

SANJEEV SETHI: So hi. I'm Sanjeev Sethi, and I'm from the Department of Lab Medicine and Pathology at the Mayo Clinic. I'm here to discuss the manuscript Monoclonal Gammopathy Associated With Proliferative Glomerulonephritis. Now, proliferative glomerulonephritis results from deposition of immune complexes and complement or complement alone. In the past, many of these cases were called idiopathic proliferative glomerulonephritis.

In a small proportion of these cases we knew the cause. Typically, the cause was a chronic infection such as hepatitis C that resulted in chronic antigen antibody complexes that are deposited in the kidney and caused a proliferative glomerulonephritis. Now, autoimmune diseases also result in circulating immune complexes that get deposited in the kidney and cause a proliferative glomerulonephritis.

Over the last few years, we have determined two new important causes of proliferative glomerulonephritis. One of them is monoclonal immunoglobulin associated proliferative glomerulonephritis, and the other one is complement-mediated glomerulonephritis. This entity is also called C3 glomerulopathy and includes two diseases, C3 glomerulonephritis and dense deposit disease, both of which actually are alike. The only difference is on electron microscopy findings. And the complement-mediated glomerulonephritis comes about from dysregulation of the alternative pathway of complement.

Now, let's talk a little bit about the manuscript which details how the monoclonal immunoglobulins cause a proliferative glomerulonephritis. In the first setting, which is fairly straightforward, is that the monoclonal immunoglobulins, whether it's resulting from a monoclonal gammopathy of undetermined significance or even a B cell neoplasm such as CLL or a low-grade B cell lymphoproliferative disorders, which cause a monoclonal gammopathy.

Now, what happens in these disorders is that the monoclonal immunoglobulins get stuck in the glomeruli and cause a proliferative GN or a proliferative glomerulonephritis. Very often the pattern is an MPGN or a membranoproliferative glomerulonephritis, and this is what is depicted in that figure. And you can clearly see in this figure that there is a proliferative glomerulonephritis. On immunofluorescence microscopy, there is staining IgG kappa and lambda is completely negative. And the electron microscopy shows you the small subendothelial or capillary wall deposits. Now, this is the straightforward mechanism, direct deposition of monoclonal immunoglobulins causes of proliferative GN.

The indirect mechanism is also important. And this results from the monoclonal immunoglobulin acting as a small mini auto-antibody. And it acts as a mini auto-antibody to a complement-regulating protein. Once it acts as this mini auto-antibody to the complement-regulating protein, these complement-regulating proteins can no longer act effectively. And this results in overactivity of the alternative pathway of complement. Again, now you have all the complement products that are deposited in the kidney, and it causes a proliferative GN. In fact, it causes a complement-mediated proliferative GN.

So in a sense, there are two arms to the monoclonal immunoglobulin causing a proliferative glomerulonephritis. One is the direct mechanism where the monoclonal immunoglobulins are deposited in the kidney. And the second, the indirect arm, where the monoclonal immunoglobulin acts as a mini auto-antibody to one of the complement-regulating proteins and causes a proliferative glomerulonephritis.

These entities are relatively newly described. There are no trials in such, but Dr. Rajkumar and I have proposed an algorithm of how to go evaluate these patients and then come up with an algorithm for treatment and management of these patients. And this is discussed in this manuscript in detail. Thank you.

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