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Unraveling IgA Nephropathy: Clinical Features and the Need for Early Diagnosis

ReachMD Announcer:

Welcome to ReachMD. This medical industry feature, titled “Unraveling IgA Nephropathy: Clinical Features and the Need for Early Diagnosis,” is sponsored by Otsuka. Your host is Dr. Jennifer Caudle.

Dr. Caudle:

This is ReachMD, and I'm your host Dr. Jennifer Caudle. And today, as part of our two-episode program focusing on IgA nephropathy, we're discussing disease progression and the urgency for early intervention.

And I'd like to welcome back Dr. Sayna Norouzi and Dr. Jared Hassler. Dr. Norouzi is an Assistant Professor of Medicine and the Director of the Glomerular Disease Clinic at Loma Linda University. Dr. Norouzi, welcome back to our program.

Dr. Norouzi:

Thank you for having me. I'm really excited for this conversation.

Dr. Caudle:

And Dr. Hassler is Associate Professor of Pathology and Laboratory Medicine at Temple University's Lewis Katz School of Medicine in Philadelphia. Dr. Hassler, thanks for joining us again today.

Dr. Hassler:

Thank you for having me back.

Dr. Caudle:

Of course. And now to start us off, Dr. Norouzi, can you describe the clinical presentation and burden of IgA nephropathy?

Dr. Norouzi:

Sure, of course. IgA nephropathy is the most common primary glomerulonephritis seen on renal biopsy globally, and the initial clinical presentation of the patients can be highly variable.¹⁻⁴ It's often diagnosed in people between 20 and 40 years of age, and sometimes incidentally during investigations for hypertension, asymptomatic hematuria, reduced kidney function with elevated creatinine, or proteinuria.⁵⁻⁸

This variability in clinical presentation is seen among different ages, ethnic and racial backgrounds, and biopsy practice patterns.^{9,10} Further complicating this is the fact that IgA nephropathy is often asymptomatic in its early stages. When symptoms do appear to the patient, hematuria is the most common.¹¹ Then, as the disease progresses, patients may experience life-affecting symptoms such as edema and fatigue, worsening kidney function leading to chronic kidney disease or CKD, and ultimately, end-stage kidney disease, which requires dialysis or kidney transplant.^{8,12-14}

One of the critical aspects of IgA nephropathy is its insidious onset as many patients are unaware of their condition until significant kidney damage has already occurred. In fact, a systematic review of 16 studies between 2010 and 2020 found that 29.1 percent of patients in the U.S. present with advanced CKD at stage four or five, which was found to be higher than other countries such as France, Spain, Poland, Norway, Italy, and Sweden.¹⁵ So the silent nature of the disease makes screening and monitoring crucial, especially in individuals with a family history of kidney disease or those presenting with unexplained hypertension or urinary changes, such as frothy urine or cola-colored urine.¹⁶

In addition to the importance of screening, the psychological burden on the patients also shouldn't be underestimated. The diagnosis of chronic disease like IgA nephropathy can lead to anxiety, depression, and a significant impact on the patient's quality of life.¹⁴ That's why managing IgA nephropathy is not just about addressing the physical symptoms, but also providing comprehensive support to help patients and their caregivers to cope with the emotional and psychological challenges of the disease.

Dr. Caudle:

Thank you so much for that detailed background, Dr. Norouzi. Turning to you now, Dr. Hassler, could you elaborate on the hematuria and proteinuria seen in IgA nephropathy?

Dr. Hassler:

Sure. Hematuria and proteinuria are common presentations of IgA nephropathy. Gross hematuria, for instance, is seen in up to 40 percent of patients, often presenting with what they describe as a "Coca-Cola"-colored urine due to red blood cells passing through the glomeruli and into the urine. This often occurs concurrently with an upper respiratory tract infection or even with a gastrointestinal infection. Bleeding in the urine can also occur without a trigger or it can also be provoked by intense exercise.^{6,12}

On the other hand, asymptomatic urinary abnormalities and microscopic hematuria, with or without proteinuria, they're often detected incidentally. And it's rare for proteinuria to occur without microscopic hematuria.¹²

Now in patients with more advanced disease, their presentation may also include chronic kidney disease with hypertension, heavy proteinuria, and even rapidly decreasing glomerular filtration rate.¹ The diagnosis of IgA nephropathy requires confirmation through renal biopsy, where I'm going to be able to see IgA immune complexes deposited within the glomerular mesangium.^{12,17}

And so the histological exam is actually critical for IgA nephropathy diagnosis. When I examine a biopsy under the microscope, I look for these characteristic deposits of IgA in the glomeruli. I also utilize the Oxford Classification system to help categorize the severity of renal injury. For instance, we assess the histopathology and then describe our findings as the MEST or MEST-C score using the Oxford Classification. This score is not only diagnostic and descriptive, but also predictive for the disease course.^{18,19}

And so to build our MEST-C score, we're going to start with 'M' for mesangial hypercellularity, or when we see more than four mesangial cells in any mesangial area of a glomerulus. So we mark this as an M0 score if this is present in 50 percent or less of glomeruli, or as an M1 if it's more than 50 percent.¹⁸

And then the 'E' stands for endocapillary hypercellularity. And that's when we observe an increased number of cells within the glomerular capillary lumen. So, a score of E0 means it's not present in any glomeruli, and E1 indicates that it is in at least one – possibly more.¹⁸

Next is 'S,' which indicates segmental glomerulosclerosis, meaning adhesion or sclerosis that doesn't affect the entire glomerulus. It's marked as an S0 if there's no presence of this and S1 if there is.¹⁸

The 'T' represents tubular atrophy and interstitial fibrosis, and that's measured by the percentage of the affected cortical area. So, T0 is 0 to 25 percent, T1 is going to range from 26 to 50 percent, and T2 is more than 50 percent affected.^{18,20}

And finally, 'C' stands for cellular or fibrocellular crescents, which are characterized by extracapillary cell proliferation. And here we'll categorize C0 for absence of crescents, C1 for affecting less than 25 percent of glomeruli, and C2 for 25 percent or more.¹⁸

And with the MEST or MEST-C score, combined with clinical, demographic, and treatment variables, we can risk stratify patients using the International IgAN Prediction Tool. This tool predicts the risk of experiencing either a 50 percent decline in eGFR or progression to kidney failure within up to 80 months from kidney biopsy. And these insights on prognosis can potentially guide disease management for the nephrologists and patients.¹⁹

Dr. Caudle:

And coming back to you now, Dr. Norouzi, what can you tell us about the progression of IgA nephropathy to end stage kidney disease?

Dr. Norouzi:

That's a really good question.

IgA nephropathy progression can be quite rapid. Over one-third of patients with IgA nephropathy have progressively worsened kidney dysfunction leading to end stage kidney disease within 10 to 20 years after diagnosis.¹² These patients also have an increased risk of mortality, up to 53 percent.²¹

Now, persistent proteinuria is a well-known indicator of progressive renal disease in patients with IgA nephropathy and serves as an early, sensitive, and widely recognized marker of progression.¹⁹ In fact, the 2023 RaDaR database study showed that elevated proteinuria over time is significantly associated with rapid loss of glomerular filtration rate and greater risk of progression to kidney failure or death in patients with IgA nephropathy.⁷ So monitoring for proteinuria is crucial in managing IgA nephropathy effectively.

Dr. Caudle:

And for those of you who are just tuning in, you're listening to ReachMD. I'm your host, Dr. Jennifer Caudle and today I'm speaking with Drs. Sayna Norouzi and Jared Hassler on disease progression in IgA nephropathy and the urgency to diagnose early.

And so, Dr. Hassler, given what Dr. Norouzi just told us about the progression of IgA nephropathy, how does this drive the urgency to treat patients?

Dr. Hassler:

So it's important to know that the burden of disease for patients with IgA nephropathy is high and it's going to worsen as the disease progresses.^{8,12,13} So, when I examine a biopsy and I calculate a MEST-C score like I talked about earlier, I'm describing the extent of the damage that's been happening in the glomerulus.^{18,19} The renal injury and the chronic inflammation ultimately result in a reduction in renal function, leading to end stage kidney disease and higher mortality.⁷ But the sooner we can intervene to prevent this damage, the more we can potentially delay disease progression.^{22,23}

And so the concept of "time is nephrons" is crucial. Early diagnosis and treatment are essential to help prevent irreversible nephron loss, which can lead to reducing proteinuria and hematuria, slowing or potentially halting progression of end stage kidney disease.^{22,23}

Early targeted treatment may also help reduce the complications associated with advanced kidney disease, such as blood pressure and other cardiovascular comorbidities, which are common in patients with chronic kidney disease.¹⁷ Additionally, early intervention may improve the patient's overall quality of life by reducing other symptoms like fatigue, edema, and anemia.²³

It's also important to consider the impact on healthcare resources. Advanced chronic kidney disease and end stage kidney disease require intensive management, including dialysis or kidney transplantation, which are costly and resource-intensive.¹⁵ But by treating IgA nephropathy early, we can potentially reduce the burden on healthcare systems and improve the efficiency of resource utilization.

Dr. Caudle:

Well, considering the importance of early intervention, Dr. Norouzi, what is the current landscape of treatment options for IgA nephropathy, and what are the unmet needs?

Dr. Norouzi:

I'm glad you asked because there's a significant unmet need for safe and effective treatment options for IgA nephropathy that can both improve symptoms and slow disease progression.^{7,24}

As per the 2021 KDIGO guidelines, first-line treatment involves optimized supportive care consisting of blood pressure management, addition of a maximally tolerated dose of an ACE inhibitor or ARB medications, lifestyle modification, and also cardiovascular risk assessment.¹⁷

For patients remaining at high risk for progression after three months of achieving recommended blood pressure, KDIGO recommends enrollment in a clinical trial, maximal supportive care, or corticosteroid treatment. And for patients with rapidly progressing glomerulonephritis, treatment with six months of cyclophosphamide and corticosteroids is recommended.¹⁷

I'd like to note that the new draft of KDIGO guidelines for IgA nephropathy have been released and we anticipate they'll be finalized in 2025. So there is a potential that new guidance for how to manage the disease may be different.²⁵

Now, despite receiving this standard-of-care of therapy, 78 percent of patients continue to have signs and symptoms of IgA nephropathy, including proteinuria and hematuria, with increased risk of end stage kidney disease. This is largely due to the fact that until a few years ago, most treatments were supportive in nature and didn't target the underlying pathophysiology of the disease.^{7,24} And so there's still a need for additional treatment options that target the IgA nephropathy pathogenic cascade and delay the onset of end stage kidney disease for our patients.^{26,27}

Unfortunately, for the past few decades, there have been no treatments specifically targeted for IgA nephropathy.^{7,24} But the future is bright with three new treatment options recently approved that are specifically indicated for IgA nephropathy, with more medications still in development—indicating the landscape is quickly evolving.²⁸ These recent developments contributed to the need for an updated

KDIGO guidelines as previously mentioned.²⁵

Additionally, key thought leaders in the field are discussing the need for additional targeted therapies, which is an exciting area of research that's providing hope towards more effective disease management strategies. For example, RAAS inhibitors and SGLT2 inhibitors address CKD, but targeted therapies aim to address the underlying pathophysiology or inflammatory process. So the future state of IgA nephropathy management may involve a combination of these strategies to better manage the disease and improve patient outcomes.^{26,27}

One of the emerging approaches that specifically targets the pathogenic four-hit cascade is discussed in our other program on this topic. But as a brief summary, inhibitors of A Proliferation-Inducing Ligand, or also known as APRIL, are being investigated for their potential to reduce the production of galactose-deficient IgA1 and subsequent immune complex formation. By intervening at the molecular level, these therapies could potentially halt the disease process.^{26,27}

Dr. Caudle:

Well thank you both for such an informative discussion today on IgA nephropathy. And as we come to a close, I'd like to thank my guests, Drs. Sayna Norouzi and Jared Hassler, for joining me to discuss the disease progression, urgency to treat, and future landscape of targeted treatments for IgA nephropathy. Dr. Norouzi, Dr. Hassler, it was great speaking with you both today!

Dr. Hassler:

Thanks for having us.

Dr. Norouzi:

Of course. Thanks so much for having me.

Dr. Caudle:

For ReachMD, I'm your host, Dr. Jennifer Caudle. This was the second episode of this two-part program focusing on IgA nephropathy, but if you'd like to learn about its pathophysiology and the four-hit cascade, please check out the first episode. Thank you for joining us!

ReachMD Announcer:

This medical industry feature was sponsored by Otsuka. If you missed any part of this discussion or to find others in this series, visit *Industry Features* on ReachMD.com, where you can Be Part of the Knowledge.

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