Ronald Falk, MD, Professor of Medicine and Chief of the Division of Nephrology, University of North Carolina at Chapel Hill: My name is Ronald Falk, and I come from the University of North Carolina. I have been selected to arbitrate the annual ASN ClinicoPathologic Conference (CPC), a spectacle matching an outstanding clinician who is trying to figure out the diagnosis with an extremely eminent pathologist who, of course, knows the diagnosis. I’m going to share with you that I’ve done this CPC twice. I did it last year, so that’s why I get the pleasure of being the moderator. The Renal Pathology Society and Bob Narins take incredible pleasure in writing these cases, providing as few data as possible and in fact adding as many extra bits of extraneous information as they possibly can. So, please for all of you who are clinicians, have empathy for the clinician who gets to do this; and now we will begin these proceedings.

Sharon Adler, MD, Professor of Medicine, David Geffen School of Medicine at UCLA, Associate Chief, Division of Nephrology and Hypertension, Harbor-UCLA Medical Center: First, let me thank the organizers for giving me this great opportunity to appear foolish before a large audience. The patient is a 42-yr-old man with oliguria, 10 d of weakness, hyperventilation, anorexia, nausea, vomiting, and intermittent back and flank pain. We are not told about any medicines he is taking, so I assume there are none. We are not given any past medical history, so I assume there is none. On physical examination, he is a little hypertensive, a little tachycardic, tachypneic, and afebrile. We are not given any past medical history, so I assume there is none. On physical examination, he is a little hypertensive, a little tachycardic, tachypneic, and afebrile. He appears acutely ill but not chronically ill. He has no skin manifestations, or at least there wasn’t any mention of his skin. You know you have to look for tricks when you’re doing a CPC.

On his laboratory examination, the most significant findings were a serum creatinine of 13.2 mg/dl on presentation and a hematuria of 30%. We are not told anything about his white blood cell or platelet count. He has a serum protein of 6.4 and an albumin of 3.1 g/dl. That is an inversion of the albumin globulin ratio. He is hyponatremic, hypochloremic, and hyperkalemic, and his serum bicarbonate is 13 mEq/L. He has an anion gap of 26. The increment in his anion gap equals the decrement in his serum bicarbonate. His chest x-ray shows congestive heart failure and volume overload despite the lack of a gallop on physical exam. We are not told anything about the cardiac silhouette. There was 420 mg/d protein on a 24-h urine collection. On urinalysis, there was trace protein, 10 to 15 red cells per high-power field, and hyaline and granular casts. There were needle-shaped crystals of varying lengths. He had a renal ultrasound that showed 11- and 12-cm kidneys with increased echogenicity and no structural abnormalities. Anti-nuclear antibodies, C3, C4, and hepatitis B and C serologies were normal or negative, and anti-neutrophil cytoplasmic antibodies (ANCA) and anti–glomerular basement membrane (GBM) antibody titers were sent off and are pending.

So, as the clinician, I looked at the case as presented and thought that if I were really there in the emergency room when this patient presented, there would have been a lot of additional data that I haven’t been provided that I would most likely have known. So I’m going to make a partial list of these data for you, because as I discuss this case, the absence of these pieces of information will come back to haunt me.

First of all, I found the symptom chronology unclear. The protocol merely said 10 days of nausea, vomiting, a little bit of abdominal pain, and intermittent flank pain. It really didn’t give me a sense, as a really good clinician would want to know, about the evolution and the progress of these symptoms over the course of those 10 days. That was concerning (and somewhat confusing) to me, and it is something we will come back to, since the lack of symptom evolution prevents me from discerning with certainty whether this a clinical syndrome and a clue to the underlying pathogenesis or a nonspecific manifestation of uremia in this patient who came in with a serum creatinine of 13 mg/dl.

We know that the patient has an anion gap acidosis. We don’t know if the patient was acidemic. There’s no blood gas. We can’t tell if he’s tachypneic from the acidosis or if he has superimposed hypoxia. We don’t know whether there’s a compensated second metabolic disorder. Assuming that he had a simple anion gap acidosis, if somebody presents with an anion gap acidosis and crystals in his urine, we routinely like to know whether there’s an osmolar gap. Interestingly enough, we haven’t been told that.

We know the patient has hematuria. I’m sure all of you have microscopes in your office or at least in your hospital, and in a patient like this with urinary red cells, you’d go to the microscope and look at the urinalysis yourself. You would be able to...
assess whether the red cells were dysmorphic or nondysmorphic, distinguishing glomerular from nonglomerular disorders, but our friends who wrote this protocol did not tell us whether this was dysmorphic or eumorphic hematuria.

There is an inversion of the albumin globulin ratio, and there is no serum or urine protein electrophoresis or immunofixation to let us know whether an abnormal monoclonal protein is present. The patient is anemic. The patient had a hematocrit of 30%, but we know nothing about the nature of this anemia. There is no description of the peripheral smear and no lactate dehydrogenase (LDH), so we don’t know whether the patient is hemolyzing. There are no iron studies, so we don’t know if the patient is sequestering blood in his lungs or losing it from some other source. We don’t know if the anemia was normochromic with normal iron stores and is just a reflection of the renal failure. We don’t know what the white cell count or platelet count was, so we don’t know if there is a primary hematologic disorder or a pattern that might suggest a vasculitis (e.g., leukocytosis, thrombocytosis, anemia). We don’t know his serum uric acid, phosphorus, or calcium. We don’t know his creatine phosphokinase, so we don’t know, for instance, whether some of this might be consequent to rhabdomyolysis.

Finally, the history is rather lacking in terms of past medical history, medication history, or toxin exposure. Taking into account all of the missing data, honing in on the diagnosis will be a challenge.

So, now I am going to crystallize this case, if you will, to its essentials. The patient has acute symptoms of weakness, anorexia, nausea, vomiting, hyperventilation, and back and flank pain. He has some key signs: Anion gap acidosis with needle-like crystals in his urine, hematuria, and mild proteinuria. He has pericarditis, pulmonary congestion, and renal failure. Taking into account what we know and we don’t know, I ended up concentrating this down to three questions:

1. Is this acute disease or chronic disease?
2. Is it glomerular or tubular?
3. Do the key symptoms and signs reflect the specific underlying clinical syndrome, or are they nonspecific manifestations of uremia?

You will see that I am going to focus on the needle-like crystalluria, which I think, in association with the anion gap acidosis, is our strongest clue to what’s going on here.

The first question was whether this is a community-acquired acute renal failure or a chronic kidney disease. The acute symptomatology supports an acute etiology. The patient is well nourished, and there is no past medical history. The renal size is adequate. The absence of broad urinary casts suggests the possibility of acute rather than chronic disease. The bicarbonate of 13 mEq/dl and the anion gap of 26 are too low and too high, respectively, for stable chronic kidney disease or ESRD, suggesting an acute process. The serum creatinine is 13 mg/dl. We weren’t told the blood urea nitrogen, and the only acute renal failure that I know of that frequently reaches 13 mEq/dl on initial presentation would be rhabdomyolysis, where creatinine is nonenzymatically generated from the conversion of creatine. Even in rhabdomyolysis, however, a creatinine of 13 mg/dl at presentation would be unusual.

In support of a chronic process, the urinalysis lacked muddy brown casts and red cell casts, which are certainly helpful when you do see them to support a diagnosis of acute renal failure. The high serum creatinine usually suggests a chronic presentation, and more information about the anemia, particularly if we knew it was normochromic and normocytic, would have supported a diagnosis of chronic renal failure. The increased renal echogenicity and the presence of anemia do not distinguish acute from chronic disease. Thus, I think that most of the data suggest that this is acute renal failure, and the case has mercifully been called “a case of acute renal failure,” so a word to the wise is sufficient, and I will assume that this is acute renal failure.

The second question is, “Is it glomerular or tubular?” To answer this, I am going to pretend that I am a medical student. A medical student would approach this in a rather rigorous algorithmic way, going through a sequential series of diagnostic paths, since acute renal failure can be prerenal, glomerular, tubular, or obstructive. Any medical student can tell you that, so I am going to actually do that. Is this patient volume depleted? He certainly was vomiting, but we’re not given his weight or orthostatic vital signs, so we don’t know if he demonstrated manifestations of prerenal azotemia. He doesn’t have a metabolic alkalosis, which you’d like to see in prerenal azotemia. We don’t know what his calcium is, so we don’t know if perhaps he has a nephrogenic diabetes insipidus; his chest x-ray looks wet; and he does have a creatinine of 13 mg/dl, so he is probably not prerenal.

What about vascular causes? I don’t think he has bilateral renal artery stenosis; there was no mention of bruit. There is no accelerated hypertension. I don’t think he has polycystic nodosa, scleroderma renal crisis, or atheroembolic disease. He had no abdominal pain or skin lesions. I don’t think that he had hemodynamic events that caused acute renal failure. He was not taking nonsteroidals, calcineurin inhibitors, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Can he have the dreaded cardiorenal syndrome? Well, I don’t think he has valvular disease; there are no murmurs described. I don’t think he has cardiomyopathy; he doesn’t have an S3 or an S4 described on physical examination. He doesn’t appear to have tamponade; he has hypertension and wet lungs, which would be rather unusual for tamponade. I don’t think that a myocardial infarction has caused what seems to be rather mild heart failure (wet chest x-ray but no gallops). He has no EKG mentioned and no cardiac enzymes measured. I suppose it is possible that he could have a viral syndrome that caused pericarditis and acute renal failure, but that would be rather unusual and wouldn’t account for the crystalluria. So, I don’t think that this patient has prerenal azotemia. I will again focus on the absence of crystalluria in addition to the other reasons cited in rejecting prerenal causes of acute renal failure.

So, we move on to glomerular causes. Clearly, the clinicians caring for this patient were thinking about rapidly progressive glomerulonephritis because they did send off for ANCA and anti-GBM antibody testing. However, I don’t think that this is...
Goodpasture syndrome. In 70% of the cases, the pulmonary hemorrhage precedes the renal disease. There is usually iron deficiency anemia from sequestration of blood in the lung. We don’t know the nature of the anemia, but I am going to make the assumption that it’s not iron deficiency. He could have anti-GBM disease without pulmonary involvement, and if that were the case, we would not be able to figure out that out prebiopsy without the appropriate serologic result. He doesn’t have dysmorphic hematuria or red cell casts, or at least they didn’t tell us that he did. A diagnosis of Goodpasture’s would not account for the profound acidosis. It would not account for the pericardial friction rub. It does not usually present with hypertension, at least early, although late in its course with advanced renal disease a BP of 170/90 mmHg, as he presented, would certainly be possible. But if we chose Goodpasture’s, it would basically imply that the clinical presentation—the nausea, the vomiting, the pericardial friction rub—were really nonspecific uremic symptoms and not tied to the underlying pathogenesis of the disease. In addition, Goodpasture’s does not present with crystalluria, so in the end, we must reject this diagnosis.

I also doubt that the patient has ANCA-associated vasculitis with crescentic glomerulonephritis. He lacks the systemic signs and symptoms of Wegener granulomatosis or microscopic polyangiitis. It is possible but unlikely that the nausea, vomiting, and abdominal pain were a prodromal syndrome leading up to overt vasculitis or even a manifestation of bowel ischemia due to vasculitis. The patient doesn’t have leukocytoclastic vasculitic skin lesions, and there are no ear, nose, or throat symptoms and no mononeuritis multiplex. These patients often have leukocytosis and thrombocytosis with anemia. We did not see that. We would expect to see dysmorphic red cells and red cell casts and a profoundly high sedimentation. This patient’s sedimentation rate was 44. A vasculitis diagnosis would not account for the profound acidosis or the friction rub. It again would imply that the clinical syndrome was uremia rather than a specific syndrome complex directly related to the underlying disease. Finally, a diagnosis of vasculitis does not account for crystalluria.

A similar argument can be made for dismissing a diagnosis of immune complex–mediated crescentic glomerulonephritis. Of course, diffuse proliferative glomerulonephritis and post-streptococcal glomerulonephritis fall into this category, but the patient lacks signs and symptoms characteristic of these disorders. This presentation would be an unusual presentation of lupus even in a young woman, and this was a middle-aged man. Furthermore, the antinuclear antibody was negative and the C3 and C4 were normal. The normal complements also imply that the clinical presentation—the nausea, the vomiting, the pericardial friction rub—were really nonspecific uremic symptoms and not tied to the underlying pathogenesis of the disease. In addition, Goodpasture’s does not present with crystalluria, so in the end, we must reject this diagnosis.

We must now consider the possibility of tubulointerstitial disease. The patient had no known hypotension, muscle injury, or sepsis to predispose him to ATN. Therefore, ATN as a primary entity is unlikely in this patient in the setting of a community-acquired acute renal failure and is probably, if present, secondary to some other primary process. It is also unlikely that the patient had acute interstitial nephritis. He had no leukocyturia, fever, or known antigen exposure. Although a skin rash is unusual in acute interstitial nephritis, if present, it is helpful; but he had no skin rash.

By a process of elimination, this forces us to consider the possibility of ATN or acute interstitial nephritis due to the ingestion of toxins. We have no toxin and no medication history in this patient at all, but we are running out of diagnoses. Radiocontrast of course is one of the most common forms of toxin-induced acute renal failure. Interestingly, toxins actually do precipitate as needle-like crystals and also as plate-like crystals on urinalysis. Examination of the urine with a polarizing light microscope would show contrast as flat rhomboidal crystals, but this is a community-acquired acute renal failure, so that is unlikely. Heavy metals, myoglobinuria, and pesticides certainly cause acute renal failure, but they don’t cause crystalluria.

How about obstruction? Postrenal obstruction is unlikely. I don’t think the patient has prostatic hypertrophy or cancer, bladder cancer, urethral strictures, stones, or papillary necrosis. An ultrasound is unremarkable except for echogenicity. There is a small percentage of acute renal failure from obstruction that is missed by ultrasound, but I doubt that is occurring here. How about obstruction? Postrenal obstruction is unlikely. I don’t think the patient has prostatic hypertrophy or cancer, bladder cancer, urethral strictures, stones, or papillary necrosis. An ultrasound is unremarkable except for echogenicity. There is a small percentage of acute renal failure from obstruction that is missed by ultrasound, but I doubt that is occurring here. How about tubulointerstitial crystals from systemic disease that might cause intratubular obstruction? We all know that light chains can cause intratubular obstruction in myeloma kidney. I searched to see if those light chains, which are seen precipitating inside tubules so nicely on renal biopsies, ever appear in the urine. I found one case (1), and the urinary crystals were hexagonal, so I don’t think this is a light-chain proteinuria case. Tumor lysis syndrome is associated with intratubular obstruction from uric acid. We were not given the serum uric acid level in this patient, and there was also no white count given, so I don’t know if this patient has a surrep-
titious leukemia or a malignancy that we’re not being told about. The most common urinary forms of uric acid are just amorphous crystals or sometimes hexagonal or football-shaped crystals. If ammonia is added to experimental synthetic urine in large amounts, uric acid will crystallize as needles (2). However, in vivo, it does not usually appear in that form in the setting of hyperuricemia. Another rare systemic disease that causes crystalluria (Charcot-Leyden crystals) is the idiopathic hyper eosinophilic syndrome. Acute renal failure is rare; it is usually a slowly progressive disorder. Crystals are more spear than needle-like (3). It culminates in eosinophilic leukemia. This is an unlikely diagnosis.

There are other molecules that can crystallize within tubules. Patients with severe liver disease sometimes have urinary crystals that are needle-shaped. Bilirubin may appear in urine as needle-like crystals. It usually sticks onto cells in clusters, so it often does not look like needles. Tyrosine, which is also present in the urine in advanced liver disease, really does look like needles. However, we don’t have any description of hepato megaly, cirrhosis, or any hepatic toxicity, so this patient is unlikely to have liver disease and needle-like crystals from that.

There are medications and intoxications that cause acute renal failure, crystalluria, and acidosis. The problem is that we don’t have any history of a medication or intoxicant ingestion, so we approach this diagnostic consideration by default, having ruled out everything else. The diagnostic dilemma continues to center around whether this patient’s symptoms reflect an underlying clinical syndrome or are nonspecific manifestations of uremia. I will focus the discussion on medications or toxins that cause crystalluria.

General overviews of crystalluria have been published (4,5). Crystalluria was the first urinary abnormality that was discovered at the advent of microscopy. For the first 50 yr of experience with urine microscopy, crystalluria was the only urinary abnormality described. Crystalluria usually doesn’t signify a problem. Physical factors influence crystallization, such as urinary concentration, pH changes, and cold temperature. Cooling causes calcium oxalate to precipitate, so a delayed urine analysis after the specimen has been on a cold lab bench may show crystallization that occurred ex vivo. Weak acids precipitate in acid urine. Hypoalbuminemia facilitates the crystallization of medications because there is more free drug present in blood and therefore more free drug filtered.

Crystalluria is common. It correlates poorly with stone formation. It often occurs ex vivo, so very often it’s not clinically significant. Certain morphologic forms are more clinically meaningful, particularly when associated with medications, toxic ingestions, inherited disorders, or, as in this case, seen in association with anion gap acidosis. Many medications crystallize in the urine as an incidental finding, including nitrofurantoin, 5-fluorocytosine, cephalaxin, aspirin, phenacetin, xylitol, and 6-mercaptopurine, the last of which causes needle-like crystals (but not anion-gap metabolic acidosis).

A number of medications are associated with crystalluria and acute renal failure. In some, the crystals are needle-like. Sulfadiazine usually organizes itself as rosettes. I assume that this case is not sulfadiazine-induced acute renal failure, since the crystals are not described as organizing in rosettes. Other drugs associated with needle-like crystals and acute renal failure include acyclovir, felbamate (for epilepsy), amoxicillin, and indinavir. In the last, the crystals are needle-like in the renal tubular lumen, but generally in the urine they form floral rosettes or plates and only rarely are needle-like. Primidone, triamterene, sulfamethoxazole, ascorbate, piridoxilate (combination of pyridoxine and glyoxylic acid used in Europe for coronary artery disease), and ciprofloxacin also cause acute renal failure, but these do not cause needle-like crystals. None of these medications would account for the large anion gap acidosis, so I am going to reject all of these medications as the underlying cause of this patient’s problem even though some of them induce needle-like crystals.

Only intoxications remain. The first intoxication that may be responsible for this illness is probably unknown to you unless you hail from Indonesia or Malaysia (6). It is due to the ingestion of djenkol (jering) beans, usually eaten between September and February. The beans have a lot of djenkolic acid, which is a sulfur-containing amino acid. They may induce acute renal failure, the pathogenesis is unknown, and mostly men are affected. The preparation of the beans doesn’t seem to be implicated in the idiopathogenesis. The affliction status of individuals is different, so at a large gathering of people eating the same beans, some will develop acute renal failure while others won’t. Furthermore, an individual’s susceptibility to acute renal failure from the bean is not fixed from one exposure to the next. Thus, it is not clear how these beans induce acute renal failure, but they certainly appear to. The chief complaint of affected patients is loin pain and suprapubic tenderness. They get nausea, vomiting, and abdominal pain, much like our patient. They get an acidosis, like our patient, and in a rat model, an anion gap acidosis. The urine and breath have a characteristic odor because of the large amount of sulfur in djenkolic acid. The urinalysis shows hematuria like our patient, glucosuria, hyaline and granular casts, and needle-shaped crystals. I don’t think that this clinical presentation is far off from the presentation of our patient. Having said that, though, I have to acknowledge that djenkol intoxication is not the most likely diagnosis and that the mostly likely diagnosis probably has something to do with oxalate.

Oxalate is the most common urinary crystal. It is derived from foods containing ascorbate, glyoxalate, and glycolate and from oxalate itself. Increased renal excretion is due to increased synthesis or increased absorption from the intestine and almost always results in precipitation of calcium oxalate. Precipitation first occurs in the proximal tubules, where oxalate is secreted, and then in the medulla, where urinary concentration and acidification play a role. Renal parenchymal deposition occurs in renal insufficiency even in the absence of an abnormality in oxalate metabolism (7). Therefore, if oxalate is present in the kidney, it is necessary to discern whether this is nonspecific deposition or whether it is pathogenetically important in the primary disease process.

There are primary and secondary forms of hyperoxaluria. The two primary forms are rare genetic disorders inducing
abnormalities in glyoxalate metabolism. Type 1 involves a mutation in alanine:glyoxalate aminotransferase and type 2 a mutation in glyoxylate/hydroxypyruvate reductase. They induce sustained elevations of plasma oxalate levels. These patients present with recurrent nephrolithiasis and progressive renal insufficiency with cardiovascular, neurologic, and skeletal morbidity from tissue deposition of oxalate in these organs. ESRD usually develops in children and young adults.

However, a case report published a few years ago is relevant to this discussion and documents an adult presentation of primary hyperoxaluria, a rare manifestation of an uncommon condition (8). This patient was a 54-yr-old woman with a distant past medical history of a renal stone having been passed 20 or 30 yr prior during a pregnancy who otherwise had been healthy for the intervening time. She presented with acute nausea and vomiting for 7 days. Her serum creatinine was 14 mg/dl, very reminiscent of our patient’s presentation, and it was documented that her serum creatinine was 1.5 mg/dl 3 mo earlier, so this was clearly acute renal failure. Her urinalysis showed red cells, white cells, and something that they called “urate crystals” (but the morphology was not actually described), and some brown granular casts. She had pleuropulmonary carditis. Our patient had a pericardial friction rub that remains unexplained. This patient developed the pleuropulmonary friction rub after dialysis was instituted, so it did not appear to be a uremic manifestation. In fact, a pleural biopsy actually demonstrated oxalate deposition in the pleura, suggesting that there probably was also oxalate deposition in the pericardium. Of interest is that this clinical presentation, which is very reminiscent of the current case, confused the doctors taking care of her at presentation, and they too were looking for a glomerular process. They too thought that maybe this was lupus or anti-GBM disease or systemic vasculitis, but these investigations turned out to be negative. A renal biopsy in this case showed deposition of crystalline material in the lumens of tubules that was birefringent on polarizing light microscopy and that was thought to be calcium oxalate. Additional studies confirmed this, including electron probe analysis of the tissue showing calcium in the crystals. Exposure of the tissue to sulfuric acid produced gas, which is consistent with the presence of calcium oxalate, and Fourier transform infrared microscopy provided a spectroscopic analysis of the crystals that showed that this was in fact monohydrate calcium oxalate crystals (9).

The clinicians then went on to demonstrate that this was primary and not secondary hyperoxaluria (8). With a normal GFR, serum and 24-h urinary oxalate measurements are diagnostic but not when the GFR is <10 ml/min. Since glycolic acid persists in serum longer than oxalic acid, the parent compound, the former can be measured, and an Italian investigator developed normative values for oxalic acid and its metabolites glycolic acid and glyceric acid, which can be measured by HPLC in plasma (10). The clinicians then did an elegant dissection of this patient’s presentation and measured oxalic acid and glycolic acid pre- and postdialysis and showed that they were very high in the patient, much higher than in healthy people and even higher than would be anticipated in patients who have secondary oxalosis. Oxalic and glycolic acid were also measured in dialysate, where they were present in excess, much more than what is obtained in patients being treated for secondary oxalosis. The clinicians concluded that this was an adult patient with a syndrome of acute renal failure, crystalluria, and pleuropulmonary carditis due to primary hyperoxaluria. This case is quite reminiscent of the case in this proceeding and raises the possibility that this is a second case of a patient with primary oxalosis presenting in an adult.

Mostly, as internists, we see acquired forms of hyperoxaluria. An overdose of ascorbic acid can cause it, but it is very rare. Nobody uses methoxyflurane anesthesia anymore, and I think that it would have been difficult for this patient to use that as an outpatient. There is no history of intestinal malabsorption syndrome in this patient. That leaves us with ethylene glycol intoxication. As we all know, this is an antifreeze, and when it is used for radiators, the preparation sometimes contains fluorescein, which appears as a bright yellow green color when it is viewed with a Woods lamp. In some emergency rooms, they actually have Woods lamps, where urine can be examined for fluorescence with long ultraviolet wavelength light. If this patient presented acutely, one might have run to the emergency room for a Woods lamp to prove that the patient had ethylene glycol intoxication.

Ethylene glycol itself actually is not toxic. Its metabolites are. Only 20% is excreted in the urine unchanged. The half-life of the metabolites ranges from 3 to 8 h. The acidosis is due to the accumulation of glycolic, glyoxylic, and oxalic acid but is also due to hydrogen ion titration from these and the formation of hippuric acid and the depletion of co-factors for the tricarboxyl acid cycle, resulting in the accumulation of lactic acid. Dihydrate envelope-shaped urinary crystals do actually occur in ethylene glycol intoxication, and they are the predominant form 4 to 5 h after intoxication. However, later, more needle-like crystals are seen (11). There is some confusion in the literature about whether these needle-like crystals in ethylene glycol intoxication are actually hippurate or oxalic acid. Nevertheless, whether its hippurate or oxalic acid, needle-like crystals do occur.

Clinically, ethylene glycolic intoxication is described as presenting in three stages. Stage 1 is a central nervous system (CNS) stage lasting from about 30 min to 12 h and is characterized by depression, ataxia, speech slurring, hallucination, convulsions, coma, and vomiting. It is at this stage that the osmolar gap is present. In our case, the only thing that we can say for sure that our patient had with respect to the CNS stage is vomiting. We were, I suppose, intentionally not given an osmolar gap, or perhaps he didn’t present within the first 12 h. Stage 2 involves the cardiorespiratory system, occurring in the second half of the first day after ingestion. Our patient had a full house of these symptoms: Tachypnea, tachycardia, metabolic acidosis, and pulmonary edema. This raises the possibility that maybe these were not nonspecific manifestations of a uremic syndrome but rather a specific clinical syndrome. Stage 3 is renal, and once again our patient expresses all of these signs and symptoms: Hematuria, low-grade proteinuria, flank pain, crystalluria, and acute renal failure. Again, this is evidence in
support of a specific clinical syndrome rather than nonspecific uremic symptoms.

Nevertheless, there are some inconsistencies in the attempt to package the patient’s symptoms into a defined clinical syndrome. The cardiopulmonary and renal stages are well represented by this patient, but the CNS stage seems to have vanished, and I would think that if this patient had a single ingestion 10 d before admission and he came in at 10 d, we might have been able to elicit more retrospective history of CNS problems on day 1. As discussed, the half-life of ethylene glycol metabolites is 3 to 8 h, so if there were a single ingestion and we have a 10-day (or 240-h) history, then on admission, 30 to 80 half-lives had passed since the ingestion. However, on day 10, there was still an anion gap acidosis and crystalluria. The crystalluria might be explained by slow release of crystals from their deposition site in the kidney, leading to a prolonged excretory phase. It is more difficult to explain the anion gap acidosis this late in the clinical syndrome. One can postulate, perhaps due to the evolving acute renal failure, that the oxalic acid metabolic products, glyoxylic acid and glyoxylate remained, resulting in persistent anion gap acidosis. Taken together, this suggests an endogenous source of oxalic acid, continuous ingestion, or significant crystal deposition in the kidney with slow release.

So what’s the diagnosis? In the end, it’s basically a gamble. There are essentially three possibilities:

1. It may be a rare disorder with an even rarer manifestation: Primary oxaluria with initial presentation as an adult.
2. It may be a more commonly occurring intoxication: Ethylene glycol poisoning. The patient lacks the CNS symptoms but has the exact cardiopulmonary and renal manifestations, along with the crystalluria and acidosis, albeit somewhat more prolonged than one might anticipate, and so ethylene glycol intoxication is a good possibility.
3. If this case were presented in Asia, I probably would have gone with jering bean intoxication. Given that we’re in St. Louis, I think I will instead go with either primary hyperoxaluria or ethylene glycol intoxication.

These three diagnoses all account for the nausea, vomiting, pulmonary congestion, pericardial friction rub, anion gap acidosis, crystalluria, flank pain, and the acute renal failure that characterized the patient’s presentation.

What should the biopsy show? It should show intraluminal and/or interstitial oxalate crystals with acute tubular necrosis. If this is primary hyperoxaluria, I would want to see chronic interstitial nephritis, potentially with superimposed acute interstitial nephritis as described in the case by Singh et al. (8) along with acute tubular necrosis.

Dr. Falk: So, to determine whether our esteemed clinician has gotten this case right, we’re going to turn to Dr. Weening.

Jan Weening, MD, PhD, Professor of Pathology, Chairman of the Department of Pathology, Academic Medical Center at the University of Amsterdam, The Netherlands: Thank you very much. I would like to first introduce a few concepts to the audience with a few slides. Do we as renal pathologists like to read a biopsy without the knowledge of clinical data, or do we like to have the clinical data? I think that differs. Some pathologists like to look at the biopsy without knowledge. I usually like to have some knowledge of the clinical data because you’re probably more efficient, but of course, you may be biased or confused by that data. The clinical data that we usually obtain from our clinicians are on a prefilled form, and we like to be informed regarding the presentation and history of the patient, the clinical differential diagnosis, physical and laboratory evaluations, some immunology parameters, some family history, and any known medication or toxin exposure. In this case, we knew that we had to deal with acute renal failure, and we can then anticipate signs of vascular obstruction, severe glomerular disease, tubulointerstitial nephritis, massive infection, disseminated intravascular coagulation, or urinary obstruction. Since these are all associated with acute renal failure, one should look for them in the biopsy.

Pathologists can indeed contribute to the diagnosis and management of this patient because we know from the literature that among the different clinical syndromes, biopsies in acute renal failure are most helpful. In patients who have acute renal failure, it has been shown that a renal biopsy contributes in over 65 to 70% of the cases to a change in management (12,13)

The biopsy consists of two cores (Figure 1). The overall architecture is preserved. The tubules are a little bit wide, but at low magnification, there is no chronic interstitial fibrosis. The vessel in the top core is difficult to interpret. It is an artery that is somewhat contracted and has signs of atherosclerosis. It is not inflamed, and I think this contraction and obstruction of the lumen is more artifact than real. But we have to look at the other vessels to make sure that this is not something significant. The glomeruli are fairly well expanded, although there is quite some space between the tuft and Bowman’s capsule. There is some acute ischemia as evidenced by capillary wall wrinkling. There are no signs of hypercellularity, inflammation, or crescents. Periodic acid–Schiff–stained sections show that other ves-

![Image](https://example.com/image.png)

*Figure 1. Light micrograph showing two cores with renal cortex with six glomeruli, an artery, and a relatively well-preserved tubulointerstitial compartment. Magnification ×40, methenamine silver stain.*
sels, including small arteries, are normal. In other glomeruli, Bowman’s space is occasionally also a little bit wide but otherwise completely normal: Not hypercellular, not inflamed, and no intravascular coagulation. In the interstitium, we can see that there is some edema and an infiltrate.

We then go to the tubulointerstitial compartment (Figure 2). Tubules are wide apart because of the interstitial edema and inflammation with plasma cells, lymphocytes, and polymorphonuclear leukocytes, and there are tubules with some proteinaceous fluid. A few tubules are dilated and show signs of necrosis. There is cellular debris in the lumen and rather severe edema in the interstitium with some infiltrate. In parts of the biopsy closer to the medulla, there is a dense infiltrate with plasma cells, lymphocytes and polys, and a lot of edema. At higher magnification, there are tubules with thin, almost necrotic tubular cells, and cast-like structures with cells in the lumen. On the trichrome stain, there is also a bit of early fibrosis, edema, and debris in the tubules.

The question of course is whether we can provide pathogenic information in addition to this picture of interstitial nephritis and tubular necrosis. And on this slide and these stains, the silver stain, the periodic acid-Schiff stain and the trichrome, I guess we cannot, but on the hematoxylin and eosin stain, there are tubules with crystals, which, when examined with polarizing light, are birefringent and typical of oxalate crystals (Figure 3). These are actually widespread through the parenchyma and at higher magnification is the typical picture of an oxalate crystal. In the semithin section that we re-cut in Amsterdam, we can see oxalate crystals within tubular cells (Figure 4). These can accumulate at the epithelial cell surface due to abnormally high concentrations, when urine flow is limited, or in young individuals, usually by hereditary congenital disease, for example by endocytotic abnormalities due to mutations of chloride channel-5 (14). In our case, it’s probably due to abnormally high concentrations caused by ethylene glycol poisoning or a solid acid poisoning, but that, of course, can’t be discerned from the biopsy.

Ethylene glycol is metabolized by alcohol dehydrogenase, the same enzyme that also metabolizes methanol and ethanol. The former is metabolized to glycolic acid, and the latter to formic acid and acetic acid, respectively. Glycolic acid is then enzymatically converted to a host of toxic products, including formic acid, oxalate, and a few others that are injurious not only to the kidney but also to the CNS and the liver. So the diagnosis should be indeed acute tubular necrosis due to calcium oxalate toxicity, possibly caused by ethylene glycol poisoning, in this adult patient as the most likely diagnosis.

Dr. Falk: Beautiful photomicrographs. So, does anybody have follow-up on this patient?

Richard Glassock, MD, Professor Emeritus, David Geffen School of Medicine at UCLA: I can give you a little more detail on the patient if you’d like. This patient arrived at Los Angeles International Airport on a gurney having been sent from an
He did not receive methoxyflurane, so by default, this just had to be, from my point of view, ethylene glycol toxicity.

Dr. Glassock: To follow-up, he was hemodialyzed for about 3 wk, slowly recovered renal function, was discharged when serum creatinine got down to 3, and he went back to his home country.

References


