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Beyond Serology: Is There Still a Value of Kidney Biopsy in Anti-Glomerular Basement Membrane Disease?

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Anti-glomerular basement membrane (anti-GBM) disease is a small-vessel vasculitis that may affect both the glomerular and alveolar basement membranes causing rapidly progressive glomerulonephritis in nearly 100% of affected patients and diffuse alveolar hemorrhage in approximately 50%.[1] It results from the production and binding of anti-GBM antibodies, mostly to epitopes of the α3 chain of type IV collagen present in basal membranes.[1] The disease has an acute course and often a dire prognosis with up to 60% to 70% of patients reaching end-stage kidney disease; however, when treatment is started urgently, approximately 80% of patients will achieve remission; therefore, rapid diagnosis is imperative.[2] Although commercial enzyme-linked immunoassay kits are available, biopsy is still considered the gold standard to diagnose anti-GBM disease. The most recent Kidney Disease: Improving Global Outcomes guidelines clearly state that, whereas "testing for the presence of anti-GBM antibodies should be done urgently using commercially available [enzyme-linked immunoassay] (…), diagnosis should be made without delay, and kidney biopsy findings should be reported to the clinician by the pathologist on the day of the biopsy."[3]

However, scoping the recent literature, we have found a number of large studies on anti-GBM disease, which had biopsies available in as low as 43% of patients, leaving the diagnosis and prognosis of the majority of patients in the hands of serology alone.[4,S5–S9] The largest of these, a study by Watanabe *et al.*[4] included patients with dialysis-dependent acute kidney injury without diffuse alveolar hemorrhage, a population of patients which ideally should have been biopsied barring any contraindication. In addition, a systematic review of anti-GBM/antineutrophil cytoplasmic antibody double-positive patients by Philip *et al.*,[S5] which included 538 patients showed that biopsy was performed in only 242 of 361 (67.0%) patients with acute kidney injury on presentation.

Prognostic Factors–Why a Kidney Biopsy is Needed

The accuracy of testing for anti-GBM antibodies in the diagnosis of anti-GBM disease is excellent, with sensitivity and specificity of 93% (95% confidence interval: 84%–97%) and 97% (95% confidence interval: 94%–99%), respectively.[S6] Although this is undoubtedly high, it might misclassify some patients as positive but, more importantly, produces about 7% of false negative results which would, without biopsy, leave a significant proportion of patients without an appropriate diagnosis and therapy.

Although anti-GBM serology provides an accurate tool for diagnosis and the dynamics of antibodies allows for monitoring therapy, especially the tailoring of extracorporeal therapy to one's individual need, controversy exists about whether the initial antibody level/titer has prognostic significance. Renal biopsy parameters have, however, been shown to be very good predictors in several studies. van Daalen *et al.*[S7] explored the long-term predictors and use of the Berden classification in anti-GBM disease, which was initially devised for antineutrophil cytoplasmic antibody-associated vasculitis and divides patients into a focal class (≥50% normal glomeruli), crescentic class (≥50% glomeruli with cellular crescents), sclerotic class (≥50% glomeruli with global sclerosis), or a mixed class (not fitting any other class). Histology proved crucial for

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prognosis with percentage of normal glomeruli and extent of interstitial infiltrate as 2 key predictors of end-stage kidney disease in anti-GBM disease.[5,7] Furthermore, patients in sclerotic class and those with 100% cellular crescents did not recover from dialysis dependency despite treatment. These findings led to the Kidney Disease: Improving Global Outcomes recommendation that patients who are dialysis-dependent at presentation and have 100% crescents or >50% global glomerulosclerosis in an adequate biopsy sample, and when pulmonary hemorrhage is absent should not receive aggressive treatment.[3] This recommendation is based on scientific evidence from larger cohort studies reported over the past years (Table 1), because it became evident that especially histopathology (the extent of chronic damage and percentage of crescents) predicts a low probability to recover independent kidney function. Most of these studies have either focused on clinical parameters (serum creatinine, dialysis-dependency, or urine output) or histopathological variables, and some are discussed in greater detail below. A study by Levy *et al.*[52] reported that patients with serum creatinine ≥500 μmol/l or dialysis dependency on presentation have a poor prognosis. Another study from the UK by Alchi *et al.*,[52] though emphasizing the strength of oliguria as a predictor and concluding that kidney biopsy may not be necessary in oligoanuric patients without pulmonary hemorrhage, still showed that, in patients who underwent kidney biopsy, percentage of crescents was the only significant predictor of renal survival with none of the patients who recovered from dialysis dependency having >75% crescents. A recent study showed that, although percentage of

Table 1. Studies published in the last 10 years (September 2013–August 2023) reporting on histologic parameters as independent predictors of renal survival in anti-GBM disease

Study first author, yr (reference)	Number of patients	Patients with biopsy performed, *N* (%)	Baseline creatinine (μmol/l)	Crescents/cellular crescents (%)	Mean or median follow-up (months)	Renal survival at 1 year/5 years/ follow-up (%)	Predictors of renal survival	
							Histologic	Other
Caillard *et al.*,[6] 2023	150	135 (90.0)	578	NR/NR	59.9	29/NR/NR	C3 deposits (non-dialysis dependent patients)	Dialysis dependency at presentation (all patients)
Floyd *et al.*,[11] 2023	174	174 (100)	6.5[a]	NR/NR	39.8	NR/NR/39.9	Percentage of normal glomeruli (cut-off: 10%)[b]	Dialysis dependency at presentation
Zhu, *et al.*,[S18] 2022	94	56 (59.6)	661.9	68.5/19.6	23.3	NR/NR/11.7	Percentage of fibrocellular crescents (increase by 10%)	Oliguria/anuria Peak creatinine Serum C3
Jia, *et al.*,[S11] 2022	448	218 (48.7)	811.1	87/NR	9	37.9/NR/NR	Percentage of crescents (increase by 20%)	Serum creatinine at diagnosis
Zahir, *et al.*,S13 2021	48	48 (100)	769.3	76.5/65.4	7	9.7/NR/NR	Severe glomerulosclerosis Severe IFTA	Oliguria/anuria Serum creatinine at diagnosis
Zhang *et al.*,[S15] 2021	65	65 (100)	477.5	NR/23.8	NR	25.7/18.5/NR	Renal tissue $CD4^+/CD8^-$	Serum creatinine at diagnosis Peripheral blood $CD4^+/CD8^-$
Marques *et al.*,[S14] 2019	119	101 (84.9)	636.6	NR/NR	44	NR/NR/33	Hyaline thrombi	Cannabis use
van Daalen *et al.*,[S9] 2018	123	123 (100)	619	NR/61[c]	46.8	NR/34/NR	Percentage of normal glomeruli Extent of interstitial infiltrate	Dialysis dependency at presentation
Alchi *et al.*,[39] 2015	43	27 (62.8)	NR	NR	27[c]	16/NR/NR	Percentage of crescents (>75%)	Oliguria (all patients)

NR, not reported.
[a]Estimated glomerular filtration rate (ml/min per 1.73 m^2).
[b]Glomeruli without any scarring, crescents, or fibrinoid necrosis within the tuft.
[c]Given for single-positive group.

crescents did not reach statistical significance in a multivariate model, patients with >50% of crescents had much lower renal survival rates at 2-year follow-up compared to those with <50% of crescents (6% vs. 49%). Moreover, 9 patients who did not develop end-stage kidney disease during follow-up had a median percentage of crescents of 47% compared to a mean of 80% in all patients.[S10] This study did not show a consistent association of serum creatinine at initial presentation with percentage of crescents and there was no difference in percentage of crescents between patients with or without alveolar hemorrhage, which further demonstrates that degree of renal impairment or diffuse alveolar hemorrhage cannot serve as predictors of histology. A recent large retrospective cohort study from China showed that percentage of crescents was the stronger one of only 2 predictors of renal survival, alongside serum creatinine at presentation. Risk of end-stage kidney disease increased by 73% for each 20% point increase in crescents. Interestingly, percentage of crescents and serum creatinine were independent of each other, providing further evidence that they reflect different aspects of disease and confirming that serum creatinine cannot be used as surrogate for histology.[S11] These studies (some are summarized in Table 1) used different cut-offs at which percentage of crescents the renal prognosis is poor; however, this number has not been consistent across studies. An international endeavor to collect histopathological data from patients with anti-GBM disease is required to likely overcome this issue. In addition, a synthesis with clinical presentation is required when deciding not to treat a patient based on histopathological data, considering serum creatinine and the urine output at the time of presentation.

Other Considerations When Evaluating a Kidney Biopsy

A study by Floyd *et al.*[5] which investigated whether the prognostic value of a modified renal risk score, initially devised for antineutrophil cytoplasmic antibody-associated vasculitis, translated well to anti-GBM disease found that the percentage of normal glomeruli outperformed all other variables, including the second component of the score, the need for kidney replacement therapy, which had long been the major predictor of prognosis in anti-GBM patients. Although this study defined normal glomeruli as those without scarring, crescents, or fibrinoid necrosis within the tuft, this predictive value is certainly due to the percentage of crescents, given that a supplementary analysis comparing patients with 100% crescents with those with up to 10% normal glomeruli showed no difference in outcomes.[5] Importantly, all of these studies also included a significant proportion of double-positive patients which tend to have a lower proportion of crescents and a better prognosis than pure anti-GBM disease. Results like these emphasize the shift from mainly diagnostic to prognostic biopsies in anti-GBM disease.

Although crescents remain paramount in predicting outcomes in anti-GBM disease, several other histologic parameters have also been shown to have predictive value, such as interstitial fibrosis and tubular atrophy, extent and composition of interstitial infiltrate, glomerulosclerosis, and hyaline thrombi.[S7,S12–S14] A recent study by Caillard *et al.*[6] showed that C3 deposition in the glomeruli was associated with lower renal survival in initially nondialysis-dependent patients and, interestingly, much higher proportion of crescentic class; and underlines the importance of complement in anti-GBM disease, further pointing to the importance of histology. Moreover, a biopsy might reveal other findings; that is, periglomerular inflammation, granuloma or thrombotic microangiopathy, and anti-GBM disease can also occur with other primary and secondary glomerular diseases (antineutrophil cytoplasmic antibody-associated vasculitis, IgA nephropathy, membranous nephropathy, monoclonal gammopathy, etc.).[S15–S17] All of these additional findings may guide alternative treatment decisions and/or impact prognosis.

Renal pathology guidelines state that routine immunofluorescence turnaround time should be up to 2 days and most centers today enable same-day immunofluorescence for rapidly progressive glomerulonephritis.[7] Contrary to this, serologic testing is not widely available and samples must sometimes be sent to reference laboratories which usually takes longer than rapid immunofluorescence.[8] Moreover, most centers offer testing for anti-GBM antibodies only once a week, given the paucity of ordering the test and in order to be cost-effective. Moreover, a relevant proportion of patients presents with a "non-classical" form of anti-GBM disease.

Given the changing landscape of therapy with several new and upcoming drugs, such as imlifidase, the importance of biopsy might even be greater in the next few years.[1] The results of the first randomized controlled trial, GOOD-IDES-02, a study which evaluates not only the safety and efficacy of imlifidase in anti-GBM disease and has biopsy as mandatory inclusion criteria, but also aims to provide new insight into renal histology and its association with outcomes, will hopefully further clarify and affirm the

prognostic value of renal biopsy parameters. In addition, there are several reports on the safety and efficacy of rituximab, not only as treatment for refractory anti-GBM disease, but also as first-line therapy in for example, younger patients in which fertility preservation is important, or those that had adverse events to cyclophosphamide. The potential prognostic value of histologic parameters needs to be elucidated in this setting and it is conceivable that histology might help stratify patients and guide therapy in these cases.

To conclude, performing a renal biopsy has proven crucial in anti-GBM disease because serology and biopsy are not mutually exclusive, and in the vast majority of cases, provide complementary information showing us a broader view, which enables a more rapid diagnosis, better prognostication, and might lead to improved patient outcomes. See supplementary references for additional research in this area. A consensus on the relevance to perform biopsies is important, and discussions around this topic will be a central part of a group of international researchers currently in the process to establish recommendations to diagnose and treat anti-GBM disease.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Atypical anti-GBM Disease.

Supplementary Reference.

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