Brad Rovin:
Hello everyone. My name is Brad Rovin and I am the Director of the Division of Nephrology at the Ohio State University Wexner Medical Center. I have been working in nephrology for a long time, and my special area of interest is how the immune system interacts with the kidney and especially how auto immune diseases affect the kidney. In that sense, I have a clinic for patients with lupus nephritis, and I work closely with my rheumatology colleagues in that clinic.

Brad Rovin:
I would like to talk to you about a very important diagnostic procedure that we do with our lupus nephritis patients called the kidney biopsy. And we will try to explain at least our views at Ohio State and what we have published in the past on the importance and relevance of the kidney biopsy to the management of patients with lupus nephritis. So to start out, I’d like to just talk a little bit about the technique of kidney biopsy and maybe this would be something you could talk to your patients about because a lot of patients are sort of scared about having a biopsy and a little bit of the explanation of the technique may help alleviate those concerns.

Brad Rovin:
For the kidney biopsy, we ask the patients not to eat after midnight. We usually try to do the biopsies in the morning. The biopsy itself is done with the patient lying on their stomachs in a prone position. And we always do the biopsy under some sort of radiologic guidance. The way we do the biopsies in my division is that the nephrologist performs the biopsy in the radiology suite using the ultrasound machine. If patients are not suitable for ultrasound guided biopsy, then we ask our interventional radiology colleagues to do the biopsy under the guidance of a CT scan.

Brad Rovin:
But most of the biopsies can be done by the nephrologist using ultrasound. The advantage of ultrasound is that there is no radiation. It is just of course, sound waves imaging the kidney. We locate the kidney with the ultrasound and we always try to go for the lower pole of the kidney away from the blood vessels. We use a small needle called the biopsy gun. The patient is asked to hold their breath. And after of course the whole area of the skin all the way down to the capsule of the kidney has been suitably anesthetized, we place the needle into the back and then all the way down to the surface of the kidney, watching the needle advance with the ultrasound.

Brad Rovin:
When the needle is at the surface of the kidney and the patient is holding their breath, we deploy the gun. It makes a little bit of a clicking noise, which we do tell patients about, so they don’t jump or get scared when they hear that noise. And the biopsy is over in literally less than a second. We do like to take two pieces of tissue so that we can do all the studies that we like to do with the pathologist. And then the patient is allowed to rest and is monitored for in our institution four to six hours. We do check the blood counts to make sure that there is not a lot of bleeding.

Brad Rovin:
Then the patients are generally allowed to go home and resume their daily activities. We do ask that patients do not do heavy lifting for a week after the biopsy. And, we do like to avoid aspirin or nonsteroidals if possible, after the biopsy and certainly we like those held for several days before the biopsy to minimize the risk of bleeding. All in all, the procedure does not take very long, but then the observation period does take a few hours. In general, the procedure is painless because the patient is numbed up and afterwards, the patient may feel like they have a bruise in their back.
Brad Rovin:
The biggest adverse event, if you will, of a kidney biopsy is that we do get hematomas or bleeding around the kidney. That is usually self-contained and is not clinically relevant. So, once we have the kidney tissue, it goes to the nephropathology division in our pathology department. They process the kidney for light microscopy, immunofluorescence, microscopy, and electron microscopy. And I know that electron microscopy is not available in all countries, but certainly is the standard of care in the United States.

Brad Rovin:
We assess the changes in the kidney, and we try to grade or classify the type of lupus a patient has using the International Society of Nephrology and Renal Pathology Association guidelines, which were published several years ago. Now, these guidelines or this classification system is undergoing an upgrade that will hopefully be more evidence-based and related to how the biopsy does in terms of prediction of clinical outcomes and also in terms of directing our therapeutic efforts. The current ISNPS guideline was done and classified mostly by histology.

Brad Rovin:
As we move forward with renal pathology, we more and more want to get a lot of information from the biopsy and really push the biopsy interpretation to give us as much clinically relevant information to help us manage the patient as possible. In that regard, it is important to understand that the biopsy is not only for the diagnosis of lupus nephritis. When I say lupus nephritis, I mean specifically an immune complex glomerulonephritis in the setting of a patient who has a systemic lupus erythematosus.

Brad Rovin:
Patients with lupus can have other kidney issues that are related to the lupus that are not lupus nephritis. So, one important thing that we do get from the biopsy is to confirm that the patient does have immune complex glomerulonephritis. Now, this may be obvious from the clinical presentation of the patient with proteinuria and hematuria and possibly impaired kidney function, but what we and our colleagues who have been doing investigation in kidney pathology and lupus nephritis have shown is that you cannot always understand what’s going on in the kidney through the clinical manifestations displayed by the patients.

Brad Rovin:
In other words, there is a discordance between the biopsy findings and the clinical findings that the patient presents with. So, this means that we often get information from the biopsy that we would not otherwise have. And that is why I think a biopsy is important to do at the very first presentation of a patient with lupus who has suspicion of kidney involvement. There is concern in the community that since most patients are currently treated with a combination of corticosteroids and mycophenolate mofetil or MMF for lupus nephritis, the diagnosis is not particularly urgent to be confirmed by pathology. I disagree with that for several reasons and I would like to discuss those briefly.

Brad Rovin:
First, because of the discordance between clinical findings and histologic findings and the fact that proteinuria, which is our most important biomarker of kidney involvement in lupus nephritis is rather nonspecific, looking at the biopsy can tell us a lot of information about the extent of damage to the kidney. It’s really important to understand how much of the kidney damage is due to active inflammatory disease, which in general is something that we can target therapeutically and get to resolve, versus chronic damage that has resulted in scar formation that we can’t really address clinically or therapeutically at this point in our understanding of how to treat lupus.

Brad Rovin:
So in other words, you can have protein in the urine because you have active inflammation in the kidney that will respond to an immunosuppression, or you can have protein in the urine because you used to have active inflammation in the kidney that’s now converted to chronic damage and the kidney leaks protein, and that will not respond to immunosuppression. It may respond to other conservative therapies like controlling blood pressure and renin-angiotensin-aldosterone system blockade or RAS inhibition, but not necessarily to immunosuppressive drugs. This is an important decision because it can influence how aggressively one would treat a patient with immunosuppression and of course, immunosuppression has its own long list of adverse events and side effects so that using immunosuppression in an informed way is probably the best course for the patient.
Brad Rovin:

In addition to immune complex glomerulonephritis, which is what we use the term lupus nephritis to describe, the kidney can be involved in patients with lupus, with thrombotic microangiopathy and clotting in the small blood vessels of the kidney or the glomerular capillaries. This occurs in about 25% or more of patients with lupus, especially those with antiphospholipid syndromes and this type of damage to the kidney requires a different approach to therapy that could include plasmapheresis and could include anticoagulation. Missing these lesions and treating only with immunosuppression for inflammation would really cause trouble down the road for patients because the thrombotic microangiopathy causes ischemic damage to the kidney and progressive renal insufficiency.

Brad Rovin:

So that is one example, and you cannot always pick this up clinically. Other examples include lupus podocytopathy, which is a manifestation of lupus that affects the podocyte on the glomerular basement membrane. The podocyte is a very important cell type that regulates the filtration barrier and what goes into the urine. These podocytopathies tend to resemble a minimal change disease that we would see in a non-lupus population or focal segmental glomerulosclerosis. The treatment of lupus podocytopathy generally is corticosteroids alone without cytotoxic agents. And these patients often respond very well.

Brad Rovin:

Having this information would be important to individualize the immunosuppressive or treatment regimen of the patient and providing them with the most benefit and the smallest chance of side effects. Podocytopathies are seen in about 5% of patients with lupus. Podocytopathy generally occurs by itself but thrombotic microangiopathy can occur by itself or with lupus nephritis making the situation even more confusing. Once you have an initial diagnosis of lupus and you have confirmed that histologically, the question arises as to whether there's benefit from a repeat biopsy. This is an interesting question and something we have been looking at for several years with colleagues all over the world.

Brad Rovin:

A repeat biopsy is not particularly enthusiastically embraced by a lot of people because kidney biopsy is an invasive procedure, but some of the data we’ve accumulated lately suggests that a repeat kidney biopsy strategically planned on a protocol basis during the course of therapy may actually help us manage patients with lupus nephritis better. In data that we’ve published and other groups have published recently, we found that at the end of maintenance therapy in patients who are doing really well clinically about 25% to 30% of patients have ongoing histologic activity in the kidney.

Brad Rovin:

If you don’t do a kidney biopsy and you don’t see that these patients have ongoing activity and you decide it’s time to wean down the immunosuppression in a patient, we hypothesized that those patients may be predisposed to having flares of lupus nephritis. Of course, one of the things that we want to do once we diagnose and treat lupus nephritis is to keep the disease quiescent because every time the patient flares, the kidney can accumulate injury and chronic damage. And eventually enough kidney parenchyma is damaged that the kidney will progress on to end stage kidney disease, even without a lupus nephritis being active.

Brad Rovin:

We did a study recently and demonstrated that patients who have ongoing activity, despite looking very much in remission clinically, but ongoing activity histologically in the biopsy have very much increased risk of having a flare of lupus nephritis over the next couple of years. We also found that if one uses the biopsy at the end of maintenance and continues therapy in patients who have ongoing inflammatory activity and tapers therapy in patients who look like they’ve resolved histologically, the flare rate in patients managed this way using histology plus the clinical metrics, is actually significantly less than patients managed only with clinical information.

Brad Rovin:

We are trying to develop protocols in which we do incorporate repeat kidney biopsies to be able to manage the long-term immunosuppression in our lupus nephritis patients. We also tend to use a repeat kidney biopsy if a patient who has been doing well quiescent off immunosuppression or have significantly reduced immunosuppression has a lupus nephritis flare. Sometimes it is very clear that the lupus in general is active. Sometimes patients who have had significant prior renal damage can have increasing proteinuria and it looks like their lupus nephritis is flaring.
Brad Rovin:

When you do these biopsies in this situation, you actually find that a lot of patients have bland histology without inflammation and those patients would not need to be treated aggressively with immunosuppression so this can save a patient another course of immunosuppression if necessary. Another use of the kidney biopsy is in the clinical trial domain. We have suggested as we help pharma develop clinical trials, that they consider having a repeat biopsy at the end of treatment so we can see what novel drugs are doing to the kidney histology and make sure that the drugs are acting in the way that we assume they are acting, based on their mechanisms of action in the laboratory and that the patients are getting histologic resolution of their lupus nephritis.

Brad Rovin:

In summary, the kidney biopsy is and continues to be relevant in the management of patients with lupus nephritis. The kidney biopsy will likely become more relevant as we have newer and newer drugs that target very specific parts of the immune system, and the kidney biopsy will likely help us understand which patients may be best treated with which drugs. In other words, personalizing the care of the patient to obtain the best response with the fewest side effects. What I did not touch on today but what I think is relevant is that we and others are moving toward a molecular analysis of the kidney biopsy to see what genes and pathways of injury are upregulated. We do know that they tend to be different in different patients and this may also enhance the value of the biopsy by again, allowing us to target very specific immunosuppressive drugs to the specific needs of the individual patients.

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