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A 71-year-old woman with shock and a high INR

A 71-YEAR-OLD WOMAN is brought to the emergency department by her neighbor after complaining of fatigue and light-headedness for the last 8 hours. The patient lives alone and was feeling well when she woke up this morning, but then began to feel nauseated and vomited twice.

The patient appears drowsy and confused and cannot provide any further history. Her medical records show that she was seen in the cardiology clinic 6 months ago but has not kept her appointments since then.

Her medical history includes atrial fibrillation, hypertension, type 2 diabetes mellitus, and osteoarthritis. Her medications are daily warfarin, atenolol, aspirin, candesartan, and metformin, and she takes acetaminophen as needed. She is neither a smoker nor a drug user, but she drinks alcohol occasionally. Her family history is significant for her mother's death from breast cancer at age 55.

The neighbor confirms that the patient appeared well this morning and has not had any recent illnesses except for a minor cold last week that improved over 5 days with acetaminophen only.

INITIAL EVALUATION AND MANAGEMENT

Physical examination

On physical examination, her blood pressure is 80/40 mm Hg, respiratory rate 25 breaths per minute, oral temperature 38.3°C (100.9°F), and heart rate 130 beats per minute and irregular.

Her neck veins are flat, and her chest is clear to auscultation with normal heart

sounds. Abdominal palpation elicits discomfort in the middle segments, voluntary withdrawal, and abdominal wall rigidity. Her skin feels dry and cool, with decreased turgor.

Initial treatment

The patient is given 1 L of 0.9% saline intravenously over the first hour and then is transferred to the intensive care unit, where a norepinephrine drip is started to treat her ongoing hypotension. Normal saline is continued at a rate of 500 mL per hour for the next 4 hours.

Cardiac monitoring and 12-lead electrocardiography show atrial fibrillation with a rapid ventricular response of 138 beats per minute, but electrical cardioversion is not done.

Initial laboratory tests

Results of basic laboratory tests in the emergency department are shown in **Table 1**.

Of note, her international normalized ratio (INR) is 6.13, while the therapeutic range for a patient taking warfarin because of atrial fibrillation is 2.0 to 3.0.

Her blood pH is 7.34 (reference range 7.35–7.45), and her bicarbonate level is 18 mmol/L (22–26); a low pH and low bicarbonate together indicate metabolic acidosis. Her sodium level is 128 mmol/L (135–145), her chloride level is 100 mmol/L (97–107), and, as mentioned, her bicarbonate level is 18 mmol/L; therefore, her anion gap is $128 - (100 + 18) = 10$ mmol/L, which is normal (≤ 10).¹

Her serum creatinine level is 1.3 mg/dL (0.5–1.1), and her blood urea nitrogen level is 35 mg/dL (7–20).

Her potassium level is 5.8 mmol/L, which is consistent with hyperkalemia (reference range 3.5–5.2).

She presents with an acute change in mental status, hypotension, pulse 130 bpm, INR 6.13, bicarbonate 18 mmol/L, and creatinine 1.3 mg/dL

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TABLE 1

Initial laboratory results

Test	Value ^a	Reference range
Serum sodium	128 mmol/L	135–145 mmol/L
Serum potassium	5.8 mmol/L	3.5–5.2 mmol/L
Serum chloride	100 mmol/L	97–107 mmol/L
Serum creatinine	1.3 mg/dL	0.5–1.1 mg/dL
Blood urea nitrogen	35 mg/dL	7–20 mg/dL
Serum glucose (random, not fasting)	194 mg/dL	70–140 mg/dL
Alanine aminotransferase	18 IU/L	7–35 IU/L
Serum albumin	4.0 g/dL	3.5–5.5 g/dL
Hemoglobin	10.1 g/dL	12.3–15.3 g/dL
Mean corpuscular volume	85 fl	80–100 fl
Mean corpuscular hemoglobin	28 pg/cell	26–34 pg/cell
Mean corpuscular hemoglobin concentration	32.5 g/dL	31–36 g/dL
White blood cell count	11.0 × 10 ⁹ /L	4.5–11.0 × 10 ⁹ /L
Neutrophils	67%	40%–75%
Lymphocytes	24%	20%–45%
Monocytes	3.5%	2%–10%
Eosinophils	5.0%	1%–6%
Basophils	0.5%	0%–1%
Platelet count	220 × 10 ⁹ /L	150–400 × 10 ⁹ /L
International normalized ratio	6.13	2.0–3.0 ^b
Partial thromboplastin time	35 seconds	30–40 seconds
Arterial partial pressure of oxygen	76 mm Hg	78–84 mm Hg (predicted for age)
Oxygen saturation	94%	
Arterial partial pressure of carbon dioxide	30 mm Hg	35–45 mm Hg
Serum bicarbonate	18 mmol/L	22–26 mmol/L
Blood pH	7.34	7.35–7.45

^a Abnormal results are shown in bold.^b Therapeutic range for patients on warfarin for atrial fibrillation.

DIFFERENTIAL DIAGNOSIS

1 Which of the following is the most likely cause of this patient's symptoms?

- Adrenal crisis
- Cardiogenic shock due to decreased cardiac contractility

- Intracranial hemorrhage
- Acute abdomen due to small bowel obstruction
- Septic shock due to bacterial toxin-induced loss of vascular tone

Our patient is presenting with shock. Given our inability to obtain a meaningful history, the differential diagnosis is broad and includes all of the above.

Adrenal crisis

The sudden onset and laboratory results that include hyperkalemia, hyponatremia, and normal anion gap metabolic acidosis raise suspicion of adrenal crisis resulting in acute mineralocorticoid and glucocorticoid insufficiency.¹

The patient's elevated serum creatinine and high blood urea nitrogen-to-creatinine ratio of 26.9 (reference range 10–20) also suggest intravascular volume contraction. Her low hemoglobin level and supratherapeutic INR, possibly due to an interaction between warfarin and acetaminophen combined with poor medical follow-up, raise suspicion of acute bilateral adrenal necrosis due to hemorrhage.

Adrenal crisis is a medical emergency that can lead to rapid deterioration and death if not diagnosed and treated promptly. Some of its manifestations (Table 2) are nonspecific and are common to various other conditions. Thus, its diagnosis requires a high index of suspicion.

Bilateral adrenal hemorrhage is one cause of adrenal crisis resulting in bilateral adrenal necrosis. Risk factors for adrenal hemorrhage include anticoagulation therapy, underlying coagulopathy, postoperative states, and certain infections such as meningococemia and *Haemophilus influenzae* infection.^{2–5} Nevertheless, in most cases the INR is in the therapeutic range and the patient has no bleeding elsewhere.⁴ Other causes of adrenal necrosis include emboli, sepsis, and blunt trauma.^{6,7}

Other causes of adrenal crisis are listed in Table 3.

Cardiogenic shock

Cardiogenic shock is caused by decreased myocardial contractility, making the heart unable to adequately pump the returning blood.

However, the metabolic disturbances in our patient and the finding of flat neck veins make this cause of shock less likely.

Intracranial hemorrhage

Intracranial hemorrhage can present with a decreased level of consciousness, but it is less likely to cause hypotension, as the cranial space is limited. If massive intracranial hemorrhage would occur, the increase in intracranial pressure would more likely cause hypertension by the Cushing reflex than hypotension.

Acute abdomen

Abdominal pain and rigidity along with fever can be presenting symptoms of both adrenal insufficiency and an acute abdomen due to intestinal obstruction.⁴ However, intestinal obstruction typically causes a high anion gap metabolic acidosis due to lactic acidosis, instead of the normal anion gap metabolic acidosis present in this patient.⁸ Moreover, her deranged electrolytes, suprathreshold INR, and absence of previous gastroenterologic conditions make adrenal crisis a more likely diagnosis.

Septic shock

Septic shock would also cause fever and hypotension as bacterial toxins induce a pyrexia response and vasodilation. However, at such an early stage of sepsis, the patient would be expected to be warm and hyperemic, whereas this patient's skin is cool and dry due to volume depletion secondary to adrenal insufficiency.⁹ Sepsis would also cause a high anion gap metabolic acidosis due to lactic acidosis, as opposed to this patient's normal anion gap metabolic acidosis. These findings, along with the metabolic derangements and the absence of a focus of infection, make sepsis a less likely possibility.

■ CASE CONTINUED: CARDIOMEGALY, PERSISTENT HYPOTENSION

Blood is drawn for cultures and measurement of troponins and lactic acid, and urine samples are taken for culture and biochemical analysis. Chest radiography shows mild cardiomegaly. The patient is started empirically on vancomycin and cefepime, and her warfarin is discontinued.

Five hours after presenting to the emer-

TABLE 2

Clinical manifestations of adrenal insufficiency by organ system^a

General

Fatigue, generalized weakness
Muscle weakness
Muscle and joint pain
Loss of appetite
Weight loss
Fever^b

Gastrointestinal

Nausea and vomiting
Abdominal pain
Acute abdomen with tenderness and rigidity^b
Constipation or diarrhea
Salt craving^c

Dermatologic

Hyperpigmentation of skin, mucous membranes, hair, and nails^c
Vitiligo^c
Dry, itchy skin
Auricular cartilage calcification (males)

Cardiovascular

Shock^b
Intravascular volume depletion
Hypotension/orthostatic hypotension
Tachycardia/orthostatic tachycardia
Tachypnea

Neuropsychiatric

Dizziness, postural dizziness
Depression^d
Memory impairment^d
Psychosis (rare)^d
Confusion^b
Decreased level of consciousness^b

Reproductive (women):

Decreased axillary and pubic hair
Decreased libido
Amenorrhea

Endocrine

Autoimmune endocrine disorders,^c eg, hypothyroidism
Other pituitary hormonal abnormalities^e

^a Clinical manifestations depend on rate of onset and severity of adrenal insufficiency.

^b Only in adrenal crisis.

^c Only in primary adrenal insufficiency.

^d Only in long-standing adrenal insufficiency.

^e Only in secondary or tertiary adrenal insufficiency.

gency department, her blood pressure remains at 80/40 mm Hg even after receiving 3 L of normal saline intravenously.

TABLE 3

Major causes of adrenal crisis

- Adrenal necrosis due to:
 - Adrenal hemorrhage
 - Sepsis
 - Emboli
 - Blunt trauma
- Sudden withdrawal of corticosteroids in a patient who is steroid-dependent
- Deterioration of previously undiagnosed adrenal insufficiency after major stress, eg, severe infection
- Failure to increase corticosteroid dosage in steroid-dependent patients on days of major stress, eg, severe infection, surgery^a
- Acute secondary or tertiary adrenal insufficiency, eg, pituitary apoplexy

^a Some animal studies suggest that continuing the maintenance dose of glucocorticoids is adequate to prevent adrenal crisis. It is common practice to provide stress doses of glucocorticoids during an acute illness.

Adrenal crisis can lead to rapid deterioration and death if not diagnosed and treated promptly

PROMPT MANAGEMENT OF ADRENAL CRISIS

2 Which of the following is the most appropriate next step in managing this patient?

- Draw samples for serum cortisol and plasma adrenocorticotropic hormone (ACTH) levels, then give hydrocortisone 100 mg intravenously
- Perform abdominal computed tomography (CT) without contrast
- Perform transthoracic echocardiography
- Increase the norepinephrine infusion
- Immediately give fludrocortisone

First give fluids

The first step in managing a patient with suspected adrenal crisis is liberal intravenous fluid administration to replenish the depleted intravascular space. The amount and choice of fluid is empiric, but a recommendation is 1 L of normal saline or dextrose 5% in normal saline, infused quickly over the first hour and then titrated according to the patient's fluid status.¹⁰

Measure cortisol and ACTH; start corticosteroids immediately

Immediate therapy with an appropriate stress dose of intravenous corticosteroids (eg, hydrocortisone 100 mg) is essential. However, this

should be done after drawing blood for cortisol and ACTH measurements.¹⁰

Do not delay corticosteroid therapy while awaiting the results of the diagnostic tests.

Cortisol and ACTH levels are useful in assessing adrenal function in critically ill patients.¹¹ While inappropriately low serum cortisol usually indicates adrenal insufficiency, measuring plasma ACTH is important to distinguish whether the adrenal insufficiency is primary (ie, due to dysfunction of the adrenal gland itself) or central, ie, either secondary (due to dysfunction of the pituitary gland) or tertiary (due to dysfunction of the hypothalamus). Primary adrenal insufficiency is associated with elevated plasma ACTH, whereas central (secondary or tertiary) adrenal insufficiency is associated with low or inappropriately normal plasma ACTH levels (**Figure 1**).

In addition, in the early phase of evolving primary adrenal insufficiency, measurement of plasma renin and aldosterone levels may be beneficial, as mineralocorticoid deficiency may predominate.^{10,12,13}

One of the most important aims of early corticosteroid supplementation is to prevent further hyponatremia by reducing a reactive increase in antidiuretic hormone secretion caused by cortisol deficiency. Corticosteroids also help to restore normal blood pressure by increasing vascular tone, as glucocorticoid receptor activation potentiates the vasoconstrictor actions of norepinephrine, angiotensin II, and other vasoconstrictors.^{14,15}

Which corticosteroid to use?

Which corticosteroid to use in previously undiagnosed adrenal insufficiency is controversial. The Endocrine Society¹⁰ and Japan Endocrine Society¹⁶ clinical practice guidelines recommend hydrocortisone in a 100-mg intravenous bolus followed by 200 mg over 24 hours.

The choice of hydrocortisone is justified by its superior mineralocorticoid activity.^{10,16} Further, hydrocortisone is preferred over dexamethasone if the patient is known to have primary adrenal insufficiency, or if the serum potassium level is higher than 6.0 mmol/L.

Some clinicians, on the other hand, recommend dexamethasone, given as a 4-mg intravenous bolus followed by 4-mg boluses every 12 hours. Their rationale is that dexa-

methasone, unlike hydrocortisone, does not interfere with subsequent serum cortisol assays if the patient later undergoes ACTH stimulation testing.¹⁷ Dexamethasone may also be preferred to minimize unwanted mineralocorticoid effects, such as in neurosurgical patients at risk of brain edema.

If hydrocortisone is used, ACTH stimulation testing can be done after withholding hydrocortisone for 24 hours once the patient is stable. (It should be restarted after the test if the results are abnormal.)

Other possible steps

Abdominal CT should be done in our patient to address the possibility of bilateral adrenal hemorrhage. However, it is preferable to wait until the patient is stabilized.

Echocardiography. Our patient is likely to have an element of cardiac failure, given her hypertension and cardiomegaly. However, decompensated heart failure is probably not the cause of her presentation. Thus, the first priority is to treat her adrenal crisis, and echocardiography should be deferred.

Increasing the norepinephrine infusion is unlikely to improve her blood pressure very much, as she is significantly volume-depleted. Further, low cortisol decreases the vascular response to norepinephrine.¹⁵

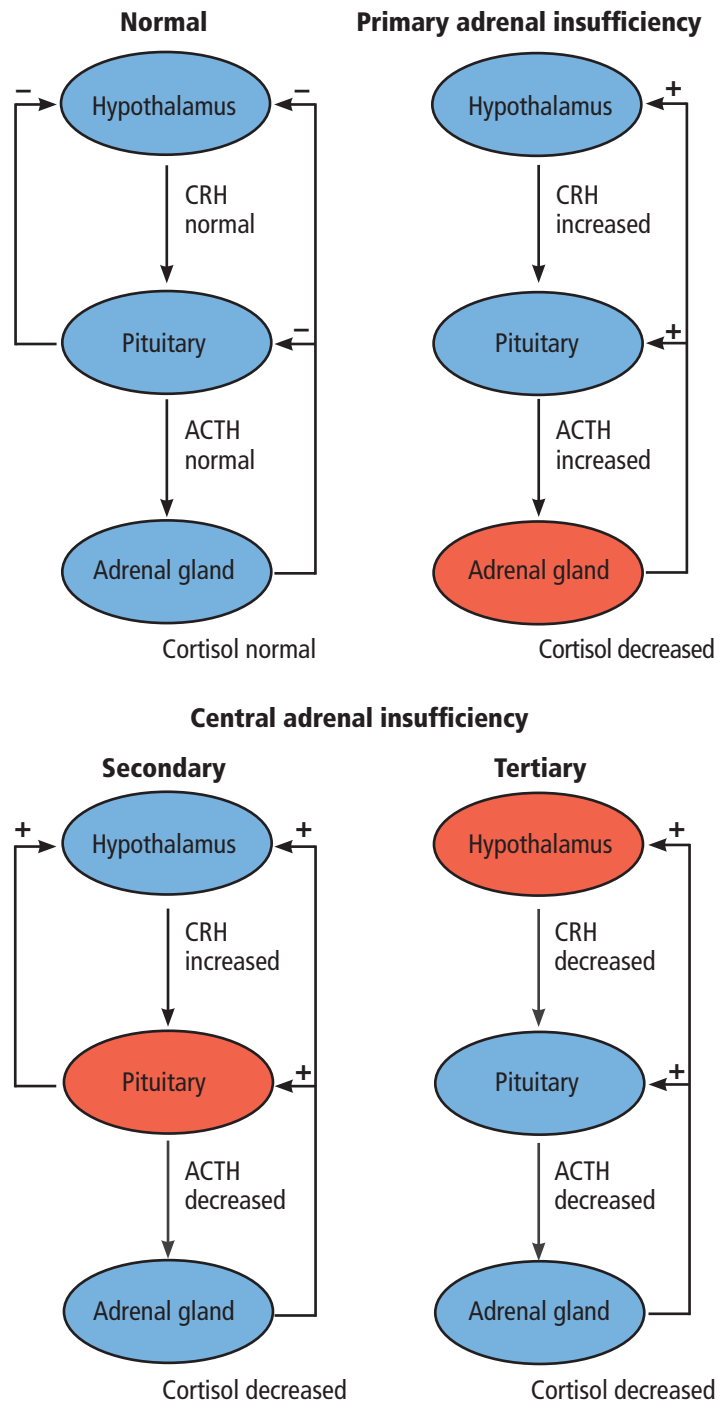
Mineralocorticoids such as fludrocortisone are used to treat primary adrenal insufficiency. However, they are not required during acute management of adrenal crisis, as 40 mg of hydrocortisone offers mineralocorticoid activity equivalent to 100 µg of fludrocortisone. Thus, the high doses of hydrocortisone used to treat adrenal crisis provide adequate mineralocorticoid therapy.^{10,18}

If dexamethasone is used, its effect along with normal saline supplementation would be sufficient to replete the intravenous space and bring the sodium level back up to normal in the acute setting.

■ CASE RESUMED: IMPROVEMENT WITH HYDROCORTISONE

The patient's blood is drawn for serum cortisol and plasma ACTH measurements. A 100-mg intravenous bolus of hydrocortisone is given, followed by a 50-mg bolus every 6 hours until the patient stabilizes.

Adrenal insufficiency



ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; a plus sign indicates stimulation; a minus sign indicates inhibition; blue indicates a normally functioning gland; red indicates a defective gland

Figure 1. Adrenal insufficiency is classified according to whether the defect lies in the adrenal gland (primary adrenal insufficiency) or centrally, ie, in the pituitary gland (secondary adrenal insufficiency) or hypothalamus (tertiary adrenal insufficiency).

TABLE 4

Laboratory findings in adrenal insufficiency

Hyponatremia
Hyperkalemia ^a
Hypercalcemia
Hypoglycemia
Normal anion gap metabolic acidosis ^a
Azotemia (prerenal) ^a
Anemia (normochromic normocytic)
Relative lymphocytosis
Eosinophilia
Mild elevation in serum thyroid-stimulating hormone
Autoantibodies against 21-hydroxylase antigen ^a

^aMay be present only in primary adrenal insufficiency.

Do not delay corticosteroid therapy while awaiting test results

Twenty-four hours later, the patient states that she has more energy, and her appetite has improved. The norepinephrine infusion is stopped 48 hours after presentation, at which time her blood pressure is 120/70 mm Hg, heart rate 85 beats per minute and irregular, and temperature 36.7°C (98.1°F). Her current laboratory values include the following:

- Serum sodium 137 mmol/L
- Serum potassium 4.3 mmol/L
- Hemoglobin 9.3 g/dL
- Serum cortisol (random) 7.2 µg/dL
- Plasma ACTH 752 pg/mL (10–60 pg/mL).

■ ESTABLISHING THE DIAGNOSIS OF ADRENAL INSUFFICIENCY

3 Which of the following is the most appropriate test to establish the diagnosis of adrenal insufficiency?

- 7 AM total serum cortisol measurement
- Random serum cortisol measurement
- 7 AM salivary cortisol measurement
- 24-hour urinary free cortisol measurement
- ACTH stimulation test for cortisol
- Insulin tolerance test for cortisol

Adrenal insufficiency can present acutely with catastrophic outcomes, such as in adrenal crisis. Alternatively, it can present insidiously with multiple vague manifestations and nonspecific laboratory findings (Table 4). But even when the diagnosis of adrenal insufficiency is apparent, laboratory tests are required for confirmation.

These tests also help determine the type of adrenal insufficiency (primary, secondary, or tertiary) and guide further management. Secondary adrenal insufficiency is caused by inadequate pituitary ACTH secretion and subsequent inadequate cortisol production, whereas tertiary adrenal insufficiency is caused by inadequate hypothalamic corticotropin-releasing hormone secretion and subsequent inadequate ACTH and cortisol production. The diagnosis of adrenal insufficiency relies first on demonstrating inappropriately low total serum cortisol production. Subsequently, serum ACTH helps to differentiate between primary (high ACTH) and secondary or tertiary (low or inappropriately normal ACTH) adrenal insufficiency.

Each test listed above may demonstrate a low cortisol level. However, in a nonacute setting, safety concerns (especially regarding insulin tolerance testing), poor diagnostic value, feasibility (ie, the difficulty of 24-hour tests), and poor sensitivity of 7 AM cortisol make the ACTH stimulation test the most appropriate test in clinical practice to establish the diagnosis of adrenal insufficiency.

7 AM serum cortisol measurement

Measuring the serum cortisol level early in the morning in the nonacute setting could be of diagnostic value, as an extremely low value (< 3–5 µg/dL) is almost 100% specific for adrenal insufficiency in the absence of concurrent exogenous steroid intake. However, the very low cutoff for this test causes poor sensitivity (about 33%), as many patients have partial adrenal insufficiency and hence have higher serum cortisol levels that may even be in the normal physiologic range.^{19–22}

Random serum cortisol measurements

Random serum cortisol measurements are not very useful in a nonacute setting, since cortisol levels are affected by factors such as stress and hydration status. Moreover, they fluctuate

during the day in a circadian rhythm.

On the other hand, random serum cortisol is a very good test to evaluate for adrenal insufficiency in the acute setting. A random value higher than 15 to 18 $\mu\text{g}/\text{dL}$ is almost always associated with adequate adrenal function and generally rules out adrenal insufficiency.^{11,23,24}

7 AM salivary cortisol measurement

The same principle applies to early morning salivary cortisol. Only extremely low values ($< 2.65 \text{ ng}/\text{mL}$) may distinguish patients with adrenal insufficiency from healthy individuals, with 97.1% sensitivity and 93.3% specificity.²⁵

Of note, early morning salivary cortisol is not routinely measured in most clinical practices for evaluation of adrenal function. Hence, morning serum and morning salivary cortisol are useful screening tools and have meaningful results when their values are in the extremes of the spectrum, but they are not reliable as a single test, as they may overlook patients with partial adrenal insufficiency.

Urinary cortisol measurement

Urinary cortisol measurement is not used to diagnose adrenal insufficiency, as values can be normal in patients with partial adrenal insufficiency.

The ACTH stimulation test

The ACTH stimulation test involves an intramuscular or intravenous injection of cosyntropin (a synthetic analogue of ACTH fragment 1–24 that has the full activity of native ACTH) and measuring total serum cortisol at baseline, 30 minutes, and 60 minutes to assess the response of the adrenal glands.

The test can be done using a high or low dose of cosyntropin. The Endocrine Society's 2016 guidelines recommend the high dose (250 μg) for most patients.¹⁰ The standard high-dose stimulation test can be done at any time during the day.²⁶ If the cosyntropin is injected intravenously, any value higher than 18 to 20 $\mu\text{g}/\text{dL}$ indicates normal adrenal function and excludes adrenal insufficiency.^{27,28} If intramuscular injection is used, any value higher than 16 to 18 $\mu\text{g}/\text{dL}$ at 30 minutes post-cosyntropin excludes adrenal insufficiency.²⁹

The ACTH stimulation test may not exclude acute secondary or tertiary adrenal insufficiency.

Insulin tolerance testing

Insulin tolerance testing remains the gold standard for diagnosing adrenal insufficiency and assessing the integrity of the pituitary-adrenal axis. However, given its difficulty to perform, safety concerns, and the availability of other reliable tests, its use in clinical practice is limited. It is nonetheless useful in assessing patients with recent onset of ACTH deficiency.^{30,31}

■ CASE RESUMED: PATIENT DISCHARGED, LOST TO FOLLOW-UP

Abdominal CT without contrast is done and demonstrates bilateral adrenal hemorrhage. Thus, the patient is diagnosed with primary acute adrenal insufficiency due to adrenal necrosis.

She is started on oral hydrocortisone and fludrocortisone after intravenous hydrocortisone is discontinued. She is counseled about adhering to medications, wearing a medical alert bracelet, giving herself emergency cortisol injections, taking higher doses of hydrocortisone if she is ill, and monitoring her INR. She is discharged home after her symptoms resolve.

The patient does not keep her scheduled appointment and is lost to follow-up. She returns 2 years later complaining of fatigue and feeling unwell. She admits that she stopped taking hydrocortisone 1 year ago after reading an online article about corticosteroid side effects. She has continued to take fludrocortisone.

■ MINERALOCORTICOID VS CORTICOSTEROID DEFICIENCY

Our patient has primary adrenal insufficiency. The presentations of primary and central (secondary or tertiary) adrenal insufficiency are similar, but there are critical differences (Table 5). Further, she has been taking her mineralocorticoid (fludrocortisone) replacement but has stopped taking her corticosteroid (hydrocortisone).

4 Which of the following is least likely to be present in this patient at this time?

- Intravascular volume depletion
- Hyponatremia
- Skin hyperpigmentation
- Normokalemia
- Elevated serum ACTH level

Hydrocortisone 40 mg offers mineralocorticoid activity equivalent to fludrocortisone 100 μg

TABLE 5

Clinical features of primary vs central (secondary, tertiary) adrenal insufficiency

Feature	Primary	Central	Possible explanation for difference
Skin hyperpigmentation	Yes	No	Adrenocorticotrophic hormone production and thus melanocyte-stimulating hormone levels are increased in primary but not central adrenal insufficiency
Gastrointestinal symptoms	More prominent	Less prominent	More prominent electrolyte disturbances in primary adrenal insufficiency may play a role in gastrointestinal symptoms
Intravascular volume depletion, hypotension	More prominent	Less prominent ^a	Decreased serum aldosterone levels only in primary adrenal insufficiency
Hyperkalemia	Yes	No	Decreased serum aldosterone levels only in primary adrenal insufficiency
Hypoglycemia	Less prominent	More prominent	Concomitant growth hormone deficiency present in some cases of central adrenal insufficiency More insidious progression in central adrenal insufficiency resulting in delayed presentation and more prominent corticosteroid deficiency symptoms such as hypoglycemia
Blood urea nitrogen elevation	More frequent	Less frequent	Intravascular volume depletion resulting in prerenal azotemia is present more frequently in primary adrenal insufficiency
Hypopituitarism, headaches, visual field defects	No	Yes	Depends on the underlying cause

^aSecondary adrenal insufficiency such as pituitary apoplexy may present with hypotension and, if not treated, may lead to azotemia. However, this may occur much more frequently in patients with primary adrenal insufficiency.

Insulin tolerance testing remains the gold standard but is difficult to perform in practice

Intravascular volume depletion

Intravascular volume depletion is the least likely to be present. This is because intravascular volume depletion is mainly secondary to mineralocorticoid deficiency rather than corticosteroid deficiency, which is not present in this patient, as she is compliant with her mineralocorticoid replacement therapy.^{32,33} However, even with sufficient mineralocorticoid replacement, mild hypotension may be present in this patient due to corticosteroid deficiency-induced loss of vascular tone.

Hyponatremia

Hyponatremia in adrenal insufficiency is not due only to mineralocorticoid deficiency. Patients with secondary or tertiary adrenal insufficiency may also exhibit hyponatremia.³⁴ ACTH deficiency in such patients is not expected to cause mineralocorticoid deficiency, as ACTH has only a minor role in aldosterone production.

It has been proposed that hyponatremia in secondary adrenal insufficiency is due to cortisol deficiency resulting in an increase of antidiuretic hormone secretion.^{35,36} The mechanisms for increased antidiuretic hormone include cortisol deficiency resulting in an increased corticotropin-releasing hormone level, which acts as an antidiuretic hormone secretagogue,^{37,38} and cortisol directly suppressing antidiuretic hormone secretion.³⁹

In our patient, volume expansion and hyponatremia are expected due to increased antidiuretic hormone secretion as a result of corticosteroid insufficiency.

Hyperpigmentation

Hyperpigmentation of the skin is present only in long-standing primary adrenal insufficiency. This is due to chronic cortisol deficiency causing an increased secretion of pro-opiomelanocortin, a prohormone that is cleaved into

ACTH, melanocyte-stimulating hormone, and other hormones. Melanocyte-stimulating hormone causes skin hyperpigmentation due to increased melanin synthesis.⁴⁰ The hyperpigmentation is seen in sun-exposed areas, pressure areas, palmar creases, nipples, and mucous membranes.

This patient has long-standing corticosteroid deficiency due to noncompliance and primary adrenal insufficiency, and as a result she is expected to have elevated serum ACTH and hyperpigmentation.

Normokalemia

Mineralocorticoid deficiency results in hyperkalemia and metabolic acidosis by impairing renal excretion of potassium and acid.⁴¹ This patient is compliant with her mineralocorticoid replacement regimen; thus, potassium levels and pH are expected to be normal.

TAKE-HOME POINTS

- Suspect adrenal crisis in any patient who presents with shock.
- Acute abdomen or unexplained fever could be among the manifestations.
- Initial management requires liberal normal saline intravenous fluid administration to replete the intravascular space.
- Draw blood samples for serum chemistry, cortisol, and ACTH, followed immediately by intravenous hydrocortisone supplementation.
- In critically ill patients, evaluate adrenal function with random serum cortisol; in a nonacute setting use the ACTH stimulation test.
- Chronic management of primary adrenal insufficiency requires corticosteroid and mineralocorticoid therapy.

REFERENCES

1. Mani S, Rutecki GW. A patient with altered mental status and an acid-base disturbance. *Cleve Clin J Med* 2017; 84(1):27–34. doi:10.3949/ccjm.84a.16042.
2. Almiani M, Gorthi J, Subbiah S, Firoz M. Quiz page November 2012: an unusual case of acute hyponatremia and normal anion gap metabolic acidosis. *Am J Kidney Dis* 2012; 60(5):xxxiii–xxxvi. doi: 10.1053/j.ajkd.2012.05.026.
3. Migeon CJ, Kenny FM, Hung W, Voorhess ML. Study of adrenal function in children with meningitis. *Pediatrics* 1967; 40(2):163–183.
4. Rao RH, Vagnucci AH, Amico JA. Bilateral massive adrenal hemorrhage: early recognition and treatment. *Ann Intern Med* 1989; 110(3):227–235.
5. Shimizu S, Tahara Y, Atsumi T, et al. Waterhouse-Friderichsen syndrome caused by invasive *Haemophilus influenzae* type B infection in a previously healthy young man. *Anaesth Intensive Care* 2010; 38(1):214–215.
6. Castaldo ET, Guillamondegui OD, Greco JA 3rd, Feurer ID, Miller RS, Morris JA Jr. Are adrenal injuries predictive of adrenal insufficiency in patients sustaining blunt trauma? *Am Surg* 2008; 74(3):262–266.
7. Xarli VP, Steele AA, Davis PJ, Buescher ES, Rios CN, Garcia-Bunuel R. Adrenal hemorrhage in the adult. *Medicine (Baltimore)* 1978; 57(3):211–221.
8. Takeuchi K, Tsuzuki Y, Ando T, et al. Clinical studies of strangulating small bowel obstruction. *Am Surg* 2004; 70(1):40–44.
9. MacKenzie IM. The haemodynamics of human septic shock. *Anaesthesia* 2001; 56(2):130–144.
10. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2016; 101(2):364–389. doi: 10.1210/jc.2015-1710.
11. Hamrahian AH, Fleseriu M; AACE Adrenal Scientific Committee. Evaluation and management of adrenal insufficiency in critically ill patients: disease state review. *Endocr Pract* 2017; 23(6):716–725. doi: 10.4158/EP161720.RA.
12. Saenger P, Levine LS, Irvine WJ, et al. Progressive adrenal failure in polyglandular autoimmune disease. *J Clin Endocrinol Metab* 1982; 54(4):863–867.
13. Coco G, Dal Pra C, Presotto F, et al. Estimated risk for developing autoimmune Addison's disease in patients with adrenal cortex autoantibodies. *J Clin Endocrinol Metab* 2006; 91(5):1637–1645. doi: 10.1210/jc.2005-0860.
14. Ullian ME. The role of corticosteroids in the regulation of vascular tone. *Cardiovasc Res* 1999; 41(1):55–64.
15. Yang S, Zhang L. Glucocorticoids and vascular reactivity. *Curr Vasc Pharmacol* 2004; 2(1):1–12.
16. Yanase T, Tajima T, Katabami T, et al. Diagnosis and treatment of adrenal insufficiency including adrenal crisis: a Japan Endocrine Society clinical practice guideline [Opinion]. *Endocr J* 2016; 63(9):765–784. doi: 10.1507/endocrj.EJ16-0242.
17. Taylor RL, Grebe SK, Singh RJ. Quantitative, highly sensitive liquid chromatography-tandem mass spectrometry method for detection of synthetic corticosteroids. *Clin Chem* 2004; 50(10):2345–2352. doi: 10.1373/clinchem.2004.033605.
18. Goldfien A, Laidlaw JC, Haydar NA, Renold AE, Thorn GW. Fluorohydrocortisone and chlorohydrocortisone, highly potent derivatives of compound F. *N Engl J Med* 1955; 252(11):415–421. doi: 10.1056/NEJM195503172521101.
19. Jenkins D, Forsham PH, Laidlaw JC, Reddy WJ, Thorn GW. Use of ACTH in the diagnosis of adrenal cortical insufficiency. *Am J Med* 1955; 18(1):3–14.
20. Hägg E, Asplund K, Lithner F. Value of basal plasma cortisol assays in the assessment of pituitary-adrenal insufficiency. *Clin Endocrinol (Oxf)* 1987; 26(2):221–226.
21. Deutschbein T, Unger N, Mann K, Petersenn S. Diagnosis of secondary adrenal insufficiency: unstimulated early morning cortisol in saliva and serum in comparison with the insulin tolerance test. *Horm Metab Res* 2009; 41(4):834–839. doi: 10.1055/s-0029-1225630.
22. Erturk E, Jaffe CA, Barkan AL. Evaluation of the integrity of the hypothalamic-pituitary-adrenal axis by insulin hypoglycemia test. *J Clin Endocrinol Metab* 1998; 83(7):2350–2354.
23. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; 348(8):727–734. doi: 10.1056/NEJMra020529.
24. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; 39(2):165–228. doi: 10.1007/s00134-012-2769-8.
25. Ceccato F, Barbot M, Zilio M, et al. Performance of salivary cortisol in the diagnosis of Cushing's syndrome, adrenal incidentaloma, and

- adrenal insufficiency. *Eur J Endocrinol* 2013; 169(1):31–36. doi: 10.1530/EJE-13-0159.
26. **Dickstein G, Shechner C, Nicholson WE, et al.** Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. *J Clin Endocrinol Metab* 1991; 72(4):773–778. doi: 10.1210/jcem-72-4-773.
 27. **May ME, Carey RM.** Rapid adrenocorticotropin hormone test in practice. Retrospective review. *Am J Med* 1985; 79(6):679–884.
 28. **Speckart PF, Nicoloff JT, Bethune JE.** Screening for adrenocortical insufficiency with cosyntropin (synthetic ACTH). *Arch Intern Med* 1971; 128(5):761–763.
 29. **Peechakara S, Bena J, Clarke NJ, et al.** Total and free cortisol levels during 1 µg, 25 µg, and 250 µg cosyntropin stimulation tests compared to insulin tolerance test: results of a randomized, prospective, pilot study. *Endocrine* 2017; 57(3):388–393. doi: 10.1007/s12020-017-1371-9.
 30. **Finucane FM, Liew A, Thornton E, Rogers B, Tormey W, Agha A.** Clinical insights into the safety and utility of the insulin tolerance test (ITT) in the assessment of the hypothalamo-pituitary-adrenal axis. *Clin Endocrinol (Oxf)* 2008; 69(4):603–607. doi: 10.1111/j.1365-2265.2008.03240.x.
 31. **Lindholm J, Kehlet H.** Re-evaluation of the clinical value of the 30 min ACTH test in assessing the hypothalamic-pituitary-adrenocortical function. *Clin Endocrinol (Oxf)* 1987; 26(1):53–59.
 32. **Charmandari E, Nicolaidis NC, Chrousos GP.** Adrenal insufficiency. *Lancet* 2014; 383(9935):2152–2167. doi: 10.1016/S0140-6736(13)61684-0.
 33. **Burke CW.** Adrenocortical insufficiency. *Clin Endocrinol Metab* 1985; 14(4):947–976.
 34. **Jessani N, Jehangir W, Behman D, Yousif A, Spiler IJ.** Secondary adrenal insufficiency: an overlooked cause of hyponatremia. *J Clin Med Res* 2015; 7(4):286–288. doi: 10.14740/jocmr2041w.
 35. **Oelkers W.** Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Engl J Med* 1989; 321(8):492–496. doi: 10.1056/NEJM198908243210802.
 36. **Ishikawa S, Schrier RW.** Effect of arginine vasopressin antagonist on renal water excretion in glucocorticoid and mineralocorticoid deficient rats. *Kidney Int* 1982; 22(6):587–593.
 37. **Wolfson B, Manning RW, Davis LG, Arentzen R, Baldino F Jr.** Co-localization of corticotropin releasing factor and vasopressin mRNA in neurones after adrenalectomy. *Nature* 1985; 315(6014):59–61.
 38. **Kalogeras KT, Nieman LK, Friedman TC, et al.** Inferior petrosal sinus sampling in healthy subjects reveals a unilateral corticotropin-releasing hormone-induced arginine vasopressin release associated with ipsilateral adrenocorticotropin secretion. *J Clin Invest* 1996; 97:2045–2050.
 39. **Kovacs KJ, Foldes A, Sawchenko PE.** Glucocorticoid negative feedback selectively targets vasopressin transcription in parvocellular neurosecretory neurons. *J Neurosci* 2000; 20:3843–3852.
 40. **Sarkar SB, Sarkar S, Ghosh S, Bandyopadhyay S.** Addison's disease. *Contemp Clin Dent* 2012; 3(4):484–486. doi: 10.4103/0976-237X.107450.
 41. **Szylman P, Better OS, Chaimowitz C, Rosler A.** Role of hyperkalemia in the metabolic acidosis of isolated hypoaldosteronism. *N Engl J Med* 1976; 294(7):361–365. doi: 10.1056/NEJM197602122940703.
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