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Challenging Cases in IgA Nephropathy and Identifying Patients for Specialized Care

ReachMD Announcer:
You're listening to ReachMD. This medical industry feature titled *Challenging Cases in IgA Nephropathy and Identifying Patients for Specialized Care* is sponsored by Otsuka. And now, here's Dr. Jaimini Patel and Dr. Sayna Norouzi.

Dr. Patel:
Hello NephU Community, and welcome to today's webinar on complex IgA nephropathy cases. My name is Dr. Jaimini Patel, and I'm currently a nephrology medical science liaison, and I'm moderating today's discussion.

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Before we begin, I'd like to review some rules of engagement. The information provided today is for informational purposes only and is not intended as medical advice or a medium for diagnosis. Those seeking medical advice should consult their healthcare providers. Our experts aim to provide viewers with non-promotional, accurate, and scientifically rigorous information that is not misleading. Finally, no CME credits will be provided.

It is my pleasure to introduce our expert for today's presentation, Dr. Sayna Norouzi. Dr. Norouzi is an Associate Professor of Medicine and a clinical nephrologist at Loma Linda University Medical Center. She completed her fellowship at Baylor College of Medicine in Houston, Texas, and is the founder and director of the Glomerular Diseases Clinics at Loma Linda. She is also the co-director of the online GlomCon glomerular diseases fellowship program. Dr. Norouzi has been selected as the Educator of the Year for three consecutive years and is a member of Alpha Omega Alpha Medical Honor Society. She has a special interest in glomerular diseases and is involved in multiple research projects and clinical trials.

Thank you so much, Dr. Norouzi, for being here today. We really appreciate your time and are excited to hear from you and learn about IgA nephropathy.

Dr. Norouzi:
Thank you, Jaimini, for the kind introduction. I'm really excited to be here and talk about IgA nephropathy, given that all the therapeutic options out there, clinical trials on IgA nephropathy, and how our uh understanding of IgA nephropathy is evolving. We're going to introduce IgA nephropathy through a review of its epidemiology and underlying pathogenesis, including APRIL and the 4-hit process. Then we're going to define what constitutes a complex IgA nephropathy case, including refractory proteinuria, declining eGFR, overlapping syndromes, or atypical pathology. We're going to review clinical markers and diagnostic findings that may suggest the need for multidisciplinary or specialty clinic referral. And then at the end, we're going to present some complex cases and discuss diagnostic considerations, including repeat biopsies or secondary IgA nephropathy features.

And uh you know, we're not able to end this discussion without uh talking about the specialty care at this point, and we're going to emphasize the value of our specialized uh care centers, including IgAN clinics and centers of excellence, in managing high-risk patients and basically helping our patients to have access to emerging diagnostics and clinical trials and new therapeutic options.

So uh IgA nephropathy is a heterogeneous disease with variable clinical presentation. And I think that this is something really important as nephrologists to be actually comfortable with seeing patients with different phenotypes, and that's something that I actually deal with every day in the clinic. Every patient comes in with different lab findings, different clinical presentations, and different needs in terms of their treatment options.

We usually diagnose IgA nephropathy in adults age 20 to 40 years and often it's an incidental finding. So it's really important to actually think about it for a moment, that you are dealing with patients that are really young at this point. They don't have a lot of symptoms, and just someone tells them that I see something on your urine that I shouldn't see, and I want you to actually follow up with a kidney doctor. They actually frequently experience disease progression despite being asymptomatic.

So again, it's a lot of responsibility on us as nephrologists to talk to our patients about the possible complications that can happen in the future, despite being asymptomatic at the time. So it's a really tricky situation, because patients are going to tell you that 'I feel fine, I don't have any symptoms.' And then you have to actually discuss the data, what we know about IgA nephropathy so far, and the risk of progression and ending up on dialysis or transplant in the near future.

And you're going to see IgA nephropathy in different ethnic and racial backgrounds, particularly like, you know, like, basically when you are dealing with different disease severity, you're going to see it in different ethnic and racial backgrounds, and that's something that you should keep yourself updated about that and uh making sure that you are, again, ready to see different phenotypes of IgA nephropathy in the clinic.

And again, you're going to see different biopsy findings on the IgA nephropathy as well, that we're going to talk about; the biopsy findings and how to interpret these results uh when you're talking to your patients uh about their biopsy findings, and how you're categorizing their IgA nephropathy in terms of the risk of progression and in terms of uh risk of ending up on dialysis or transplant in the future.

We do have um a graph here that you see about the clinical characteristics of patients with IgA nephropathy at the time of diagnosis. As you see, a lot of patients are going to show up with protein in the urine, hematuria, which is blood in the urine, edema, fatigue, pain. It could be some flank pain that they have, and then a lot of uh possible CKD symptoms such as, you know, um they might have lost their appetite, nausea. Uh Sometimes they say, like uh um even like vomiting, muscle ache. And then they can have, like, migraines and headaches as well.

Hematuria and proteinuria are common presentations of IgA nephropathy. You can actually have patients that they come in and say that 'I actually see blood in my urine,' and that macroscopic or visible hematuria, and it can be present in up to 40 to 70% of patients. It can actually happen at the time that they are dealing with a respiratory tract infection or a GI infection. So you have to be ready about hearing that your patients might tell you that 'I was just dealing with cold-like symptoms, some cough, some sore throat,' and—or 'I was dealing with diarrhea recently.' And this bleeding may also occur without a trigger. They might tell you that 'I don't remember being sick recently. I just have protein in my urine. I was told that I have blood in my urine, and I don't remember dealing with anything recently.' And that's okay as well, and it doesn't have to be linked to a recent infection for sure.

And then the proteinuria can be present in about 75% of patients. It's a well-known early and sensitive indicator of the disease progression in the setting of IgA nephropathy. It's an accepted endpoint in clinical trials per our guidelines, and that's one of the biomarkers that we follow up in the clinic for our patients, for uh prognosis of the disease and also how our patients are responding to the treatment as well.

It's rare for proteinuria to happen without microscopic hematuria, but we—for sure—we see these patients in the clinic as well. So if you see only proteinuria, that does not rule out uh IgA nephropathy.

Dr. Patel:
So Dr. Norouzi, with the majority of patients presenting with some degree of proteinuria with or without hematuria, I imagine it can be easy to fall into a pattern of managing patients to reduce those symptoms with the therapies that we have available to us. But what exactly is the disease pathogenesis that leads to the proteinuria and hematuria? And how can we begin to address the root cause of the disease?

Dr. Norouzi:
Of course, that's a really good question. And of course, we're going to urine protein to creatinine ratio is one of the major endpoints that we actually look into that uh in the clinical trials. And also that's an endpoint when we are actually uh putting our patients on new treatment options. We always want to see that, if they are responding or not, and proteinuria is one of them.

We're actually going to uh talk about the disease pathogenesis in a minute, and we're going to basically go into the details and see that how IgA nephropathy actually happens in our patients. And that's, um I think it's really important for both uh nephrologists and patients to understand how IgA nephropathy happens. And the more you understand about the pathogenesis of the disease, uh you're going to be more comfortable about using the medications, prescribing the medications, and following up the patients, because if you feel like the medication makes sense from the pathogenesis standpoint, then you feel like, okay, I'm just going to give time. I'm going to um trust

the clinical trial data, and I'm going to follow up the endpoints that we have on biomarkers that we have and see my patient—if my patients is going to respond.

From the patient side, uh they're going to feel more comfortable as well. The more you explain the pathogenesis of the disease to them and how the medication works, they feel more confident in the uh therapy option that they're choosing, and they're going to be more patient. They're going to be more compliant.

So that's one of my favorite parts. Every time that I see a patient, I just go over the pathogenesis with them in a really simple language to make sure that they understand, like, what we are treating, what we are targeting, and how the medication works.

So this is um a really famous hypothesis that we've been hearing about uh IgA nephropathy. So um we do have data about the 4-hit process as well. So um now we are able to actually measure galactose-deficient IgA1, and that's really important, and that's really helping us to understand the 4-hit process much better than before.

So the way that we are thinking about the pathogenesis of IgA nephropathy is that um it's basically a cascade of immune process coming together to induce kidney injury. How does it happen?

So in hit 1, we know that something happens to our immune system. For example, like in a stressful event, you maybe you're dealing with an infection. So your body is producing a lot of –uh a lot of IgA's, IgG's, like sounding like you're fighting something uh stressful that could be an infection. And uh meanwhile, as you're producing IgA, you—for some reason, your body is going to produce uh galactose-deficient IgA1. This uh type of IgA, as we say, is deficient in galactose. So our body doesn't recognize galactose-deficient IgA1 and is trying to remove that from our body. So we're going to produce anti-galactose-deficient IgA1 autoantibodies.

So these autoantibodies are trying to remove galactose-deficient IgA1. They're going to form immune complexes. And these immune complexes, they're going to deposit in our gloms in our kidneys. And by deposition of these immune complexes on the kidneys, we're going to see more inflammatory process on the kidneys, and which going to cause um fibrotic tissue, which can cause injury over time, and that's the reason that our kidney function drops over time.

So um it's not that simple. So as we talk about the 4-hit process and say that, okay, there is this galactose-deficient IgA1, then you have autoantibodies, immune complexes. But of course, our immune system is much more complex, and there are going to be more factors actually affecting 4-hit process.

And one of them is A proliferation-inducing ligand, or APRIL, in IgA nephropathy, which is a really interesting compound. And the more you understand about this, uh it makes it more interesting to actually look into the pathogenesis of IgA nephropathy.

So basically, APRIL plays a key role in the pathogenic cascade of IgA nephropathy. How it works is that it's an important initiating and sustaining factor in IgA nephropathy progression. You basically see a factor that we are introducing here that is going to basically promote the production of pathogenic galactose-deficient IgA1 and immune complexes. So it's really interesting that you basically realize that it's not as easy as you think that galactose-deficient IgA1 is being produced, but how you are producing galactose-deficient IgA1 and what factors are affecting uh production of galactose-deficient IgA1 is really interesting and could be a target for the treatment of IgA nephropathy as well.

We actually know that the serum APRIL levels are higher in patients with IgA nephropathy uh patients. And the higher APRIL levels that you have, it's going to be associated with higher levels of galactose-deficient IgA1 and also more rapid progression to kidney failure.

So again, science is really interesting, and you realize that there are more into the cascade of IgA nephropathy pathogenesis, and there is a molecule that actually you can measure, and it is actually associated with rapid progression of kidney failure in the setting of IgA nephropathy. So um that makes it more interesting, and that makes it um like a good start to think about, do we have more therapeutic options for patients for IgA nephropathy, and should we look into it and see that uh maybe by suppressing APRIL we can decrease the chances of um kidney disease progression for our patients with IgA nephropathy.

So I want to give you more details on how APRIL works and why APRIL is actually associated with the levels of galactose-deficient IgA1. So APRIL basically is known that has, like, a really important role in development of B cells and antibody class switching. How does that work, is that, um so again, we are dealing with an antigen in our body in the uh beginning of the disease processes. So basically, you are dealing with an infection, a stressful event, something, and you basically have your body has this antigen encounter.

So once you have this antigen encounter, your antigen-presenting cells, or APCs, they're going to actually come and capture the antigen because they want to remove that from your body. So these APCs, they're going to become activated. And when we say APCs, what are these APCs? These are dendritic cells. It could be macrophages that they are trying to come and swallow the antigen because they want to remove that from your body. We don't recognize the antigen, and your body and your immune system is trying to remove that

and resolve the issue for you.

So once these APCs are becoming activated, they're going to release something that is called APRIL. APRIL is going to promote cell survival, and it's going to prevent the apoptosis of immature B cells. We all know that our immat—uh our B cells are actually uh playing a really important role in our immunity. So these B cells are becoming active because they are hearing that there is an antigen that they have to fight out with uh—with the antigens. So APC is already trying to capture the antigens, and they are trying to present that to our immune system. They're going to produce something that is called APRIL. And APRIL is going to help the immature B cells to become mature naive B cells. So basically, APRIL is pushing our immature B cells to become mature B cells.

Once you have the B cell activation, APRIL is not done at this point. It's going to basically enhance survival. It's going to enhance proliferation and differentiation of these activated B cells. So not only APRIL is pushing our immature B cells to become mature naive B cells, it's not going to—like APRIL not going to let go of the B cells at this point; it's going to push these B cells to actually differentiate, to prolifer—uh to have the proliferation and become even more active.

So once we have the differentiation of the B cells, APRIL is actually going to push these B cells to induce—uh it's going to induce antibody class switching in activated B cells. So basically, it's going to help us to maintain the plasma cell survival and sustain antibody production, so um not letting go. So APRIL continues to stay active. And now we have activated B cells, APRIL is going to push these activated B cells to actually produce antibodies, and it's actually going to help you to sustain the antibody production as well.

And this is something that, in the setting of IgA nephropathy, we don't want to see that happening, right? Because your body—by mistake, like your body, is super activated. Your immune system is super activated for no good reason at this point, and your plasma cells at this point, they are producing the galactose-deficient IgA1. So sending this signal to the activated B cells that we want you to remain active and produce more galactose-deficient IgA1 is exactly what we don't want to see in the setting of IgA nephropathy.

And um again, this APRIL molecule that uh starts to um act, um gets produced from the APCs, and remains active throughout the B cell maturation and throughout the B cell activation and differentiation is something that is showing us a lot of activity in the setting of IgA pathogenesis.

So let's look at the KDIGO guidelines and see that, what are the considerations for the diagnosis of IgA nephropathy. We know that um a lot of these patients with IgA nephropathy, historically, they were labeled as IgA nephropathy because they had hematuria and proteinuria. But actually, KDIGO guidelines are telling us this is not the way that you diagnose IgA nephropathy; you really need to have a kidney biopsy.

So that's the gold standard, and you really need to do the biopsy on these patients. And that's something that, as nephrologists, we really, if you're not adopted, if we haven't adopted this kind of practice, we really need to adopt it at this point, because we do have therapeutic options for our patients with IgA nephropathy, and we need to establish a good diagnosis. We need to make sure that what we are dealing with. And that's going—that's only going to happen with a kidney biopsy.

IgA nephropathy is basically, uh when you do the biopsy, you're going to see uh on the immunofluorescence, you're going to see that IgA is deposited on the kidneys, and this is the way that you're going to diagnose IgA nephropathy.

But it's not only about the diagnosis. The biopsy is going to give us some features that is called MEST-C score, and it's going to help us to guide about how aggressive is the disease. So MEST-C score is verified um to help us to basically um decide about the prognosis of IgA nephropathy. It's not verified at this point to help us to decide what treatment options we're going to choose, but it's going to help us to have a better understanding of what kind of IgA nephropathy we are dealing with.

And uh MEST-C scores basically stand for M is mesangial hypercellularity. E is endocapillary hypercellularity. S stands for segmental sclerosis. And T stands for tubular atrophy or interstitial fibrosis. And then C is crescents.

So basically, assessment of IgA nephropathy uh requires a kidney biopsy. We want to see IgA-dominant staining in glomeruli by immunohis—histology or immunofluorescence, that we see that, and assessment for secondary causes of IgA nephropathy as well, because we know that uh sometimes you can see IgA staining on the biopsy, and it could be secondary to um maybe a recent infection. It could be secondary to um some patients with uh cirrhosis and—and liver issues. They can have IgA staining as well. So you really want to rule out secondary causes before you actually approach to a patient with primary IgA nephropathy.

Currently, there are no validated uh diagnostic serum or urine biomarkers, uh and that's really unfortunate, and that's the reason that we are relying a lot on the kidney biopsies to diagnose IgA nephropathy. However, there is um—there are some ongoing research on novel biomarkers, and uh hopefully we're going to have some validated biomarkers in the future that's going to help us to diagnose and also follow up—uh for the follow-up on the patients with IgA nephropathy. Because once you start the treatment for your patients, you really um basically rely on even a repeat kidney biopsy or urine protein to creatinine ratio, eGFR. So having additional biomarkers—serum or

urine biomarkers—that's going to be really helpful, and it's going to be really mean—meaningful as well, to see if the patient is responding to the treatment options that you choose.

So uh our understanding of IgA nephropathy is evolving really fast. So one of the major studies that actually gave us a lot of information about uh the IgA nephropathy prognosis in the future is a really huge study that is called the RaDaR study. This is a registry of patients from UK, and um it actually gave us some information about the prognostication of IgA nephropathy in the setting of different levels of um urine protein to creatinine ratio.

Um this study overall, it actually shows us that most patients with IgA nephropathy, they develop end-stage kidney disease within 10 to 15 years of diagnosis. And that's huge because, as we said, most of our patients are being diagnosed in their 20s, 30s, 40s. So ending up on dialysis in 10 to 15 years, that's a big deal for our patients, because they are still young at that time. So no one wants to deal with complications of dialysis or even thinking about kidney transplant in their 40s, 50s, 60s, like they are still young at that time. And uh that's something that I usually discuss uh with my patients. I have a printed version of the RaDaR study in my clinic, and a lot of times I show this graph to my patients, and I tell them that I know that you feel fine at this point. And our goal of like treatment at this time, the reason that we are starting treatment for you at this time, is just that we want to prevent complications for you. And complications in 10 to 15 years might be too far for you at this time. But at the time that they're being diagnosed, imagine diagnosing someone age of 25. In 15 years, they're still super young. And tell them that in your 40s, you really don't want to deal with dialysis or transplant. And that's the reason that it's really important to get on the treatment and uh control the disease as much as possible.

So um we traditionally, and based on the previous guidelines, there was a lot of attention on patients with IgA nephropathy who had proteinuria more than 1 gram. With the RaDaR study, we actually see that about 30% of patients that have proteinuria between 0.5 to 1 gram per day, they actually are at high risk for ending up on dialysis as well. And 20% of those that they had less than 0.5 gram per day, they are at risk of ending up on dialysis as well. So again, this is a huge number in medicine. So imagine if I tell you that there is 1 to 2% of ending up on dialysis, uh you're going to freak out. And I'm talking about 20%, 30%.

So that's a huge number in uh medicine, and that's something that shows us that uh we really have to be more careful about uh when to start treatment for our patients, being more um basically uh trying to save time for our patients by diagnosing them as early as possible. So when you see patients and you feel like this is probably a patient with IgA nephropathy, considering the amount of proteinuria, hematuria, how they are acting, um it's really recommended to consider the kidney biopsy as soon as possible to diagnose these patients in a timely manner.

And then once you diagnose these patients, and once you calculate the risk of ending up on dialysis for them, if they are considered high-risk patients, then consider certain treatment as soon as possible as well, so we can prevent complications for them.

I really hope at some point, when we go to dialysis units to see our patients, we don't see these young patients. And it always breaks my heart to see the younger patients, and then you ask them, like, what happened? And they've been diagnosed with IgA nephropathy. And I know in the past we didn't have good treatment options for them, but now it has changed. Time has changed, and we do have treatment options for these patients. So it's up to us as nephrologists to basically diagnose early and um basically discuss uh treatment options for our patients as soon as possible once you diagnose them.

So this is the MEST-C score. And uh MEST-C score again, uh because of IgA nephropathy being a hot topic, is getting a lot of attention as well these days. As we said, uh when you do a biopsy in the setting of IgA nephropathy, it's not just about diagnosing the patient; it's going to give you some information about the uh prognosis of your patient as well.

So uh the way that your pathologist is going to report the MEST-C score is based on how much of the activity they see on the biopsy. We are talking about when you're talking about M, you're talking about mesangial hypercellularity. So basically, when it's M0, it means that less than or equal to 50% of the gloms are basically involved.

When you're talking about E0, basically they don't see any endocapillary hypercellularity. So if you see only one of like you know—uh one of the gloms is basically involved, that's going to be E1. So any presence is going to be giving you a score of 1 on endocapillary hypercellularity.

And then uh segmental sclerosis, any presence is going to be S1 for you. So when the patient comes back with S1, it means that your pathologist saw even like segmental sclerosis in one of the gloms and is reporting maybe 1 or maybe more. So that's one of the limitations of the MEST-C score. But any presence is going to get S1.

And uh T1 score is when you're about 25% to 50% of your gloms is involved, and that stands for tubular atrophy or interstitial fibrosis. And we all know as nephrologists, that's not good news, and uh you really want to see less fibrotic tissue at the time that you diagnose your patients. That shows that you have more viable tissue to basically save for your patients.

And crescents is always bad news for us, and it shows that the disease is super active at the time. And C1 basically is less than 25% of the gloms, and C2 is more than or equal to 25% of the gloms.

So basically, um these findings on the biopsy can serve as a valuable early prognostic tool. Again, it's not going to help us to decide what kind of treatment option you're going to choose for your patient, but it's going to help you to understand if you're dealing with an aggressive form of IgA nephropathy or not. And um this is something that you basically can discuss with your patients when you're discussing the biopsy findings.

But uh you're going to be surprised that you're—uh most of my patients, they really love to hear about their biopsy findings in details. And they usually ask really interesting questions from me. They really want to know uh the chronicity of the disease. They ask questions about how active it is, and it helps them to understand their disease state much better. And it helps them to feel like they are part of uh this process of deciding about treatment options, and um I think that's really important. The more you tell your patients, they feel more empowered to uh advocate for themselves, and they feel like they are part of the decision-making at this point. And that's the reason that I feel like it's really important to spend a lot of time with our patients with IgA nephropathy at this point.

Dr. Patel:
Dr. Norouzi, thank you so much for sharing that wonderful background on IgA nephropathy and really illuminating the urgency in managing and diagnosing this disease, frankly, early on, so we can really help our patients kind of mitigate that kidney damage that occurs as the disease progresses.

I imagine in your practice, you see a variety of patients with IgA nephropathy who present on a spectrum of disease severity. Would you care to share with us some cases of patients presenting with a complex and challenging IgA nephropathy picture, and kind of walk us through your thought process when designing a therapeutic regimen for them?

Dr. Norouzi:
Sure. Of course. I love a good case-based discussion, and our clinic is really busy with a lot of GN patients, especially IgA nephropathy, for some reason. So um that has given me a lot of experience um seeing these patients and uh dealing with different phenotypes of IgA nephropathy, which is um really interesting, and it gives you a really good perspective of, like, not every patient is just going to be the same. And um patients are going to need different treatment options. They might not respond to specific treatments, and you might need to change the course.

Um so uh we're going to dive into case 1. This is a 36-year-old female patient. Uh she has biopsy-proven IgA nephropathy, and her blood pressure has been almost controlled, 135/79. Her current medications are SGLT-2 inhibitors, ACE inhibitor. She is actually getting an uh aldosterone receptor antagonist as well. She doesn't want to have kids. She's not interested in getting pregnant, and she was referred to the GN clinic for a second opinion.

At the time that I saw the patient, her urine protein to creatinine ratio was 2.5 grams per day, and um her eGFR was around 30 to 33 for the past uh 3 to 4 months.

So let's look at the biopsy images that we have uh from the um initial biopsy that she had for diagnosis of IgA nephropathy. So as you see, she has some fibrotic tissue. She has some—um you see that a lot of cells here, that you see some proliferation here as well. So obviously not a normal biopsy. So it raises suspicious about something is going on. It's—uh could be IgA nephropathy at this point, but we know that she's had—she's been dealing with some chronic—like it's chronic, because you see some chronic changes on the biopsy as well.

Here you see some uh FSGS, and you see some um basically E1 here, maybe it's endocapillary hyperproliferation. And this is like you see a lot of cells here, and you see some mesangial proliferation as well.

Um IgA is super positive on immunofluorescence here, so our pathologist read it as 3 to 4+ uh IgA here. So it's super positive for IgA nephropathy, and this is um one of the major ways of diagnosing IgA nephropathy from the kidney biopsies.

This is the electron microscopy. And as you see, you have uh mesangial deposits uh on the gloms as well here, which is uh usually something that you see in the setting of IgA nephropathy.

So basically, this uh biopsy was read as M1, E1, S1, T1, C0 by our pathologist, and that gave me a lot of information about what kind of IgA nephropathy I'm dealing with. Uh I went over the biopsy findings with my patient in detail, as she wanted to know uh what's showing and uh what are the risks of ending up on dialysis or transplant for her. This is a patient that we are starting with lower eGFR. Her eGFR was fluctuating between 30 to 33. She had more than 2 grams of proteinuria at the time that she came to my clinic. So uh in my opinion, she is considered high risk. And if you actually calculate the risk of um uh ending up on dialysis, like the prognosis of IgA nephropathy

with the calculator, she's going to actually get considered as a high-risk patient as well.

So at this point, um we do have a couple of options for treatment of IgA nephropathy. Per KDIGO guidelines, 2025 guidelines, uh basically guidelines are recommending us and suggesting to basically uh target the CKD care and the pathophysiology of IgA nephropathy at the same time. In order to do CKD care, we consider ACE inhibitors or ARB, SGLT-2 inhibitors, and now we do have newly FDA-approved medications, dual endothelin inhibitors as well, that you can consider instead of ACE and ARB, or sometimes you can add it on to ACE and ARB if you're talking about endothelin inhibitors.

So um on the other side, for the pathogenesis of the disease, then you can think about how you're going to tackle the uh decreasing the production of galactose-deficient IgA1, or basically uh managing the disease processes um going after the 4-hit process, right? So basically, either you want to decrease the production of galactose-deficient IgA1, or you want to decrease the inflammation on the site, on the gloms, on hit 4 as well.

And we do have a couple of uh options. One of them is targeted uh steroid. Uh we do have complement inhibitors, and now we do have the option of anti-APRIL as well, uh which makes me really happy to uh have multiple options for my patients in having—uh considering combination therapy for my patients that are really high risk as well.

Uh this patient is considered high risk, obviously, with the amount of proteinuria, with the decreased eGFR at this time, with the active disease on the kidney biopsy, and we already see some fibrotic tissue on her biopsy as well, which is not surprising, because we see her eGFR is already has dropped to 30 to 33, so it's fluctuating. She's already on the lower side, and she's really young. She's in her 30s, and um dialysis or transplant is basically the last thing that she wants to deal with.

A lot of times, you might feel like, okay, um eGFR had already dropped, then, uh you know, uh patient is going to end up on dialysis anyways. But it's really important for the patients when they are dealing with the complications, are you dealing with dialysis and transplant in your 30s, 40s, or 50s? And that's going to be a huge change in their lifestyle, their life goals. A lot of them are trying to have, like, family plannings, like, you know, uh getting married, uh choosing a job at this point. So uh going up on dialysis or transplant, that's going to be a huge change, and it's going to impact their lives. So um again, at this point, it's going to be basically a discussion with the patient, and you're going to come up with a treatment option in a shared decision model.

I want to add on that there is still, like, we do have ongoing clinical trials as well, so I always discuss that uh with my patients as well. There are some patients that would like to try clinical trials in the beginning, and then if it doesn't work out, or if they feel like they can just, like, they can change their mind, basically, as part of the clinical trial as well. So um that's another option that patients have. Uh but again, with having the FDA-approved medications, um that's something that I usually discuss all the options with the patients um really clearly. We spend a lot of time, and then we come up with the decision.

Uh these medications require compliance, meaning that patients need to take them every day or every week. It's going to be uh anti-APRIL as an injection. So it requires um collaboration between the physician and the patient. So that's the reason that you really need to make these decisions with the patients, to make sure that they actually follow through, they actually take the medication. Otherwise, it's not going to work out.

So uh we're going to discuss another case. Um this is a 47-year-old Hispanic male. He had biopsy-proven IgA nephropathy 7 years ago, had a history of CKD stage 3b uh 5 years ago, and now is progressing to stage 4. Hypertension that's longstanding, but is well controlled with ACE inhibitor, and he's been uh on the maximally tolerated dose for the past 5 years. When he came to the clinic, his eGFR was 29, his uPCR was 1.1, and his creatinine was 2.8.

So he came to the GN clinic with one question, 'How can you just keep my kidney function as it is as long as possible? I understand that uh I'm at risk of ending up on dialysis. I know that I've lost a huge portion of my kidney function.' His amazing community nephrologist already educated him about his disease state. He knew that his IgA nephropathy had progressed. Uh he knew that his eGFR is lower than usual that we see in clinical trials. But he came in with one hope, that what can I do at this point uh to preserve my kidney function, just for a little bit while longer, 'because I do have young kids at this point. I don't want to go on disability. I don't want to go on dialysis. I'm not mentally ready for even thinking about uh transplant.'

This is his uh kidney biopsy, and um we do have—I love the arrows on this one, that they can actually clearly see the mesangial hypercellularity in the biopsy here. So basically, obviously, this patient is M1. We do not see any endocapillary hypercellularity, so he got E0. He doesn't have any active crescents, and that was C0. It was a really good biopsy. We had 40 gloms, and he had 20 to 25% interstitial fibrosis, which is not surprising to me with the degree of kidney disease that he has; 25% of fibrotic tissue at this point uh is not surprising at all. So basically, his um kidney biopsy was reported as M1, E0, and um he had some fibrotic tissue so S1, and uh T0, and C0.

This is some segmental sclerosis that you see. This is S1. And these are the IgA deposits in the mesangium that, as you see is clearly positive, and again, it's diagnostic in the setting of uh IgA nephropathy. Uh this is electron microscopy, and you see some mesangial deposits, as usual in the setting of IgA nephropathy, GBMs are normal, and then you see some partial foot process effacement as well.

So basically, as we said, his biopsy was reported as M1, E0, S1, T0, C0. And um there was, like, uh it was reported that there is no features of lupus nephritis. For some reason on the biopsy, we weren't thinking about lupus nephritis for this guy; he was um really typical the way that he presented as um IgA nephropathy. Um he had some mild arterial nephrosclerosis as well. He had longstanding hypertension and um yeah, so uh basically, he didn't have—there is no mass-forming lesion or on renal imaging. He didn't have any other concerns for any other findings. Eventually, he got diagnosed with primary IgA nephropathy, and uh that's the reason that he was actually referred to our clinic.

And again, this is the electron microscopy and the mesangial deposits.

So uh let's see what we did for our patients. So um of course, for any patients with IgA nephropathy, when he came to our clinic, he was already on ACE inhibitor for a long time for his blood pressure, and his blood pressure was well controlled. We started him on SGLT-2 inhibitor as well, because that's one of part of the CKD care in the setting of IgA nephropathy, and then we discussed options for him. So at this time, again, we had the option of um targeted steroids. Uh we had the option of uh basically complement inhibitors. And uh at the same time you do for the CKD care, you can consider dual endothelin inhibitors as well.

Uh this patient in particular, uh after we discussed options, and especially that I saw this patient a while back about a year ago, so we didn't have the option of anti-APRIL at that time. We did have ongoing clinical trials, but he didn't qualify for the clinical trials based on his eGFR at the time. Um after discussing all the options, he decided to choose um targeted-release steroids. And uh he continued the medication for, as you see, for more than 9 months, and it helped him to control his um proteinuria at the time.

So the question comes out, like if you see this patient today, um uh considering that you have other options you have anti-APRIL, would you consider that for your patients? And do you think that if that can help the patient? In my opinion, that could be a potential option for the patient. And I would definitely discuss that with my patients and um tell them that, you know, I know the data is kind of limited on the lower eGFR. But um you know, in real life, uh patients do not care that they're 29 or 31 because, you know, the clinical trials are enrolling eGFR more than 30 or 35.

And we do have a lot of variation. The reason that I'm including the data on eGFR here is that eGFR in real life has a lot of variation as well. A lot of times it depends on um the diet, like how much hydration they had, if they had a recent sickness or something. So you do see a lot of variation in the eGFR as you're following these patients. So um he wanted to try a treatment, and at this point, and when—if he comes to my clinic um at this point uh with the initial like a consult, I would discuss different options with him, and I would offer him anti-APRIL as well. And I'll make him like, you know, ask him to see like which one is going to suit his life better, his lifestyle, his goals, and uh which ones appears to be easier for him to adopt, because eventually I want him to be compliant with his regimen, whatever he chooses. And uh I want him to come back for the follow-ups and have a close follow-up with me to make sure that he's responding or not responding. Because, you know, patients might not respond at some point uh and you might need to switch treatments for them as well. So, and um that's something that is helping us to evolve our understanding of IgA nephropathy at this point as well.

Dr. Patel:
Dr. Norouzi, thank you so much for sharing those wonderful cases. They were truly, certainly eye-opening, and give us a real glimpse into how challenging these patients can really be to manage, and not only considering the new therapeutic options we have, but what really suits their lifestyle, and including the patient, kind of in that decision-making for their own care.

Um you know, because IgA nephropathy is—it's not only a rare disease, it's incredibly heterogeneous in presentation, as you mentioned, and with the approval of several new medications, all from a variety of drug classes, I imagine for the clinician it's becoming increasingly imperative that per—patients receive very specialized care. Can you share your thoughts on the value of specialty GN clinics and when patients should be referred?

Dr. Norouzi:
Of course. Um this is a really good question. Honestly, in my own experience, every time that we get a new approval for a new medication for IgA nephropathy or any GN uh disease, uh my referrals actually doubles, because um it's getting, like, really complex to decide about patients. And as nephrologists, um if you feel like, uh you know, I'm not sure if I'm offering all the options out there to my patients, you kind of feel ethically obligated to get, like, a second opinion. And you see that um a lot now. Like, with um sitting in the GN clinic, I get a lot of second opinions, because it's really hard to navigate treatment options for IgA nephropathy.

I know that KDIGO guidelines is giving us, like, a framework, but eventually, like, at the end of the day, patients are going to present

with different phenotypes. They're going to have different needs, and uh with having so many new medications out there, it's going to be really hard to navigate the best treatment options for the patients.

So um I think the role of uh GN clinics and centers of excellence from now on is going to be really prominent. It's going to be really important to give that uh peace of mind to both—like, to physicians, to nephrologists, and patients—that they are on the correct treatment, and they know about all the options as well. Because it's not just about the therapeutic options. You do have clinic—uh many, many clinical trials right now as well. Uh you can get enrolled into GN registry studies as well. There are so many other clinical uh research opportunities that actually can actually support your patients throughout the treatment as well.

So uh by seeing uh a physician as a second opinion or experts opinion at the GN clinic or center of excellence, I think that's going to um honestly improve care and also making it easier for nephrologists that they have focus on different areas. Because nephrologist uh—like, nephrology is becoming really subspecialized. I might be focused - I'm focused on rare kidney diseases, and then when it comes to management of uh peritoneal dialysis, I might actually reach out to one of my colleagues who are actually uh dealing with peritoneal dialysis patients more than me, maybe like rounding in different PD units every day, every minute.

And this is how I actually tell my community nephrologists that, you know, when I'm dealing with another topic, and it's just so subspecialized that I'm going to reach out to you. And um at this point, I'm just really focused on rare kidney diseases, and I'm trying to keep myself updated. And this is how we work together, right? Um I seek out your advice for different topics. You seek out my advice for different topics as well. So this is how it's been working and collaborating, and I think that's going to be the fundamental of centers of excellence for GN. It doesn't mean that um the experts at the centers of excellence, they know everything about uh nephrology better than everyone else. It means that they're just more focused on uh GN care and IgA nephropathy at this point, and they're spending a lot of time to keep themselves updated. So um basically, that's the reason that centers of excellence are going to play a really important role in how we navigate treatment for IgA nephropathy.

The other thing is that when you go to a center of excellence or a GN clinic, you know that you have access to other specialties as well. So if you need transplant evaluation, that's going to be much faster. If you're basically dealing with other GN diseases, for example, lupus, you're going to be able to see a rheumatologist easier, because we have this multidisciplinary care at the GN uh clinics and centers of excellence that makes it easier to refer and get second opinions from other specialties as well.

Um pregnancy care is really important, because now we do have patients—I get a lot of referrals for IgA nephropathy, lupus nephritis, the patient is pregnant. It's more complex. At this point with the new therapeutic options, you want to know if they're safe during pregnancy. Or if they were taking the medication and they become pregnant, you want to know how to navigate care during pregnancy as well.

So these are, again, topics that are really sensitive and requires a lot of basically um a lot of effort to basically keep yourself updated. And I honestly am going to say that by attending only one conference or two conferences per year on IgA nephropathy, at this point, you're not going to be able to keep up with everything that's going on in the field. And that's the reason that we work uh in collaboration together.

And again, me spending a lot of time on rare kidney diseases, it's going to probably um make me to actually ask help for other areas of nephrologies, and um that's completely fine. And probably at some point, we're going to have centers of excellence in different areas of nephrology, and um that should be the way that we are going to look at this specialty, nephrology, that the same as cardiology, they have EP, heart failure, transplant. So um this is the way that we should look at it, and um this is the way that we can actually work together and improve care together as a community.

Dr. Patel:
Thank you so much, Dr. Norouzi, for kind of going through, you know, why specialty GN clinics are incredibly important. I know they're kind of on the horizon, and I think it's a really exciting option uh for our patients to receive that really focused care, so that they're getting that well-rounded care for something like uh a rare kidney disease. And that collaboration, I think, is certainly important. We, like you mentioned, we see it in a lot of other specialties, and I think uh nephrology is no exception to that. And it's a wonderful thing, I think, for patients to have that um at their disposal, um to be able to kind of, you know, piggyback on a variety of nephrologists um for their total care.

Um this was an incredibly informative uh presentation and a wonderful resource, I think, for our nephro—NephU Community. I certainly learned a lot um from your presentation. Um so thank you so much for your time. We really appreciate it.

Um and to stay up to date on our upcoming events, uh please visit nephu.org um /events, and you can also download the NephU app from Google Play or the Apple App Store.

To our NephU viewers, thank you so much for joining us today. Um you can now download your certificate of completion on NephU under Manage Your Profile in your account. Thank you again for tuning into the webinar today, and—and we hope you enjoyed it. Take care.

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