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Editorial Comment

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Anti-glomerular basement membrane nephritis: why we still 'need' the kidney biopsy

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Anti-glomerular basement membrane (GBM) nephritis is a rapidly progressive glomerulonephritis (RPGN) due to autoantibodies directed against the noncollagenous 1 domain of type IV collagen in the GBM. The eponym 'Goodpasture's syndrome' is used in cases of renal and pulmonary involvement, typically in the form of pulmonary hemorrhage. The disease can be diagnosed clinically in a patient with a RPGN––defined as at least 50% decline in renal function in <3 months with evidence of glomerular injury via hematuria and proteinuria [1]––if circulating anti-GBM antibodies are detectable by an enzyme-linked immunosorbent assay (ELISA). However, a firm diagnosis can only be made by a renal biopsy demonstrating a crescentic glomerulonephritis on light microscopy and diffuse, linear localization of IgG along the GBM on immunofluorescence (IF).

A question that recurrently arises is whether a biopsy is 'needed' in cases of RPGN with positive serologic testing. This question may apply not only to anti-GBM disease but also to anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis and lupus nephritis. As a clinician who has the privilege of working in an academic center with a world-renowned renal pathology division, the answer for me is always an obvious, resounding 'yes'. Indeed, most renal pathologists today are so skilled––both in diagnostic accuracy and turnaround time––that very often the biopsy results arrive days before the results from serologic tests, which are often sent out to reference laboratories. Again, using our hospital as an example, our pathologists routinely do same-day IF staining on kidney biopsies, so that a RPGN biopsied in the morning can be tentatively signed out as a pauci-immune, immune-complex, or anti-GBM crescentic glomerulonephritis by the afternoon. It is hard to imagine any laboratory turning around an anti-GBM serologic test that quickly.

The three case reports of anti-GBM nephritis with negative serologic testing in the current issue of *Clinical Kidney Journal* highlight the importance of renal biopsy beyond just quick turnaround time. These unusual cases of RPGN were instances in which the diagnosis could only be made by a kidney biopsy. Moulis *et al.* [2], Dash *et al.* [3] and Kussman and Gohara [4] all describe classic clinical presentations of RPGN with negative serologic testing for circulating anti-GBM IgG autoantibodies (as well as negative testing for other causes of RPGN, such as ANCA and lupus) but firm diagnoses of anti-GBM nephritis made by kidney biopsies. Interestingly, the case reported by Moulis *et al.* [2] showed on IF linear staining that was stronger for IgA than for IgG, prompting the authors to re-test their patients for anti-GBM IgA autoantibodies, which were positive. In this instance, the renal biopsy not only made the diagnosis but also informed serologic testing (as anti-GBM IgA autoantibodies are not routinely tested) that in turn guided treatment (plasma exchange until negative serologic testing for anti-GBM IgA).

Of course, a renal biopsy never truly 'makes' a diagnosis. The histopathology, rather, presents a pattern of injury that in turn allows the treating physicians to seek out an etiology behind that pattern. Routine IF staining of kidney biopsies does not stain specifically for anti-GBM autoantibodies, but a linear deposition of IgG along the GBM suggests that the IgG, which is 'lighting up,' is from anti-GBM autoantibodies. Serologic testing for circulating antibodies then confirms the presence of such autoantibodies. The ELISA techniques used to detect circulating anti-GBM antibodies are quite robust, particularly when combined with western blot analysis, yielding ∼98% sensitivity [5]. Yet, as was recently pointed out in a discussion from the *New England Journal of Medicine* of another case of serum antibody-negative anti-GBM nephritis, 'even a test that is 98% sensitive will be negative in 2% of patients with anti-GBM disease' [6].

In some instances, a false-negative serology in anti-GBM nephritis can be explained by antibodies that bind to the kidney with high affinity but circulate in levels too low for the ELISA. These autoantibodies may be detectable by a more sensitive biosensor analysis [5], available only in research settings and not employed in any of the three current case reports. Speculatively, this type of analysis may have been able to detect circulating antibodies in the cases reported by Dash *et al.* [3] and Kussman and Gohara [4]. Alternatively, as in the case reported by Moulis *et al.* [2] and the 11 similar cases reviewed in their discussion, ELISA testing for IgG anti-GBM autoantibodies

was negative because the disease was mediated by IgA autoantibodies. Anti-GBM nephritis thus exemplifies the glomerular disease whose firm diagnosis relies on a combination of clinical, serologic and histopathologic findings.

As our understanding of the pathophysiology behind glomerular diseases has grown, the armamentarium of serologic tests at our disposal has likewise expanded. These advances extend well beyond just RPGNs, such as anti-GBM nephritis, and raise questions about the role of kidney biopsy. For example, in the not-too-distant future, all patients with new onset nephrotic syndrome will likely undergo serologic testing for antibodies to the M-type phospholipase A2 receptor (PLA2R), the target antigen in the majority of cases of primary membranous nephropathy [7]. Will a patient with nephrotic syndrome and positive PLA2R antibodies still 'need' a kidney biopsy? Likewise, the patient who presents with normal renal function but persistent hematuria and low-grade proteinuria may be tested for elevated serum levels of IgA1 with truncated galactose-deficient hinge region *O*-glycans (Gd-IgA1) as a screening assay for IgA nephropathy [8]. If Gd-IgA1 levels are increased, is a biopsy still 'necessary?' Conceivably, the issue of whether a biopsy is 'needed' when serologic testing is positive may eventually apply to all glomerular diseases. As with anti-GBM disease, we should not expect biopsies to fall out of favor or decline in importance just because a serologic test is available. The information gleaned from a biopsy will continue to complement the clinical and serologic data, guiding diagnostic and treatment decisions.

A thorough kidney biopsy report not only suggests or confirms a pathologic diagnosis but can also provide information on the severity of the injury, activity versus chronicity of the lesion, and the presence of other, significant renal or vascular abnormalities [9]. In other words, a well-read kidney biopsy can tell the nephrologist what the patient has and whether there is a reasonable chance of recovery with successful therapy. There is no serologic test that can impart that degree of information.

Conflict of interest statement. None declared.

(See related articles by Moulis *et al.* IgA-mediated anti-glomerular basement membrane disease: an uncommon mechanism of Goodpasture's syndrome. *Clin Kidney J* 2012; 5: 545–548; Kussman and Gohara. Serum antibody-negative Goodpasture syndrome with delta granule pool storage deficiency and eosinophilia. *Clin Kidney J* 2012; 5: 572–575, and Dash *et al*. Renal injury due to anti-GBM antibody-mediated glomerulonephritis without circulating antibody. *Clin Kidney J* 2012; 5: 591–594)

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