## CASE 1

A 29-year-old woman who was involved in a motor vehicle accident is brought to the emergency department, where she is found to be hypotensive with severe internal bleeding. She is given several units of blood by transfusion and sent to the intensive care unit for monitoring. Within 36 hours, a slight decrease in urine output and an increase in blood urea nitrogen (BUN) are noted, and by 72 hours there is a dramatic drop in urine output. Laboratory studies at 72 hours are as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium:</td>
<td>5.1 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>25 mg/dL</td>
</tr>
<tr>
<td>Serum creatinine:</td>
<td>2.5 mg/dL</td>
</tr>
<tr>
<td>Urinalysis:</td>
<td>Mild hematuria, mild proteinuria, granular casts, and renal tubular epithelial cells in sediment</td>
</tr>
<tr>
<td>Fractional excretion of sodium ($\text{Fe}_\text{Na}$):</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

### What is the most likely diagnosis?

The patient most likely has acute tubular necrosis (ATN) secondary to renal ischemia as a consequence of shock due to the accident. ATN is the most common cause of acute kidney injury and is a result of direct injury to the renal tubular epithelia.

### What are common causes of this condition?

Renal ischemia and nephrotoxins are the two general classes of causes of ATN. Hypotension and other prerenal diseases can cause renal ischemia. Common nephrotoxins include antibiotics (eg, aminoglycosides, amphotericin, foscarin), radiopaque contrast, immunosuppressants (eg, cyclosporine, tacrolimus), chemotherapy agents (eg, cisplatin), and myoglobin (eg, in rhabdomyolysis).

### What is the cause of the patient's azotemia?

ATN involves direct damage to renal tubular epithelial cells (the proximal tubule is particularly vulnerable to ischemic injury because of its high demand for adenosine triphosphate). In addition, the sloughing of intact tubular cells and necrotic cellular debris into the tubular lumen blocks the urinary luminal tract. This leads to a back leak of the filtrate and, consequently, a decrease in the glomerular filtration rate (GFR).

### How do the laboratory findings help distinguish this condition from prerenal disease?

The microscopic findings on urinalysis and the BUN/creatinine values can help distinguish simple prerenal disease from ATN as follows:

- Muddy brown epithelial and granular cell casts in the urine are almost always pathognomonic for ATN.
- The BUN/creatinine ratio is approximately normal (10–20:1) in ATN but elevated (> 20:1) in prerenal disease.
- $\text{Fe}_\text{Na}$ is usually < 1% in prerenal states, while the $\text{Fe}_\text{Na}$ is usually > 1% in ATN.

### Why is the BUN/creatinine ratio elevated in prerenal disease but not in intrinsic renal disease?

Urea is a water-soluble molecule that is passively reabsorbed in the proximal tubule (the area of the kidney most sensitive to hypoperfusion) where volume depletion increases reabsorption of sodium and water in parallel with an increase in BUN.

Creatinine is not reabsorbed in the proximal tubule; hence, when there is volume depletion, there is not a commensurate rise in serum creatinine. Creatinine is freely filtered, and then gets secreted in the tubules.

Thus, in cases of upper gastrointestinal bleeding or other causes of hypoperfusion, BUN is elevated but creatinine is normal.

### What is the natural course of this condition?

Within 36 hours of injury, ATN undergoes an initial phase, during which time urine output decreases and BUN increases. Within 2–6 days, a maintenance phase begins, where urine output falls dramatically and there is a significant risk of death without treatment. Finally, the recovery phase typically occurs within 2–3 weeks.
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Renal
A 70-year-old man visits his primary care physician after going to a health fair and discovering that his blood pressure is 170/100 mm Hg. The previous year, his blood pressure was 135/85 mm Hg. The man also has a history of hypercholesterolemia. At the physician’s office, his blood pressure is 150/100 mm Hg and heart rate is 80/min. An abdominal bruit is detected in the epigastric region to the right of midline. Laboratory findings are significant for a serum sodium level of 147 mEq/L and a serum potassium level of 3.3 mEq/L.

What is the most likely diagnosis?
The man most likely suffers from renal artery stenosis. The bruit described is in the region of the renal artery; this finding, in addition to the sudden increase in blood pressure and hypokalemia supports the diagnosis of renal artery stenosis. Imaging confirms the diagnosis.

What is the pathogenesis of this condition in this patient and how would it differ in a young woman?
In the elderly population, renal artery stenosis is seen more often in men and is mostly caused by atherosclerotic plaques (secondary to hypercholesterolemia). For younger patients, fibromuscular dysplasia of the renal arteries, seen more in females, would be the likely cause.

What changes in renin secretion from each kidney are likely?
The kidney ipsilateral to the stenosis will increase renin secretion in response to a perceived decrease in arterial pressure due to decreased flow to the juxtaglomerular apparatus. The contralateral kidney will respond to the patient’s resulting hypertension by decreasing its renin secretion (Figure 12-9).

How does elevated plasma renin lead to hypertension?
In the plasma, renin converts angiotensinogen (produced in the liver) to angiotensin I. This is converted to angiotensin II by angiotensin-converting enzyme (ACE), which is secreted by pulmonary and renal endothelial cells. Angiotensin II acts on vascular smooth muscle to increase blood pressure. Angiotensin II also acts on the adrenal cortex to stimulate the release of aldosterone, which increases renal absorption of sodium to increase blood volume and thus blood pressure.

What electrolyte abnormalities are associated with this condition?
As seen in hyperaldosteronism, the sodium reabsorption is isotonic; therefore, the serum sodium is normal but hypertension ensues, and hypokalemia is expected as a consequence of renal potassium losses.

What is the medication of choice for this condition?
To correct the increased angiotensin II, an ACE inhibitor (such as captopril) or an angiotensin II receptor blocker (such as losartan) would be the medication of choice. Caution should be used with these drugs when renal artery stenosis is bilateral.

What four classes of antihypertensive drugs directly target the effects of renin?
- ACE inhibitors (captopril, enalapril, and lisinopril).
- Angiotensin II receptor blockers (losartan).
- Aldosterone-antagonizing diuretics (spironolactone).
- Renin inhibitors (aliskiren).
A 37-year-old woman presents to her rheumatologist complaining of increased fatigue, periorbital edema, and swelling of her lower extremities of 3 days' duration. One month earlier she started on prednisone and hydroxychloroquine for her newly diagnosed lupus. Her previously normal urinalysis now reveals hematuria, proteinuria, dysmorphic RBCs, and RBC casts. Her serum creatinine is 2.5 mg/dL. Physical examination at this visit reveals a temperature of 38.3°C (100.9°F), a blood pressure of 150/90 mm Hg, and a weight increase of 5 kg (11 lb). Moderate ascites and lower-extremity pitting edema up to her thighs are present.

What classification of renal disorders do these symptoms represent?
Hematuria with RBC casts, dysmorphic RBCs, and proteinuria on urinalysis in the setting of hypertension and edema indicate a nephritic syndrome. Causes of nephritic syndrome include rapidly progressive glomerulonephritis (RPGN), poststreptococcal GN, IgA nephropathy, lupus nephritis, and mesangial proliferative GN.

The next day, the patient is oligo-anuric, and her serum creatinine rises to 3.2 mg/dL. What is the most likely diagnosis?
This patient most likely has RPGN, a clinical diagnosis characterized by a doubling of serum creatinine in a 3-month period and rapid progression to acute renal failure. RPGN can result from a primary glomerulopathy or a secondary glomerulopathy mediated by a systemic disease, such as lupus in this case, or a streptococcal infection.

Kidney biopsy is also performed the next day (Figure 12-8). How does it aid in the diagnosis of this condition?
Kidney biopsy remains the gold standard for diagnosis. Light microscopy (LM) demonstrates the typical crescent formation of RPGN (Figure 12-8). Immunofluorescence microscopy of a renal specimen distinguishes three major patterns of immunoglobulin deposition, representing three diagnostic categories:
- Immune-complex glomerulonephritis is categorized by scattered granular deposits of immune complexes. This is the typical “lumpy bumpy” pattern. It can be seen in Henoch-Schönlein purpura and lupus among others.
- Anti–glomerular basement membrane disease shows smooth, linear deposition of immunoglobulin as seen in Figure 12-4.
- Pauci-immune glomerulonephritis (the most common type) manifest sparse or absent immunoglobulins. It can be seen idiopathically or in the setting of anti–neutrophilic cytoplasmic antibody vasculitides.

What is the pathogenesis of this condition?
RPGN is on the spectrum of immunologically mediated PGN. Lupus-associated RPGN is rare but likely shares a mechanism similar to other types of lupus renal diseases. Mesangial and subendothelial deposition of immune complexes, primarily composed of DNA-anti-DNA, are present. Subsequent activation of complement initiates the immune response.

How does the morphology of urine erythrocytes distinguish upper and lower urinary tract disorders?
Dysmorphic RBCs suggest upper tract bleeding or inflammatory glomerular or tubulointerstitial disease. RBC casts are also an indication of a glomerular disorder. Normal erythrocytes or eumorphic RBCs suggest lower urinary tract bleeding.

Should this patient receive treatment or will the condition self-resolve?
Untreated RPGN typically progresses to end-stage renal disease over weeks to months; therefore, prompt treatment is essential. Although treatment varies based on underlying etiology, empiric steroids should be given to all RPGN patients, sometimes with cyclophosphamide.
CASE 19

A 64-year-old woman presents to her physician with sudden onset of nausea and severe back pain on her right side. The patient is in acute distress and is unable to find a comfortable position. She has no prior history of back pain. Her temperature is 36.9°C (98.4°F), her heart rate is 90/min, and her blood pressure is 130/80 mm Hg. Relevant laboratory findings are as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>140 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>100 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4 mEq/L</td>
</tr>
<tr>
<td>Phosphoric acid</td>
<td>2.1 mEq/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.8 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>100 mg/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>13 mg/dL</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>25 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>15 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1 mg/dL</td>
</tr>
</tbody>
</table>

Urinalysis shows RBCs

What is the most likely diagnosis?
Nephrolithiasis (kidney stones). Acute back/side pain (especially related to movement or that waxes and wanes) with elevated calcium and RBCs in the urine indicates kidney stones.

How is this condition classified?
Approximately 85% of renal calculi are calcium oxalate stones (Figure 12-10), which are strongly radiopaque. The second most common kidney stones are struvite (ammonium magnesium phosphate), which are radiopaque and associated with Proteus vulgaris and Staphylococcus aureus infection. Other, less common stones include uric acid stones (radiolucent) and cystine stones (moderately radiopaque). This patient most likely has calcium oxalate stones given her hypercalcemia and normal temperature.

What is the pathogenesis of this condition?
Calcium oxalate stones can be caused by hypercalciuria, hyperoxaluria, or hypocitraturia (citrate is a potent inhibitor of calcium precipitation/stone formation).

What is the pathogenesis of the other three classifications of this condition?
Struvite stones form in the presence of alkaline urine, created by urease-splitting organisms such as Proteus vulgaris, Klebsiella, or Staphylococcus aureus. Uric acid stones are associated with hyperuricemia, which is seen in gout and conditions with high cell turnover such as leukemia or myeloproliferative disease. Cystine stones are observed in congenital cystinuria.

What is the appropriate treatment for this patient’s condition?
Treatment consists of analgesics, hydration, and if obstructed or infected, antibiotics ± stenting. Thiazide diuretics are contraindicated in this patient because of her hypercalcemia. Extracorporeal shockwave lithotripsy may be necessary for stones that do not pass spontaneously as a minimally invasive surgical intervention is usually indicated for stones > 5 mm.

What hormonal imbalance can cause the electrolyte abnormalities seen in this condition?
Hyperparathyroidism should always be considered in a patient with calcium stones. The high calcium concentration and low phosphate concentration may be a result of excess parathyroid hormone (PTH). High PTH level increases renal reabsorption of calcium and decreases renal reabsorption of phosphate. It also stimulates renal activation of vitamin D, which increases calcium and phosphate absorption from the gastrointestinal tract.
A 60-year-old man with a 30-year smoking history presents to his physician with complaints of cough, fatigue, and a recent 9.1-kg (20-lb) weight loss. X-ray of the chest reveals a 2-cm hilar mass that is identified on biopsy as small cell lung cancer. On physical examination, the patient has some cachexia but normal skin turgor, no edema or jugular venous distention, and no orthostatic hypotension. Relevant laboratory findings are as follows:

Serum:
- Sodium: 128 mEq/L
- Potassium: 4 mEq/L
- Blood urea nitrogen (BUN): 8 mg/dL
- Glucose: 90 mg/dL

Urine:
- Sodium: Normal
- Osmolality: 610 mOsm/kg H₂O

What is the most likely diagnosis?
Hyponatremia.

How is the etiology of this condition determined?
Volume status is assessed first. Although sodium loss can cause hyponatremia, excessive retention of water is usually the cause. A thorough history and physical examination can help correlate the patient's volume status to a cause of hyponatremia, and laboratory values can be used to confirm volume status. The cause of fluid loss can be determined by history (e.g., vomiting, diuretics, diarrhea) and physical findings of low volume (e.g., decreased skin turgor, low jugular venous pressure). Signs of excessive fluid retention include peripheral edema.

What laboratory findings can help determine a patient's volume status?
Serum and urine osmolality and sodium concentration can help confirm a patient's volume status. Most hyponatremic patients have a decreased serum osmolality; however, renal failure and hyperglycemia are two important causes of hyponatremia that accompany normal or increased serum osmolality.

In patients with low plasma osmolarity, urine osmolarity can differentiate primary polydipsia (low/normal urine osmolarity) from impaired water excretion (high urine osmolarity, as in the majority of patients).

In patients with hypo-osmolar serum and hyperosmolar urine, urinary sodium can then distinguish between hyponatremia caused by circulating volume depletion (e.g., from heart failure, cirrhosis, hypovolemia leading to decreased urinary sodium) and euvolemic hyponatremia (e.g., syndrome of inappropriate secretion of antidiuretic hormone [SIADH] leading to normal urinary sodium).

In this case, what is the most likely etiology of the patient's volume status?
This patient's small cell lung tumor raises the likelihood of SIADH (a paraneoplastic syndrome for small cell lung cancer). Physical findings and lab values are also consistent with SIADH.

What are the major causes of this condition?
- Ectopic ADH production by a tumor, particularly small cell (oat cell) carcinoma of the lung.
- Intracranial pathology, such as trauma, stroke, tumors, or infection.
- A wide range of drugs.
- Major surgery, pain.
- HIV infection.
- SIADH may also be idiopathic.

What is the mechanism of action of ADH?
ADH is the main regulator of serum osmolality. ADH causes water channels (e.g., aquaporin-2) of the principal cells of the kidney's collecting ducts to translocate to the cell membrane, thereby allowing more water to be reabsorbed. Its release from the posterior pituitary is stimulated by hyperosmolality and by decreased effective circulating volume.

What are the appropriate treatments for this condition?
Treatment consists of tumor resection. If evidence of SIADH persists or resection is not possible, treatment involves restriction of free water intake or use of hypertonic saline with loop diuretics or demeclocycline.