ISSN: 2475-6296

Case Report

Journal of Clinical & Experimental Immunology

# Anti-Gbm Disease in Children: Outcomes and Association with Systemic Vasculitis

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**Submitted**: 17 Nov 2018; **Accepted**: 22 Nov 2018; **Published**: 30 Nov 2018

## Abstract

*Anti-Glomerular Basement Membrane (anti-GBM) disease is a rare autoimmune disorder affecting the glomerular and alveolar basement membranes. Diagnosis is based on the detection of anti-GBM autoantibodies, along with renal or lung biopsy. Some patients are both anti-GBM and ANCA positive, reflecting an association with systemic vasculitis that has been reported only in some adult cases. Dual positivity of anti-GBM and ANCA is associated with poorer prognosis and higher relapse rates therefore more aggressive and longer treatment is essential. In this case, series we report four cases of children diagnosed with anti-GBM disease that we also screened for signs of systemic vasculitis.*

**Keywords:** Anti-Glomerular Basement Membrane Disease; Systemic Vasculitis; Anti-Neutrophil Cytoplasmic Antibodies; Glomerulonephritis

## Introduction

Anti-Glomerular basement membrane (anti–GBM) disease is an autoimmune disorder caused by autoantibodies against the NC1 domain of the alpha-1 chain of type IV collagen, which is largely present in the glomerular and alveolar membrane [1]. The disease is not common in adults, and is extremely rare in children [2]. Patients typically present with rapidly progressive glomerulonephritis, with or without pulmonary haemorrhage and general symptoms [3]. Diagnosis of anti-GBM disease is largely based on detection of anti-GBM antibodies, and this is often accompanied by renal or lung biopsy [3]. Other serological testing, such as anti-neutrophil cytoplasmic antibodies (ANCA) can be carried out, and several reports have been made of patients being both ANCA and anti-GBM positive, though this finding is rare. Both p-ANCA and c-ANCA can be seen, but p-ANCA is more prevalent [4]. Also, it has been reported that anti-GBM disease and systemic vasculitis can co-exist [5]. Though this dual existence is rare, several cases have been reported and their symptoms are similar, indicating that it is important to consider both in either condition.

Herein, we report the cases of four patients diagnosed with anti-GBM disease. We describe disease manifestations, laboratory parameters, autoantibody profile, biopsy results and treatment. Table 1 provides a summary of the patients identified.

## Cases

Patient 1 is a fifteen-year-old female presenting with a one-month history of haemoptysis, 2 episodes of epistaxis, lethargy, headaches, nausea and vomiting. She was initially treated as a chest infection. On admission, she was found to have poor renal function (creatinine 513 micromole/L). Examination showed bilateral renal angle tenderness and urine dip revealed 3+ blood and 4+ proteins. Initial investigations showed increased C–reactive protein (CRP) (115 mg/L) and low haemoglobin (3.0 g/L). Renal ultrasound showed increased echogenicity of renal cortex with loss of medullary differentiation bilaterally. Anti-GBM level was 96.5 U/ml and renal biopsy that followed showed crescentic glomerular nephritis and IgG staining along the glomerular basement membrane. The patient had 2 units of blood transfused and in total had 7 transfusions over the 2-week admission. Treatment of double-filtration plasmapheresis (DFPP) was commenced and continued for 10 sessions over 2 weeks. Pulsed IV methyl-prednisolone 1 g was commenced for 5 days and was then switched to an oral prednisolone taper. One IV dose of cyclophosphamide 500 mg/m2 was given during admission, and in total, she received 4 doses over a four-month period, until a negative anti-GBM titre was reached and renal function recovered. Mycophenolate mofetil (MMF) 500 mg BD was added for a total of 8 months before being discontinued.

Patient 2 is a 2-year-old female who presented with a one week history of fever >39 °C. She was previously treated with trimethoprim for a urinary tract infection based on symptoms and positive microscopy and culture of *E coli*. Despite this, she continued to spike fevers and had abdominal and left loin pain, so consequently was admitted. Renal ultrasound demonstrated features of bilateral pyelonephritis so she was given IV cefuroxime. The fevers continued and did not respond to a change in antibiotics (teicoplanin and meropenem). CRP at this point was 152 mg/L. Further investigations did not elicit another cause. Repeat urinalysis showed haematuria 3+ and proteinuria 1+ and a diagnosis of vasculitis with renal involvement was considered, so IV methylprednisolone 300 mg/m$^2$ was started for 3 days, leading to a fall in temperature and CRP. She was found to be

hypertensive with systolic BP ranging from 108-143 mmHg, despite often having a negative fluid balance. She continued to have central abdominal pain, raised BP, microscopic haematuria and minimal proteinuria, and this time a possible diagnosis of polyarteritis nodosa was considered. However, neither angiography nor renal biopsy showed evidence of vasculitis, though renal biopsy showed 75% crescentic nephritis. Anti-GBM antibodies were checked at this point and were significantly positive; hence, a diagnosis of anti-GBM disease with systemic inflammatory response was given. DFPP was commenced, for duration of 10 sessions over 2 weeks, and she was commenced on 30 mg (2 mg/kg) of prednisolone on a reducing regime. One IV dose of cyclophosphamide was given, and she was then continued on oral cyclophosphamide 30 mg (2 mg/kg) for 2 months. Azathioprine 30 mg (2 mg/kg) was commenced on discharge from hospital and her anti-GBM levels were decreasing but continued to be monitored. Renal function normalised quickly, having previously been moderately abnormal.

Patient 3 is a 17 year-old female initially presenting with a four-day history of tonsillitis and a three day history of worsening macroscopic haematuria. Blood urea and creatinine levels increased (11.5 to 16.1 and 153 to 300 micromol/L respectively) consistent with a rapidly progressive nephritis. Both post-streptococcal glomerulonephritis and IgA nephropathy were considered as differential diagnosis for which she was put on a fluid restriction of 1.5 L. Renal biopsy showed florid nephritis and linear IgG staining along the basement membrane. Anti-GBM was tested at this point showing a level of 10.1 U/ml so anti-GBM disease was diagnosed. Treatment consisted of pulsed methylprednisolone, switching to oral prednisolone 80 mg after 3 days. DFPP was also commenced for 9 sessions, and a first dose of IV cyclophosphamide 500 mg/m$^2$, causing a decrease in creatinine to 154 micromol/L and anti-GBM antibodies. The patient was discharged on 60 mg oral prednisolone on a reducing dose and had a further 3 doses of monthly IV cyclophosphamide. The patient was then commenced on MMF 250 mg BD and continued to have a negative anti-GBM titre. Renal function resolved along with the resolution of symptoms.

Patient 4 is a 16 year-old male with a four-month history of intermittent haemoptysis, described as fresh as well as altered blood. High resolution CT showed extensive alveolar shadows due to haemorrhage, and biopsy following this showed extensive alveolar damage including collapsed air spaces, macrophages, inflammation, haemorrhage and fibrosis, but no evidence of malignancy. Anti-GBM was raised at 22 U/ml, and the patient consequently received IV methylprednisolone and 2 cycles of DFPP, which were to be continued. Risk factors for this patient included being a smoker (30 cigarettes/day) and various illicit drugs. The patient was switched to oral prednisolone 60 mg OD and received blood transfusions due to low Hb (7.3 g/L). Haemoptysis and shortness of breath on exertion continued, though cough and wheeze had improved. He was started on hydroxychloroquine and had one dose of IV cyclophosphamide. On discharge, the patient had an improved fibrinogen, and undetectable anti-GBM. He had received 10 sessions of DFPP in total. Haemoptysis had resolved and renal function remained stable. IV cyclophosphamide was to be continued monthly for 6 months. MMF was commenced, though the patient was found to be intolerant so it was switched to oral azathioprine 100 mg OD (2 mg/kg). Anti-GBM titre remained negative; only 4 doses of cyclophosphamide were given. Oral prednisolone continued to be tapered off, and in absence of lung or systemic disease, the immunosuppressants were discontinued.

## Disclosure

The authors declare that there is no conflict of interest.


## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.


**Table 1: Summary of cases discussed**

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---|---|---|---|---|
| **Age at presentation, Gender** | 15<br>Female | 2<br>Female | 17<br>Female | 16<br>Male |
| **Presentation** | Haemoptysis, epistaxis, lethargy, headaches, nausea, vomiting and dyspnoea | Continuous fevers, abdominal and left loin pain, microscopic haematuria | Macroscopic haematuria consistent with rapidly progressive nephritis | 4 month history of haemoptysis |
| **CRP (mg/L)** | 115 | 152 | 19 | 19 |
| **Antibodies**<br>c-ANCA/p-ANCA<br>MPO<br>PR3<br>Anti-GBM | <br>**p-ANCA** positive<br>negative<br>negative<br>positive | <br>**c-ANCA** positive<br>negative<br>negative<br>positive | <br>**p-ANCA** positive<br>negative<br>negative<br>positive | <br>**p-ANCA** positive<br>negative<br>negative<br>positive |
| **Biopsy** | **Kidney** - Crescentic glomerulonephritis; IgG deposition on glomerular basement membrane | **Kidney** - Crescentic glomerulonephritis with around 75% crescents; IgG deposition along tubular basement membrane | **Kidney** - Focal segmental necrotising glomerulonephritis with 33% crescent rate; IgG deposition along the capillary loops | **Lung** - Extensive alveolar damage – collapsed air spaces, macrophages, inflammation, haemorrhage, fibrosis |

| | | | | |
|---|---|---|---|---|
| **Treatment**<br>All patients received blood transfusions as they were severely anaemic<br>Cyclophosphamide was given until a negative anti-GBM titre was detected | • 10 cycles DFPP<br>• 4x 500mg/m$^2$ cycles cyclophosphamide<br>• MMF 8 months 500mg BD<br>• IVMP followed by oral prednisolone | • 10 cycles DFPP<br>• 1x 500mg/m$^2$ cycle cyclophosphamide<br>• followed by 2 months 30mg OD oral<br>• Azathioprine 30mg OD<br>• IVMP followed by oral prednisolone | • 9 cycles DFPP<br>• 4x 500mg/m$^2$ cycles cyclophosphamide<br>• MMF 6 months 500mg BD<br>• IVMP followed by oral prednisolone | • 10 cycles DFPP<br>• 4x 500mg/m$^2$ cycles cyclophosphamide<br>• Azathioprine 100mg OD, reduced to 50mg after 3 months (MMF intolerant)<br>• IVMP followed by oral prednisolone |

**Anti – GBM**, anti – Glomerular Basement Membrane; **c – ANCA**, cytoplasmic – anti-neutrophil cytoplasmic antibodies; **CRP, C** – reactive protein; **DFPP**, Double filtration plasmapheresis; **MMF**, Mycophenolate mofetil; **MPO**, Myeloperoxidase; **p – ANCA**, perinuclear - antineutrophil cytoplasmic antibodies; **PR3**, Proteinase–3

## Discussion

All four patients at diagnosis were screened for clinical features of systemic vasculitis, marked inflammatory response, as well as characteristic histology and autoantibodies. Two patients did have particularly high inflammatory markers at presentation. None had definite histological features of vasculitis other than anti-GBM disease on renal biopsy. Biopsy findings suggestive of the disease include crescent formation due to membranous nephropathy and linear IgG deposition along the glomerular basement membrane, though the absence of IgG staining does not exclude the disease [6]. It can also be seen in other autoimmune diseases such as systemic lupus erythematosus, diabetic nephropathy and Alport's disease after renal transplantation [1]. Primary small vessel vasculitides such as granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) should be considered when pauci-immune glomerulonephritis is seen on immunofluorescence. Where there are granular deposits that would indicate immune complex formation, disorders such as Henoch–Schönlein purpura or systemic lupus erythematosus should be considered [7]. It should also be noted that the presence of crescents is an indicator of more severe disease, especially with more than 25% crescents. This therefore suggests that immune complex glomerulonephritis is generally a less severe form that anti-GBM glomerulonephritis [8]. Pulmonary biopsy can be considered, but findings of IgG deposition are not as consistent with anti-GBM disease as those observed in renal biopsy [9].

All four patients were positive for ANCA, but all were lacking specificity of proteinase -3 (PR3) or myeloperoxidase (MPO). It is known that those with both ANCA and anti-GBM positivity have a higher relapse rate than patients only presenting with anti-GBM antibodies [10]. These patients have had often a worse pattern of disease and early treatment is necessary to improve outcomes. Therefore, it was important for us to check that our patients did not elicit these features, and if they had, a different management plan might have been initiated. Early diagnosis was vital, and there have been several reports of a correlation between early interventions with a better outcome [11, 12]. There have previously been reports of a coexistence of anti-GBM disease and systemic vasculitis in children; in particular, much of the literature concerns ANCA associated vasculitides with a positive anti-GBM titre [12, 13]. The majority of the literature takes place in the form of case reports, due to the rarity of the disease. Many of the reported cases have been in the adult population, where those patients with dual positivity and features of systemic vasculitis have poor recovery of renal function, potentially linked to greater glomerular damage due to the presence of both antibodies [14].

A theory for the coexistence is one in which ANCA development is the initial event, with ANCA-associated mechanisms leading to the exposure of the otherwise hidden alpha3 NC1 type 4 collagen antigen and triggering anti-GBM antibody production [15]. There is a high incidence of this dual positivity of ANCA and anti-GBM, which has a pathogenic link [10]. Pure anti-GBM disease is monophasic and non-relapsing. With ANCA, associated vasculitis there is a 30-60% relapse rate and this double positive suggests a higher relapse rate. Therefore, early diagnosis and indicator for monitoring is needed and although rare in children there have been suggestions that it may take a different clinical course [5].

The management of anti-GBM disease in children is largely based on the treatment for adults. Treatment is intense, with plasmapheresis for 10-14 days to remove the antibody from circulation, until a negative anti-GBM titre is detected. The method used in our centre is DFPP, which has the advantage of removing antibodies, without the need for replacement blood products. Immunosuppression is vital, including both IV 500 mg/m2 cyclophosphamide monthly and IV pulsed methylprednisolone, followed by oral prednisolone on a reducing dose. The anti-GBM titre is monitored over this time, until a negative reading is achieved on two occasions [1, 7]. The disease is commonly monophasic, indicating that the immunosuppressants can usually be discontinued within a few months, as occurred in the cases described. In contrast, those patients with both ANCA and anti-GBM positivity are likely to receive immunosuppression on a maintenance regime [16].

Summarising our patients, one had renal features only, two had both renal and pulmonary features, and one had only pulmonary features of anti-GBM disease. All patients were severely anaemic, and consequently received blood transfusions. Plasmapheresis was used as initial treatment, along with cyclophosphamide for three to four months. Remission was achieved after a maintenance period of up to eight months. All four patients had a monophasic pattern of disease.

In conclusion, the management of anti-GBM disease and anti-GBM disease combined with systemic vasculitis is similar, but their coexistence may play a significant part in their prognosis. For future cases, our strategy would be checking for signs of systemic vasculitis in patients presenting as anti-GBM disease, as treatment plan and duration may need to be reconsidered.

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