Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the master consultant.

Nephron What do you have for us today, my dear apprentice?

Henle I have a 67-year-old white man with a history of type 2 diabetes mellitus, with an elevated hemoglobin A1c (8.1%) and a history of moderate hypertension, who is now here with proteinuria.

Nephron Stop… why are you talking like a textbook today?

Henle Trust me; you are going to love this one!

Nephron It better be a case of some exotic chemotherapy causing thrombotic microangiopathy (TMA) and not diabetic nephropathy—although sodium-glucose cotransporter-2 (SGLT2) inhibitors have made diabetic nephropathy interesting as well. Nevertheless, go on!

Henle (*curious*): Hmm.... what is with everyone and TMA these days? Getting back to the case, he was in his usual state of health until a few months ago, when he noticed his blood pressure getting worse, requiring more than two medications for management.

Nephron What was his creatinine 6 months ago?

Henle It was 0.7 mg/dL 1 year ago and 1.3 mg/dL 6 months ago.... thank you for your interruption. Also, his urine albumin-to-creatinine ratio 3 months ago was 0.3 g/g.

Nephron (*angry*): And let me guess: now the creatinine is 1.6 mg/dL, and he has proteinuria of 5 g/24 h.

Henle (*surprised*): There you go again—you are stealing my thunder. Yes, and yes, but it is 6 g/24 h. You are off slightly. Only trace edema on examination. Cholesterol is stable, and serum albumin is slightly low at 3.4 g/dL.

Nephron Is there any hematuria?

Henle Yes, a bit, and some red blood cell casts as well. Hmm….

Nephron I am sure they did serologies before they called you.

Henle Better yet, I even got you a kidney biopsy!

Nephron (*startled*): Stop right there. Before we go any further, let me summarize this. You have a diabetic patient with worsening renal function and rising proteinuria. Wait... I can't say "renal" any more—kidney function.

Henle (*wondering to himself about quick decision by Nephron*): Yes; correct. By the way, no new medications, such as quinine, nonsteroidal anti-inflammatory drugs, hydralazine, or protein pump inhibitors. Just on the usual: glipizide, metformin, lisinopril, and amlodipine. Of course, no SGLT2 inhibitors.

Nephron Oh, oh, no! This is a good one. Glad you brought this case to me. I am assuming this is paraproteinemia related, since you think I am reading too much onconephrology these days.

Henle (*trying to remember*): Ha-ha… perhaps not. The kidney biopsy was done, and it showed….

Nephron (*jumping in*): TMA.

Henle (*with a smirk*): Hmmm. You are too much. Stop interrupting. The mesangial areas showed diffuse and focal nodular expansion by matrix material with segmental mesangiolysis and microaneurysm formation. A few glomeruli displayed variable ischemic changes. The arteries displayed moderate intimal fibrosis, and the arterioles showed prominent afferent and efferent hyalinization. Immunofluorescence was negative for significant glomerular immune complex deposition. Electron microscopy revealed glomerular basement membranes with global thickening. Segmentally, there was subendothelial widening with segmental glomerular basement membrane duplication and mesangial cell interposition. Focally, within these areas there was an accumulation of flocculent and electron-lucent debris with mild layering of new basement membrane material. Basically, the pathologic findings showed renal TMA in a background of diabetic nephropathy.

Nephron (*shocked*):This is impressive! What are you: a poetic renal pathologist? And thank you for reading the pathology report verbatim. You could have saved a lot of words and ink and said, "diabetic nephropathy with superimposed TMA." I trust you.

Henle (*jumping in*): As I mentioned earlier, no secondary cause—no cancer found, no rheumatologic disease. No paraproteinemia to explain the TMA finding. To my knowledge, diabetes should not do this. With the diagnosis of TMA, a review of peripheral blood smears and laboratory parameters was undertaken. Peripherally, there were no schistocytes, and the vitamin B12 level was 770 pg/mL. The von Willebrand factor-cleaving protease (ADAMTS13) was 110% of reference range activity, ruling out any ADAMTS13 deficiency and thrombotic thrombocytopenic purpura. No diarrhea was noted, which suggests that there was no typical hemolytic uremic syndrome, or evidence for the presence of Shiga toxin. The platelets remained in normal range despite the drop in hemoglobin over the course of the year.

Nephron Good work, apprentice, on your search for the cause of TMA. We often forget to do that. How do you categorize TMA?

Henle (*not sure*): Well, most of the world likes to call this stuff hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), or atypical HUS. I think the better way is to define it by the pathophysiology, such as ADAMTS13-mediated TMA, complement-mediated TMA, Shiga toxin–mediated TMA, drug-induced TMA, metabolism mediated (cobalamin deficiency), coagulation mediated, and finally secondary systemic diseases–associated TMA. Interestingly, there are two mechanisms of drug-induced TMA: immune mediated (quinine) and direct endothelial injury. Some of the chemotherapies and targeted therapies might fall into that category.

Nephron Perfect! Pathobiology-based discussion is always the best way to discuss anything, rather than names like TTP, HUS, and atypical HUS.

Henle But here I am confused. We checked for all potential causes in our patient. Complements were normal, but in complement-mediated TMA 60% of patients might have normal complements. The entire complement cascade workup was performed, but—you know—I will get the results in 2022.

Nephron (*interrupting*): Is there anything on his physical examination?

Henle Nothing specific except for some trace edema bilaterally in the lower extremities. His blood pressure was high at 150/90 mm Hg.

Nephron Use of tonic water? Because that might contain quinine, which leads to an immune-mediated TMA.

Henle Perhaps this patient has a complement cascade factor deficiency and a "second hit" occurred. But what is that second hit?

Nephron Any diabetic neuropathy or retinopathy?

Henle Yes, diabetic retinopathy. Big deal.…

Nephron Let's go to his bedside

Henle and Nephron exit.

Nephron Sir, we have a question for you. Do you get any specific injections for your diabetic eye disease?

Patient "Yes, Avastin."

Henle responds with shock.
A few hours later:

Henle He had experienced progressively blurry vision and was seen by an ophthalmologist, who prescribed intravitreal vascular endothelial growth factor (VEGF) inhibitor therapy a year ago. He was receiving intravitreal injections of bevacizumab (Avastin) (1.25 mg) in both eyes (2.5 mg injected total) every 2 months until he had a more severe episode of recurrent macular edema. This necessitated switching to monthly intervals. This was also deemed necessary because of the possible development of early central retinal vein occlusion, which could impair vision. According to this dosing schedule, the patient received bevacizumab at a total of 20 mg in both eyes to date.

Nephron Fascinating information. So, you think this intravitreal bevacizumab can cause renal-limited TMA? If so, you are going to give some retina specialists a heart attack.

Henle, puzzled, leaves the room. He returns a day later.

Nephron And?

Henle The US Food and Drug Administration never approved bevacizumab for intravitreal use but did approve aflibercept (Eylea) and ranibizumab (Lucentis) for intravitreal use. The label inserts asserted that the serum drug levels with intravitreal injections were 200-fold lower than the levels achieved by systemic administration, and thus VEGF inhibition would be minimal. So why do we get renal TMA?

Nephron (*jumping in*): New data have shown that intravitreal absorption could be significant (≥50% inhibitory concentration) and result in very significant inhibition of systemic VEGF for days to weeks after intravitreal injections. Ranibizumab may be considered as a lower-risk option for diabetic retinopathy in patients with proteinuria because of lower serum levels, shorter t½, and much less VEGF disruption.

Henle (*surprised*): There are now published cases that show worsening hypertension, proteinuria, and glomerular disease after intravitreal VEGF inhibition. Kidney biopsy findings range from renal-limited TMA, collapsing glomerulopathy, and FSGS. Most of these findings are in the background of diabetic nephropathy.

Nephron The pattern of injury is exactly what is expected with VEGF blockade systemically. Temporal clarity is important to make these associations. An important clinical lesson from these cases is that diabetes per se cannot be blamed for the abrupt rise in serum creatinine and rapid rise in proteinuria.

Henle Assumptions are bad in medicine. A systematic process is important for a differential diagnosis in every case, and asking about nontraditional medications is now more important in medicine than ever.

Nephron These are also useful teaching cases to dissect the causes of nondiabetic glomerular disease in diabetic patients. These cases are extremely challenging to diagnose, and it is useful to consider the role of intravitreal VEGF blockade in every diabetic patient. Retina specialists should consider measuring urine protein in addition to monitoring blood pressure to document the effect of VEGF depletion on the kidney. Would they do that? I assume that we will see more of this to come.

Henle The patient was instructed to talk with his retina specialist. But balance is important in medicine. Loss of vision is far more important to some patients than having to use dialysis. Continuing the agent was the final decision made by this patient. His serum creatinine is now 3.4 mg/dL.

Nephron Well done, apprentice. Keep an open mind; never assume. Make sure you have looked at all aspects of your differential diagnosis. Just because someone has a history of diabetes does not mean that the rising creatinine and proteinuria is from diabetic nephropathy. And it is cool that I got to discuss TMA. I think that it is a fascinating diagnosis.

Henle (*with a wink*): Do you think hypertension causes TMA or TMA causes hypertension?

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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