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Unmasking IgAN: From Suspicion to Timely Diagnosis

Announcer:
Welcome to CME on ReachMD. This activity, titled “Unmasking IgAN: From Suspicion to Timely Diagnosis” is provided by Medtelligence.

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Dr. Latus:
Early diagnosis and renal biopsy are essential in the diagnosis of IgA nephropathy, and providers need to use a systemic approach, which includes histopathology. In addition, the mechanisms of action of some IgA nephropathy therapies may result in additional advantages that we need to be aware of.

Join us for an exploration of these important clinical topics using a patient case study.

This is CME on ReachMD and I'm Dr. Jörg Latus.

Dr. Cheung:
And I'm Dr. Chee Kay Cheung.

So we're talking about how to unmask the glomerular disease IgA nephropathy. We can only achieve an earlier diagnosis when we know what to look for. So, Jörg, I understand you have a patient case?

Dr. Latus:
Yes, I would like to start with a case presentation of a 40-year-old female whom she was diagnosed with an IgA nephropathy 10 years ago and, at the beginning, she has no symptoms. Later on, she presented to her primary physician with a high blood pressure, and later on a proteinuria and hematuria was detected, and a biopsy was done.

Focusing on the medical history of my patient, I believe she is, let's say, a typical patient, because many people or patients with an IgA nephropathy may not have any symptoms at first. Therefore, the early diagnosis of the disease of these patients is not that easy, and as the disease advances, symptoms usually start to appear.

It's very important that an IgA nephropathy can only be diagnosed with the kidney biopsies, and there is no validated diagnostic serum or urine biomarkers for IgA nephropathy.

Dr. Cheung:
What features would you say a pathologist and a clinician are looking out for on that biopsy?

Dr. Latus:
So in IgA nephropathy, the disease is characterized by specific histological features observed on the light microscopy, immunofluorescence, and electron microscopy.

And the key features include the mesangial hypercellularity, the endocapillary hypercellularity.

They look for segmental glomerulosclerosis and accretion formation within the biopsies.

And of course, in regard to the chronic changes, they look for tubular interstitial changes in the light microscopy.

Then of course, the immunofluorescence is the hallmark of IgA nephropathy diagnosis, and it's critical for confirming the diagnosis. And the key feature is IgA deposition predominantly in the mesangium, often with the complement C3 and sometimes with IgG and/or IgM. And it's, again, these 3 deposition reflects the complement activation commonly seen along with the IgA nephropathy and fibrin and other immune complexes; they can also be seen in more advanced stages of the disease.

And you get, later on, the electron microscopy helps to further characterize the deposits and structure changes, the electron-dense deposits found primarily in the mesangium. There's a mesangial proliferation and matrix expansion and podocyte changes, with the effacement of food processes may be observed, especially in more severe cases.

So the Oxford classification of IgA nephropathy includes 4 key histological parameters assessed by light microscopy, which are used to predict the prognosis. So it's MEST and the C.

So 5 years ago a second biopsy was done, and the biopsy showed a mesangial proliferative IgA nephropathy without intra- or extracapillary proliferates. **Using** the MEST score it was M1, E0, S1, T0, and C0.

So later on she had persistent proteinuria and microhematuria, and then she was treated with systemic steroids for 2 years. Later on, she was put on an ACE inhibitor and an SGLT2 inhibitor, and this was the way she presented to me in December last year, with a kidney function with an EGFR of 75 mL/min, and then proteinuria of 3 g/g creatinine.

Dr. Cheung:
And I think we really have to be on the lookout for these cases of suspected glomerular disease because we know that we're diagnosing most of our patients with IgA nephropathy and their GFR in the 40s to 50s, when there's already a significant amount of nephron loss. So the earlier we can make that diagnosis, I think, the better outcomes there can be by starting our treatments earlier to preserve as much kidney function as possible.

And we know that one of the strongest risk factors for long-term kidney outcomes is the degree of proteinuria.

So that's been shown in several registry studies, most recently the UK RaDaR Registry studies, which really demonstrated a very strong association with heavier degrees of proteinuria and increased risk of kidney failure. But interestingly, as you know, Jörg, in this study, even those with lower degrees of proteinuria, less than 1 g/day, and this is a group that was traditionally thought to be, actually, at low risk, we know that the outcomes of that group were still at significant risk of developing kidney failure within 10 years, with around 1 in 4 of that group developing the endpoint.

Now that we have the diagnosis from the pathologists, what are the next steps that should be followed?

Dr. Latus:
After we have the result of an IgA nephropathy, there is an algorithm published in the KDIGO guideline for the initial assessment and management of patients with IgA nephropathy. First of all, we need the diagnosis, and therefore, we need the kidney biopsies. And then you have to consider secondary causes like IgA vasculitis and IgA nephropathy secondary to viable, or let's say, inflammatory bowel diseases.

And if you excluded the secondary causes, you can make the diagnosis of an idiopathic IgA nephropathy, and then you need the MEST-C score. And then there is a risk stratification for the patient using clinical and histological data, and therefore you can quantify the progression risk at diagnosis using the International IGN Nephropathic Prediction Tool to inform and discuss with the patients the possible third-party options and make a shared decision-making.

So I think we have to keep up, and it's completely in line with the data you presented from the RaDaR Registry, that even in patients with a proteinuria lower than 1 g, they're at high risk to become a dialysis patient.

Dr. Chung:
Actually, the UK RaDaR Registry data also shows us that the outcomes are very poor with IgA nephropathy. So that median kidney survival in adults was only 11 years from diagnosis to kidney failure.

And there's actually been a more recent analysis of the UK RaDaR registry that compared the IgA nephropathy cohort with other cohorts of rare disease. So the IgA nephropathy cohort was compared against a cohort with ANCA-associated vasculitis, and both of these cohorts where patients' cohorts were enrolled with a similar median baseline eGFR. But what we saw was that actually in the IgA

cohort, the rates of progression to kidney failure were much quicker compared to the ANCA-associated vasculitis cohort. I think that really speaks to the lack of effective therapies at that time to slow the progression of kidney disease.

There's also some urgency as well, because the median window between baseline to hitting an eGFR below 30 in that IgA cohort was only 4 years from diagnosis to eGFR below 13. We know that once the eGFR reaches that stage, you're probably faced with advanced kidney disease, which is going to be much less likely to be responsive to therapies.

Dr. Latus:
And we talk about younger patients who stay on dialysis for several years, and we're not talking about patients with diabetic nephropathy with a high cardiovascular risk, so of course, we have to treat them in a very strict way.

Dr. Cheung:
We're diagnosing most patients with IgA nephropathy in their 30s and 40s. So you've got to think that these patients have another 40 years, on average, of life ahead of them. We really have to be protecting that kidney function over that lifetime. And there's data, again from the RaDaR study, that shows that we need to slow the rate of kidney disease progression to less than 1 mL/min/year. And I think to do that, we're going to need a number of therapies, effective therapies, and much more than what we've had available to us for so long in terms of just ACE inhibitors or angiotensin receptor blockers. We're going to need more effective therapies.

Dr. Latus:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jörg Latus, and here with me today is Dr. Chee Kay Cheung. We are reviewing the histopathological features of IgA nephropathy and how an earlier diagnosis may lead to better outcomes for patients.

So this patient case really highlights how to implement a systemic diagnostic approach when histopathological features on real biopsies have you suspecting IgA nephropathy.

So now, Chee Kay, what would you providers be thinking about in terms of therapies, and do some have advantages over others?

Dr. Cheung:
Thanks, Jörg. So I think as you mentioned before, the first line is to really think about the holistic picture and optimizing supportive care, thinking about good control of blood pressure, and addressing those lifestyle factors and cardiovascular risk factors. But as we've already discussed, long-term outcomes for IgA nephropathy are poor despite the therapies that we've had for a long time, and really they were very much restricted to treatments like ACE inhibitors or angiotensin receptor blockers, really highlighting the need for new therapies.

I think your earlier case really demonstrated, as well, a good point about corticosteroids, because although, perhaps, there could have been some early control in that patient, we know the effects of corticosteroids are not sustained so that when you stop steroids, after some time, the proteinuria can return back to baseline.

So I'm going to talk a little bit about sparsentan. So this is a novel dual-endothelin and angiotensin receptor antagonist. It works by blocking 2 receptors, so it has 2 mechanisms of action. One is the endothelium A receptor, and the other one is the angiotensin II type 1 receptor.

Signaling through these receptors is strongly upregulated in patients with IgA nephropathy. And we know that signaling for both of these works synergistically to drive a lot of the damaging effects we see in IgA nephropathy. So they work to drive vasoconstriction, increasing glomerular hyperfiltration, which can contribute to proteinuria. They also have specific effects on cells within the glomerulus, so those receptors on mesangial cells. So they drive mesangial cell proliferation, cytokine release, extracellular matrix production. Signaling through both these receptors also can cause podocyte injury, podocyte cell loss, and also have effects on the endothelial glycocalyx, damaging that glycocalyx, which can increase proteinuria as well. And then downstream signaling through both of these receptors can also drive tubular interstitial inflammation and fibrosis.

And we're now going to watch a video about its mechanism of action.

[MOA video plays.]

So you can see that signaling through the endothelium receptor and also the angiotensin type 2 receptor can drive a lot of damaging effects in IgA nephropathy. And sparsentan has been developed, really, to tackle both of these issues at the same time. So I think this is why this is a very interesting and exciting development for the treatment of IgA nephropathy.

And there's a number of other exciting therapies coming through as well. We have an alternative complement pathway inhibitor, iptacopan, which is a factor B inhibitor, which is in a phase 3 trial at the moment called the APPLAUSE trial. Interim results from that study showed a significant proteinuria reduction of 9 months compared to placebo, and we're waiting for results to come through for

eGFR data at the end of 2 years of that study.

We also have drugs that block the cytokines BAFF and APRIL. These are cytokines that drive IgA production from B cells and also galactose-deficient IgA, the pathogenic IgA that's deposited within the kidneys in IgA nephropathy, and inhibitors of these have been shown to effectively reduce galactose-deficient IgA, reduce proteinuria, and preserve kidney function. But these are a bit earlier in their development, these data from phase 2 studies, and they're being studied in phase 3 clinical trials at the moment. And hopefully we'll get some results from these compounds in the near future.

So atrasentan is another oral selective endothelin A receptor antagonist, so it blocks the endothelin A receptor only and doesn't have that dual component that blocks the angiotensin receptor blocker that sparsentan does. Atrasentan has, again, been studied in a phase 3 clinical trial. We saw data presented at the ERA Congress this year, showing that 9 months' treatment was able to significantly reduce proteinuria, and we're waiting for further results to come out from the ALIGN trial to show its effects on GFR. But again, really, this data from this trial is really emphasizing the potential for endothelin receptor blockade for the treatment of IgA nephropathy.

Dr. Latus:
As you mentioned, I think, we have to keep in mind that we have 2 different diseases. So we have to treat, first of all, the autoimmune disorder and the CKD.

And as you mentioned previously, the PROTECT study with sparsentan was an international, multicenter, randomized, double-blind, parallel-group, active-control, phase 3 trial. And I believe the active-control phase is very important because if we look at the study data, we should start by focusing on the decline of kidney function in the placebo group in the previously published trials.

So we have to keep this in mind when we talk about the results, and the results of the PROTECT trial, I think, very good results. The primary endpoint was met at the 36-week interim analysis with the between-group relative reduction in proteinuria of 41%, and the long-term clinical benefit of sparsentan was confirmed by eGFR chronic slope, which showed a statistically significant treatment effect compared with irbesartan, so I think very interesting and good results.

So we asked the question what kind of effects does sparsentan have in patients treated with a maximally tolerated RAAS inhibition and SGLT2? And what we saw was a 40% to 50% relative reduction of proteinuria in our patients, very rapid decrease in proteinuria, and we had a very good safety profile in regard to edema and blood pressure lowering.

So now the question is, should we start with sparsentan first in all of our patients, instead of ACE inhibitors?

Dr. Cheung:
I think sparsentan is a really good treatment option for our patients. And we've seen through the phase 3 PROTECT trial that treatment with sparsentan was superior compared to angiotensin receptor blockade alone. So I think it could be a very good foundational therapy for most of our patients with IgA nephropathy, as we've seen, due to its effectiveness. And I think that effectiveness also accrues over the long term as well. So sure, I can see sparsentan being a good foundational therapy for our patients with IgA nephropathy. And then, if patients still have persistent disease or relapsing disease despite that, maybe they'll need cyclical or other therapies on top of sparsentan.

Dr. Latus:
Yes, absolutely in line with you, because if you see the slope is less in the sparsentan group compared to the irbesartan group. So that means a lot of years later on dialysis for many patients. So yes, I'm absolutely in line with you. Could be in first-line treatment.

Dr. Cheung:
Before we sign off, Jörg, what's your one take-home message for our audience?

Dr. Latus:
IgA nephropathy can only be diagnosed with a kidney biopsy, and there are no validated diagnostic serum or urine biomarkers for IgA nephropathy. And nowadays, new third-party options are available for our patients, but you need a diagnosis and, therefore, you need the kidney biopsy.

Dr. Cheung:
I think my take-home message would be that the clinical trial data that really shows that sparsentan is a very good treatment option for patients with IgA nephropathy, especially those with proteinuria and progressive IgA nephropathy. I think it's a treatment that's suitable for most patients with IgA nephropathy, and that has now shown proven benefits against angiotensin receptor blockers alone. They're safe to use in the long term, and I think this could be a very good foundational therapy for our patients with IgA nephropathy.

Dr. Latus:

I want to thank our audience for listening and thank you, Dr. Chee Kay, for joining me and sharing your insights.

Dr. Cheung:
Thank you very much and goodbye.

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