A Case of Licorice-Induced Pseudoaldosteronism

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A 76-year-old woman was referred to our emergency department (ED) by her primary care provider out of concern for a severely low potassium level of 2.0 mEq/L. The patient had a history of controlled hypertension (for which she was taking atenolol, 25 mg once daily, and losartan, 25 mg once daily), hypothyroidism, and borderline diabetes. The patient and her husband were recovering from a diarrheal illness that had developed 3 days prior. For the past 2 weeks, the patient had noted dyspnea on exertion, fatigue, intermittent palpitations, and worsening leg edema. She was a nonsmoker and drank 3 to 5 glasses of wine per week. Her family history was unremarkable. Physical examination findings were remarkable for uncontrolled hypertension (blood pressure, 166/65 mm Hg) and 3+ to 4+ peripheral edema.

Results of laboratory tests are summarized in the **Table**.

The random urine potassium level was 15.6 mEq/L. The 24-hour urine potassium level was significantly elevated at 77 mEq/L (with a 24-hour urinary creatinine level <13 mg/dL), indicating renal potassium wasting. The random cortisol level was 9.4 µg/dL (reference range, 5-25 µg/dL), with an adrenocorticotropic hormone level of 14 pg/mL (reference range, 6-50 pg/mL) collected on hospital day 2. The plasma renin level was low at 0.04 pg/mL (reference range, 0.25-5.82 pg/mL), and the aldosterone level was less than 1 ng/dL (reference range, 3-16 ng/dL in the supine position).

Electrocardiography showed nonspecific ST-T segment abnormalities, sinus bradycardia at 59 beats/min, and a corrected QT interval of 394 milliseconds. Echocardiography indicated normal left and right ventricular thickness and function but severe aortic and mitral regurgitation. Nuclear medicine cardiac stress test findings were negative for ischemia. The patient was started on intravenous and oral potassium and magnesium replacement therapy.

Differential diagnosis considered for the patient's extreme hypokalemia, metabolic alkalosis, recently worsening hypertension, and peripheral edema were primary or secondary aldosteronism or pseudoaldosteronism.

Licorice is the dried root of *Glycyrrhiza glabra*, a slow-growing woody shrub.

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Table. Laboratory Test Results[a]

Analyte	Value	Reference Range
Sodium	140 mEq/L	136-145 mEq/L
Potassium	*1.5 mEq/L*	3.5-5.1 mEq/L
Chloride	95 mEq/L	95-110 mEq/L
Bicarbonate	*40 mEq/L*	21-32 mEq/L
Urea nitrogen	10 mg/dL	0-18 mg/dL
Creatinine	0.83 mg/dL	0.40-1.00 mg/dL
Glucose	105 mg/dL	70-99 mg/dL
Aspartate aminotransferase	*60 U/L*	0-37 U/L
Alanine aminotransferase	44 U/L	0-60 U/L
Alkaline phosphatase	71 U/L	26-137 U/L
Bilirubin	1.4 mg/dL	0.0-1.4 mg/dL
Albumin	*2.9 g/dL*	3.2-4.7 mg/dL
Thyrotropin	4.9 mIU/L	0.4-5.2 mU/L
N-terminal pro brain-type natriuretic peptide	741 pg/mL	0-1800 pg/mL for age ≤35 y
Troponin I every 6 h	*0.38, 0.36, 0.33 ng/mL*	0.00-0.36 ng/mL
Calcium	8.1 mg/dL	8.5-10.1 mg/dL
Magnesium	*1.4 mg/dL*	1.8-2.4 mg/dL
Serum osmolality	292 mOsm/kg	275-295 mOsm/kg
Urine osmolality	*194 mOsm/kg*	300-900 mOsm/kg
Stool *Clostridioides difficile*, norovirus, stool cultures	Negative	Negative

[a]Abnormal values are indicated with italics.

Primary aldosteronism is characterized by excess aldosterone production, usually by an adrenal adenoma, with resulting renin suppression. Abdominal computed tomography scans to evaluate for adrenal nodules were negative in our patient.

Secondary aldosteronism occurs as a result of overall increased activation of the renin-angiotensin-aldosterone system (RAAS) secondary to renal hypoperfusion or ischemia, such as in renal artery stenosis, diarrhea, and abuse of diuretics or laxatives. In our patient, results of a comprehensive 12-diuretic urine screening test were negative, and her diarrhea was mild and self-limited.

Pseudoaldosteronism is characterized by a clinical syndrome of aldosteronism but suppressed renin and aldosterone activity, as seen in our patient. Pseudoaldosteronism occurs in hereditary disorders such as Liddle syndrome and Gitelman syndrome (both of which were unlikely, given the patient's age) and because of hereditary or acquired deficiency of 11β-hydroxysteroid dehydrogenase (11β-HSD).

The patient continued to require extremely high doses of potassium (>240 mEq/d). Spironolactone was started on hospital day 5, and the losartan dose was up-titrated to manage her blood pressure.

On hospital day 6, the patient presented a bottle of a liver support supplement (Advanced Liver Support, distributed by Advanced Bionutritionals) that she had started taking 3 months prior. The daily dose of the supplement had 1000 mg of dried licorice root extract with a minimum of 20% glycyrrhizic acid. The patient's last ingestion had been 1 week ago, immediately before her presentation to our ED for hypokalemia.

The patient was advised to stop taking the supplement. She was discharged without potassium supplementation on hospital day 7 with a serum potassium level of 4.5 mEq/L and with a prescription for daily spironolactone. A random urine potassium level at discharge was 10.3 mEq/L, indicating renal conservation. A follow-up basic metabolic panel was ordered. The patient had no recurrence of hypokalemia at follow-up 6 weeks later, her blood pressure remained controlled, and she had only trace

peripheral edema. Spironolactone was continued, as were her usual antihypertensives.

DISCUSSION

Licorice is the dried root of *Glycyrrhiza glabra*, a slow-growing woody shrub (**Figure**). It has been used historically as a sweetener and a thirst quencher. The primary active ingredient is glycyrrhizin, which is a mixture of potassium and calcium salts of glycyrrhizic acid (GZA).[1] Glycyrrhizin is 50 times sweeter than sucrose.[2] It is used as a flavoring agent in candies, tea, and flavored cigarettes. It has been used in traditional medicine for its anti-inflammatory and estrogenic properties.[2]

Upon ingestion of licorice, glycyrrhizin is barely detectable. GZA, the active ingredient, reaches the intestine and is hydrolyzed by intestinal bacteria to glycyrrhetic acid.[1,3-6] Glycyrrhetic acid inhibits 11β-hydroxysteroid dehydrogenase,[3,7] an enzyme located in the distal tubule of the kidney adjacent to mineralocorticoid receptors. This enzyme regulates cortisol metabolism by converting the biologically potent endogenous cortisol to the inactive cortisone. By inhibiting this enzyme, glycyrrhetic acid leads to an increased cortisol level. Usually, both cortisol and mineralocorticoids bind to the mineralocorticoid receptors with same avidity.[4,5] But the excess cortisol thus produced will bind with high affinity to the mineralocorticoid receptors and act as a mineralocorticoid.

Additionally, glycyrrhetic acid likely inhibits the hepatic metabolism of aldosterone by suppressing 5β-reductase activity in the liver,[8] thus prolonging its effects. Thus, the metabolites of licorice can lead to a syndrome of apparent mineralocorticoid excess,[7,9] as seen in our patient, that can present as hypokalemia, metabolic alkalosis, low plasma renin activity, hypertension, and edema. Hypokalemia in turn can induce polyuria secondary to nephrogenic diabetic insipidus,[10] accounting for polyuria (4946 mL/24-h urine in our patient) and low urine osmolality, which was also noted in our patient.

Recommended safe limits of daily ingestion have varied from 1 to 10 mg of glycyrrhizin (which corresponds to 1000 to 5000 mg of licorice[11]) to 100 mg per day.[12] Our patient had been taking 1000 mg of licorice daily for 3 months. Susceptibility to glycyrrhizin is influenced by baseline health status, with some patients developing manifestations of toxicity with intake of smaller amounts over a given period.[13] Patients with baseline decreased level of 11β-HSD may develop toxicity with intake of small amounts.[2] Other risk factors include old age, female sex, hypertension, and hypokalemia due to diarrhea or diuretic therapy.[2]

Emphasis should be placed on careful history about a patient's diet and use of supplements. Licorice ingestion must be considered in any patient presenting with hyperaldosteronism. Fortunately, pseudoaldosteronism induced by licorice is completely reversible with cessation of consumption. Spironolactone or eplerenone therapy may play a role in treatment due to their aldosterone antagonist effects.[14] Glycyrrhetic acid has a long half-life, and the RAAS may take up to 6 months to normalize after discontinuation.[15] ■

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