A 53-year-old man with a history of hypertension presented to an urgent care clinic due to 2 to 3 weeks of lightheadedness and generalized weakness. Associated symptoms included diffuse myalgias and daily low-grade fevers. He denied any palpitations, syncope, or changes in urine or bowel movements. Initial laboratory evaluation showed a creatinine level of 2.8 mg/dL and a potassium level less than 2 mmol/L, so he was referred to the emergency department.

Examination in the emergency department revealed an afebrile, well-nourished man with moist mucous membranes, clear lung sounds, and no peripheral edema. Vital signs demonstrated blood pressure of 135/75 mm Hg and a heart rate of 70 beats/min. Laboratory evaluation showed the following results (reference ranges provided parenthetically): potassium, 1.8 mmol/L (3.6 to 5.4 mmol/L); blood urea nitrogen, 13 mg/dL (8 to 24 mg/dL); creatinine, 2.76 mg/dL (0.7 to 1.4 mg/dL); bicarbonate, 32 mEq/L (22 to 29 mEq/L); and hemoglobin, 10.7 g/dL (13.2 to 16.6 g/dL). The patient’s creatinine level was 0.8 mg/dL 1 year before presentation.

1. What is the most appropriate next step in the evaluation of this patient?
   a. A 24-hour urine study consisting of creatinine clearance and protein
   b. Serum protein electrophoresis with immunofixation
   c. Renal biopsy with light microscopy, immunofluorescence, and electronic microscopy
   d. Urinalysis with microscopy, urine electrolytes, and creatinine
   e. Helical computed tomography of the abdomen and pelvis

A 24-hour urine study can provide more accurate data, including measured (vs estimated) glomerular filtration rate and quantitative proteinuria, compared with a spot urinalysis. However, it is time-consuming and can delay this patient’s care, and it would be unlikely to change diagnostic or therapeutic management at this step in his work-up.

Serum protein electrophoresis should be performed in patients with renal dysfunction that is suspected secondary to a monoclonal gammopathy of renal significance (MGRS). Although cast nephropathy resulting in acute kidney injury (AKI) remains in the differential diagnosis, a serum protein electrophoresis would not be the best initial step for a comprehensive evaluation.

Although a renal biopsy is indicated when an underlying parenchymal disease is suspected, it would be too aggressive at this juncture due to its associated risks (primarily bleeding).

Urinalysis with microscopy, urine electrolytes, and creatinine is the best next step. Urinalysis is a fast and simple diagnostic test that can quickly narrow the differential diagnoses of renal disease. Urinalysis
with microscopy includes semiquantitative information about the presence of cells, casts, crystals, glucose, ketones, hemoglobin, urine osmolality, and proteinuria. These results assist the clinician in rapidly determining whether there is a glomerular, tubular, interstitial, or vascular renal problem. The urine electrolytes can also help with evaluation of his multiple metabolic disturbances. Urine sodium and the fractional excretion of sodium can be further used to differentiate among prerenal, intrinsic, and postrenal etiologies in patients with oliguric severe AKI. The urine sodium level is usually less than 10 to 20 mEq/L, and the fractional excretion of sodium is usually less than 1% in prerenal etiologies.

Helical computed tomography of the abdomen and pelvis provides structural information, but it requires radiation, with potential intravenous (IV) contrast exposure, and is more expensive. Renal ultrasound is generally the first imaging test of choice in a patient with unexplained kidney injury because it incurs no irradiation, can be quickly performed at the bedside, and can quickly provide significant structural imaging data that can exclude anatomical or obstructive causes of renal insufficiency.

Urine studies showed the following values (reference ranges provided parenthetically): urine pH 6.6; osmolality, 191 mOsm/kg (150 to 1150 mOsm/kg); protein, 70 mg/dL (<26 mg/dL); predicted 24-hour protein, 3247 mg (1031 to 10,229 mg); and a bland microscopy. Random urine electrolytes showed sodium, 49 mEq/L; potassium, 17 mmol/L; chloride, 49 mEq/L; and creatinine, 58 mg/dL. The patient had adequate urine output of at least 0.5 mL/kg per hour. A renal ultrasound with Doppler showed an 11.5-cm right kidney and a 12.0-cm left kidney with preserved renal cortical thickness, bilateral increased echogenicity, patent renal arteries and veins, and no hydronephrosis, with a normal bladder.

The results are most consistent with an acute intrinsic renal etiology. Findings arguing against a prerenal AKI include euvoolemia, a blood urea nitrogen to creatinine ratio less than 20:1, and a urine sodium level of 49 mEq/L. The renal ultrasound did not show a postrenal obstructive AKI, and the normal renal sizes with preserved cortical thickness further support a subacute rather than a chronic etiology for his renal dysfunction. Urinalysis showed proteinuria without sediments, suggesting acute tubular necrosis or acute interstitial nephritis.

2. What is the most appropriate next step in the work-up for this patient’s elevated bicarbonate level?
   a. Arterial blood gas (ABG)
   b. Genetic work-up for Bartter and Gitelman syndromes
   c. Overnight oximetry study
   d. 24-hour urine sodium and creatinine
   e. Diuretic screen

An ABG would be the best next step for evaluation of this patient’s elevated bicarbonate level because it can help differentiate between a primary metabolic alkalosis and secondary compensation. Bartter syndrome and Gitelman syndrome are uncommon genetic causes of metabolic alkalosis and hypokalemia that mimic loop and thiazide diuretics, respectively. Gitelman syndrome typically presents earlier in life but should remain in the differential diagnosis while working up more common causes first.

An overnight oximetry study should be considered if a patient has chronic respiratory acidosis with compensatory metabolic alkalosis, but an ABG is needed first to confirm respiratory acidosis.

A 24-hour urine sodium with creatinine (confirms adequate specimen collection) is useful in the evaluation for hypertension, hyperaldosteronism, renal stones, and other renal diseases, but it is unnecessary at this time because we already have a spot urine sodium level. Surreptitious diuretic use should be in the differential diagnosis for metabolic alkalosis, but this would not be the best next step because it does not evaluate for other
secondary causes of alkalosis, and the results are delayed compared with an ABG.

The patient’s ABG showed the following results (reference ranges provided parenthetically): pH 7.51 (7.35 to 7.45); Pco₂, 37 mm Hg (35 to 48 mm Hg); and Po₂, 72 mm Hg (83 to 108 mm Hg), consistent with a primary metabolic alkalosis. In this case, it can be difficult to differentiate whether the hypokalemia or the metabolic alkalosis was the primary inciting factor because the 2 processes can contribute to each other. Hypokalemia can cause potassium to move from the intracellular to the extracellular compartment, and, consequently, hydrogen ions to move conversely from the extracellular to the intracellular space, generating a metabolic alkalosis. This hypokalemic effect also leads to intracellular acidosis that can increase renal ammoniagenesis, resulting in further maintenance of metabolic alkalosis. Metabolic alkalosis, on the other hand, can cause hypokalemia by shifting potassium into cells and renal potassium wasting.

3. In addition to aggressive repletion of his potassium, what is the most appropriate next step in work-up for this patient’s hypokalemia?
   a. Urine chloride level
   b. Spot urine potassium to creatinine ratio
   c. Serum parathyroid hormone level
   d. Serum thyrotrpin and free thyroxine levels
   e. Morning cortisol level

   A urine chloride level is helpful for the evaluation of metabolic alkalosis by differentiating between renal vs extrarenal etiologies, but it is not as useful for the initial evaluation of hypokalemia.

   A spot urine potassium to creatinine ratio would be the most appropriate next step because it will further evaluate whether renal potassium loss is present. A urine potassium to creatinine ratio greater than 13 mEq/g suggests renal potassium wasting. A 24-hour urine study with urine potassium level would be ideal but can be inaccurate when this patient is receiving large amounts of IV potassium supplementation.

   Parathyroid hormone can affect extracellular potassium disposition but more commonly causes hyperkalemia in patients with chronic renal failure, which does not apply to the present patient.

   Disturbances in thyroid function (thyroid hormone can cause potassium to shift intracellularly) and excess adrenal activity (cortisol has mineralocorticoid activity) are potential causes of hypokalemia. Evaluation for hormonal disturbances would be more appropriate after confirmation of renal potassium wasting.

   Hyperaldosteronism is another endocrine cause for hypokalemia, hypertension, and metabolic alkalosis. Initial testing for hyperaldosteronism includes serum renin and aldosterone levels, instead of morning cortisol levels.

   A spot urine potassium to creatinine ratio was 29 mEq/g. A 24-hour urine study showed the following results (reference ranges provided parenthetically): sodium, 250 mEq/L (41 to 227 mEq/L); potassium, 68 mmol (17 to 77 mmol); protein, 1399 mg (<229 mg); calcium, 45 mg (<250 mg); and phosphorus, 541 mg (<1100 mg). Additional laboratory studies showed plasma renin activity of 1.1 ng/mL per hour (reference range, 0.6 to 3.0 ng/mL per hour) and a serum aldosterone level less than 4.0 ng/dL (reference range, <21 ng/dL).

   The spot and 24-hour urine potassium levels are both consistent with inappropriate renal potassium loss. Results of the 24-hour urine studies also suggest renal losses of sodium, protein, and phosphorus. In patients with hypophosphatemia, a 24-hour urine phosphate level greater than 100 mg is consistent with renal phosphate wasting.

   The patient continued to receive oral and IV repletion of potassium, in addition to repletion of magnesium and phosphorus. On the second morning of hospitalization, the patient’s serum potassium level was 2.5 mmol/L, and he continued to note muscle weakness. After receiving 160 mEq of potassium over the second day, his serum potassium level on the third morning was 2.7 mmol/L.
4. What is the best next step in the management of this patient’s hypokalemia?
   a. Stop potassium repletion due to risk of rebound hyperkalemia
   b. Start propranolol therapy
   c. Start thiazide diuretic therapy
   d. Start amiloride therapy
   e. Transition to oral potassium supplementation alone

   Although the risk of potassium overcorrection is increased in patients with a reduced glomerular filtration rate, this patient should continue to receive potassium repletion because he has severe and symptomatic hypokalemia with ongoing renal loss. In estimating the potassium deficit, each 0.3 mmol/L reduction of serum potassium is equivalent to a total body deficit of 100 mmol.6 Therefore, this patient still has a deficit of approximately 433 mmol (not accounting for ongoing daily loss).

   Nonselective β-blockers, such as propranolol, can be used in patients with refractory hypokalemia secondary to thyrotoxic periodic paralysis because they reduce excessive stimulation of the sodium-potassium adenosine triphosphatase and the resultant drive of potassium into cells. This patient’s pathology is primarily due to renal potassium wasting rather than transcellular shift and would be better addressed by repleting the deficit and decreasing ongoing renal loss.

   Starting a thiazide diuretic would be inappropriate because thiazides can exacerbate hypokalemia.

   Potassium-sparing diuretics (amiloride, triamterene, spironolactone, or epleronone) should be considered in patients with renal potassium wasting who have an inadequate response to potassium supplementation alone, and would be an appropriate choice for this patient with refractory hypokalemia.

   Potassium repletion at standard doses often may not be sufficient to correct hypokalemia in patients with renal potassium wasting. In severe (potassium level, <2.5 to 3.0 mmol/L) or symptomatic (arrhythmia, muscle weakness) hypokalemia, administration of IV potassium at a maximum rate of 10 to 20 mEq/h in addition to oral potassium is reasonable until the serum potassium level is persistently greater than 3.0 mmol/L and symptoms have resolved.

   The patient was started on amiloride, 5 mg daily, in addition to potassium repletion. With close monitoring, he subsequently had improvement in his serum potassium level and muscle weakness.

5. Which of the following processes would be most likely to account for this patient’s overall etiology of AKI and clinical presentation?
   a. Primary hyperparathyroidism
   b. Hyperaldosteronism
   c. Severe vitamin D deficiency
   d. Amyloidosis
   e. Renovascular disease

   Primary hyperparathyroidism is typically associated with prominent hypercalcemia and mild hypophosphatemia. This patient presented with profound hypophosphatemia and an only borderline elevated serum calcium level.

   Primary hyperaldosteronism can be associated with hypertension, hypokalemia, and metabolic alkalosis. Although the present patient has hypokalemia and metabolic alkalosis, his clinical presentation with mild hypertension on a single-drug regimen and presence of other electrolyte abnormalities is inconsistent. Furthermore, initial screening laboratory studies for hyperaldosteronism are typically associated with an elevated plasma aldosterone concentration (usually >15 ng/dL) and suppressed plasma renin activity, resulting in an aldosterone to renin ratio greater than 20 to 30.7

   Vitamin D deficiency can cause hypocalcemia and severe hypophosphatemia due to increased urinary excretion from secondary hyperparathyroidism and decreased gastrointestinal absorption. Vitamin D deficiency can also be associated with proximal tubule dysfunction, leading to multiple electrolyte abnormalities, such as the hypokalemia, hypomagnesemia, hypophosphatemia, and hypouricemia seen in the present patient.
Amyloid light-chain amyloidosis is an MGRS that is usually associated with nephrotic syndrome, heart failure, peripheral neuropathy, and hepatomegaly. Conversely, MGRS cast nephropathy more frequently presents with AKI associated with abnormal serum or urine protein electrophoresis and serum free light chains.

Bilateral renal artery stenosis can result in severe and refractory hypertension associated with hypokalemia due to an activated renin-angiotensin-aldosterone system, resulting in renal potassium loss. The patient’s previous renal ultrasound with Doppler did not show evidence suggestive of significant renal artery stenosis.

Further testing showed the following values (reference ranges provided parenthetically): parathyroid hormone, 64 pg/mL (15 to 65 pg/mL); repeated serum calcium, 8.3 mg/dL (8.6 to 10.0 mg/dL); 1,25 dihydroxy-vitamin D, 8.8 pg/mL (18 to 64 pg/mL); 25-hydroxyvitamin D (total), 8.1 ng/mL (20 to 50 ng/mL); normal serum and urine protein electrophoresis with immunofixation, and normal kappa/lambda free light chain levels and ratio. The heavy metal screen result was nonsignificantly elevated. The patient subsequently received vitamin D repletion therapy at 50,000 IU weekly for 8 weeks, and then continued vitamin D supplementation. Repeated vitamin D levels several months later were 30 ng/mL, his creatinine level returned to 0.93 mg/dL, and he had no hypokalemia or other electrolyte abnormalities.

**DISCUSSION**

In summary, this patient was a previously healthy man with hypertension who presented with several weeks of generalized weakness and lightheadedness. He was found to have subacute, nonoliguric renal failure associated with severe hypokalemia, severe hypophosphatemia, and metabolic alkalosis. His profound electrolyte abnormalities were determined secondary to renal wasting from proximal tubular dysfunction, likely secondary to severe vitamin D deficiency. His subacute renal failure was suspected primarily due to hypokalemic nephropathy.

This case outlines the diagnostic work-up and management for patients with acute to subacute renal failure combined with metabolic abnormalities such as metabolic alkalosis and severe hypokalemia. Noninvasive testing with a urinalysis with microscopy, urine electrolytes, and urine creatinine is a good starting point for initial work-up. In patients with hypokalemia where the etiology is not readily apparent by history or physical examination, the spot urine potassium to creatinine ratio or 24-hour urine potassium levels can be used to assess inappropriate renal potassium loss. In patients in whom the urine sodium level is less than 30 mEq/L or urine osmolality is lower than serum osmolality, a spot urine potassium concentration without urine creatinine can be misleading. When hypokalemia is refractory to a large amount of potassium repletion, potassium-sparing diuretics should be considered as adjunctive measures. If combination therapy is used, close monitoring of the serum potassium level is required to avoid hyperkalemia. In patients with hypokalemia secondary to renal loss with evidence of Fanconi syndrome, vitamin D deficiency should be in the differential diagnosis.

Renal potassium wasting caused by vitamin D deficiency has been reported in the literature. The mechanism is not completely understood, but there are rare reports of vitamin D deficiency associated with type 2 renal tubular acidosis or Fanconi syndrome. Vitamin D deficiency also decreases intestinal absorption of calcium and phosphorus, leading to a compensatory elevation of the parathyroid hormone levels that can reduce the bicarbonate absorption in the proximal tubule. Increased bicarbonate delivery to the distal tubules leads to further increased renal potassium loss. Hypokalemia, on the other hand, results in transcellular shifts that cause intracellular acidosis. This subsequently causes production of ammonia and secretion of hydrogen ions into the renal tubules, leading to reclamation of bicarbonate that contributes to maintenance of metabolic alkalosis and a cycle that leads to more profound hypokalemia.
Note that proximal tubulopathy with Fanconi syndrome is typically associated with a metabolic acidosis, not an alkalosis, due to bicarbonate wasting from the proximal tubule. In this patient, in addition to hypokalemia causing metabolic alkalosis through transcellular shifts and increased distal hydrogen secretion, there may yet be an additional unknown pathophysiologic mechanism. In severe hypokalemia, a study described persistent high urinary excretion of chloride that is saline resistant until the hypokalemia correction is partially corrected. Overall, however, this is an uncommon case, and Fanconi syndrome should be classically associated with a metabolic acidosis.

Chronic hypokalemia can lead to hypokalemic nephropathy, which is characterized by vacuolar lesions in the epithelial cells in the proximal tubules, and more severe cases have noted interstitial nephritis and fibrosis, and tubular atrophy. When it is subacute, hypokalemic nephropathy is reversible with potassium repletion. However, with prolonged hypokalemia, more severe and irreversible renal insufficiency can occur.

Potential Competing Interests: The authors report no competing interests.

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REFERENCES

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