Special Feature

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Introduction

A 39-year-old African-American man presents with an upper respiratory infection, and urinalysis reveals 4+ proteinuria, trace blood. Serum creatinine is 1.7 mg/dl. He is referred for nephrology consultation. The past medical history is notable only for a chronic skin infection that is being treated with tetracycline. There is no known history of diabetes, sickle cell disease, or hypertension. He has no known drug allergies. The social history is remarkable for the patient’s occupation in battery recycling. He is single and in a monogamous sexual relationship. He denies use of intravenous drugs, cocaine, alcohol, and tobacco. The family history is negative for kidney disease. His mother has hypertension. On detailed review of systems, the patient has no physical complaints and specifically denies leg swelling, joint pain, skin rashes, dysuria, hematuria, difficulty passing urine, passage of stones, pain, fever, and night sweats.

On physical examination, he appears well. His vital signs include a temperature of 35.7°C, BP of 140/80 mmHg, and a heart rate of 82 beats per minute. His neck is supple, and there is no lymphadenopathy. His cardiac and pulmonary examinations are normal. There is no hepatosplenomegaly. He has no signs of edema, arthritis, or rash. The laboratory data are summarized in Table 1.

Dr. Ajay K Singh. To summarize, this is a 39-year-old African-American battery recycler with kidney disease that was detected during routine evaluation of an acute respiratory infection. The renal dysfunction and the proteinuria could be compatible with either a tubulointerstitial or a glomerular etiology. Glomerular range proteinuria is usually >3 g/24 h, whereas “tubular” range is in the 1 to 2 g/24-h range. Since our patient has a urinary protein excretion of 2 g/24 h, I favor either a tubulointerstitial process or, at most, a mild glomerular disease. The absence of any prior measures of renal function makes it difficult to assess acuity. I favor a more acute or subacute process because of the absence of broad urinary casts and lack of metabolic and hematologic derangements common in a more chronic process (hypobicarbonatemia, low normal calcium and elevated phosphorus, and anemia). Compatible with acute etiology, the renal ultrasound shows relatively intact kidney size (Table 1).

My differential diagnosis is listed in Table 2. The history of a chronic skin infection raises the possibility of reactive amyloidosis. The occupational history of recycling batteries suggests possible exposure to heavy metals such as lead or cadmium. Common things being common, focal segmental glomerulosclerosis and membranous nephropathy need to be considered. Review of the laboratory data reveals a low anion gap and abnormalities consistent with incomplete Fanconi syndrome, raising the possibility of exposure to outdated tetracycline or a proximal tubulopathy from a paraprotein. High rates of type AA amyloidosis have been reported in patients with chronic suppurative skin infections. Menchel and co-workers (1), in a prospective survey of 150 addicts examined at autopsy, reported seven cases of renal amyloidosis. In all cases, the amyloid was AA-protein-related. These authors suggest that 26% of addicts with chronic suppurative skin infections have renal amyloidosis. However, AA amyloidosis secondary to chronic inflammatory dermatoses, in the absence of drug-associated “popping,” is rare (2,3). We are only provided limited information about whether the skin infection is of a suppurative nature in this case. As well, the patient denies intravenous drug addiction and has no physical evidence of skin “popping.” Consequently, I believe AA amyloidosis is an unlikely explanation for the patient’s presentation.

This patient has laboratory features consistent with incomplete Fanconi syndrome, reflecting dysfunction of the proximal tubule. There are many causes for Fanconi syndrome (Table 3). It has been known since 1960 that breakdown products of tetracyclines used after their shelf life are toxic and cause Fanconi syndrome (4). In 1963, Gross (5) and Frimpter et al. (6) identified the major degradation products present in the outdated tetracycline capsules. Subsequent animal studies by Benitz and Diermeier (7) evaluated the toxicity of three separate tetracycline degradation products, demonstrating that epianhydrotetracycline was the most toxic. In reported cases glucosuria, aminoaciduria, phosphaturia, and proteinuria occurred in most, if not all, of the patients. Acidosis was common, and azotemia and hypokalemia were sometimes observed. Some of these clinical features are present in our patient. However, these derivatives of tetracycline develop only in hot, moist, acid conditions. Because citric acid is no longer used in the production of tetracycline, tetracycline-associated Fanconi syndrome is now rare. I would be very
surprised if this was the explanation for our patient’s presentation.

The occupational history of battery recycling raises the specter of heavy-metal poisoning from lead or cadmium as a possible cause of his renal disease. Gonick provides an excellent review of this topic (8). We are not told about the type of batteries being recycled, or the duration of exposure. Nor, for that matter, do we know whether the patient worked in an open smelter, where he could have been exposed to one or more heavy metals, or in a modern factory. Since almost 90% of lead acid batteries are recycled, there is a possibility of lead exposure in this patient because of his occupation.

Lancereaux was the first to report lead nephrotoxicity in a paper published in 1863 (9). He noted substantial atrophy of the renal cortex and tubular fibrosis in the kidney in an artist who habitually held paintbrushes in his mouth. In the late 1920s, an epidemic of chronic nephritis due to childhood lead poisoning brought to light the full spectrum of lead-induced nephropathy (10). Subsequently, reports of lead nephropathy have appeared among distillers of illegal corn whiskey in the United States (11,12) and among industrial lead workers (13). Nowadays, lead nephropathy from the western hemisphere is largely historical since industrial hygiene has markedly improved. In our patient, lead nephropathy is implausible because of the absence of certain clinical features that are sine qua non for the diagnosis, including hypertension, gout, slowly progressive decline in kidney function with minimal proteinuria, an elevated uric acid level, and contracted kidneys on ultrasound. Renal dysfunction, in our case, appears subacute or acute in tempo, hypertension and gout are absent, proteinuria is significant, uric acid level is on the lower side, and kidney size is normal. All of these make lead nephropathy an unlikely diagnosis.

Again, because of his occupation, I also considered the possibility of cadmium nephrotoxicity, which can cause renal dysfunction and Fanconi syndrome (8,14,15). Acute exposure to cadmium fumes may result in flu-like symptoms, including chills, fever, and muscle aches, sometimes painful, and severe enough to hospitalize and cause death (15). Cadmium nephrotoxicity may be associated with lead nephropathy. The kidney is the major route of cadmium excretion and a high percentage of body cadmium burden resides in the kidney (16). It has been suggested that the kidney might have a protective role in cadmium toxicity (17). However, there is no evidence that cadmium exposure resulted in renal dysfunction in our patient.

Table 1. Laboratory data

| Urinalysis: 2+ protein, occasional RBC, 3–5 WBC, 0 casts, glucose 2+, ketones negative |
| Sodium 137 mEq/L, potassium 4.3 mEq/L, chloride 101 mEq/L, bicarbonate 29 mEq/L, Serum creatinine 1.7 mg/dl, blood urea nitrogen 15 mg/dl, creatinine clearance 52 cc/min. Glucose 90 mg/dl |
| Total bilirubin 0.8, calcium 9.8, phosphorus 3.4, cholesterol 245, uric acid 3.2. AST 29, ALT 39, alkaline phosphatase 84, triglycerides 150 |
| Hemoglobin 13.9 g/dl, hematocrit 45%, white blood count 3.1 K, platelets 283,000 |
| RPR nonreactive. PSA 0.7. |
| ANA 1:80 speckled nucleolar pattern, anti-DNA negative. Hepatitis B surface Ag and Ab negative, hepatitis C Ab negative, HIV negative, RPR negative. ESR 13. |
| C3 132, C4 60. |
| 24-h urine volume 800 cc, creatinine 1.4 g, protein 2 g/day. |
| SPEP–TP 7.8, albumin 3, alpha-1 globulin 0.2, alpha-2 globulin 0.7, beta-globulin 1.3, gamma-globulin 1.0. |
| Imaging: chest x-ray normal; sonogram without hydronephrosis, kidneys 12.8 and 11.7 cm. A renal biopsy is performed. |

Table 2. Differential diagnosis

Amyloidosis AA secondary to suppurative skin infection
Heavy-metal-associated renal disease
lead or cadmium
FSGS
Proteinuric glomerular disease
Outdated tetracycline
Amyloid AA, amyloid AL, monoclonal immunoglobulin deposition disease
Kappa light chain tubulopathy with incomplete Fanconi syndrome and possibly light chain deposition disease glomerular disease

FSGS, focal segmental glomerulosclerosis.

Table 3. Classification of Fanconi syndrome

Inherited
inborn errors of metabolism
hereditary fructose intolerance
galactosemia
Wilson’s disease
cystinosis
Acquired
Drugs
outdated tetracycline
aminoglycosides
cisplatin
ifosfamide
6-mercaptopurin
valproic acid
tenovir
Toxins
mercury
lead
cadmium
uranium
Tubular toxicity
multiple myeloma
amyloidosis
light chain nephropathy
benign monoclonal gammopathy

AST - aspartate aminotransferase; ALT - alanine aminotransferase; RPR - Rapid plasma reagin test; PSA - Prostate-specific antigen.

referred to as “the cadmium blues” (14). More chronic cadmium exposure causes chronic respiratory problems such as emphysema, rhinitis, and anosmia. In this case, there is no history of acute occupational exposure and our patient did not present with a chronic respiratory ailment. Furthermore, patients with cadmium toxicity frequently have evidence of osteomalacia. The best example of cadmium intoxication of a large population is itai-itai-byo, or “ouch-ouch” disease, so named because of the crippling and painful osteomalacia (8,16), endemic to the Jinzu River basin in Japan. The typical patient was a middle-aged postmenopausal, multiparous woman who had lumbar pains, leg myalgia, a duck-like gait, and typical findings of osteomalacia. I very much doubt that cadmium is the cause of this man’s presentation, because modern industrial practices have minimized occupational exposure to cadmium, and this patient does not have prominent chronic respiratory or bone-related symptoms.

Rather than a tubulointerstitial etiology, one could argue this patient has an early glomerular lesion. The presence of proteinuria would be consistent, but the 2 g per day of proteinuria would not be typical, unless one invoked the possibility of secondary focal segmental glomerulosclerosis (FSGS) or mild idiopathic membranous nephropathy. The history does not support secondary FSGS or membranous nephropathy as etiologies; both are unlikely in our patient.

The laboratory workup provides us with two relatively subtle laboratory abnormalities that cannot be ignored and are key to my diagnosis. First, the low anion gap, and second, the glucosuria and the lowish phosphorus and uric acid levels suggesting incomplete Fanconi syndrome. A low-serum anion gap is an uncommon finding. Data from two large clinical laboratories suggest that the prevalence of a low anion gap is between 0.8% and 3% (17,18). The causes of a low-serum anion gap are discussed in detail elsewhere (19). The most common reason for a low anion gap is laboratory error (20). Other causes include an increase in unmeasured cations or a decrease in unmeasured anions. An IgG or IgA paraproteinemia will cause deviations in the serum anion gap. IgA tends to be anionic and increases the anion gap. In general, IgG tends to be cationic, and there is a strong inverse correlation between the level of the serum anion gap and the concentration and net positive charge of IgG paraproteins. The glucosuria in the absence of hyperglycemia, and the lowish serum phosphorus level and the low uric acid level, are compatible with Fanconi syndrome, likely of the incomplete type, because not all of the features of the Fanconi syndrome are evident in our patient.

In 1954, Sirota and Hamerman were the first to publish a report of an adult with Fanconi syndrome and multiple myeloma (21). Many reports and series characterizing adult Fanconi syndrome in patients with a paraproteinemia have since been published. A common finding is the deposition of crystalline material in lysosomes in proximal tubular epithelial cells and a clinical presentation of Fanconi syndrome. In rare cases, there is deposition into histiococytes and the condition is termed crystal-storing histiocytosis, with a clinical picture dominated by acute kidney injury, rather than Fanconi syndrome. Occasionally, there is even more widespread renal involvement with crystal deposition in renal tubular epithelial, visceral epithelial cells, parietal epithelial cells, and, even more rarely, involvement of mesangial cells and glomerular endothelial cells.

Maldonado et al. (22) published the first substantive series of proximal tubulopathy with kappa-associated crystalline deposition. Bence Jones protein of the kappa type was a constant finding. However, just like the current case, there were no serum protein monoclonal abnormalities detected. In half of the patients, crystalline cytoplasmic inclusion bodies were present in lymphoplasmacytic bone marrow elements and renal tubular cells. More recently, Messina and co-workers (23) reported a series with heterogeneity in the clinical features. The majority of patients (seven of the 11) had Fanconi syndrome and low-mass myeloma or monoclonal gammopathy of undetermined significance (MGUS). However, three patients who presented with full-blown Fanconi syndrome had myeloma kidney; one patient of this group also had numerous crystals in proximal tubule cells. One of the 12 patients with Fanconi syndrome had no evidence of crystals in proximal tubule cells, even after electron microscopy. Contrasting with the clinicopathologic heterogeneity, all of the patients had a paraprotein of the kappa type, and eight of nine belonged to the V kappa I variability subgroup, which indicates that Fanconi syndrome light chains are related by the sequence of their variable regions.

The largest reported series of patient’s with Fanconi syndrome originates from the Mayo Clinic. Ma et al. (24) presented the clinical features and outcomes in 32 patients diagnosed with Fanconi syndrome. In their series, 31% had multiple myeloma, 6% had Waldenstrom macroglobulinemia, 19% had smoldering multiple myeloma, and 44% had MGUS. A monoclonal light chain was detected in the urine of all patients at diagnosis; 91% had kappa light chains, and the other 9% had lambda light chain Bence Jones proteinuria. Notably, and very much like our patient, at the time of diagnosis, a serum monoclonal protein was found in only 69% of patients and a positive SPEP is not always seen. Ma et al. (24) also reported that incomplete Fanconi syndrome was the rule rather than the exception. While glucosuria was a constant finding, hypokalemia (44%), hypophosphatemia (50%), and hypouricemia (66%) were observed in only a fraction of patients. Of the 32 patients, 17 had a renal biopsy performed, and eight had characteristic crystal structures in the cytoplasm of the epithelial cells of the proximal renal tubules. Taken collectively, then, the presence of an IgG kappa paraproteinemia provides a parsimonious explanation for most, if not all, of the clinical findings.

The pattern of the renal disease in dysproteinemic disorders depends on where the paraprotein deposits in the kidney (Table 4). This, in turn, determines the clinical presentation. Heher et al. and Markowitz et al. provide excellent reviews on this topic (25–27). A kappa light chain nephropathy results from deposition in the glomerular basement membrane and presents with proteinuria or the nephrotic syndrome. Rarely, a proliferative glomerulonephritis has also been reported. A kappa tubulopathy presenting with Fanconi syndrome may occur when the prox-
The normal serum protein electrophoresis (SPEP) may be reduced by 2.3 mEq/L. The SPEP result in our patients suggested some lowering in the anion gap (for every 1-g/dl decrement in serum albumin concentration, the serum anion gap could have accounted for a decrease in albumin was 3 on the SPEP) could have accounted for a lowering in albumin concentration. The serum anion gap reflects the difference between the sum of cations and the sum of anions in the body fluid. A low anion gap is usually due to metabolic acidosis, such as lactic acidosis, or due to the presence of a cationic substance in the body fluid. A very small amount of very cationic paraprotein could have resulted from the kidney absorbing the plasma could have resulted from the kidney absorbing the cationic paraprotein. A feature that has been reported previously. I am postulating that the low levels in serum-free light chains (31). In a paper by Keren et al., monoclonal gammopathy was correctly detected by SPEP only 88% of the time (32). My explanation for the “negative” SPEP is that the paraprotein has a very high affinity for the kidney, a feature that has been reported previously. I am postulating that the low levels in the plasma could have resulted from the kidney absorbing all of the circulating, highly reactive, and nephrotoxic paraprotein. A very small amount of very cationic paraprotein could have caused the low anion gap. On a separate but related note, it is also possible that a low albumin (the albumin was 3 on the SPEP) could have accounted for some lowering in the anion gap (for every 1-g/dl decrement in serum albumin concentration, the serum anion gap is reduced by 2.3 mEq/L). The SPEP result in our patients points to a lower-than-normal serum albumin concentration.

In summary, my diagnosis in this patient is an incomplete Fanconi syndrome from a kappa proteinemia, and my hope is that Dr. Racusen will show us a kappa chain proximal crystalline tubulopathy on renal biopsy.

**Dr. Lorraine Racusen.** I have been asked to provide “The Answers,” the traditional role for the pathologist in the CPC (clinopathologic correlation) exercise. The clinical history available for this patient was succinct, as the patient was quickly referred for renal biopsy. However, Dr. Singh has done a superb job of analyzing the available data and arriving at a diagnosis.

The renal biopsy on this patient was received as two tissue cores, with cortex containing numerous glomeruli and blood vessels. By light microscopy, glomeruli were normocellular, with delicate mesangium and capillary walls, which stained with silver and PAS (Periodic Acid Schiff) stains in a normal pattern, without evidence of abnormal deposits. Interstitial areas contained no inflammation or fibrosis. No pathologic changes were seen in arteries or arterioles.

The most striking feature in the biopsy was accumulation of eosinophilic crystalline material in tubular epithelial cells (see Figure 1). Crystals were silver- and PAS-negative but stained orange on Masson trichrome stain (see Figure 1B). Crystals were largely in proximal tubule epithelial cells and were associated with cell swelling and focal cell necrosis. Congo Red stain for amyloid was negative.

Immunofluorescence staining was performed on frozen tissue containing seven glomeruli. Protein in tubular epithelial cells stained for IgG (1+) and kappa (1+) light chain, with some albumin as well (2+). Arterioles stained for C3 (1+), and some interstitial fibrinogen was detected. Stains for lambda light chain, IgA, IgM, and C1q were negative. Immunoperoxidase stain for kappa light chain was positive (see Figure 2), and lambda light chain was negative.

Electron microscopy revealed numerous needle-like crystals and crystalline arrays within proximal tubule epithelial cells (see Figure 3), with rare crystals in mesangial cell cytoplasm. Glomerular epithelial cells were remarkable for focal effacement of foot processes, with some cytoplasmic vacuolization and microvillous change. No dense, granular, or fibrillary deposits were detected. Immunoelectron microscopy was performed with gold-labeled antibody for kappa and lambda light chains. Crystals stained strongly for kappa light chain, (see Figure 4) with staining for lambda light chain negative and staining of normal control tissue negative.

Since SPEP is not as sensitive as immunofixation (IFE) or assay for free light chains (31,32), and as a follow-up to the elevated β-globulin with asymmetric appearance on SPEP, IFE of the serum was performed and revealed a faint band in the kappa region. Urine protein electrophoresis revealed a spike in the gamma region, with a monoclonal kappa light chain on IFE of the urine. A bone marrow biopsy revealed greater than 50% plasma cells, kappa light chain positive. Bone marrow aspirate revealed immature plasma cells with crystalline intracellular granules, apparently immunoglobulin. Congo Red stain for amyloid was negative. Injury to renal tubular epithelium is a common lesion in...
light chain-induced renal disease. A common manifestation is failure of reabsorption of small molecules by the proximal tubules, which may result in Fanconi syndrome, but patients may present with acute kidney injury as well.

Free light chains are freely filtered by the glomerulus and avidly absorbed by proximal tubular epithelial cells. They bind to the megalin-cubulin tandem scavenger receptor system (33) and are endocytosed via the clathrin-dependent endosomal/lysosomal pathway (34). Intracellular light chains in turn inhibit Na-K-ATPase in proximal tubular cells (35) and lead to a range of cytotoxic effects (36,37).

Nephrotic potential is widely variable among light chains, with kappa light chain more commonly associated with tubular injury. Most cases of crystal-associated tubulopathy have been associated with kappa light chains, especially the Vh1 subgroup (38), as noted. A transgenic

Figure 1. (A) Eosinophilic crystalline material in proximal tubular cells (arrows) (H&E staining). (B) Crystals stain orange on trichrome stain (arrows) (Masson trichrome).

Figure 2. Immunoperoxidase stain for kappa light chain revealing positive staining of intracellular crystals.

Figure 3. Electron micrograph revealing intracellular spiculated crystals in tubular epithelial cells.

Figure 4. Electron micrograph with immunogold labeling for kappa light chain. Particles are deposited on the intracellular crystals.
animal model created using a V kappa J kappa rearranged gene from a patient with myeloma-associated Fanconi’s syndrome demonstrated proximal tubule crystallopathy; crystals diminished on conditional deletion of the human V kappa (39). Mutations in the CDR L1 loop may confer protease resistance, with the light chain serving as a nidus for crystal formation. In other cases, lattice-like arrays or large proteinaceous aggregates in lysosomes have been reported in proximal tubular cells (e.g., Kapur et al. [40]). In some cases, a pattern of acute tubular injury with prominence of lysosomes and atypical lysosomes without crystals or inclusions is seen (41). Immunostaining, including ultrastructural immunolabeling, may be critical in making an accurate diagnosis (42), and the pathologist should be alert to the range of patterns of injury. Crystals in proximal tubular cells are often associated with crystals in bone marrow cells, as in this case.

Most patients with light chain–associated proximal tubulopathy do well in the absence of overt malignancy. In the current case, however, multiple myeloma was diagnosed, with a large number of malignant plasma cells in the bone marrow. A skeletal survey at the time of diagnosis was negative for lytic lesions. The patient was started on a cytoreduction therapy. A bone marrow biopsy at 5 years revealed less than 5% plasma cells, staining for both kappa and lambda light chains. At latest follow-up 13 years posttransplant, his creatinine was 1.5 and SUN 10. However, at 15 months after diagnosis, the patient had a bone marrow biopsy with atypical positive plasma cells. Approximately 2 years after initial diagnosis, he underwent an autologous bone marrow transplant following cytoreduction therapy. A bone marrow biopsy at 5 years revealed less than 5% plasma cells, staining for both kappa and lambda light chains. In the intervening years, he had developed diabetes mellitus, hypertension, and hyperlipidemia, and was on a range of medications, but without evidence of recurrence of myeloma.

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Disclosures
None

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