Diagnostic and Management Challenges in Goodpasture's (Anti-GBM) Disease

SR Henderson, AD Salama.

Centre for Nephrology, Division of Medicine, University College London, Royal Free Hospital, London, UK

Correspondence to: Prof Alan Salama
UCL Centre for Nephrology
Royal Free Hospital
London NW3 2PF
Email: a.salama@ucl.ac.uk

SH is a Medical Research Council Clinical Training Fellow

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Abstract

Goodpasture's or anti-glomerular basement membrane (GBM) disease is classically characterised by the presence of circulating autoantibodies directed against the non-collagenous domain of the α3 chain of type IV collagen(α3(IV)NC1), targeting glomerular and alveolar basement membranes, and associated with rapidly progressive crescentic glomerulonephritis, with alveolar haemorrhage in over half the patients. However, there are increasing examples of variants or atypical presentations of this disease, and proposed novel therapeutic options, which nephrologists should be aware of. The pathophysiology of this condition has been understood through molecular analysis of the antibody-antigen interactions and the use of HLA-transgenic animals, while the association of anti-GBM antibodies with anti-neutrophil cytoplasm antibodies (ANCA) and their combined impact on disease phenotype is increasingly recognised, providing some insights into the basis of glomerular damage and autoimmunity.

Introduction

Goodpasture's or anti-glomerular basement membrane (GBM) disease is characterised by the presence of circulating autoantibodies directed predominantly against the non-collagenous domain of the α3 chain of type IV collagen (α3(IV)NC1) (1), found in both glomerular and alveolar basement membranes, resulting in rapidly progressive crescentic glomerulonephritis, and alveolar haemorrhage in over half the patients. Although uncommon, with an incidence of 0.5- 1.6 cases/million/year (2), approximately 20% of cases of rapidly progressive glomerulonephritis (RPGN) are caused by anti-GBM disease, with isolated renal involvement occurring in 40% of patients (1). Peak incidence is in the third and sixth decades and there is a male preponderance, reflecting increased alveolar haemorrhage in younger men. If untreated, anti-GBM disease is life-threatening with irreversible kidney damage and respiratory failure. Since the introduction of modern treatment protocols, based on antibody removal by plasma exchange and use of glucocorticoids and cyclophosphamide (see table 1), patient outcomes have been transformed (3). Additionally, there has been increasing awareness of atypical anti-GBM nephritis and complex clinical variants. Despite the widespread availability of diagnostic tests, delayed establishment of the correct diagnosis and thus transfer to treatment centres, results in many patients requiring permanent renal replacement th erapy. In part this is due to the rarity of the disease and confounding clinical factors that can potentially explain the cause of AKI, prompting physicians to defer performing serological tests. Improving patient outcomes therefore requires increasing awareness of the condition and consideration of its variants as well as more urgent diagnostic strategies. For example, increasing use of electronic acute kidney injury alerts could prompt more rapid (and automated) serological analysis to exclude the diagnosis. This review will highlight recent findings, including environmental influences, appreciation of clinical variants and advances in clinical management.

Autoantigens

Type IV collagen contains 6 different subunits, alpha chains (α1 – α6), forming a triple helical structure in the N-terminal and middle regions, and folding to form a C-terminal globular domain (non-collagenous(NC)1) (4). The main antibody target in anti-GBM disease is α3(IV)NC1 which interacts with the triple helical promoter α3α4α5(IV) allowing it to remain cryptic and evade immune surveillance under normal conditions. Denaturing conditions disrupt the molecular structure of type IV collagen exposing the antigen and enabling epitope recognition, which has been shown to be conformation dependent. Critical amino acid residues were identified and immunodominant conformational epitopes characterized by various groups (5, 6), defining the most critical as E_A and E_B (5).

Predisposing Factors

Anti-GBM disease is strongly associated with polymorphisms of MHC class II genes, with disease susceptibility correlating with Human leukocyte antigen (HLA) DRB1 alleles. DRB1*1501, DRB1*03 and DRB1*04 confer a susceptibility for disease while DRB1*01 and DRB1*07 confer a protective effect (7). The molecular basis for this HLA effect has in part become clearer following investigations using HLA-transgenic mice, which demonstrated that immunodominant α3(IV)NC1 antigens are presented on DR15 susceptibility alleles but not on DR1 resistance alleles, and only in DR15 transgenic mice immunized with the α3 peptides, does clinical disease develop (8). Susceptibility HLA-DR15 alleles are common in the healthy population, yet disease is rare, supporting the notion that a second hit in the form of one or more environmental influences is required for disease development. Previously suggested triggers have included cigarette smoking or inhaled hydrocarbons, damaging the alveolar basement membrane and exposing type IV collagen epitopes(9). Additionally, seasonal variation has been reported in small patient cohorts (10, 11) suggesting potential infectious triggers. Spatial and temporal clustering of disease incidence at a national level has been recently described (2). Over an 11 year period, incidence of anti-GBM disease was 1.6 (range 0.4 to 2.8) per million population per year in Ireland. Temporal clustering occurred over a 3 month winter period, supporting previous anecdotal reports and in keeping with Ernest Goodpasture's first description of what he thought was an influenza-related condition (12). Lung involvement affected only 20% of the Irish patients, 80% of whom were male, while the majority (72%) reached end stage renal failure. Spatial clustering in a rural county was identified, in which none of the 7 presenting patients had lung disease, but the majority (71%) had detectable anti-GBM antibodies with dual positivity for anti-neutrophil cytoplasm antibodies (ANCA)(2). Understanding the HLA allelic variation in this region and the exposure to a common environmental influence would be vital to further dissect out disease aetiology, while the disproportionate occurrence of dual antibody positivity could represent a difference in disease pathogenesis.

Diagnosis

Early detection of circulating anti-GBM antibodies in the context of an acute kidney injury, with or without pulmonary haemorrhage can direct timely initiation of treatment and improve patient outcome. Many physicians are increasingly relying on serology to confirm or refute the diagnosis, feeling that renal biopsy may

be unnecessary, but there are reasons to be cautious of this approach. Positive anti-GBM serology may be occasionally associated with pathology that is pauci-immune (for example in the context of ANCA dual positivity, and see atypical cases below), potentially changing the prognosis for renal recovery and propensity for relapse. In addition, false positive anti-GBM antibody tests may be found in states of polyclonal activation such as in hepatitis C or HIV infection and with diverse renal pathologies. Finally, rare cases of anti-GBM disease without circulating anti-GBM antibodies have been reported, which may result in diagnostic delay, until a renal biopsy is performed. Serological diagnosis relies on ELISA or luminex based technologies which have become the standard methods for antibody detection using denatured recombinant NC1 portion of α3(IV) as the antigenic target. Specificity and sensitivity of assays have been reported to range from 90 -100% and 94.7 – 100% respectively (13). However, there are several important variants that need to be considered when interpreting anti-GBM antibody results.

Clinical Variants

False positive or negative antibody Anti-GBM Disease

1. Ig class and subclass variants

IgG1 subclasses are predominantly detected by commercial methods but four subclasses of human IgG exist according to their heavy chains (IgG1, IgG2, IgG3 and IgG4) and each can bind to the GBM (14, 15). IgG1 and IgG3 subclass restriction is most frequently found in patients both in sera and glomeruli and is more closely associated with disease severity; IgG3 has the greatest ability to activate complement and both IgG1 and IgG3 have the greatest affinity for binding Fc receptors (15, 16). However, IgG4 subclass antibodies have also been found to be pathogenic both in isolation and co-existing with other immunoglobulin subclasses in atypical anti-GBM disease and are not detected by standard ELISA (14, 17). Additionally, IgA anti-GBM antibodies are also not detected by standard methods and have been shown to bind various α(IV)chains (including α1,2,5 and 6) (18, 19), which may not be represented in standard assays using α3(IV) (Figure 1). Antibodies bound to glomeruli have a longer half-life than their circulating counterparts and if combined with a low level of antibody titer, may make antibody detection in serum difficult (17, 20). Other factors affecting antibody detection can include low level antibody affinity and the presence of high levels of circulating polyclonal antibodies contributing to false negative or positive results. Finally, rare cases in which circulating anti-GBM antibodies may only be detected by highly sensitive techniques such as resonance biosensors have been reported, and it remains unclear why these are not picked up on standard assays (21).

2. Antigen variants

Early detection methods used solubilized GBM containing all of the α(IV) chains, but modern assays use recombinant α3(IV), therefore different antibody target epitopes (contained within α1 or α4(IV) collagen chains, or directed against α5 (IV) in cases of Alport nephritis patients developing anti-GBM disease post transplantation) may be not be not detected by standard methods . More recently cases of circulating but not deposited anti-GBM antibodies have been reported, potentially due to differences in expression of glomerular cryptic epitopes not exposed in vivo (Sadeghi-Alavijeh et al, 18th ANCA vasculitis workshop).

It is therefore possible to miss a diagnosis of anti-GBM disease based solely on initially 'negative' serological assays while positive circulating anti-GBM antibodies may not always be associated with linear staining crescentic glomerulonephritis, and gold standard immunohistochemical staining of GBM is vital to establish the glomerular pathology.

'Double Positive' Anti-GBM and ANCA Disease

The co-existence of anti-neutrophil cytoplasm antibodies (ANCA) with anti-GBM antibodies has been increasingly recognised with detection rates varying from 21% to 38% (22-25). In contrast, anti-GBM antibody detection in ANCA positive samples has only been found in 8 - 14% of patients (23, 25, 26). Double positive patients have broader antigenic specificity, preferential binding of anti-GBM antibodies to α5 chains of type IV collagen, and lower levels of antibodies to α3(NC1)compared to anti-GBM disease alone(27). ANCA directed against myeloperoxidase (MPO) predominates in double positive patients with reported frequencies of 66 to 81% (26, 28). However, there is greater reactivity to MPO in anti-GBM sera if MPO is deglycosylated (29). Using exoglucosidase and endoglucosidase treatment to generate aberrant glycosylated MPOs, more than 50% of patients with single anti-GBM antibody positivity demonstrated reactivity to 1 or more aberrant glycosylated MPOs, with the greatest rate of detection(over 60%) seen in double positive patients. However, it is worth noting that antibodies to aberrant glycosylated MPOs are also seen in a smaller proportion of patients with IgA nephropathy, minimal change disease and end-stage renal disease (29). The clinical significance of these observations remains to be clarified.

Double positive patients are affected later in life, somewhat different to anti-GBM disease (median 62 years and 44 years respectively) but in keeping with ANCA-associated vasculitis (AAV) (median 65 years) and there appears to be a male preponderance (25). Demographic data on the incidence of dual antibody positivity is lacking but a single center case series estimated incidence at 0.47 per million people per year (22). Analysis of HLA associations in dual positive antibody patients is limited, but HLA DRB1*1501 and DRB1*0405 carriage has been reported (30).

Clinical presentation is almost indistinguishable from patients with only anti-GBM antibody positivity but clinical course often differs. This is most evident when considering renal recovery. Despite standard immunosuppression regimens, dialysis-dependent dual antibody positive patients have reduced renal recovery compared with only ANCA positive patients, in keeping with typical anti-GBM disease. In fact, there appears to be an inverse relationship between renal recovery and titres of anti-GBM and anti-MPO- antibodies (28). It is possible that this may relate to the progression of glomerular lesions where the presence of circulating ANCA may cause crescentic lesions of various ages, compared to predominantly acute active lesions in disease mediated by anti-GBM antibodies alone (31, 32). Although low in number, relapse in double positive patients tends to be associated with subsequent positive ANCA but negative anti-GBM antibody serology, further supporting the pathogenic role of ANCA (22, 33).

Crescentic Membranous Nephropathy

Crescent formation in membranous nephropathy is rare and so co-existent anti-GBM disease or ANCA-associated vasculitis must be considered. The presence of linear immunoglobulin GBM staining and circulating anti-GBM antibodies on a background of membranous nephropathy supports the diagnosis of anti-GBM disease. However, membranous nephropathy can also occur after the onset of anti-GBM disease in the context of glomerular immune complex deposition (34). A single center case series evaluated the clinical, pathological and immunological data of 8 patients with membranous nephropathy superimposed on anti-GBM disease with particular focus on the co-existence of antibodies to M-type phospholipase A2 receptor (PLA_2R) and anti-GBM antibodies (35). Clinical features were more in keeping with membranous nephropathy with a higher degree of proteinuria, less crescent formation and less severe renal injury compared to anti-GBM disease alone. Antibody specificity was narrower with circulating antibodies in all patients recognizing α3(IV)NC1 and minimal reactivity to other alpha subunits, unlike age and sex matched anti-GBM disease controls. All patients with membranous nephropathy and anti-GBM disease reacted with E_A epitope but less so to E_B. Whilst IgG4 is implicated in the pathogenesis of primary membranous nephropathy, IgG3 and, to a lesser extent, IgG2 were detected on renal biopsies in a subset of patients by immunohistochemistry, while serological reactivity to PLA_2R was not demonstrated and glomerular expression was only detected in 1 patient (36).

De novo anti-GBM antibody formation that occurs in the context of membranous nephropathy may be due to mechanical or inflammatory GBM damage, exposing neo-epitopes and driving autoantibody formation. Sub-epithelial immune complex deposition and complement activation could disrupt the GBM and promote antigen release, and form *in situ* complexes with exposed GBM antigens (37). The effect of phospholipase A2 receptor antibody disrupting the GBM and inducing a conformational change to unveil neo-epitopes may still be important.

Anti-GBM following immunotherapy

The role of regulatory T cells in maintaining and re-stablishing immune tolerance to the autoantigen has been suggested as a reason for lack of disease in healthy individuals and paucity of relapses in treated anti-GBM (38) , unlike that found in ANCA vasculitis where regulatory cell deficiencies have been identified (39, 40). In keeping with this concept, depletional biologic agents that can effectively remove all T cell subsets (Alemtuzumab, anti-CD52) have been found to trigger de-novo anti-GBM disease (41, 42). Although no other case reports of other depletional biologic agents promoting anti-GBM disease have been published, increasing use of biologic agents that can alter the balance of effector and regulatory T cell subsets, such as check point inhibitors (anti-PD1, anti-CTLA4) may make this more common and should prompt rapid investigation to exclude anti-GBM disease in those patients treated with such agents and presenting with rapidly declining renal function and/or new onset urinary abnormalities.

Atypical Anti-GBM Nephritis

The pathological hallmark of anti-GBM disease is linear immunoglobulin GBM staining on immunohistochemistry and necrotizing crescentic glomerulonephritis is the characteristic histological lesion. However, indolent disease and different patterns of injury with reduced crescent formation may also occur (17). In 20 cases identified in a 7 year study period, (accounting for 11.8% of total anti-GBM disease cases) crescent formation was only seen in 40% of cases and on average affected only 18% of glomeruli. Fibrinoid necrosis affected 7% of glomeruli. Acute tubular necrosis was present in half of cases with mild and focal interstitial inflammation in 65%. Segmental membranous nephropathy was seen in 2 patients. Mesangial and/or endocapillary hypercellularity occurred in all cases and endocapillary proliferative glomerulonephritis was the most common finding. Gold standard immunofluorescence linear IgG GBM staining was seen in 17 patients with IgM and IgA binding in the remaining patients. Interestingly, the presence of crescent formation was more commonly associated with polytypic IgG antibody profiles (deposits staining for both kappa and lambda light chains) compared to monotypic binding. Renal recovery and patient outcomes were better than typical anti-GBM disease, likely due to the pattern of renal injury but also the absence of lung involvement in this cohort (17). Finally, a number of dual positive (ANCA and anti-GBM) patients appear to have a predominant pauci-immune glomerulonephritis with relatively good rates of renal recovery.

Management

Antibody removal

The main goals of therapy in anti-GBM disease are rapid removal of circulating anti-GBM antibodies and suppression of autoantibody formation. This is most commonly achieved using plasma exchange and immunosuppression (glucocorticoids and cyclophosphamide) respectively. Timely initiation of treatment is critical as renal recovery is much more likely in the early phase of disease, for example before oliguria or dialysis-dependency occurs. A treatment regimen historically established by the Hammersmith group remains at the forefront of therapy (Table 1). Prednisolone (1mg/kg tapered over 6-9 months) and cyclophosphamide for 2 – 3 months are used in combination with daily plasmapheresis for 14 days, or until the anti-GBM antibody is no longer detectable (3, 43). This approach has transformed patient and kidney survival. Long-term follow-up of patients requiring dialysis at presentation found patient and kidney survival to be 65% and 8% respectively at 1 year and 44% and 13% at 5 years. However, in patients not requiring dialysis, patient and kidney survival at 1 year was reported to be 100% and 95% respectively and both 94% at 5 years (43).

Despite overwhelming evidence outlining the benefits of immunosuppression and plasma exchange, most reported studies are uncontrolled with only a single randomized prospective study conducted to date (44). Nevertheless, over a 5 year period Johnson *et al* showed that immunosuppression (oral prednisolone 2 mg/kg daily for 1 week; oral cyclophosphamide 2mg/kg daily for 3 months tapering to 1mg/kg) in combination with

plasma exchange every 3 days (compared to daily therapy described in the Hammersmith treatment regimen) was more effective than immunosuppression alone. Although not well matched for severity of renal injury at presentation, measured by percentage of crescentic lesions and serum creatinine, which was a clear prognostic factor, adjunctive plasma exchange improved outcome. Anti-GBM antibodies were more rapidly removed when immunosuppression and plasma exchange were combined and this was associated with better renal recovery, measured by serum creatinine and dialysis requirement (44). A large retrospective study supported these findings with improved patient and kidney outcome in patients treated with immunosuppression and plasma exchange compared to those treated with immunosuppression alone (45).

Although plasma exchange is an invasive procedure with potential complications relating to venous access, and reactions to replacement fluid, it is generally well-tolerated and only associated with minor complications (46). Albumin is the replacement fluid of choice but fresh frozen plasma (FFP) has to be added in some patients, if there is a bleeding risk, for example after renal biopsy, or in patients with pulmonary haemorrhage. FFP is typically collected in anticoagulant citrate dextrose solution (ACD) and so must be exchanged at a lower rate than albumin; bicarbonate production and reduced renal excretion after citrate metabolism poses a risk of metabolic alkalosis (47).

Immunoadsorption (IAS) is an alternative method of removing antibody from the circulation and is used in the treatment of several autoimmune diseases. In renal disease, IAS is most frequently used in ABO incompatible and highly sensitized renal transplant recipients, in antibody-mediated rejection, and in SLE (using DNA-binding columns) while advocates have proposed IAS as a therapy in other glomerular disease, notably focal segmental glomerular sclerosis, ANCA-associated vasculitis and anti-GBM disease (48). IAS has additional benefits to plasma exchange, including selective high affinity binding of IgG subclasses 1, 2 and 4 (but variable binding of IgG 3, IgA and IgM), requires no FFP or albumin and allows a greater plasma volume to be processed. Processing of 2.5 plasma volumes has the capacity to remove up to 87% IgG, with multiple sessions increasing IgG clearance to >98% (48).

The role of IAS in anti-GBM disease has not been widely evaluated with only case reports described prior to a retrospective review of 10 patients treated with IAS and immunosuppression. Antibody levels were 71 to 84% lower after the first IAS treatment and were within normal range after 2 – 9 treatments (49). Long-term patient and kidney survival was reported to be 90% and 50% respectively at a mean of 84 months, somewhat better than previous reports using plasma exchange and immunosuppression but not comparable to larger patient cohorts (43). Therefore, IAS offers an effective therapy for direct removal of circulating anti-GBM antibodies and is non-inferior to plasma exchange although this needs to be more thoroughly evaluated.

Plasma exchange and IAS can remove circulating but not tissue-bound anti-GBM antibodies. This problem can be targeted by virtue of the properties of bacterial proteins secreted by *Streptococus pyogenes*, specifically IgG-degrading enzyme of *S.pygoenes* (IdeS) and endoglycosidase S (EndoS). IdeS cleaves the heavy chain of human

IgG resulting in one F(ab')2 and two monomeric Fc fragments thereby directly affecting IgG effector functions. In comparison, endoglycosidase hydrolysis of all IgG subclass glycans diminishes C1q binding and complement activation as well as IgG-mediated opsonization by impairing IgG FcγR binding. IgM and IgA are resistant to both enzymatic activities (50).

The efficacy of IdeS and EndoS degradation of circulating autoantibodies (51, 52) and tissue-bound anti-GBM antibodies has been shown (53). In an experimental murine model of glomerulonephritis, IdeS removed glomerular Fc fragments of anti-GBM antibodies and was associated with a reduction in leukocyte infiltrate and complement activation as well as complete prevention of albuminuria. This effect was not seen with EndoS treatment even although albuminuria was reduced (53). Following safety studies (54), IdeS trials have progressed mainly in kidney transplantation, but a clinical trial is also underway in anti-GBM disease, evaluating the efficacy of IdeS in removing pathogenic tissue-bound anti-GBM antibodies (GOODIdeS).

Immunosuppression

Glucocorticoids and cyclophosphamide continue to be the mainstay of immunosuppressive treatment in anti-GBM disease. However, there are circumstances where alternative agents may be required most likely relating to the potential risks and tolerability of cyclophosphamide. Rituximab has been used in this instance with good effect, albeit described only in up to twenty case reports (55). Mycophenolate mofetil has also been used, again described only in a handful of case reports but appears to be beneficial in refractory or relapsing disease (56-58). In all cases duration of therapy after induction treatment is unclear and is directed by clinical symptoms and achieving persistently negative anti-GBM antibodies. In cases in whom renal recovery is deemed unlikely (oligoanuria, dialysis dependent with 100% crescents on renal biopsy) and there is no associated pulmonary haemorrhage, immunosuppression may be avoided. However, rare cases of renal recovery despite dialysis dependency have been reported, in which kidney injury may have a significant contribution from severe tubular injury or milder glomerular damage (59, 60). Anti-GBM antibodies will disappear naturally over two years on average. In cases where potential living kidney donors are forthcoming, more rapid antibody removal may be warranted to allow earlier transplantation. We have used both rituximab and cyclophosphamide in these cases and rates of antibody decline appear similar, however, they are significantly faster when combined with plasmapheresis. Although no comparison trials are available we suggest six months of anti-GBM antibody negativity prior to transplantation, and this strategy has resulted in no cases of recurrent disease in our transplant populations, although very rare cases have previously been reported (61) in which other provoking factors may have contributed.

Conclusion

There are clearly challenging clinical variants of anti-GBM disease. Recognizing different patterns of disease and therefore understanding mechanism of injury is more complex. Increasing awareness of different pathogenic immunoglobulin classes and subclasses as well as antigen specificities can make interpreting

immunological findings difficult. The archetypal crescentic glomerulonephritis with linear antibody deposition may not always be present making clinical diagnosis even more problematic. However, the principles in management remain the same; rapid removal of pathogenic antibodies and prevention of their re-synthesis. Whilst direct removal of circulating antibodies by plasma exchange, or perhaps immunoadsorption, are very effective, there are potential new therapies which may also target tissue-bound antibodies persisting in glomeruli and driving disease.

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Table 1

Current treatment protocols	Potential variants without substantial cohort evidence to date (see text)
1. Glucocorticoids 1mg/Kg Prednisolone/day; max 60 mg; tapering weekly 45mg, 30 mg, 25, 20 mg; followed by slower taper(2.5 mg /fortnight) up to month 6	
2. Immunosuppression Oral cyclophosphamide 2-3 mg/Kg, adjusted for WCC (to keep above 4). Reduced dose in elderly (1.5-2mg). 3 months of treatment, possibly shorter in elderly if adequate clinical and immunological response.	IV cyclophosphamide as per ANCA vasculitis protocol, care in timing with plasma exchange, give after Plasma exchange(Pex) session and wait 24 hours, before next Pex. Rituximab 1g x 2 doses
3. Plasma exchange 60 mls/Kg, max 4 litres, daily for 14 days or until anti-GBM titre normalized. Using 5% human albumin alone with additional FFP if risk of bleeding (recent invasive procedure or pulmonary haemorrhage).	Immunoadsorption IdeS therapy
4. Prophylaxis Co-trimoxazole (or in case of intolerance Dapsone, or monthly pentamidine); Anti-fungal(nystatin or fluconazole) Proton pump inhibitor or H2 antagonist Calcium/vitamin D	

Figure 1

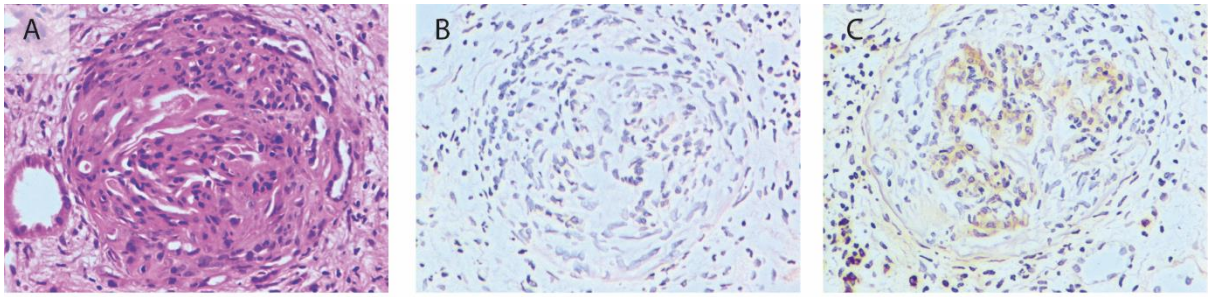

Figure 1 – Renal biopsy tissue from a patient with IgA anti-GBM disease stained with haematoxylin and eosin (A) and by immunohistochemistry for IgG (B) and IgA (C)(all x400). A large circumferential cellular crescent is present in the glomerulus and is associated with compression of the glomerular tuft (A). Linear glomerular basement membrane IgG is not seen by immunohistochemistry (B) but linear IgA (C) is demonstrated within the crescentic lesion.