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The Hidden Danger of IgAN: Pathogenesis and Unmet Needs

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**Dr. Barratt:**
This is CE with GLC, and I'm Dr. Jonathan Barratt. We begin today by talking about the pathogenesis of IgA nephropathy.

IgA nephropathy is an immune complex-mediated glomerular disease. Anyone who's been to a kidney biopsy meeting will have seen those IgA immune complexes light up by immunofluorescence in a kidney biopsy. We can see them on electron microscopy, and we know that the presence of those immune complexes within the glomerular mesangium and capillary loops drives an inflammatory and scarring process within glomeruli that ultimately leads to loss of kidney function. We think these immune complexes form because there's an excess of mucosal-derived IgA in the circulation.

The genetic studies that have been undertaken on global populations have consistently shown that the predominant pathways impacted by genetic risk alleles in IgA nephropathy affect the mucosal production of IgA, particularly within the gastrointestinal tract, and it's believed there is a subtle mucosal immune system dysregulation that results in an excess of mucosal-type IgA that enters the circulation.

This IgA is prone to self-aggregating. It's prone to bind to other proteins in the circulation, and there are anti-glycan antibodies that are likely developed against general microbial pathogens that can cross-react with this mucosal-type IgA, amplifying these immune complexes.

This disease is a chronic disease. These immune complexes have likely been in the circulation for a very long time before they cause appreciable loss of kidney function. The first thing that happens when we have the immune complex deposition is low-grade glomerular inflammation, which results in damage to the glomerular basement membrane, with the leakage of red blood cells into the urine, giving invisible hematuria and the beginnings of proteinuria with low-grade albuminuria and then overt proteinuria. These effects are largely asymptomatic, which means patients can often accrue significant glomerular damage before they come to the attention of a clinician.

Often, patients present late. Patients present with the consequences of significant nephron loss, that being hypertension or an impaired serum creatinine. Occasionally, we do pick up patients who, for some reason, have had their urine dipsticked, and they're found to have blood and protein in the urine at that earlier stage of disease before there's significant nephron loss. And rarely, certainly in adult practice, do we see episodes of visible hematuria in the setting of mucosal immune system activation. This is much more common in pediatric practice and particularly in teenagers.


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So the challenge, even though we do understand so much better the pathogenesis of this disease, is that in many of its phases it is a silent disease, such that when patients finally present to us, they often have had the disease for many, many years. They've accrued significant glomerular injury and a loss of kidney function, and we are playing catch-up from the very beginning in terms of trying to manage this disease and the consequences of this disease in terms of glomerular and kidney damage.

What you will see when you look at the KDIGO update that was published in 2025, in the recent commentary is that the nephrology community are trying really hard to promote early diagnosis, not just of IgA nephropathy, but other rare kidney diseases that present late. So we are trying to promote discussions with primary and secondary care colleagues to increase awareness of glomerular disease, increase awareness of minor abnormalities in serum creatinine, early development of high blood pressure, modest changes in urinalysis in terms of blood and protein, because we want to diagnose this disease early. We want to diagnose this disease when those immune complexes are driving a response that we can reverse because once those glomeruli have developed fixed scarring, once the tubular interstitium is scarred, we cannot reverse that. We have to deal with the consequences of persistent chronic kidney damage.

And so the wonderful new therapies we're seeing are targeting many different aspects of that pathogenic cascade I just talked to you about. And they're offering us real hope of being able to manage both the immunological aspects of this disease, but as we've seen with other forms of chronic kidney disease, manage those generic downstream consequences of nephron loss that we use in all forms of CKD.

So we're making great progress. Our priority needs to be to intervene early and to diagnose this disease as quickly as we possibly can.

So that's all for today. Thank you for listening.

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