Detective Nephron

Detective Nephron, world-renowned for expert analytic skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. Mackenzie Ula Densa, a budding nephrologist, plans to present a new case to the master consultant.

Nephron 2022 is almost here. What do you have for us today, my dear apprentice?

Mac I have a 76-year-old man with AKI….

Nephron (*excited*): AKI…we haven't done that in a while. What is the serum creatinine?

Mac Trust me, you are going to love this one! Serum creatinine is 6 mg/dL, up from his baseline of 1.0 mg/dL just a few weeks ago.

Nephron Come on, spill the *details*….

Mac Hmm...hold your horses. He has a history of benign prostate hypertrophy and small bowel resection many years ago and presented with gradual onset of decreased urinary output, fatigue, anorexia, and confusion that had gradually progressed over the preceding 3 weeks.

Nephron Stop…nice! What an amazing topic…. Nephrologists love AKI, but I am tired of COVID-19-related AKI.

Mac Yes, it's AKI….

Nephron Why? This is obstruction…stop right there….

Mac (*laughing out loud*): Serum c-ANCA, p-ANCA, ANA, and complement C3 and C4 levels were within normal values. There was no serologic evidence of hepatitis B or C infection. SARS-CoV-2 PCR ×2 negative. No proteinuria.

Nephron (*angry*): Normal renal function...or some folks want "kidney function"...a few weeks ago and now such rapid AKI. Only three things come to mind: obstruction, obstruction, obstruction….

Mac (*surprised*): Shhh….Well, acute interstitial nephritis or severe acute tubular injury can also lead to rapid AKI…but yes, obstruction.… Let me tell you a bit more before you lose interest. We did a bedside sonogram, and no signs of distal or proximal obstruction. A radiologist also confirmed that.

Nephron (*bored, rolling his eyes*): Oh yes, the Hocus POCUS—seems like nephrology is doing all crazy things now.... I am sure the potassium is high, and sodium is low. You know we can still have obstruction despite your POCUS and official sonogram showing non-obstructive findings.

Mac Yes, potassium is 5.5 mg/dL, and sodium is at 134 mM. There is obviously some metabolic acidosis, and BUN is 80 mg/dL. Urinalysis showed 24 WBCs/hpf, 1264 RBCs/hpf, and muddy brown casts.

Nephron (*winking*): Did you spin it?

Mac No, he is not on dialysis.

Nephron (*laughing*): No, I meant spin the urine, not starting dialysis. I thought only surgeons called getting dialysis spinning.

Mac The urine sediment had muddy brown casts, no WBC casts, no RBC casts…but…

Nephron But what? You saw some crazy crystals?

Mac (*trying to remember*): None really.

Nephron (*jumps in*): And I assume you ruled out myeloma, NSAID use, PPI use…all that….

Mac (*surprised*): Obviously! I even have a biopsy finding….

Silence

Mac Hmm. Do you want to know it?

Nephron (*shocked*): Not used to such a drastic turn of events. Usually, L.O. Henle wouldn't tell me things after a kidney biopsy. He would wait for me to tell him. You have surprised me…. Interesting….

Mac (*jumps in*): The kidney biopsy showed tubular and interstitial damage with large calcium oxalate crystals in tubular lumens, epithelial cells, and interstitium. There is moderate interstitial fibrosis and tubular atrophy. IF and EM didn't add much to the diagnosis.

Nephron So why are you here? You have a diagnosis…oxalate nephropathy.

Mac (*sure*): Yes, but why? Why does this patient have oxalate nephropathy? We always make a diagnosis like this and forget to find out why.

Nephron Perfect! This is fascinating and often missed. Oxalate nephropathy can be as high as 4% in all kidney biopsies. Rarely studied, but most cases have nonspecific nephrosclerosis and diabetic nephropathy with the diagnosis as well. Causes, as you are aware, can be vast. Pathologists make the diagnosis, but many times as nephrologists, we are not thinking of oxalate nephropathy in our differential diagnosis.

Mac (*confused*): Well, he can't have primary hyperoxaluria. That is an autosomal recessive disease with more of a pediatric age group and too late for this presentation. That is due to overproduction of oxalate and oxalate precursor glyoxylate leading to systemwide deposition of calcium oxalate.

Nephron (*interrupting*): Excellent, but never say never! Rarely, primary hyperoxaluria can present in adulthood too. But more importantly, remember surgeries…. As internists, we often forget surgical interventions. Normally, calcium binds oxalate in the bowel to form insoluble calcium oxalate that is excreted in the feces. In a state of fat malabsorption, calcium is bound by free fatty acids and becomes unavailable for oxalate binding. There is then increased soluble oxalate available to be absorbed by the bowel. An intact colon appears likely important for oxalate absorption, and hyperoxaluria in enteric hyperoxaluria has generally not been observed in patients where the colon is not utilized such as in patients with ileostomies after colectomy. The risk of calcium oxalate precipitation is likely worsened by volume

depletion from diarrhea as well as bicarbonate loss, which can lead to metabolic acidosis and hypocitraturia. Both nephrolithiasis and oxalate nephropathy were frequent complications of one of the first surgical treatments for obesity—jejunoileal bypass. Even the more recent Roux-en-Y gastric bypass, which replaced jejunoileal bypass as the procedure of choice for malabsorptive bariatric surgery, has been recognized as a cause of oxalate nephropathy. Orlistat, a weight-loss agent that also causes fat malabsorption, has similarly been recognized to cause hyperoxaluria and oxalate nephropathy. For those onconephrologists out there, keep in mind, oxalate nephropathy after pancreatic exocrine insufficiency is described, and there are emerging data for risk after pancreatectomy for pancreas adenocarcinoma as well from single-center studies. Clearly, the pancreas has some role here but not clear data.

Mac Although our patient had not undergone such a surgery, he had undergone small bowel resection for intestinal obstruction many years ago. It can be speculated that his impaired fat absorption increased fat in the intestine, which decreased free Ca^{2+} due to binding of Ca^{2+} to the intestinal fat. This may have caused calcium oxalate to decrease and free oxalate to increase, which increased absorption of oxalate in blood, leading to deposition of oxalate in renal tissue. I also read that patients who get even cholecystectomy can cause aggravation of enteric malabsorption of fat, thereby causing the deposition of oxalate. To me, it seems like any history of a potential GI surgery should raise some red flags to us as nephrologists.

Nephron Good work, Mac! I think that we often ignore that "surgical history" component and think, "Why would that affect the kidney?" But as you know, all things affect the kidney…but can that abrupt rise be explained by his prior surgery?

Mac (*nodding*): No recent infections either. It has been suggested that antibiotic use, especially antibiotics that deplete intestinal *Oxalobacter formigenes*, which metabolizes oxalate, could lead to hyperoxaluria. Depletion of gut Oxalobacter was associated with increased urinary oxalate, especially in kidney stone-forming patients. He didn't have any history of kidney stones.

Nephron (*puzzled*): Who comes up with these names of organisms in infectious diseases? Between the new chemotherapy names and organism names, medicine has become challenging to pronounce these names…ugh! I can give an entire talk on that….

Mac So that is out. He has been very careful regarding SARS-CoV-2 and has received both his mRNA vaccine shots. Yes, we have heard of podocytopathies and ANCA disease from it. Now don't tell me you think his oxalate nephropathy is from the vaccine?

Nephron Hahaha…no way…but let's go ask him about a few other things he may be taking to prevent getting the virus. I have a hunch on what he might be taking.

Mac and Nephron exit to visit the patient at the bedside. They have a long conversation and return back to the office with an answer.

Nephron Mac! Bedside rounds are the best! Brilliant!

Mac (*confused*): Going back to the patient and getting more history of present illness are so key in several cases.

Nephron Fascinating information. Who takes such massive doses of vitamin C?

Mac People will do anything to prevent themselves from getting COVID-19…despite lack of evidence.

Nephron (*jumps in*): Oxalate nephropathy can be seen with excessive intake of high oxalate foods or mega doses of vitamin C, although some cases have been reported involving more moderate amounts, especially with chronic intake. *NEJM* even published a case called "Iced-Tea Nephropathy." Juicing of vegetables can also cause it. It has been speculated that juiced oxalate foods may be more effectively absorbed in the intestine via the paracellular pathway via solvent drag and because of dilution of calcium by water. Vitamin C is likely a more bioavailable source of oxalate than food. Oral intake of 2–7 g of vitamin C and obviously IV vitamin C, which was given during inpatient COVID-19 treatments, can lead to oxalate nephropathy. Our patient was taking 4 g of vitamin C daily for the last year to prevent infection from the virus. That coupled with the chronic resected small bowel likely caused the oxalate nephropathy.

Mac (*surprised*): I have heard that even star fruit, *Averrhoa bilimbi* (a fruit in parts of Southeast Asia), high intake of peanuts and cashews, rhubarb, and black iced tea can cause it. Interestingly, spinach and purslane have the highest oxalate (milligram) content per 100 g.

Nephron Fantastic! Those causes are mainly case reports and case series. I think surgeries are the bigger culprit coupled with ingestions in most cases of oxalate nephropathy.

Mac For your information, he told me something else. He said that in the last month, he has been worried about his health, and he started eating more purslane, as it is "full of antioxidants."

Nephron Well done, apprentice. Keep an open mind. Again, never assume. Make sure you have gone over all aspects of your differential diagnosis. A detailed history led to the cause of the oxalate nephropathy.

Mac (*with a wink*): For treatment, I assume stopping these agents will help. I assume agents like pyridoxine, vitamin C intake, and citrate intake may not help much here. Glad that drugs like lumasiran are approved for primary hyperoxaluria...but here, not so helpful. Hydration and stopping of agents likely will do it.

Nephron Yes. Treatments for secondary oxalate nephropathy are tough. Data are limited to basically nothing….

A few weeks later…

Mac (*with excitement*): With hydration and time, his serum creatinine is 1.8 mg/dL and stable. Not back to normal completely, but we can live with that. Too much of anything is not good for you—even your vitamins!

Nephron (*laughing*): Don't even get me started on that one…. Let's leave that for a discussion over my favorite New York-style coffee…. ■

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