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Diagnosing IgA Nephropathy: The Role of Immunofluorescence and Immunohistochemistry

**Announcer:**
You're listening to *On the Frontlines of IgA Nephropathy* on ReachMD. And now, here's your host, Dr. Gates Colbert.

**Dr. Colbert:**
Welcome to *On the Frontlines of IgA Nephropathy* on ReachMD. I'm Dr. Gates Colbert, and joining me to discuss the diagnostic pathology of IgA nephropathy, or IgAN for short, is Dr. Agnes Fogo. Dr. Fogo is a renal pathologist as well as a Professor of Pathology, Microbiology, and Immunology at Vanderbilt University School of Medicine in Nashville, Tennessee. Dr. Fogo, thanks for being here today.

**Dr. Fogo:**
It's my pleasure. Thank you.

**Dr. Colbert:**
To start us off, Dr. Fogo, what are the most critical biopsy findings that indicate a patient has IgA nephropathy?

**Dr. Fogo:**
This is dependent upon immunofluorescence examination or, in some places, immunohistochemistry to show that there are IgA deposits. It's a very logically named disease. And to meet criteria for IgA nephropathy, we need to have IgA staining—that typically is in the mesangium but may extend to the capillary loops—that is IgA dominant or codominant compared to the other immunoglobulins. There are other things that can cause IgA staining. For instance, in lupus nephritis or (IgA)-dominant infection-associated glomerulonephritis, that could be in the differential, and we would include light microscopic, electron microscopic, and clinical findings to distinguish. But the simple answer is we've got to have IgA to make a diagnosis of IgA nephropathy.

**Dr. Colbert:**
And can you explain how IgA deposits in renal biopsies are differentiated from other glomerular diseases?

**Dr. Fogo:**
Yes. I alluded already to the differential diagnosis in lupus nephritis. Typically, IgG is dominant or could be codominant, but in contrast to IgA nephropathy, we have what we call a full-house pattern of staining with all three immunoglobulins—IgG, IgA and IgM—and both C3 and C1q complement, and very often reticular aggregates also called tubuloreticular arrays, a sign of high interferon levels seen by EM in the endothelial cells. This would, in addition to the clinical history, indicate that the IgA is part of a lupus nephritis. With (IgA)-dominant infection-associated glomerulonephritis, we will, in the acute phase, have an exudative appearance, meaning numerous PMNs within the glomerular tuft along with the deposits and very strong C3 and hump-type deposits by EM. In more chronic cases, the distinction may be more subtle as we have fewer humps and fewer PMNs, and then we would rely on very strong C3 or askew with kappa more than lambda rather than the lambda dominance that we see in IgA nephropathy and, of course, as always, clinical correlation to suggest that the IgA process may be infection-related rather than the usual IgA nephropathy. The other differential is IgA vasculitis, which we used to call Henoch-Schonlein purpura, and this cannot be uniquely demonstrated to be that diagnosis by renal biopsy. We need the clinical correlation as the findings morphologically overlap completely between IgA vasculitis and IgA nephropathy.

**Dr. Colbert:**
And as a quick follow-up to that, what are the challenges in differentiating IgA nephropathy from other diseases like lupus nephritis?

**Dr. Fogo:**
As I just indicated, in lupus nephritis, there is full-house staining. We have reticular aggregates, also called tubuloreticular arrays, by electron microscopy, and we will typically have IgG be dominant or sometimes codominant. The key findings then would be the C1q staining, which we don't see in IgA nephropathy; the reticular aggregates; and having deposits in all compartments. In IgA nephropathy, it is very unusual to have subepithelial deposits, whereas in lupus, you would have mesangial, subendothelial, and potentially subepithelial deposits depending upon the class of lupus that we are dealing with.

**Dr. Colbert:**
For those just tuning in, you're listening to *On the Frontlines of IgA Nephropathy* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Agnes Fogo about the diagnostic pathology of IgA nephropathy.

Continuing our discussion, Dr. Fogo, how does mesangial hypercellularity affect disease progression in IgAN?

**Dr. Fogo:**
This was a surprise in the initial Oxford IgA nephropathy group, which I was part of, named Oxford because we had many of our meetings at Oxford University in the UK. We looked at lesions in a cohort of about 250 or so patients, adult and children. If you had diagnosis of IgA nephropathy, we had long-term follow-up, and we scored things that could reliably be scored and looked to see if they, independent of the clinical course, correlated with outcome. To our surprise, mesangial hypercellularity, which we scored at different levels, at a level of only greater than 4 mesangial nuclei in the most cellular mesangial part of the glomerulus away from the vascular pole, was correlated with worse GFR loss than if there were no such mesangial hypercellularity lesions. When this lesion was present in more than half of the glomeruli, there was a GFR loss of 2.2 ml per minute normalized per square meter per year, compared to 0.7 if there was no hypercellularity, so this was a surprise. Whether or not this can be influenced by many of the new therapies that are evolving has not been tested prospectively. Many of the clinical trials have biopsies that are remote in time from the initiation of therapy, so we don't yet have controlled data to know whether this morphologic marker of activity is changed by therapy and then changes the outcome, but it does associate with worse outcome independent of other features and of clinical parameters in the patients.

**Dr. Colbert:**
And how has the Oxford classification improved IgA nephropathy diagnosis and prognosis?

**Dr. Fogo:**
The Oxford IgA nephropathy doesn't have anything to do with making a diagnosis, but in cases that meet the diagnostic criteria that we talked about, it gives additional morphologic features in this archival cohort with all varying treatment associated with different outcomes. The features that initially were found to be associated with worse outcomes independent of clinical parameters were the mesangial hypercellularity we just discussed, and even just one glomerulus with endocapillary hypercellularity also suggested with worse loss of GFR over time, segmental stenosis or adhesion even in just one glomerulus, and significant tubulointerstitial fibrosis greater than 25 percent. Surprisingly, in that first cohort, we didn't find that crescents were associated with worse outcome, but we could show that patients with crescents more often were treated with immunosuppression.

In the second big study led by Mark Haas, published in *JASN* 2017, over 3,000 patients were studied who had IgA nephropathy, and there we included a broader range of patients. A third of these had some crescents. And in that study, we could find that if you had crescents greater than a quarter of the glomeruli involved, there was a worse outcome. If you had less than a quarter of glomeruli involved with cellular or fibrocellular crescents, there was a worse outcome if the patients did not have immunosuppression, but if they were treated with immunosuppression, we do not see a worse outcome. So again, we do not have prospective controlled trial data for all of these, but in these archival large- and medium-sized biopsy studies, we have found that these morphologic markers give some indication of injury that is associated archivally with varied treatments with worse outcomes.

**Dr. Colbert:**
Thank you for that. And before we close, Dr. Fogo, do you have any final thoughts to leave with our audience today?

**Dr. Fogo:**
IgA nephropathy has evolved so much in terms of our recognition of its long-term consequences. Eons ago, when I was a medical student, in my very old *Robbins Pathology* textbook, it said that Berger's disease was a disease of no significance long-term because there wasn't long enough follow-up. And now we recognize that this is the most common glomerular disease in kidney biopsies in the world, and we recognize that there are different ways that this can be treated and attacked as we begin to understand more about pathogenesis, about abnormal IgA1 hinge region glycosylation, about a possible role for various perturbances, including complement, and there are so many trials going on to look for better ways to treat the IgA nephropathy patients. And I think the pathology helps not only with diagnosis but to stratify those patients who may have the greater risk and may be be able to have personalized treatment for

them. This is what I hope that we can accomplish in the next few years.

**Dr. Colbert:**
Yes, I totally agree. And with those takeaways in mind, I want to thank my guest, Dr. Anges Fogo, for joining me to discuss the diagnostic pathology of IgA nephropathy. Dr. Fogo, it was great having you on our program.

**Dr. Fogo:**
It was my pleasure and honor. Thank you very much.

**Announcer:**
You've been listening to *On the Frontlines of IgA Nephropathy* on ReachMD. To access this and other episodes in our series, visit *On the Frontlines of IgA Nephropathy* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!