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A Case of Anti-Glomerular Basement Membrane Disease with Renal and Ocular Involvement Treated with Anti-VEGF Injections

Daniela Potter¹, Gerald Liew² and Bruce Cleland¹¹Liverpool Hospital, Liverpool, NSW, Australia²Westmead Hospital Retina Associates, Australia*Corresponding author: Daniela Potter, Liverpool Hospital, Liverpool, NSW, Australia, E-mail: daniela.potter@health.nsw.gov.au

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Abstract

Context: Anti-Glomerular Basement Membrane (GBM) disease is a rare disease, with limited population data. It is estimated to affect 0.5-2 cases per million of the population and makes up 1-5% of patients with glomerulonephritis. Patients classically present with renal and/or pulmonary involvement, however additional manifestation have rarely been reported.

Case Report: A 45yr old female presented with fever, haematuria and acute renal failure necessitating haemodialysis. She was diagnosed with anti-glomerular basement membrane disease (anti-GBM, Goodpasture's) on the basis of elevated antibody titres and renal biopsy demonstrating a rapidly progressive crescentic glomerulonephritis with positive immunofluorescence. During the course of her management she developed blurred vision in the left eye, which was found to be due to choroidal neo-revascularisation.

Conclusion: The alpha 3 subunit of type IV, the target of the anti-GBM antibody, is primarily found within the kidney and lung however can also be isolated in other sites including the eye. Here we describe a case of anti-GBM disease affecting the kidney and eye. Our patient was successfully treated with anti-VEGF injections, the first time this has been described for this indication.

Context

Anti-Glomerular Basement Membrane (GBM) disease is a rare disease, with limited population data. It is estimated to affect 0.5-2 cases per million of the population and accounts for up 1-5% of patients with glomerulonephritis [1,2]. Patients classically present with renal and/or pulmonary involvement. It has a poor prognosis with a one year overall survival rate of 70-80% of those patients who present with dialysis dependant renal failure [3,4].

Case Report

A 45 year old female presented with a 1 week history of fever and haematuria. Her past medical history was significant for mitral valve *Staphylococcus aureus* endocarditis with a resultant bioprosthetic mitral valve replacement 6 months prior. Clinical examination revealed the presence of a new aortic regurgitant murmur without peripheral stigmata of infective endocarditis. She had a low grade temperature of 37.5°C with hypertension at 144/80 mmHg. Biochemistry demonstrated acute renal failure with a creatinine of 254 µmol/L (reference range 40 µmol/L-80 µmol/L), urea 12.7 mmol/L (reference range 3.0 mmol/L-8.0 mmol/L), sodium of 140 µmol/L (reference range 135µmol/L-145 µmol/L), potassium of 4.4 µmol/L (reference range 3.5 µmol/L -5.5 µmol/L) and bicarbonate of 19 mmol/L (reference range 20 mmol/L-32 mmol/L). Full blood count demonstrated a haemoglobin of 108 g/L (reference range 120 g/L -160 g/L), white cell count of 12.5 × 10⁹ /L (reference range 4.5-11.0 × 10⁹/L) and platelet count 326 × 10⁹ /L (reference range 150-450 × 10⁹ /L). Urine microscopy demonstrated a white cell count of 10-100 × 10⁶ /L (ref <10 × 10⁶/L), red cell count >100 × 10⁶ /L (reference range <10 × 10⁶ /L) and epithelial cell count of 10-100 × 10⁶ /L (reference range <10 × 10⁶ /L). A 24 hour urine collection demonstrated protein excretion of 0.73 g/day (reference range <0.3 g/day).

Initial diagnostic considerations included recurrence of infective endocarditis with associated glomerulonephritis. An echocardiogram confirmed aortic valve leaflet perforation without evidence of vegetation and blood cultures were negative. She was initiated on intravenous flucloxacillin, however, as her renal function failed to improve a renal biopsy was performed which demonstrated a florid rapidly progressive crescentic glomerulonephritis and features of concurrent acute interstitial nephritis. Initial immunofluorescence staining was negative (**Figure 1**). Antibiotic therapy was modified, and prednisolone was initiated in view of the finding of interstitial nephritis, however her renal function continued to decline with worsening fluid status and hypertension. A repeat renal biopsy demonstrated ongoing features of rapidly progressive crescentic glomerulonephritis, however at this time, immunofluorescence was now positive with linear IgG deposition (**Figure2**).

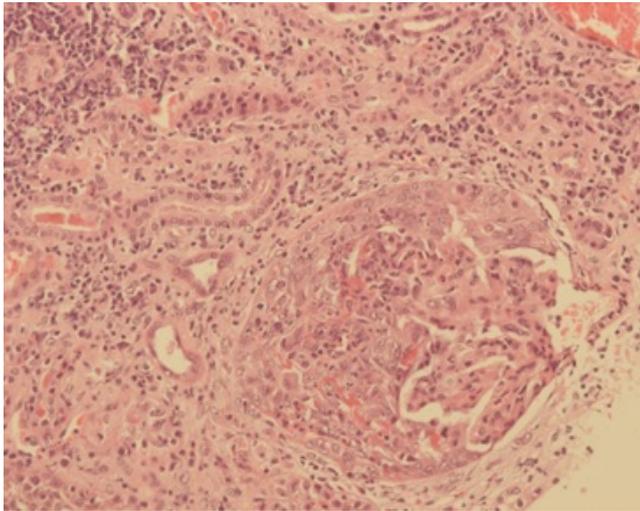


Figure 1. Renal biopsy demonstrating active glomerular crescentic lesion with cellular infiltrate.

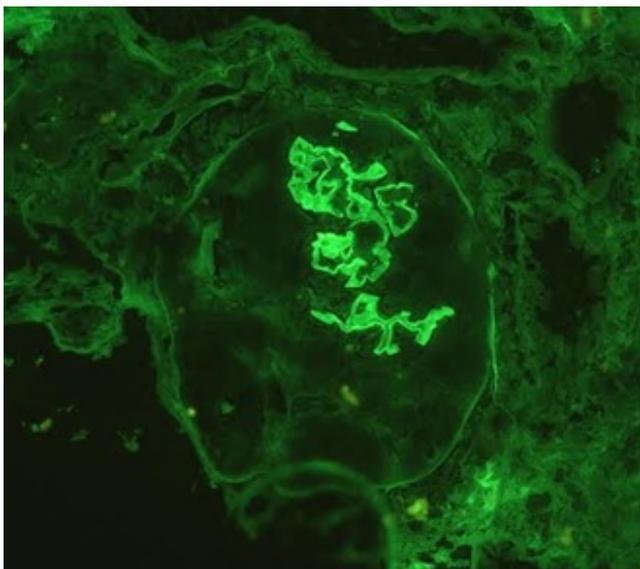


Figure 2. Positive immunofluorescence with linear IgG staining.

Serum immunology was negative for ANCA, ENA, ANA, C3, C4 and dsDNA, however anti-GBM antibody was strongly positive at an initial titre of >200IU/ml (reference range <7IU/ml). This finding, along with her second renal biopsy, was consistent with anti-Glomerular Basement Membrane disease (anti-GBM). It was felt the initial immunofluorescence was a false negative result. She had no pulmonary symptoms and computed tomography scan of the chest did not show evidence of pulmonary haemorrhage.

A course of methylprednisolone, plasma exchange and intravenous cyclophosphamide was initiated with limited improvement in renal function. Despite reduction in anti-GBM titre from >200IU/ml to 22IU/ml she required intermittent haemodialysis.

Following 6 weeks of treatment she developed new blurred vision in her left eye. Ophthalmology review found evidence of choroidal neo-revascularisation within the retina, with visual acuity of 20/20 right and 20/100 left. She had no history of eye disease and vision had previously been normal. Optical Coherence Tomography imaging demonstrated disruption of Bruch's membrane and invasion of a choroidal neovascular membrane into the retina with retinal haemorrhage (**Figure 3**).

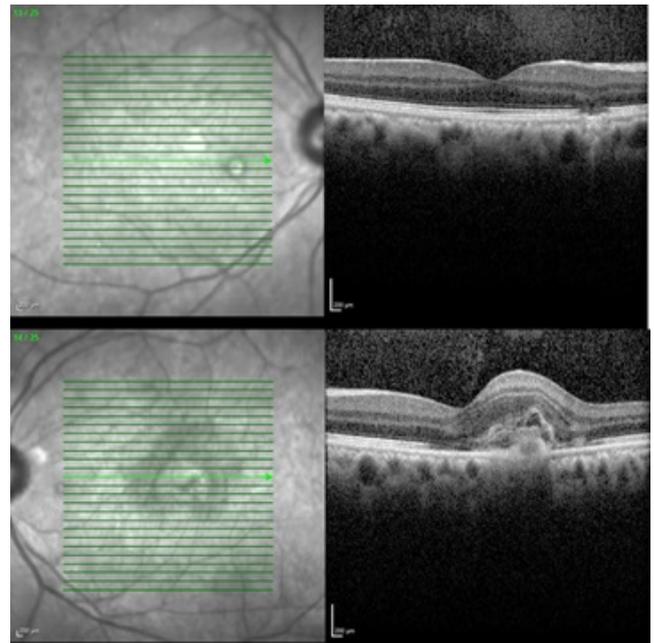


Figure 3. Upper image demonstrating the normal right eye. Lower image demonstrated the abnormal retina of the left eye.

In the context of her active GBM disease we hypothesise active antibody deposition secondary to her anti-GBM disease within Bruch's membrane of the eye caused disruption of the blood-retina barrier and permitted invasion of choroidal vessels into the retina causing her visual disturbance. Given she was at risk of progression of the neo-revascularisation and further retinal haemorrhage; we commenced treatment with intravitreal injections of bevacizumab an Anti-Vascular Endothelial Growth Factor (Anti-VEGF) agent at a dose of 1.25 mg/0.05 ml. This is the established treatment for choroidal neovascularisation. Following a single dose, her neo-vascularisation regressed and visual acuity improved to 20/40. At her last follow up visit 3 months later, the choroidal neo-vascularisation remained quiescent and did not require further treatment.

This is the first report we are aware of choroidal neovascularisation in anti-GBM and treatment for this indication.

Discussion

The term "anti-glomerular basement membrane disease" was proposed by Wilson et al to recognise the presence of an

autoantibody as a defining feature of this condition and replaced the use of Good pasture's Disease [1]. The autoantibody is directed against the alpha 3 subunit of the type 4 collagen and classically causes crescentic glomerulonephritis and pulmonary haemorrhage due to the restricted distribution this subunit of type IV collagen [5-7].

Tissue distribution of the alpha 3 (IV) NC1 subunit has been studied using mouse monoclonal antibody and autoantibodies from patients with anti-GBM. Linear binding within the lung basement membrane and kidney, in particular the glomerular basement membrane, Bowman's capsule and distal tubular basement membrane has been shown. Additional sites of binding have been demonstrated, but are limited, to the membranes in the choroid plexus, lens capsule, choroid and retina of the eye and cochlea [8,9]. Thyroid, adrenal, breast and liver have demonstrated binding on indirect immunoperoxidase only [7].

Eye disease has rarely been reported as a manifestation of anti-GBM disease. In some cases it has been described as part of a wider vasculitic process, such in the presence of anti-neutrophil cytoplasmic antibody in patients who are "double" antibody positive. The effects of a rapidly progressive glomerulonephritis, namely hypertension secondary to renal failure can induce ocular pathology. There are, however, limited historic case descriptions of direct ocular injury induced by the anti-GBM antibody [6]. The first report of the development of subretinal neovascular membranes comes from series of 14 cases in 1994 looking for ophthalmic features of anti-GBM disease [6]. Of the 13 other cases of anti-GBM disease evaluated two patients had features of ocular disease but had concurrent diagnoses of longstanding diabetes mellitus and hypertension.

In this report we demonstrate the first case of confirmed choroidal neo-revascularisation of the eye in the context of anti-GBM disease. Choroidal neovascularisation occurs in other eye diseases such as myopic degeneration, trauma and age-related macular generation, but the patient did not have myopia, had no history of trauma and was too young to develop macular degeneration, which occurs in patients over the age of 60. The unilateral nature of her ocular changes may reflect an asymmetric predisposition. Choroidal neovascularisation occurs in a response to ischaemic insult following tissue damage. Our patient may have developed sub-clinical changes due to evolving

hypertension, fluid shifts due to her severe renal failure and possible micro embolization from endocarditis. The presence of endothelial injury may have allowed antibody contact with the active subunit, initiating a chain of injury. The additional knowledge gained regarding the antibody binding supports the mechanism of direct ocular blood-retina basement membrane injury secondary to antibody binding. The use of anti-VEGF, in this case to good effect, is also the first documented episode for this indication.

We suggest that clinicians caring for patients with anti-GBM disease consider the possibility of extra renal and pulmonary manifestations of the disease and assess for ocular pathology if patients report change in vision.

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