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Anti-glomerular basement membrane(GBM) antibodies are highly specific for Goodpastures disease, in which they are generally directed against the non-collagenous (NC1) domain of the alpha 3 chain of type IV collagen(alpha 3(IV)). Less commonly, antibodies may be found with reactivity toward the alpha 4(IV) or alpha 5(IV) chains, which together form hexamers of the triple helical structure in specialised basement membranes in the glomerulus and alveolus. Generally the Goodpasture antigen within the hexamers are cryptic and not accessible to the immune system, unless they are broken down to monomers. Alterations in the complex triple helical structure allows novel epitopes to be exposed with subsequent antibody binding and the pathognomic feature of linear localisation of the antibodies along glomerular and alveolar basement membranes.

Previous cases of atypical presentations with glomerular binding but no circulating anti-GBM antibodies by conventional testing have been reported. Here we report for the first time another important variant of the clinical syndrome with circulating high titre anti-GBM antibodies, crescentic glomerulonephritis (in some cases associated with ANCA) but no linear antibody deposition by immunohistochemistry. Importantly, patients sera bound recombinant alpha 3(IV) and fixed primate kidneys with linear glomerular staining, suggesting that in the patients, the cryptic epitopes had not been exposed within the kidney. We have identified 4 subjects with this pattern of disease (Table 1), 75% of whom had concurrent ANCA and 75% of whom have done well following immunosuppressive treatment recovering good independent renal function. Previous reports of double positive (anti-GBM and ANCA) patients have shown that those biopsied all showed linear staining of IgG along the GBM. Variations in hexamer constituents in alveolar basement membranes allowing or preventing antibody binding have been suggested to explain variations in pulmonary haemorrhage. Our data has implications for clinical diagnosis suggesting we should not rely solely on serology, but obtain histological confirmation of the disease pattern, as this has important prognostic information. In addition, it may improve our understanding of the pathophysiology of crescentic glomerulonephritis, induced by mechanisms other than antibody and may explain some of the variations in disease outcomes.

Table 1

Age	Gender	Anti-GBM titre at presentation(NR<10)	ANCA/Subtype	Peak creatinine at presentation(μmol/l)	Last follow up creatinine (μmol/l)	Follow up/months
79	F	28	Yes/MPO	446	195	11
64	M	33	Yes/MPO	666	127	21
66	F	359	Negative	271	105	50

70	F	200	Yes/MPO	809	HD	48