergone 2 cycles of immunotherapy and was due for his third cycle, but he had become progressively confused and eventually minimally responsive at home. Emergency medical services was called and brought the patient to the emergency department.

En route, the patient had a systolic blood pressure of 95 mm Hg and had an episode of nonbloody, nonbilious emesis. He was resuscitated with intravenous (IV) fluids by emergency medical services. In the emergency department, initial assessment of vital signs revealed a temperature of 36.8°C, heart rate of 84 beats/min, blood pressure of 97/60 mm Hg, and respiratory rate of 24 breaths/min. His initial hypoxia (oxygen saturation, 89% to 91%) improved with supplemental oxygen via nasal cannula. On physical examination, the patient was hypovolemic and difficult to arouse. His skin was dry with normal turgor, and he had moist mucous membranes. Heart and lung sounds were both normal. His abdomen was diffusely tender to palpation. Laboratory work-up revealed the following (reference ranges provided parenthetically): sodium, 130 mmol/L (135 to 145 mmol/L); potassium, 7.9 mmol/L (3.6 to 5.2 mmol/L); chloride, 91 mmol/L (98 to 107 mmol/L); bicarbonate, 19 mmol/L (22 to 29 mmol/L); serum urea nitrogen, 39 mg/dL (8 to 24 mg/dL); glucose, 88 mg/dL (70 to 140 mg/dL); and creatinine, 2.56 mg/dL (0.74 to 1.35 mg/dL; patient baseline, 1.4 mg/dL). Venous blood gas measurement revealed a pH of 7.26 (7.35 to 7.45), PCO2 value of 49 mm Hg (35 to 48 mm Hg), and bicarbonate level of 22 mmol/L (22 to 29 mmol/L). Electrocardiography revealed normal sinus rhythm with slightly peaked T waves and normal QRS interval. Chest radiography revealed a right lower lobe infiltrate. No acute intracranial abnormalities were noted on computed tomography (CT) of the head.

1. Which one of the following diagnoses is most consistent with the patient’s presentation?

   a. Adrenal insufficiency (AI)
   b. Hypovolemic hyponatremia
   c. Aspirin overdose
   d. Gastroenteritis
   e. Syndrome of inappropriate antidiuretic hormone secretion

   Adrenal insufficiency is the most likely diagnosis based on the patient’s nausea and vomiting as well as hypotension in the setting of hyponatremia and hyperkalemia. Primary AI results in destruction of the zona glomerulosa and subsequent mineralocorticoid deficiency leading to hyponatremia and hyperkalemia. Secondary AI can also cause hyponatremia due to inappropriately high desmopressin in that setting, but it would not typically cause hyperkalemia alone. Hypovolemic hyponatremia is unlikely because the patient had adequate fluid status on examination. Moreover, the causes of hypovolemic hyponatremia are not likely...
to cause the notable hyperkalemia seen in this patient. Aspirin toxicity typically causes an early respiratory alkalosis followed by a mixed metabolic acidosis—respiratory alkalosis anion gap metabolic acidosis, whereas this patient appears to have an acute respiratory acidosis. Moreover, aspirin toxicity would not be likely to cause hyponatremia or hyperkalemia. Gastroenteritis could explain the patient’s gastrointestinal tract (GI) symptoms on admission, but electrolyte derangements including hypochloremia, hyponatremia, and hyperkalemia as well as hypotension would only result from severe GI losses, which were not apparent in this patient. The syndrome of inappropriate antidiuretic hormone secretion would explain the patient’s hyponatremia but does not account for his hyperkalemia or elevated serum urea nitrogen.

The patient received medical treatment for the hyperkalemia with calcium carbonate, insulin, and dextrose, which improved potassium levels. Piperacillin/tazobactam was administered, and the patient was admitted to the hospital for community-acquired pneumonia. Overnight, he became anuric. The next morning, he had worsening somnolence. Laboratory tests revealed a potassium level of 7.3 mmol/L, sodium value of 130 mmol/L, chloride concentration of 91 mmol/L, and bicarbonate level of 19 mmol/L, and venous blood gas analysis revealed a pH of 7.26, PCO2 value of 49 mm Hg, bicarbonate concentration of 22 mmol/L, and Po2 level of 25 mm Hg.

2. Based on symptoms and laboratory results, which one of the following is the best next step in management?

   a. Sodium polystyrene sulfonate, 15 g
   b. Emergent dialysis
   c. Normal saline, 1-L bolus
   d. Hypertonic saline, 1-L bolus
   e. Furosemide, 40 mg IV

   Sodium polystyrene sulfonate has been used to correct hyperkalemia, but the time to effect is prolonged and would only mildly correct the elevated potassium level. Dialysis is the best next step because it would most rapidly correct the patient’s electrolyte derangements as well as address possible fluid overload because the patient is anuric. Fluid administration with either normal or hypertonic saline would not be advisable because the cause of the patient’s anuria and hyponatremia are unknown at this point, and fluid administration could further exacerbate the laboratory abnormalities. Moreover, the patient had adequate fluid status on physical examination, making hypovolemic hyponatremia less likely. Diuresis with furosemide would not be advised because it could worsen his electrolyte derangements, notably the hyponatremia and hyperkalemia. A furosemide challenge could be attempted as a prognosticator for the recovery of the renal function in this context.1

   In the medical intensive care unit, the patient required vasopressors because of persistent hypotension. He continued to be anuric with altered mentation and had persistent diarrhea. His potassium level remained elevated despite treatment with furosemide, insulin, dextrose, and daily dialysis. Findings on a GI pathogen panel including *Clostridium difficile* testing were negative. Abdominal CT yielded unremarkable findings. The nephrology service was consulted, and emergent hemodialysis was subsequently initiated. On hospital day 2, laboratory tests revealed a sodium level of 130 mmol/L, potassium value of 5.4 mmol/L, chloride concentration of 95 mmol/L, and bicarbonate level of 17 mmol/L. The AM total cortisol concentration was 4.9 μg/dL (5-25 μg/dL).

3. Which one of the following would be the best next test to evaluate for possible AI?

   a. Metyrapone stimulation test
   b. Brain magnetic resonance imaging (MRI)
   c. Corticotropin measurement
   d. Renin and aldosterone measurement
   e. Adrenal CT

   A metyrapone stimulation test can be used to evaluate defects in pituitary corticotropin secretion by blocking cortisol production, but this test would not be the best next
step in evaluating the cause of the patient's low cortisol levels. Moreover, metyrapone administration can lead to nausea, vomiting, and hypotension in patients with AI and thus is not recommended in this population. Brain MRI can be used to look for intracranial abnormalities that may be contributing to a pituitary disorder, such as a pituitary mass, causing secondary AI. However, the diagnosis of secondary AI should be further investigated via laboratory testing before imaging. Corticotropin measurement concurrent with cortisol measurement is the best next step because it can help differentiate primary from secondary AI. Measuring serum renin and aldosterone levels may be useful once primary AI is confirmed to diagnose mineralocorticoid deficiency, but this test would not be indicated before the diagnosis of primary AI was established. Adrenal CT may reveal abnormal adrenal findings such as hypertrophy or atrophy, depending on the type of AI, but these findings are nonspecific and would not be recommended before determining whether the AI is primary or secondary.

Corticotropin testing revealed a value of less than 5.0 pg/mL (7.2-63 pg/mL). Subsequently, secondary AI was diagnosed, thought to be due to his immunotherapy agents for renal cell carcinoma. The endocrinology service was consulted for further recommendations regarding treatment options.

4. For this patient, which one of the following would be the most appropriate treatment regimen?
   a. Hydrocortisone
   b. Aldosterone
   c. Hydrocortisone and fludrocortisone
   d. Fludrocortisone
   e. Dehydroepiandrosterone

   Hydrocortisone alone can help provide baseline glucocorticoid activity for patients with secondary AI such as our patient. Hydrocortisone is typically provided, after a diagnosis is made, with maintenance dosing between 15 and 20 mg divided between 2 to 3 daily doses. However, if a patient presents with acute AI, stress dosing should be provided. Aldosterone replacement is not required because the renin-aldosterone axis is typically not affected by secondary AI. Fludrocortisone is often given at a dose of 0.05 to 0.2 mg daily in addition to hydrocortisone to provide mineralocorticoid effect in cases of primary AI, but mineralocorticoids are not recommended in cases of secondary AI because these patients do not have an impacted renin-aldosterone axis. In cases of secondary AI, medication review and medication taper of the offending agent would be the appropriate treatment. Although dehydroepiandrosterone production from the adrenal cortex is controlled by corticotropin, replacement of this hormone would not help maintain the glucocorticoid and mineralocorticoid effects requiring replacement after AI; however, it has been reported in some studies to help with some aspects of quality of life and sexual function in women.

   Hydrocortisone, 50 mg IV every 6 hours, was initiated for treatment of AI. After 3 doses of IV hydrocortisone, the patient exhibited notable neurologic improvement. His alertness and orientation improved to baseline, and he conversed with family and health care workers. His sodium and potassium levels progressively normalized over the course of the day and remained in appropriate ranges by hospital day 4. His renal function improved, and he was no longer anuric, with subsequent urinalysis revealing elevated white blood cell counts, white blood cell casts, and eosinophiluria.

5. Which one of the following occurs in the setting of primary AI but not secondary AI?
   a. Skin hyperpigmentation
   b. Weight loss
   c. Hypoglycemia
   d. Eosinophilia
   e. Hypercalcemia

   In primary AI, there is an excess of corticotropin resulting from lack of negative feedback from the adrenal glands. In response, proopiomelanocortin, a precursor to corticotropin and
melanocyte-stimulating hormone, is produced, leading to increased levels of corticotropin and melanocyte-stimulating hormone that bind to melanocyte receptors, causing excess melanin production. It may be worth noting that hyperpigmentation can occur at varying levels and in the setting of primary AI can resolve somewhat with glucocorticoid administration. In secondary AI, corticotropin levels are decreased, resulting in no skin hyperpigmentation. Weight loss, hypoglycemia, eosinophilia, and hypercalcemia all occur in both primary and secondary AI.

The patient’s clinical status continued to improve overall. His electrolyte abnormalities progressively corrected during his hospitalization. His hypotension was thought to be due to secondary AI, whereas his encephalopathy was metabolic in origin, resulting from his severe electrolyte derangements. Specifically, his hyponatremia and hyperkalemia were attributed to a combination of secondary AI and acute renal failure resulting from acute interstitial nephritis from his immunotherapy medications as well as prerenal azotemia from decreased oral intake prior to admission. Of note, the patient had no history of exogenous corticosteroid exposure before admission, making his immunotherapy medications the likely cause of his AI. The endocrinology service was consulted for recommendations regarding glucocorticoid management as well as further work-up for other programmed cell death ligand 1 (PD-L1)—related endocrinopathies, which were continued in the outpatient setting and ultimately revealed an elevated prolactin level of 18.5 ng/mL (4.0 to 15.2 ng/mL), a follicle-stimulating hormone value of 21.9 IU/L (1.2 to 15.8 IU/L), and a luteinizing hormone concentration of 34.6 IU/L (1.3 to 9.6 IU/L). The patient was followed up in the outpatient setting by an oncologist, who recommended starting immunotherapy with cabozantinib for continued management of his renal cell carcinoma.

DISCUSSION
The immune system contains immune checkpoints that are regulated by both costimulatory and inhibitory molecules that control the activation of T cells. Several immune checkpoints lead to negative regulation of the proliferative and functional effects of T cells. Programmed cell death ligand 1 is a transmembrane protein that is involved in suppression of the immune system. The binding of PD-L1 to programmed cell death 1 causes an inhibitory reaction reducing the development of T cells. This interaction exerts its effects during the initial activation and expansion of autoreactive T cells by attenuating self-reactive T-cell response during presentation of self-antigen by dendritic cells. Similarly, cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) is a receptor molecule that, when bound to CD80 or CD86, acts to down-regulate the immune system.

In a normal immunologic response, tumor cells create mutated antigens that are captured by dendritic cells, leading to a priming and activation of cytotoxic T cells against the tumor cells. However, many cancers have evolved to evade the immune system using these methods. Programmed cell death ligand 1 overexpression on tumor cells interacts with programmed cell death 1 expressed on T cells, leading to a reduction in T-cell function against the tumor cells. In a similar way, CTLA-4 on T cells binds CD80 and CD86 on T cells, regulating the immune response. As such, immunotherapy agents that target the immune response against tumor cells have become a novel method for treating certain malignancies. However, these agents have been linked to numerous adverse effects and immune-related adverse events (irAEs) that can lead to serious complications.

Ipilimumab, a CTLA-4 inhibitor, was the first immune checkpoint inhibitor demonstrating efficacy and was approved by the US Food and Drug Administration in 2011. Since its initiation as a therapeutic modality, meta-analyses have revealed rates of irAEs and high-grade irAEs at 72% and 24%, respectively. Immune-related adverse events most commonly associated with immunotherapy agents include diarrhea, colitis, rashes, hepatitis, and endocrine disorders including thyroiditis and hypophysitis. Of note, immunotherapy-induced hypophysitis (IIH)
was the most common endocrine-related adverse event. Autoimmune hypophysitis after ipilimumab use was first documented in 2003, and since then the medication is the most common immunotherapy agent linked to this adverse event. Nivolumab, a PD-L1 inhibitor, was approved by the Food and Drug Administration in 2014 and has been associated with IIH less commonly than CTLA-4 inhibitors; however, combined use of CTLA-4 and PD-L1 inhibitors has been associated with overall higher rates of IIH than either agent alone (8%).

The pathology of IIH stems from a process of immunologic activation at the pituitary level. The use of CTLA-4 inhibitors results in a deposition of complement components in lactotropes and thyrotropes and production of antibodies against adenohypophyseal endocrine cells. Cytotoxic T lymphocyte-associated antigen 4 expression has been reported in humans with normal pituitary function, which leaves the pituitary gland cells susceptible to attack by high levels of activated T cells induced by CTLA-4 inhibition. Caturegli et al reported biopsy findings of patients in whom IIH developed from CTLA-4 inhibitors that included macrophage infiltration, lymphocytic activation, and complement fixation likely contributing to a type II and type IV hypersensitivity response against the pituitary gland.

Immunotherapy-induced hypophysitis usually appears 8 to 10 weeks after treatment initiation, although it has been reported to occur up to 19 months after treatment completion. Because symptoms can be nonspecific, hypophysitis is likely underdiagnosed. Common symptoms include headache, visual changes, dizziness, and nausea. Hyponatremia is the most common laboratory abnormality at diagnosis. Abnormal imaging findings have been reported in up to 80.2% of patients with IIH. Findings most commonly described include generalized, uniform enlargement of the pituitary gland. However, it should be noted that a normal pituitary appearance on MRI does not rule out IIH, especially when mass effects are absent or if MRI is performed after the initial inflammation of the pituitary gland.

The management of adverse effects resulting from immunotherapy agents can pose a challenge because irAEs can develop at any time during the course of treatment and months afterward. Before starting therapy, performing a baseline hormone study in all patients to evaluate overall endocrine function and monitor changes in levels after initiating treatment can provide helpful information in recognizing and managing endocrine-associated irAEs when they develop. In both symptomatic and asymptomatic patients with laboratory abnormalities consistent with irAEs, a complete pituitary hormone study and pituitary MRI are recommended to rule out IIH. The treatment of choice is corticosteroids and replacement of the underlying hormone affected by the endocrinopathy.

Different regimens have proposed increased doses of corticosteroids with increasing severity of symptoms. For patients with mass effects like headache, vomiting, or visual field defects, one review suggests initiating prednisolone at 1 to 2 mg/kg or an equivalent dose in IV form. If patients are hyponatremic, IV therapy is warranted with a corticosteroid taper over 2 to 4 weeks followed by hormone replacement after symptomatic improvement. Following the resolution of mass effects and hypotension, hydrocortisone is commonly prescribed at replacement doses of between 15 and 25 mg/d. Complete recovery of pituitary function after IIH varies widely, with persistence of overall function in reports varying between 13% and 87%. Abnormalities on magnetic resonance imaging usually resolve within 40 days, but there are case reports describing persistent pituitary abnormalities on imaging as high as 78%. Overall, the use of immunotherapy agents requires shared decision making with patients, with emphasis on the risks and benefits. Physicians should have a low threshold for evaluation for possible acute endocrine dysfunction in patients undergoing immune checkpoint inhibitor therapy and other adverse effects resulting from these new therapeutic agents used in oncology.
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Correspondence: Address to Alice Gallo De Moraes, MD, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (gallodemoraes.alice@mayo.edu; Twitter: @gallodemoraesMD).

REFERENCES

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