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Multiple metabolic renal manifestations of a systemic disease

A 39-YEAR-OLD WOMAN with a history of depression, anxiety, and recurrent nephrolithiasis with calcium phosphate and calcium oxalate stones presented to the emergency department after 5 days of generalized weakness and right-upper-quadrant abdominal pain. She complained of having had dyspnea, arthralgia, and dry eyes and dry mouth for a long time. She did not have chest pain, fever, nausea, vomiting, abdominal pain, or diarrhea.

She had been taking sertraline 100 mg twice a day, bupropion 150 mg daily, clonazepam 1 mg daily, trazodone 300 mg at bedtime, and ibuprofen 200 mg twice a day as needed. She noted smoking half a pack of cigarettes per day but denied using alcohol or any recreational drugs. She worked as a teacher. Her family history was unremarkable.

On physical examination, her temperature was 99.9°F (37.7°C), blood pressure 118/67 mm Hg, heart rate 90 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 100% on room air. Her eyes and oral mucosa were dry, and she had excessive dental caries. Her first and second heart sounds were audible, and there were crackles in both lungs. Her abdomen was soft and nontender with no masses, splenomegaly, or hepatomegaly. There was clubbing in her fingers and toes but no edema. The results of her neurologic examination were normal except for generalized weakness.

Table 1 shows the patient's initial basic laboratory values, arterial blood gas values, and urine electrolyte concentrations. Results of urinalysis were unremarkable, and her urine pH was 6.0. Her 24-hour urine citrate excretion was 104 mg (reference range > 320), and her 24-hour urine calcium excretion was 360 mg (< 250).

Her electrocardiogram was unremarkable. Computed tomography of the chest and abdomen showed ground-glass and consolidative opacities in both lungs consistent with interstitial lung disease, multiple nonobstructive bilateral renal calculi, and nephrocalcinosis.

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CHARACTERIZING HER ACID-BASE DISORDER

1 What is the most likely cause of this patient's acid-base disorder?

- ☐ Vomiting
- ☐ Diarrhea
- ☐ Distal (type 1) renal tubular acidosis
- ☐ Proximal (type 2) renal tubular acidosis

First, let's characterize her acid-base disorder, using a stepwise approach:

- **Acidemia or alkalemia?** Our patient's blood pH was 7.34, indicating acidemia.
- **Metabolic or respiratory?** Her partial arterial pressure of carbon dioxide was 40 mm Hg, which was not elevated (reference range 35–45), and her serum bicarbonate level was low at 20 mmol/L (21–32). Therefore, the primary metabolic disorder was metabolic acidosis.
- **Normal anion gap?** The anion gap can be calculated as the serum sodium concentration minus the sum of the serum chloride and bicarbonate concentrations. The values for our patient were 148 – (115 + 20) = 13 mmol/L, with normal being 12 to 14. This supported the diagnosis of normal anion gap metabolic acidosis.
- **Is there appropriate compensation?** According to the Winter formula, the expected partial arterial pressure of carbon dioxide should be 1.5 times the bicarbonate level, plus 8, plus or minus 2. The patient's values were (1.5 × 20) + 8 = 38 ± 2 mm Hg. Her measured value was 40 mm Hg, so she was within the expected range and had appropriate respiratory compensation.

TABLE 1
Laboratory results

Tests	Results[a]	Reference range
Sodium	**148 mmol/L**	136–145
Potassium	**3.1 mmol/L**	3.5–5.1
Chloride	**115 mmol/L**	98–107
Bicarbonate	**20 mmol/L**	21–32
Blood urea nitrogen	**24 mg/dL**	7–18
Creatinine	1.0 mg/dL	0.6–1.3
Glucose	74 mg/dL	60–99
Calcium	9.2 mg/dL	8.4–10.5
Hemoglobin	**10.2 g/dL**	13.9–16.3
White blood cell count	5.99 × 10^9/L	4.5–11.0
Neutrophils	67.6%	46.2%–80%
Lymphocytes	18.5%	10.3%–40.5%
Monocytes	12.7%	3.0%–14%
Eosinophils	1.0%	0.0%–-5.0%
Basophils	0.2%	0.0%–1.0%
Platelet count	311 × 10^9/L	150–350
Alanine aminotransferase	50 U/L	6–65
Aspartate aminotransferase	26 U/L	3–37
Alkaline phosphatase	87 U/L	45–117
Bilirubin, total	< 0.2 mg/dL	0.2–1.2
Albumin	3.7 g/dL	3.5–5.0
Magnesium	2.3 mg/dL	1.8–2.4
Serum osmolality	**303 mOsm/kg**	275–295
Phosphorus	**2.1 mg/dL**	2.5–4.9
Thyrotropin	1.59 mIU/L	0.5–4.5
Arterial blood gasses		
pH	**7.34**	7.35–7.45
Partial pressure of carbon dioxide	40 mm Hg	35–45
Partial pressure of oxygen	95 mm Hg	75–100
Urine		
Random sodium	67 mmol/L	20–214
Random potassium	**8 mmol/L**	17–95
Random chloride	53 mmol/L	24–255
Random urea	207 mg/dL	132–1,629
Osmolality	165 mOsm/kg	50–1,200

[a]Abnormal results are in boldface.

Therefore, our patient had primary normal-anion-gap metabolic acidosis with appropriate respiratory compensation. As for the answer choices, vomiting is associated with chloride-responsive metabolic alkalosis, not acidosis. Diarrhea and renal tubular acidosis can both cause normal-anion-gap metabolic acidosis and can be differentiated by calculating the urine anion gap, calculating the urine osmolal gap, and checking urine pH.

The urine anion gap can be calculated by adding the urinary sodium and potassium concentrations and then subtracting the chloride concentration. Normally, ammonium is the major unmeasured urinary cation. In metabolic acidosis caused by diarrhea when the urinary acidification mechanisms are intact, urinary excretion of ammonium and chloride is significantly increased to maintain electroneutrality, leading to a negative urine anion gap because urinary chloride would then exceed the sum of urinary sodium and potassium.

The urine osmolal gap is an indirect measure of ammonium excretion and can be used to diagnose and determine the type of renal tubular acidosis. In distal renal tubular acidosis, the urinary acidification mechanisms are impaired and the urine osmolal gap is less than 150 mOsm/kg, while it is usually more than 400 mOsm/kg in other disorders in which the renal response to acidemia remains intact, such as diarrhea.[1]

Urine pH is another important factor in diagnosing and determining the type of renal tubular acidosis. Normally, in metabolic acidosis of any type, the urine pH is 5.3 or lower as a compensatory mechanism. Distal renal tubular acidosis, caused by impaired hydronium secretion in the alpha-intercalated cells in the distal nephron, is characterized by an inability to lower the urine pH to less than 5.5 under the stimulus of systemic acidosis. It is associated with hypokalemia, nephrolithiasis, nephrocalcinosis, and hypocitraturia.[2] On the other hand, proximal renal tubular acidosis is characterized by reduced reabsorption of bicarbonate in the proximal tubule, with preservation of the distal acidification mechanisms and the ability to lower urine pH below 5.5.

Our patient's urine anion gap was 22 mmol/L, urine osmolal gap 59 mOsm/kg, and urine pH 6.0. She was diagnosed with distal renal tubular acidosis in view of the following findings:

- Normal-anion-gap metabolic acidosis
- Positive urine anion gap
- Urine osmolal gap less than 150 mOsm/kg
- Urine pH greater than 5.5
- Hypokalemia
- Recurrent nephrolithiasis
- Nephrocalcinosis
- Hypocitraturia.

TABLE 2
Causes of primary and secondary distal renal tubular acidosis

Primary distal renal tubular acidosis
Sporadic (idiopathic)
Inherited (due to a congenital mutation)
Secondary distal renal tubular acidosis
Hypergammaglobulinemia
Autoimmune disorders (eg, lupus erythmatosus, Sjögren syndrome, rheumatoid arthritis)
Chronic renal allograft rejection
Obstructive uropathy
Medullary sponge kidney
Autoimmune hepatitis
Primary biliary cholangitis
Lithium, amphotericin B, ifosfamide
Sickle cell anemia

Based on information in reference 2.

WHAT ELSE DOES SHE HAVE?

2 In view of the patient's diagnosis of distal renal tubular acidosis and her clinical symptoms, for which possible additional disorder should we screen her right now?

- ☐ Multiple myeloma
- ☐ Sickle cell anemia
- ☐ Primary biliary cholangitis
- ☐ Sjögren syndrome

Causes of distal renal tubular acidosis are listed in **Table 2**.[2]

Multiple myeloma results from excessive production of monoclonal immunoglobulin by the plasma cells. It often presents with back pain, weight loss, fatigue, generalized weakness, anemia, hypercalcemia, increased total serum protein, and acute renal failure.

Acute kidney injury is seen in 50% of cases at the time of the diagnosis and can be secondary to light chain cast nephropathy or hypercalcemia.[3] Other renal manifestations include proximal renal tubular acidosis and Fanconi syndrome due to the toxic effects of the excessive excreted light chains on proximal renal tubular cells. Isolated distal renal tubular acidosis has been reported, although it is less common in multiple myeloma.

Our patient had anemia and distal renal tubular acidosis. However, she did not have any other features to support the diagnosis of multiple myeloma.

Sickle cell anemia and primary biliary cholangitis can be associated with distal renal tubular acidosis.

TABLE 3
Serology workup

Tests	Results	Normal range
Antinuclear antibody	1:80	< 40 = Negative
dsDNA antibody	Negative	Titers < 10 = Negative
Anti-Ro52 (SS-A) IgG	366	< 20
Anti-La (SS-B) antibody	< 3	< 20
Anti-Ro60 IgG	< 5	< 20
Cryoglobulin	Negative	Negative

ds = double strand; Ig = immunoglobulin; SS = Sjögren syndrome

However, our patient had no symptoms or laboratory findings suggestive of sickle cell anemia or primary biliary cholangitis (ie, no hyperbilirubinemia or elevated alkaline phosphatase level).[4]

Sjögren syndrome. Our patient had chronic xerostomia, which could be explained by her use of sertraline, bupropion, clonazepam, or trazodone. However, it is very uncommon for these medications to cause dry eyes, whereas xerostomia and dry eyes could be signs of Sjögren syndrome.

Renal manifestations of Sjögren syndrome include distal and proximal renal tubular acidosis, tubulointerstitial nephritis, nephrogenic diabetes insipidus, and membranoproliferative glomerulonephritis. However, renal involvement in Sjögren syndrome is rare, affecting fewer than 10% of patients, and it is very unusual to find multiple manifestations simultaneously.[5]

Our patient had recurrent nephrolithiasis with calcium oxalate and calcium phosphate stones and distal renal tubular acidosis. In addition, she had other symptoms such as weakness, depression, and dyspnea that could have been due to extrarenal features of Sjögren syndrome, which include peripheral neuropathy (distal sensory and sensorimotor neuropathies), central nervous system manifestations (eg, depression, focal central lesions, encephalitis, motor disorders), interstitial lung disease, inclusion-body myositis, annular erythema, and salivary gland enlargement. For all these reasons, she was screened for Sjögren syndrome.

FURTHER WORKUP

Our patient underwent further serologic workup (**Table 3**). On the Schirmer test, done as part of an ophthalmologic evaluation, 0 mm of the paper was wet, suggesting severely decreased lacrimation. Other

TABLE 4
2016 American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) classification for primary Sjögren syndrome

Inclusion criteria	Exclusion criteria
At least 1 symptom of ocular or oral dryness, defined as a positive response to at least 1 of the following questions: Have you had daily, persistent, troublesome dry eyes for more than 3 months? Do you have a recurrent sensation of sand or gravel in the eyes? Do you use tear substitutes more than 3 times a day? Have you had a daily feeling of dry mouth for more than 3 months? Do you frequently drink liquids to aid in swallowing dry food? Or suspicion of Sjögren syndrome based on glandular enlargement or the presence of characteristic extraglandular involvement	Prior diagnosis of any of the following conditions: History of head and neck radiation treatment Active hepatitis C infection (with positive polymerase chain reaction) Acquired immunodeficiency syndrome Sarcoidosis Amyloidosis Graft-vs-host disease Immunoglobulin G4-related disease

ACR/EULAR classification criteria for primary Sjögren syndrome[a]

Criteria	Score
ACR/EULAR classification criteria for primary Sjögren syndrome	3
Anti-Ro/SS-A positive	3
Ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) in at least 1 eye	1
Schirmer test ≤ 5 mm at 5 minutes in at least 1 eye	1
Unstimulated whole saliva flow rate ≤ 0.1 mL/minute	1

[a]The classification of primary Sjögren syndrome applies to any patient who meets the inclusion criteria, does not have any of the conditions listed as exclusion criteria, and has a score ≥ 4.

Adapted from reference 7.

tests that can be used to assess dry eyes include ocular surface staining, tear breakup time (< 10 seconds), and tear osmolarity (> 308 mOsm/L in either eye).[6] In view of her weakly positive antinuclear antibody titer and dry eyes, salivary gland biopsy was offered to confirm the diagnosis of Sjögren syndrome and rule out alternative diagnoses. However, the patient refused to proceed with salivary gland biopsy.

Alternatively, the 2016 American College of Rheumatology and European Alliance of Associations for Rheumatology classification for primary Sjögren syndrome (**Table 4**)[7] can be applied to our patient. She met the inclusion criteria, did not have any of the exclusion criteria, and had a score of at least 4. For all these reasons, our patient likely had primary Sjögren syndrome. Her abdominal pain was likely related to nephrolithiasis.

Sjögren syndrome is associated with B-cell lymphoma and hypergammaglobulinemia.[8,9] Therefore, it is important to screen the patient for those disorders, particularly in view of her anemia. Computed tomography of the chest and abdomen did not reveal any lymphadenopathy, and results of serum and urine electrophoresis were unremarkable, with a normal serum free light chain ratio. The patient refused to undergo any biopsy or invasive procedures.

Regarding her clubbing, generally, clubbing can be congenital or acquired. Acquired clubbing is associated with pulmonary disease, cardiovascular disease, malignancy, and liver cirrhosis. Our patient's clubbing was acquired and was likely secondary to interstitial pulmonary fibrosis. This diagnosis was supported by the findings on computed tomography and by her respiratory symptoms, which suggested long-standing hypoxia, although she did not have any respiratory disorder based on her arterial blood gasses.

TREATMENT

3 What is the most appropriate treatment for this patient?

- ☐ Symptomatic treatment plus azathioprine
- ☐ Hydroxychloroquine and corticosteroids
- ☐ Symptomatic treatment
- ☐ Corticosteroids

Treatments for sicca manifestations include saliva substitutes and artificial tears. Topical cyclosporine A has been used in severe cases of keratoconjunctivitis. Because xerostomia is associated with increased risk of caries, remineralizing rinses are recommended. Pilocarpine can be used as well to stimulate salivary flow.

Although not evidence-based, hydroxychloroquine can be used for extraglandular manifestations such as inflammatory arthritis. Its onset of action varies widely, so a delay in its effect should be anticipated.[10,11] Immunosuppressive agents such as corticosteroids, cyclophosphamide, and azathioprine are reserved for systemic manifestations including pulmonary disease (interstitial lung disease), central nervous system, sensory ganglionopathy, and cryoglobulinemic vasculitis. It is unclear whether immunosuppressive agents limit renal tubular acidosis in Sjögren syndrome.

Our patient had systemic manifestations that included lung and renal involvement. We did not give her corticosteroids, in view of her psychiatric history. Therefore, she should have been treated with azathioprine or cyclophosphamide along with symptomatic treatment. However, the patient declined immunosuppressive medications. Therefore, she was started on hydroxychloroquine 200 mg daily and supportive care including artificial tear eye drops, caries care, and saliva substitutes.

For her hypocitraturia and history of calcium kidney stones, she was advised to increase her fluid intake and follow a diet with a normal calcium content but low in oxalate and animal protein. She was also started on potassium citrate with a plan to watch her urine pH closely, but she did not tolerate it due to nausea and vomiting.

Her joint pain and generalized weakness improved. However, she was noted to have polyuria, with a urine output of 3 to 4 L per day.

POLYURIA

4 What was the most likely cause of the polyuria in this patient?

- ☐ Primary psychogenic polydipsia
- ☐ Osmotic diuresis
- ☐ Hypercalcemia
- ☐ Diabetes insipidus

Primary psychogenic polydipsia could be suspected in this patient, who had a substantial psychiatric history. However, primary psychogenic polydipsia usually presents with hyponatremia and low urine osmolality. It is less likely in our patient, given her high serum osmolality and high serum sodium concentration. A water deprivation test was not done, to avoid interfering with her eating disorder treatment.

Osmotic diuresis occurs when certain substances such as glucose, protein, or mannitol are secreted in the tubules and cannot be reabsorbed owing to a pathologic reason, secretion of a large amount of the substance, or the nature of the substance. This leads to impairment of reabsorption of water and to hypernatremia. Urine osmolality is usually higher than 300 mOsm/kg in patients with osmotic diuresis. Our patient's urine osmolality was 165 mOsm/kg, which argues against this mechanism.

Hypercalcemia causes nephrogenic diabetes insipidus, likely due to downregulation of aquaporin expression in the medullary collecting duct as well as to a decrease in renal outer medullary potassium channel activity in the thick ascending limb of the kidney. This leads to a decrease in potassium availability for the sodium-potassium-chloride transporter, diminishing its activity.[12] This patient did not have elevated serum calcium.

Diabetes insipidus. Our patient had polyuria with low urine osmolality and elevated serum sodium. Given these findings, diabetes insipidus was most likely the cause of her polyuria.

Diabetes insipidus can be central, ie, secondary to inadequate vasopressin production from the posterior pituitary, or nephrogenic, ie, secondary to inadequate renal response to vasopressin. Sjögren syndrome is known to cause nephrogenic diabetes insipidus in some patients, but it is uncommon to find multiple renal manifestations in the same patient.[13,14] The patient also had hypokalemia, which can cause a defect in urinary concentration ability and lead to nephrogenic diabetes insipidus. The exact mechanism of hypokalemia-induced nephrogenic diabetes insipidus is still unclear.

Our patient received desmopressin, but her urine volume and urine osmolality did not change significantly, which confirmed the diagnosis of nephrogenic diabetes insipidus and ruled out central diabetes insipidus. We recommended that she continue oral hydration driven by thirst and that she always have water available. Her sodium level remained stable between 140 and 145 mmol/L.

TAKE-HOME POINTS

- Renal manifestations of Sjögren syndrome include distal and proximal renal tubular acidosis, tubulointerstitial nephritis, nephrogenic diabetes insipidus, and membranoproliferative glomerulonephritis.

- It is uncommon to find multiple renal manifestations secondary to Sjögren syndrome in the same patient.
- Distal renal tubular acidosis is caused by impaired hydronium secretion in the alpha-intercalated cells in the distal nephron. It presents with normal-anion-gap metabolic acidosis, a positive urine anion gap, a urine osmolal gap less than 150 mOsm/kg, and urine pH greater than 5.5, and is associated with hypokalemia, nephrocalcinosis, and hypocitraturia.
- Extrarenal features of Sjögren syndrome include peripheral neuropathy (distal sensory and sensorimotor neuropathies), central nervous system manifestations (eg, depression, focal central lesions, encephalitis, motor disorders), interstitial lung disease, inclusion-body myositis, annular erythema, and salivary gland enlargement.
- Sjögren syndrome is associated with B-cell lymphoma and hypergammaglobulinemia.
- Immunosuppressive agents are reserved for systemic manifestations such as interstitial lung disease, central nervous system involvement, sensory ganglionopathy, and cryoglobulinemic vasculitis.

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