Refractory Hypokalemia: A Quiz
Lyle Wesley Baker and Christopher Trautman

Clinical Presentation
A 57-year-old woman with a history of diabetes mellitus, hypertension, and chronic obstructive pulmonary disease with a >40 pack-year smoking history was admitted to the hospital for generalized weakness and muscle cramping. She had been hospitalized 4 months prior with similar presenting symptoms, which were attributed to severe hypokalemia, as she had an undetectable (<1.5 mmol/L) admission plasma potassium level. She denied diarrhea, vomiting, laxative use, diuretic use, or alcohol abuse. She continued to smoke 2 packs per day. Her home medications included potassium chloride, 40 mEq twice per day, and rare ibuprofen use. Her vital signs at admission showed she was hypotensive (89/55 mm Hg). The physical examination was significant for 4/5 muscle strength of upper and lower extremities. The admission laboratory findings are shown in Tables 1 and 2. The electrocardiogram showed sinus arrhythmia, flattened T waves, and prolonged QT interval of 667 ms.

What is the differential diagnosis for this patient’s electrolyte and acid-base disturbances?
What further evaluation should be pursued in this patient to determine the cause of these disturbances?
How should this patient be treated?

Discussion
What is the differential diagnosis for this patient’s electrolyte and acid-base disturbances?
The patient’s admission laboratory findings revealed a normal anion gap metabolic acidosis with positive urine anion gap—suggestive of renal tubular acidosis (RTA). The differential diagnosis includes proximal and distal RTA, given this patient’s hypokalemia with renal potassium wasting. Markedly elevated urinary excretion of β₂-microglobulin and retinol-binding protein support a proximal tubulopathy.

Proximal RTA is caused by reduced reabsorption of filtered bicarbonate in the proximal convoluted tubule, which leads to renal bicarbonate wasting. In addition to decreased bicarbonate reabsorption, proximal RTA is commonly associated with other solute reabsorption impairments including phosphate, glucose, and amino acids. This generalized proximal tubulopathy is called Fanconi syndrome.1,2 Most causes of proximal RTA are acquired, but inheritable causes of primary isolated proximal RTA can occur, as well as secondary proximal RTA with familial Fanconi syndrome in certain hereditary diseases (Wilson disease, cystinosis, Lowe syndrome, Fanconi-Bickel syndrome, Dent disease, etc).1,2 Acquired proximal RTA in adults is commonly caused by injury to the proximal tubule secondary to paraprotein disease, autoimmune disease (Sjögren syndrome), medication toxicity, or heavy metal toxicity.1,4 Severe vitamin D deficiency can also cause
proximal RTA. Box 1 summarizes the causes of proximal RTA.

**What further evaluation should be pursued in this patient to determine the cause of these disturbances?**

Given the patient’s proximal tubulopathy and absence of any known family history of potential hereditary causes, the patient was evaluated for acquired causes of proximal tubulopathy. Testing for paraprotein disease with serum protein electrophoresis with immunofixation, serum free light chains, and urine protein electrophoresis with immunofixation was unremarkable. Likewise, testing for autoimmune disease with antibodies against antinuclear and extractable nuclear antigens was unremarkable. Her 25-hydroxyvitamin D level was within normal limits.

The review of this patient’s current and past prescriptions and over-the-counter medications did not identify any offending agent. A heavy metals screen was ordered to evaluate for potential heavy metal toxicity, including arsenic, cadmium, mercury, lead, copper, and zinc. The patient was found to have severe cadmium toxicity, with 4.4 μg in a 24-hour urine collection (reference range, <0.7 μg), corresponding to a cadmium-creatinine ratio of 6.24 μg/g.

**How should this patient be treated?**

Cadmium is a heavy metal that can cause both severe acute and chronic toxicity. The kidneys are a primary target organ for chronic cadmium toxicity. Sources of cadmium exposure include smoking cigarettes, eating contaminated foods (rice and grains farmed with cadmium-containing fertilizer), and occupational exposure. The main source of cadmium exposure in smokers is inhalation of tobacco smoke, as opposed to ingestion of contaminated foods in never-smokers. Smoking doubles the lifetime body burden of cadmium.

Daily intake of cadmium through contaminated food in the United States is around 30 μg, of which only 1%-10% is absorbed. A single cigarette has around 2 μg of cadmium, of which up to 10% is inhaled through smoking. Inhalation from smoking 1 pack (20 cigarettes) daily is between 1 and 3 μg. The critical urinary cadmium-creatinine ratio associated with onset of renal tubular injury is 2-10 μg/g—our patient had a ratio of 6.2 μg/g.

After systemic absorption by inhalation or ingestion, cadmium is freely filtered across the glomerulus and reabsorbed by proximal tubular cells while bound to metallothionein. Metallothionein is degraded by lysosomes within tubular cells, releasing free cadmium that generates reactive oxygen species, which result in proximal tubulopathy and RTA. Chronic cadmium toxicity can progress to Fanconi syndrome. Progressive loss of kidney function from cadmium toxicity does not commonly occur. Nephrologists and other providers should be aware of the potential risk of chronic cadmium nephrotoxicity and signs of proximal tubule impairment in patients with long-term history of tobacco use.

Management of this patient’s proximal tubulopathy and RTA starts with avoiding the offending agent: in this case, smoking cessation is required. Our patient reported smoking 2 packs per day—exposure to approximately 2-6 μg of inhaled cadmium daily. The patient received education on the cause of her proximal tubulopathy and the link between cigarette smoking and cadmium toxicity.

Unfortunately, tubular injury from chronic cadmium toxicity is typically irreversible, even after cessation of exposure. After correction of this patient’s severe hypokalemia using intravenous potassium, she was prescribed potassium citrate with split dosing throughout

---

**Box 1. Causes of Proximal RTA**

- **Hereditary causes**
  - Primary isolated proximal RTA
  - Secondary proximal RTA
    - Wilson disease
    - Cystinosis
    - Lowe syndrome
    - Fanconi-Bickel syndrome
    - Dent disease
    - Glycogen storage disease type I
    - Fructose intolerance
    - Tyrosinemia
- **Acquired causes**
  - Paraprotein disease
  - Amyloidosis
  - Light chain disease
  - Multiple myeloma
  - Autoimmune disease
    - Sjögren syndrome
  - Medication toxicity
    - Carbonic anhydrase inhibitors (topiramate, acetazolamide)
    - Iosfamide
    - Valproic acid
    - Tenofovir
    - Aminoglycosides
    - Oxaliplatin/cisplatin
    - Expired tetracycline
  - Vitamin D deficiency
  - Heavy metal toxicity
    - Arsenic
    - Cadmium
    - Mercury
    - Lead
    - Copper
    - Zinc
- **Idiopathic causes**
the day for treatment of her proximal RTA and to maintain normokalemia. Bicarbonate supplementation in patients with proximal RTA can result in increased urinary bicarbonate excretion with resultant worsening of hypokalemia.1 Potassium levels must be monitored closely with alkali therapy; concurrent potassium supplementation is often required.

Final Diagnosis
Cadmium toxicity causing proximal tubulopathy with proximal renal tubular acidosis and severe symptomatic hypokalemia.

References