EDITORIAL

Will laboratory markers replace kidney biopsy in patients with nephrotic syndrome?

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Since its introduction in the 1950s,[1] the renal biopsy has become an important tool in the diagnosis and treatment of patients with kidney disease, allowing precise classification and a well-informed estimation of severity, duration and prognosis of the disease involved.[2,3]

In some patients with renal symptoms, a presumed diagnosis can be made without knowledge of the renal histology, e.g. in a young child with sudden onset nephrotic syndrome (probably minimal change nephropathy); in an adolescent with acute renal dysfunction one or two weeks after a streptococcal throat infection (post-infectious glomerulonephritis); or in a patient with intermittent gross haematuria with an otherwise normal renal function without proteinuria (thin basement membrane disease or uncomplicated IgA nephropathy).

In most patients with proteinuria with or without nephrotic syndrome, histology-based diagnosis of the underlying glomerular injury is important to guide treatment and allow a rational prognosis. The biopsy findings may be as diverse as diabetic nephropathy, amyoidosis due to plasma cell dyscrasia, autoimmune disease such as lupus erythematosus, or genetically dysregulated glomerular podocytes.

Also in patients with acute or rapidly progressive renal dysfunction, a renal biopsy is crucial: it may reveal widespread interstitial injury due to drug-induced allergic reactions or toxic cellular injury; acute or extracapillary glomerulonephritis related to infectious disease or an autoimmune reaction; or severe vascular injury in the context of systemic vasculitis or thrombotic microangiopathy. In transplant patients, knowledge of renal histopathology guides us through the confusing field of rejection, drug toxicity, viral and other infections, recurrence of the original injury or development of a *de novo* form of renal disease.

Notwithstanding the important contribution of the renal biopsy for immediate and unequivocal diagnosis in most patients with kidney disease, other diagnostic tools may be helpful in postponing the procedure, allowing for an early start of treatment. Patients who enter the hospital with rapidly evolving renal failure, signs of glomerular disease such as proteinuria and erythrocyturia and a high *ANCA (anti-neutrophil cytoplasmic antigen)-antibody titer,* may be started on cytotoxic and immunosuppressive treatment while awaiting a renal biopsy. A subsequent biopsy provides the physician with precise information of the extent and severity of renal injury. This is helpful in providing reassurance for the highly toxic treatment and gives a better insight into how much recovery can be hoped for.[4]

Similarly, in a patient with high titres of anti-DNA autoantibodies, multisystem signs of systemic lupus erythematosus (SLE) and symptoms of renal involvement with loss of renal function, proteinuria and haematuria, a renal biopsy is not decisive in making the diagnosis of active SLE, and therefore treatment can be started without delay. However, a biopsy is still necessary for classifying the type of renal disease in this patient and for estimation of activity and chronicity of the changes, allowing appropriate treatment choices.[5]

In membranous nephropathy (MN), the most frequent form of proteinuric renal disease in adults, the renal biopsy has always been central in distinguishing it from other causes of nephrotic syndrome such as minimal change glomerulopathy, focal and segmental glomerulosclerosis, diabetic nephropathy, amyloidosis and light chain disease. MN can be secondary to infectious disease, malignancy and systemic lupus, but in most cases it is idiopathic. Until three years ago, the underlying cause of the formation of subepithelial immune deposits in the glomerular capillary wall in idiopathic MN was unknown, although experimental work had long hinted at an autoimmune mechanism involving one or more podocyte proteins as antigen targets.[6] In 2009, the enigma was solved by Beck *et al.*,[7] who demonstrated that an autoantibody response to phospholipase A2-receptor causes the disease in 75%

of cases of MN – the other cases being secondary to e.g. infectious diseases, malignancy or systemic autoimmune disease. Further studies revealed the underlying genetic susceptibility, based on polymorphisms in the PLA2R and HLA-DQ genes that act together in the development of this autoimmune disease.[8] Several diagnostic tests are being developed to detect circulating anti-PLA2R autoantibodies in serum samples, which will be important for diagnosis, evaluation of therapeutic intervention, and follow-up in patients with native renal disease and after transplantation. In the perspective of this new exciting knowledge, in the current issue of our journal Hofstra and Wetzels[9] discuss the clinical value of the currently available serum test and the renal biopsy in the nephrotic patient who tests positive for circulating anti-PLA2R antibodies. In their view it is still too early to go without renal histopathology and to rely on the serum test only, because most studies so far have been retrospective and more robust tests should be developed allowing quantification. Different tests should be compared and specificity and sensitivity of these tests to identify idiopathic MN have to be established in prospective studies. Furthermore, there are still several questions to be answered regarding the pathophysiology of the PLA2R-binding antibodies and the role of Ig isotypes and complement.

Finally, possible concomitant diseases may be missed when a biopsy is omitted and there is an additional need for estimating the evolution of the lesion over time (MN is usually classified in four stages from early to late) and the extent of chronic damage such as glomerulosclerosis and interstitial fibrosis, since these pathological changes may have an important effect on prognosis and the need for further treatment.

The exciting discovery in the field of idiopathic MN has solved many of the questions related to the cause and pathogenesis of this renal disease and holds great promise for the patient, but it seems too soon after the seminal observation of Beck and colleagues to rely on a preliminary test in order to distinguish between idiopathic and secondary forms of MN and to discard the cornerstone of its diagnosis: the renal biopsy.

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