Detective Nephron

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

Nephron

It’s been a while, Mac. What do you have for me?

Mac

I have a 68-year-old with a kidney transplant and now with chronic diarrhea.

Nephron

(excited) Whoa! Stop right there—that is a GI consult. I am sorry, but I am a nephrologist.

Mac

Trust me, you are going to love this one! You are like a king when it comes to figuring out non-nephrology stuff. Aren’t transplant nephrologists the kings and queens of all internists?

Nephron

Well, in that case, we may have to put on my transplant hat or call a friend over for some NY-style coffee. I think I shall invite my friend, Dr. Graft Guardian. He is just a phone call away;

Mac

Hmm…oh well. I can totally relate to that one.

Paused as Dr. Graft Guardian enters.

Guardian

Dear Nephron and Mac, please continue to discuss the case. The “Transplant Guru” has arrived.

Mac

This is a 68-year-old male with a history of deceased donor kidney transplant in 2008 for end stage kidney disease secondary to hypertension (or as some believe). He had a history of bilateral, native kidney nephrectomies for renal cell carcinoma and was on maintenance immunosuppression therapy with mycophenolate sodium 360 mg p.o. b.i.d. [by mouth, two times a day], tacrolimus 1 mg b.i.d. (with a goal level of 4–6 ng/mL), and prednisone 5 mg p.o. daily. His baseline creatinine was 1.7 mg/dL.

Nephron

Stop…nice! What an amazing topic. Nephrologists love and hate hypertension. Didn’t we have an editorial in the September issue of Kidney News on who should own hypertension?

Mac

(laughing out loud) Can we move on? The focus is diarrhea.

Guardian

(trying to remember) As part of the malignancy workup, an esophagogastroduodenoscopy was done, which was unremarkable except for peptic duodenitis. A stool PCR test for Shiga toxin 1 and 2, Cryptosporidium, Giardia, Cyclospora, Campylobacter, Verminia enterocolitica, adenosirus, and rotavirus was negative as well.

Nephron

Pre-renal AKI resolved. Great…done. We can sign off!

Mac

I am sorry, but I cannot sign off on a transplant patient’s case. This is my forte, regardless of what part of medicine it is. This is the best part of being a transplant nephrologist. I think we know more ID [infectious diseases] than ID docs, more heme-onc [hematology-oncology] than hematologists, and more immunology than immunologists.

Nephron

Talk about modesty! Hmm….

Guardian

(jumping in) I think what you have done is a very good workup.

Mac

Yes, it was. Stool cultures and ova and parasites (O+P) evaluations are important. Conventional stool cultures are also useful, especially in bacterial causes. The yield is low, with acute, watery diarrhea. With bloody stools, the laboratory should be requested to look for Shiga toxin-producing Escherichia coli. With seafood ingestion, the laboratory should be requested to look for Vibrio. A stool can be tested for Campylobacter, Cyclospora, and Cryptosporidia, and a stool may also be implicated in causing diarrhea, as solid organ transplant patients often receive many medications, such as other antibiotics. Other, less common causes of diarrhea in transplant recipients include post-transplant lymphoproliferative disorder (PTLD), inflammatory bowel disease, colon cancer, and bacterial overgrowth syndromes.

Nephron

(winking) Dr. Guardian, are we done with your medicine lecture yet?

Mac

(laughing) Let me tell you more to explain the situation. He was admitted to the hospital for supportive care, and an extensive workup for his symptoms was undertaken. Hydration resolved his AKI. Stool Cladirum difficile toxins A and B were negative. Stool culture was negative for growth of any routine enteric pathogens and Vibrio cholerae, and a qualitative fecal test to rule out malabsorption was negative. Serums cytomegalovirus (CMV) polymerase chain reaction (PCR), Epstein Barr virus PCR, and cryptoccocal antigen were negative. HIV and tuberculosis T-SPOT testing were negative as well. A cancer antigen 19-9 level was obtained, which was normal. His last colonoscopy done 6 months ago did not detect any concerning lesions. There were no masses on a chest x-ray and on ultrasound imaging, and his nephrectomy beds were negative for any recurrent or remnant disease. Echocardiography showed normal ejection fraction and no valvular vegetation. Now what?

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Detective Nephron: shocked. Let me guess, it’s SARS-CoV-2.

Nephron: No, no, it’s not COVID-19-induced this time around. Although, adding that to the title of any publication would probably lead to quicker acceptance of a paper on this case.

Guardian: Go on with the real stuff of the harder part of the case, and let’s leave SARS-CoV-2 out of this. In all seriousness, we lost many of our patients to the pandemic. Please respect the virus.

Silence

Mac: (decisively) Norovirus (NoV) PCR is positive on the stool PCR. The repeat value confirms this.

Guardian: Hmm…fascinating. NoV infections are the most common cause of acute gastroenteritis worldwide. In the transplant population, NoV infections can result in chronic diarrhea, which has long-standing after-effects on nutrition/hospitality of life, elevated tacrolimus levels, and resultant toxicity and graft dysfunction. Even though the first cases were reported in 2009, awareness about this infection and approaches to its management leave room for improvement.

NoV binds to antigens on enterocytes, causing edema and severe enterocyte injury resulting in diarrhea. Clinical manifestations of NoV/ sapovirus gastroenteritis in patients who are immunocompromised include non-bloody; watery diarrhea; nausea; vomiting; abdominal discomfort; bloating; weight loss; and wasting. Fever is unusual. It spreads mainly via the food-borne, fecal-oral routes but also through person-to-person contact or contaminated surfaces. Both T cell and B cell responses are required to clear NoV infection, and immunosuppressive therapy is a risk factor for prolonged infection. In kidney transplant recipients, because of iatrogenic immunosuppression, NoV symptoms can be prolonged and chronic, with periods of symptom exacerbation and remission. If not treated, kidney graft dysfunction can occur due to severe dehydration. The diarrhea can also disrupt the P-glycoprotein efflux pump, leading to supra-therapeutic tacrolimus levels, further worsening the AKI. Also, patients are at higher risk of rejection due to immunosuppression reduction that is done to allow the host immune response to eliminate the infection.

Nephron: (sighing off) Good point. A 2021 study by Gäckler et al. in Transplantation addressed the gaps in our understanding of the clinical characteristics of NoV infections post-kidney transplantation. The study enrolled 60 patients with kidney transplants diagnosed with NoV infection by a positive stool PCR test. It aimed to identify the characteristics of chronic NoV infections in kidney transplant recipients and their effect on allograft function. The study also evaluated the safety and efficacy of using intravenous immunoglobulin (IVIg) as a therapeutic measure in 18 patients with chronic diarrhea. NoV gastroenteritis occurred a median of 52 months after transplant, resulting in a cumulative median hospital length of stay of 8 days for patients admitted with acute gastroenteritis. Thirty-one of the 60 patients were found to have chronic infection. Compared with those with acute infection, patients with chronic infections stayed longer in the hospital (10 vs. 7 days), and they were hospitalized more frequently for their illness (17 patients vs. 1 patient). Multivariate analysis showed that both diabetes mellitus and the administration of lymphocyte-depleting induction therapy were independent prognostic factors for the development of chronic NoV infection among kidney transplant recipients.

Guardian: (jumping in) Nephron, you just stole those lines from the March Kidney News issue, in which it was highlighted as an important topic.

Mac: IVIg! Interesting… Why not hold MMF and start nitazoxanide?

Nephron: Do all of the above: start nitazoxanide therapy, give a few doses of IVIg, and hold MMF. I doubt he will reject his kidney these many years out with an elevated tacrolimus level.

Mac: You are so dramatic!

Guardian: (Laughing out loud) On a serious note, he may be correct. As I had mentioned, currently, there is no single, proven therapy to cure NoV in the kidney transplant population who are immunocompromised.

T reatment with medications such as nitazoxanide and Ig has proven effective in limited cases. Reducing immunosuppression for the patient’s immune system to clear the infection may lead to renal transplant rejection, so we must be careful.

Nephron: Mac! What are you going to do? The ball is in your court.

Mac: (confidently) We will hold MMF, give nitazoxanide, and eventually monitor for renal function and graft rejection. IVIg may have a role in the next few weeks if clinically there is no improvement, and symptoms don’t resolve.

Guardian: Sometimes, you must make tough decisions in transplant nephrology. No evidence is going to help guide you; it will be your clinical acumen.

Nephron: (jumping in) Yes, of course. Tell the team your plan.

Mac: A few days later

Mac: (surprised) Well, we did as we planned. He did clear his virus, and kidney function remained stable at 1.8 mg/dL. We did do a protocol renal biopsy, and no rejection was noted.

Nephron: Fantastic! I assume he stays off MMF?

Mac: For now.

Guardian: Preventive measures for NoV are important given the morbidity associated with the infection. Hand hygiene is of paramount importance.

Silence

Nephron: You sound like a joint commission surveyor.

Mac: (winking)

Nephron: (laughing) There you go again! Fascinating diagnosis and treatment, Mac, and special thanks to our transplant nephrologists in helping us with this tough case. I must say, transplant nephrologists are truly the best internists on the planet. Now, let’s have some NY-style coffee.

Dr. Graft Guardian takes a bow and winks. 

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