



EXCEPTIONAL CASE

Human leucocyte antigen-associated anti-glomerular basement membrane disease in siblings

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ABSTRACT

We report a case of anti-glomerular basement membrane (GBM) disease in association with human leucocyte antigen (HLA) DRB1 15:01. A 71-year-old woman presented with oligoanuric acute kidney injury accompanied by high titre anti-GBM antibodies. Renal biopsy revealed a severe crescentic glomerulonephritis. Her brother had presented 6 years earlier with oligoanuric acute kidney injury. He was dual positive for MPO ANCA and anti-GBM antibodies. Renal biopsy was not performed. Both had an absence of pulmonary involvement. Tissue typing confirmed both were heterozygous for HLA DRB1 15:01 and DRB1 04:03.

Keywords: acute kidney injury, anti-GBM, familial, Goodpasture syndrome, hereditary

BACKGROUND

Anti-glomerular basement membrane (anti-GBM) disease is rare. It has an incidence of <1.63 cases/million/year and is usually associated with a rapidly progressive glomerulonephritis [1].

The condition is associated with antibodies against the $\alpha 3$ chain of type 4 collagen which is highly expressed in the alveoli and GBM.

Genetic factors, particularly those related to the *human leucocyte antigen (HLA)* gene are implicated in its pathogenesis, but familial occurrence has only been reported once before.

CASE REPORT

A 71-year-old woman presented with oligoanuric acute kidney injury and a 2-week antecedent history of lower respiratory tract-type symptoms that were not improved with antibiotic therapy. She denied haemoptysis, haematuria or epistaxis.

There was a past medical history of untreated hypertension. She was an ex-smoker.

At presentation, her blood pressure was 163/83 mm/Hg and temperature 37.4°C.

Her biochemistry showed creatinine 872 μ mol/L (normal 45–84), urea 32.2 mmol/L (normal 2.5–7.8), potassium 4.5 mmol/L (normal 3.5–5.8), anti-GBM titre >680 U/L (normal <1.0) and anti-neutrophil cytoplasmic antibodies (ANCA) was negative. Her haemoglobin was 89 g/L (normal 115–165). Her chest X-ray was normal.

The patient was commenced on renal replacement therapy and treated with pulsed intravenous (IV) methylprednisolone, IV cyclophosphamide and daily plasma exchange.

She underwent an urgent renal biopsy that demonstrated cellular crescents in 15 of 15 glomeruli, many segmental necrotizing lesions and linear immunoglobulin G deposition on immunofluorescence (Figure 1).

In view of the extensive crescentic change and ongoing oliguria in spite of initial aggressive treatment, further

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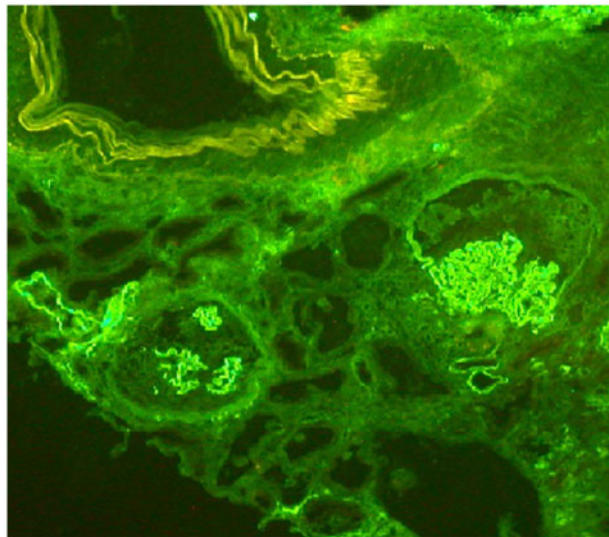


FIGURE 1: Renal biopsy demonstrating linear immunoglobulin G deposition.

immunosuppression was discontinued and she was established on maintenance haemodialysis.

On further questioning, the patient revealed that her brother was also under the care of our renal department.

Six years previously, at the age of 60 years, her brother presented similarly with oligoanuric acute kidney injury, with a 4-week history of feeling generally unwell, nausea, diarrhoea and epistaxis. He did not have haemoptysis or frank haematuria. The patient was an ex-smoker for 10 years. His past medical history was not significant.

Vital signs at presentation revealed a blood pressure of 146/93 mmHg and a temperature of 36.8°C.

Urine dip was active with blood 4+, protein 3+ and glucose 1+.

Presenting biochemistry showed a creatinine of 1726 $\mu\text{mol/L}$ (normal 59–104), urea of 48.9 mmol/L (normal 2.5–7.8) and potassium of 6.8 mmol/L (3.5–5.3).

Immunology showed anti-GBM of 287 U/L (normal <1.0) with weakly positive myeloperoxidase-specific ANCA.

He was started on renal replacement therapy and received IV methylprednisolone, IV cyclophosphamide and daily plasma exchange. Despite this, the patient remained dialysis dependent and anuric. A renal biopsy was not performed. Immunosuppression was discontinued and he was established on maintenance haemodialysis.

A diagnosis of familial anti-GBM disease was suspected based on family history. Both subjects underwent tissue typing and were shown to be heterozygous for HLA DRB1 15:01 and DRB1 04:03 alleles.

DISCUSSION

Anti-GBM disease is a rarity and familial clustering is virtually unreported. This is the second documented case of siblings with anti-GBM disease [2].

It is the first documented case in which both siblings have HLA typing confirming heterozygosity for DRB1 15:01 and DRB1 04:03. Both siblings shared a common childhood environment and both now live in the same geographic area as adults, supporting the hypothesis of an environmental trigger for the condition. Spatial and temporal clustering can occur in anti-GBM disease as shown by Canney et al. [1].

There is a known positive association between HLA DRB1 15:01 and DRB1 04. The hierarchical association of positivity is more so with HLA DRB1 15:01 than with HLA DRB1 04 [3].

DRB1 15:01 is present in 10–15% of the Caucasian population. DRB1 04:03 was shown to be present in 13% of one population in England.

The DR4 allele appears to exert its influence in the presence of DR15.

DRw15 and DR4 contain six amino acid motifs that may make patients susceptible to anti-GBM. These motifs are not seen on DR1. In contrast, DR1 is protective for the condition [4].

Ooji et al. [5] showed the protective effect of DR1 by antigen-specific regulatory T cells. This is associated with a shift in the phenotype of $\alpha 3$ (IV) chain 135–145-specific CD 4⁺ T cells from a pro-inflammatory to a tolerogenic phenotype [5].

In conclusion, we report the second familial case of anti-GBM disease associated with HLA DRB1 15:01 and the first with heterozygosity for DRB1 15:01 and DRB1 04:03 alleles. Again, this case highlights the interplay of a possible environmental provoker(s) with a susceptible HLA type and the subsequent production of pro-inflammatory T cells that is critical for the development of this condition. Finally, a thorough family history remains important.

ACKNOWLEDGEMENTS

Informed verbal consent was obtained from both patients.

CONFLICT OF INTEREST STATEMENT

None declared.

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