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https://reachmd.com/programs/cme/igg4-rd-case-conversations-the-peculiarities-of-kidney-involvement/24302/

Released: 06/05/2024
Valid until: 06/05/2025
Time needed to complete: 15 minutes

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IgG4-RD Case Conversations: The Peculiarities of Kidney Involvement

Dr. Quattrocchio:
Hello to everybody. I am Dr. Giacomo Quattrocchio. I am a Nephrologist, and I work in Turin, Italy at the San Giovanni Bosco Hospital, and it's really a great pleasure for me to be here with Lynn.

Dr. Cornell:
And I am Lynn Cornell. I'm a Renal Pathologist at Mayo Clinic and Professor of Laboratory Medicine and Pathology.

Here are our disclosures.

And today we have two IgG4-related disease case conversations related to the kidney.

Our first case is a 74-year-old man who had progressive chronic kidney disease for several years. The serum creatinine was 1.7 mg/dL. He had trace blood and no protein in the urine. The medical history was significant for abnormal liver enzyme tests, cholangitis, and biliary stasis, which was found 3 years previously. Also 3 years ago, he had some imaging studies done that showed abnormal kidneys with several areas of decreased signal activity in the cortex, and the radiologist at that time suggested possible infarcts in the kidney.

A kidney biopsy was done. And you can see here, in this example, there's diffuse interstitial inflammation. So throughout this whole sample, you see inflammation. Here is a glomerulus for reference. On higher magnification, you can see that the infiltrate is composed of plasma cells. You can see several here. Eosinophils, you can see these pink cells here, as well as mononuclear cells. On a trichrome stain, we can see that there's increased interstitial fibrosis, which shows this blue staining pattern in the interstitium. And on the silver stain, you can see residual damage tubules here that are atrophic as well as tubulitis, and that's when we see inflammatory cells within the tubules, in addition to the interstitial inflammatory cells. An IgG4 stain shows increased IgG4-positive plasma cells in the kidney.

On kidney biopsies, we also routinely do immunofluorescence on electron microscopy, if it's done for kidney dysfunction or proteinuria, if it's a medical kidney biopsy, as opposed to a tumor kidney biopsy. And in this case, immunofluorescence showed granular tubular basement membrane deposits. And you can see corresponding electron-dense immune deposits by electron microscopy.

So the diagnosis here is IgG4-related tubulointerstitial nephritis. So in addition to using the features on the kidney biopsy, we also correlated this with the patient's history, which was consistent with IgG4-related disease involving other organs.

Now, tubulointerstitial nephritis, in general, is a disease pattern in the kidney where we can see interstitial inflammation and tubulitis, and we can see varying degrees of interstitial edema or fibrosis, or both. And we divide these into – or put these cases along a spectrum of acute interstitial nephritis to chronic interstitial nephritis, which has either less fibrosis and more inflammation, or more fibrosis in chronic interstitial nephritis. And this, in general, can be due to any cause.

And if we look at the different categories of interstitial nephritis, we categorize these by the cause of that pattern of injury in the kidney. Most causes of interstitial nephritis are drugs, but autoimmune disease is another potential cause, as well as infection, hereditary, toxic, metabolic, mimics, and other types of interstitial nephritis. And today we're focused on a particular type of autoimmune interstitial nephritis, and this category includes IgG4-related interstitial nephritis.

So both our group and Mayo Clinic and Japanese groups have proposed diagnostic criteria of IgG4-related interstitial nephritis. And both of these diagnostic criteria use criteria from different categories. One is the histology or immunophenotype, and that includes a plasma cell rich interstitial nephritis, as we saw in this example. A second criterion is increased IgG4-positive plasma cells in the tissue. And another histologic or immunophenotypic feature is a presence of tubular basement membrane immune complex deposits, as we saw in this case. This was a helpful criterion to make this diagnosis, but not required for the diagnosis.

We also have proposed imaging serology and other organ involvement criteria, particular types of radiographic features, by the imaging criteria that have been described in IgG4-related disease in the kidney, serology includes elevated serum, IgG4, or total IgG level, and other organ involvement includes autoimmune pancreatitis, salivary gland involvement, and other types of IgG4-related disease organ involvement.

And importantly also, to make this diagnosis in the kidney, we need to exclude other potential causes of interstitial nephritis.

Dr. Quattrocchio:
Thanks, Lynn. So what are the laboratory and radiological investigations that the clinician has to do to investigate the renal involvement in IgG4-related disease, in particular, in tubulointerstitial nephritis? As you can see in this slide, at least we have to do for our patients, creatinine, electrolytes, liver and pancreatic enzymes, urinalysis, albumin, creatinine ratio, and protein creatinine ratio on the urine, serum protein electrophoresis, total immunoglobulins, IgG4 and Ig levels, particularly important are C3 and C4 levels, antinuclear antibody, rheumatoid factor, and ANCA. And we'll see later why is it also important to look for ANCA positivity.

And from a radiologic point of view, ultrasonography is warranted, but very useful and sometimes necessary are CT or MRI scan with contrast media, and to exclude or to look for other organ involvement, a PT/CT scan.

What is the laboratory presentations of patients with IgG4-related kidney disease? Well, patients can go towards nephrologists for an acute kidney disease. Or, as we have already just seen with Lynn, for a chronic kidney disease or rapidly progressive renal failure. From a urinary point of view, we can find proteinuria or hematuria, but, and this is very important, also minimal or no urinary abnormalities.

From a immunologic point of view, the majority of patients will show hypergammaglobulinemia, elevated IgG4 levels, as we have seen in the case of Lynn. Hypocomplementemia, C3 and/or C4, in nearly half the cases, elevated Ig levels, eosinophilia, antinuclear antibodies in 20-30% of cases, and rheumatoid factors in about 1/3 of patients.

Dr. Cornell:
So I just wanted to draw the attention to an important mimicker of IgG4-related disease, and that is mass-forming ANCA disease. And this can involve the kidney and can involve other organs. And you can see in this example, we can have fibrosis, plasma cell rich interstitial inflammation, increased IgG4-positive plasma cells, and also mass lesions in the kidney and other organs. So in that way, it's a great mimicker of IgG4-related disease, and it's really important to do ANCA studies, and specifically anti-MPO and anti-PR3, if you are considering a diagnosis of IgG4-related interstitial nephritis that has histologic and immunophenotypic and radiographic features that are suggestive of this diagnosis.

To help distinguish ANCA disease from IgG4-related kidney disease, there are particular histologic features, and these are interstitial carrier or necrosis, granulomatous inflammation we should essentially never see an IgG4-related kidney disease, increased neutrophils. If you see many neutrophils, think of ANCA. And if you see a necrotizing or crescentic glomerulonephritis, that also would favor ANCA disease. So lab testing for anti-MPO and anti-PR3 is needed if you suspect IgG4-related disease.

Dr. Quattrocchio:
So we have diagnosed that IgG4-related tubulointerstitial nephritis. And how we treat our patients? First-line treatment, as for other forms of IgG4-related disease, is based on steroids. In particular, prednisone 0.61 mg/kg per day for at least 2 to 4 weeks, followed by a gradual tapering, tapering in 2 to 4 weeks, and with the goal to discontinue completely steroids in a 2-4 month period. Steroids are usually very effective also in tubulointerstitial nephritis, and in inducing particularly responses in inflammatory stage. But very frequently, in about 2/3 of cases, we can see relapse in our patients. And as we all know, steroids are full of adverse effects.

In these cases, we can try to add DMARDs. This is modifying drugs like azathioprine or mycophenolate, that are effective in some cases. But really, really effective in our patients, the treatment with anti-CD20 cells have demonstrated in several reports. In particular, the schedule is based on rituximab 1 gram per 2, 2 weeks apart in the effusion.

And what is the follow up for our patients after induction therapy? Of course, all our patients must receive a regular follow-up with the following laboratory investigations. Every 6 to 12 months, we have to repeat creatinine, serum, potassium, urinalysis, albumin creatinine ratio, protein creatinine ratio, total immunoglobulins, IgG4, and Ig levels, and C3 and C4 levels, because if we see a decrease after normalization of C3 and C4 levels, we must suspect a relapse.

Dr. Cornell:
Case 2 that we'll discuss is a 56-year-old man. He initially presented with abdominal pain, distension, and ascites. He had some radiology studies performed, which showed diffuse pancreatic enlargement with a hypodense rim, peripancreatic fluid collection, and no biliary, renal, or aortic involvement.

So the CT scan showed pancreatic disease. The serum IgG4 was elevated, so the patient was diagnosed clinically with autoimmune pancreatitis, also known as IgG4-related pancreatitis.

The patient was treated with prednisone for 2 months. His symptoms improved, and he also had additional courses of prednisone, six additional courses that were 3 months long each.

Four years later, he was found to biliary involvement with narrowing of the portal vein, diffuse pancreatic enlargement which represented relapse of the IgG4-related pancreatitis, and mild retroperitoneal fibrosis on imaging studies. Also around this time, the patient had frothy urine, so he was referred to nephrology. The creatinine was 1.1 mg/dL, so not very elevated. He had 4 grams per day proteinuria, and a kidney biopsy was performed.

So if you look at this kidney biopsy from low magnification, it looks different from that first case we showed. There isn't any interstitial inflammation here, and you can see many glomeruli in the sample. Looking closer at the glomeruli on this PAS stain section, we are not seeing hypercellularity. And again, you can see absence of interstitial inflammation. On a silver stain section on higher magnification, you can see that the glomerular basement membranes are thickened, and it looks like there are deposits in these glomerular basement membranes which are pink. And on the trichrome stain section, we can see those deposits which are staining blue. So the histologic pattern of injury that we say this is, is a membranous glomerulonephritis.

We of, course, do immunofluorescence on our medical kidney biopsies, and we can see here there's global granular glomerular basement membrane staining for IgG, C3, kappa, and lambda. When we have a membranous pattern of injury, we do another stain for PLA2R, and that's an antigen in most cases of primary membranous nephropathy. In this case, it's negative. So we would be thinking of a secondary type of membranous nephropathy.

By electron microscopy, we also see these immune complex deposits in a subepithelial location along the glomerular basement membranes. Here, there's a tubuloreticular inclusion in an endothelial cell that can suggest autoimmune disease in some patients.

So the diagnosis here, given the history of IgG4-related disease involving other organs is IgG4-related membranous glomerulonephritis. And of interest, this case shows no concurrent IgG4-related tubulointerstitial nephritis.

So as I mentioned, membranous glomerulonephritis can be primary or secondary. It can be secondary to autoimmune disease, infections, medications, cancers, other conditions. And most of these cases of primary membranous glomerulonephritis are due to anti-PLA2R antibodies. And we can do staining in the kidney for PLA2R, or do a serum test.

Membranous glomerulonephritis is also the most common disease in Ig – most common glomerular disease in IgG4-related disease. And it's interesting because it's a different disease pattern of involvement; it's not the usual inflammatory involvement that we see in the kidney and interstitial nephritis or in other organs.

Overall, in IgG4-related kidney disease, about 95% of patients have IgG4-related tubulointerstitial nephritis, and about 15% of patients have IgG4-related membranous glomerulonephritis. And these patterns can overlap, so you can have both together on the same kidney biopsy.

We recently had a paper accepted on clinical pathologic features of IgG4-related kidney disease based on tissue samples that were seen at Mayo Clinic. This included 125 patients with IgG4-related kidney disease. Most of the patients were male, with the mean age of 65 years. The primary indication for biopsy in most cases was acute or chronic renal failure. Other patients had proteinuria or a mass lesion as a primary indication for the biopsy. Most of the patients had increased serum IgG or serum IgG4, and just over half had hypocomplementemia. And even though the mass – a mass lesion, wasn't necessarily the primary indication for biopsy, about half of the patients had abnormal radiographic features. And this is interesting, because the sample was mostly patients who underwent a kidney biopsy for medical purposes, not for a tumor.

Dr. Quattrocchio:
Thanks, Lynn. So what is the diagnostic workup in patients with membranous glomerulonephritis? It's a little bit different from tubulointerstitial nephritis, because first of all, we must exclude a primary form, and we must look for anti-phospholipase A2 receptor. Then, based on the age of our patients, we must look for cancer with, for example, looking for a fecal occult blood test, chest x-ray, abdominal ultrasonography, mammography in females. And we must exclude, as already Lynn has explained to us, infections, mostly

hepatitis B and hepatitis C viruses, and rheumatologic diseases such as lupus or connective tissue disease, and drug exposure, particularly nonsteroid antiinflammatory drugs.

What is the therapy? Well, even if we know that membranous glomerulonephritis is less responsive to steroids than tubulointerstitial nephritis, one course over 2 to 3 months with prednisone at the same dosage as for tubulointerstitial nephritis must be tried. If the proteinuria that is the examinations that we must strictly follow doesn't show any decrease within 2 to 3 months, we can add DMARDs. In particular, mycophenolate or cyclophosphamide or cyclosporin, effective in some cases, or even better, rituximab with the same schedule as for tubulointerstitial nephritis.

And here is the laboratory follow-up. Proteinuria in the dose for the 24 hours is mandatory to identify relapse or incomplete response, together with serum protein electrophoresis and total immunoglobulins, and also IgG4 and Ig levels, and C3 and C4 levels. Again, we have seen from Lynn that about 50% of patients with or without tubulointerstitial nephritis have decreased levels of C3 and C4.

Dr. Cornell:
So we have several take-home messages from these cases. First, IgG4-related kidney disease is not that rare. It can present without other organ involvement, so we need to keep it in mind. In our study, we found that about 20% of patients have kidney-alone involvement in IgG4-related disease. Renal biopsy is a safe and easy diagnostic tool. We need to make sure that the kidney biopsy diagnosis is correct. So consider IgG4-related disease and mimickers. The diagnosis of IgG4-related kidney disease may require additional clinical history and laboratory and radiographic evaluation. Sometimes the pathologist may just see an interstitial nephritis with many plasma cells, and then we need to ask the nephrologist to go back and ask the patient if there's any history of inflammatory conditions, and as well as doing these additional laboratory tests.

Dr. Quattrocchio:
Again, acute or progressive renal failure with or without proteinuria or radiologic lesions are red flags for us nephrologists. Treatment with the steroids and/or rituximab aimed at avoiding end-stage kidney failure is very effective. And our goal is this one, avoid end-stage kidney failure. And finally, regular follow-up is mandatory.

Dr. Cornell:
Thank you.

Dr. Quattrocchio:
Thank you to everybody. And thank you, Lynn.