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ANTI-GLOMERULAR BASEMENT MEMBRANE (ANTI-GBM) DISEASE: THE CHALLENGES IN DIAGNOSIS AND THE CHOICE OF TREATMENT

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ABSTRACT

Anti–glomerular basement membrane (anti-GBM) antibody disease is an autoimmune disorder. The majority of patients develop widespread glomerular crescent formation, presenting with features of rapidly progressive glomerulonephritis (RPGN). The etiology is unclear. The treatment depends on the creatinine level at presentation, dialysis dependency, and pulmonary involvement to decide on plasmapheresis, glucocorticoid, and immunosuppressive therapy. We report a case of a 17-year-old lady who presented features of RPGN requiring intermittent dialysis, renal biopsy, and serology showing features of anti-GBM glomerulonephritis (GN).

Keywords: *Anti-GBM disesase, glomerulonephritis, rapid progressive glomerulonephritis, end stage kidney disease*

INTRODUCTION

Anti–glomerular basement membrane (anti-GBM) is a disorder in which the circulating antibodies are directed against an antigen normally present in the GBM and alveolar basement membrane, specifically the alpha-3 chain of type IV collagen. Most patients will be presenting with systemic signs such as fever, arthralgia, malaise, loss of weight in the prodromal period, and then signs and symptoms of acute glomerulonephritis (GN). From there, we will think of causes of rapidly progressive glomerulonephritis (RPGN) without pulmonary involvement, such as post-streptococcal GN, immunoglobulin A (Ig A) vasculitis, antineutrophil cytoplasmic autoantibodies (ANCA) associated disease and anti-GBM disease. To establish the diagnosis, a series of investigations included a serological assay of serum anti-GBM antibodies and renal biopsy. Treatment is to aim to remove pathogenic autoantibodies rapidly and start early. Treatment response depends on the severity of the renal involvement, with or without pulmonary involvement, and the treatment choices, including plasmapheresis with immunosuppressive therapy or supportive care.

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CASE REPORT

A 17 years old lady, presented with haematuria for a month, one week of fever and pain in the left lumbar. Upon further history, she had haematuria at the age of 12, but she did not seek medical attention, in which it resolved after two days. She has no regular medications but she had been taking herbs – pudina and moringa leaves for the past 6 years. She has no significant connective tissue disease related symptoms, denies recent upper respiratory tract infection. During the first admission, the physical examination was unremarkable. Her haemoglobin level was 9.4 g/dL, white blood count was 20 x 103 /µl, platelet 279 x109 /L, urea 9.9 mmol/L, creatinine 271 µmol/L, potassium 3.9 mmol/L, and C-reactive protein (CRP) of 107 mg/L, urine protein and creatinine ratio 0.53 g/mmol . Antinuclear antibody (ANA), C3, C4, and anti-streptolysin O (ASOT) titer were negative. The initial impression was acute pyelonephritis with non-oliguric acute kidney injury (AKI), with probable Immunoglobulin A (IgA) nephropathy, and was given antibiotic - IV Tazocin, and IV Methylprednisolone for one week. She has undergone temporary haemodialysis for worsening uraemia and hyperkalaemia. The patient was counselled for a kidney biopsy but was not keen at that point of time and she requested to be discharge.

After a week from the discharge, she presented to our hospital with frothy urine and haematuria, uraemic symptoms (nausea and vomiting), and bilateral lower limbs swelling. On examination, she has bilateral lower limb swelling with pitting oedema up to mid-shin, other systemic review is unremarkable.

She has elevated blood pressure. Further blood and urine investigations are showed in Table 1 and 2. She has nephrotic range of proteinuria, her creatinine level has worsen, urine culture and sensitivity of extended-spectrum β-lactamases (ESBL) Klebsiella pneumoniae. There was no evidence of obstructive uropathy in the ultrasound kidney urinary bladder with a normal size of both kidneys and no evidence of thrombosis from renal doppler. Chest X Ray was normal. Anti-GBM titer and ANCA were sent but the results were still pending. The result of ASOT titre was the first serology to be available, the titer was elevated (6400 IU/ml). Thus, the patient was treated as post-streptococcal GN. The renal function was never recovered despite completed total of two courses of methylprednisolone with adequate antibiotic coverage.

Test Type	Value	Normal Range
WBC (x 10^3/µl)	9.9	4-10
Neutrophil (%)	78	55-70
Lymphocyte (%)	13	20 - 40
Hemoglobin (g/dL)	8.00	12-15
Mean Cell Volume (fl)	78.40	83-101
Mean Cell Hemoglobin (pg)	25.1	27-32
Platelets (x10^9/L)	577	150 - 400
Urea (mmol/L)	22.1	2.8 – 7.2
Creatinine (µmol/L)	668	45-84
Na (mmol/L)	137	136-145
K (mmol/L)	4.0	3.5-5.1
Cl (mmol/L)	104	98-107
Calcium (mmol/L)	2.01	2.20-2.65
C-reactive protein (CRP) (mg/L)	71.60	0-5.0
Phosphate (mmol/L)	2.06	1.20-2.26
C3 (g/L)	1.31	0.83-1.31
C4 (g/L)	0.28	0.15-0.57
Venous blood gas	pH 7.332, bi-carbonate 18.6, Lactate 1.5	
Urinalysis	Blood 3+, Protein 2+, Leucocytes -ve	
Urine PCR (g/mmol)	0.53	0.00-0.03

Table 1 shows blood and urine investigations of second admission.

µL- microliters; g/dL- grams/deciliter; mmol/L – millimoles per liter; µmol/L – micromole per liter; mg/L – milligrams per liter; fl – femtoliter

Test type	Result
ANA	Negative
ANCA	Negative
Anti-GBM	Positive (452.502 U/ml)
ASOT	Positive (6400 IU/ml)
PLA2R Antibody	Negative

Table 2 shows autoimmune workup.

ANA – Antinuclear antibody; ANCA – Anti-neutrophil Cytoplasmic; Anti-GBM – Anti- Glomerular Basement Membrane; ASOT – Anti-Streptolysin O Titer; PLA2R antibody – Phospholipase A2 receptor antibody

Renal biopsy was performed but it was delayed in view of the infection (Figure 1 and 2). The result showed a crescentic and necrotizing lesion with diffuse sclerosing (15/23, 65% global glomerulosclerosis) pattern. The anti-GBM autoantibody titer, in which was available after the renal biopsy result, showed 452.502 U/ml (positive), while ANCA is negative. Correlate with serology and immunofluorescence findings, an certain diagnosis was made - Anti-GBM disease. Also, there is evidence of acute tubulointerstitial nephritis with acute tubular injury in the background of moderate (60%) chronic tubulointerstitial damage, as possibility results from herbal taking or the medications.

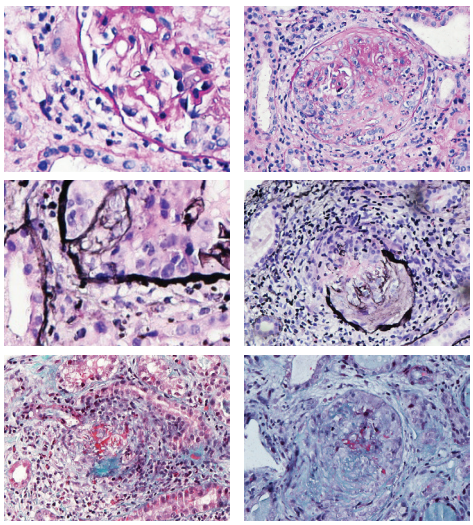

Figure 1: Renal histopathology in anti-GBM GN. (A-B) Periodic Acid Schiff stain, X40 magnification demonstrated (A) segmental sclerosis of the glomerulus and crescent within the glomerulus; (B) fibrocellular crescent within the glomerulus. (C-D) Silver stain, X40 magnification (C) demonstrated dilated tubules lined by reactive atypia and contains granulocytes in the lumen and glomerulus with cellular crescent; (D) A few of the glomeruli show destruction of the Bowman capsule. (E-F) Masson Trichrome stain demonstrated fibrinoid necrosis and a few neutrophils.

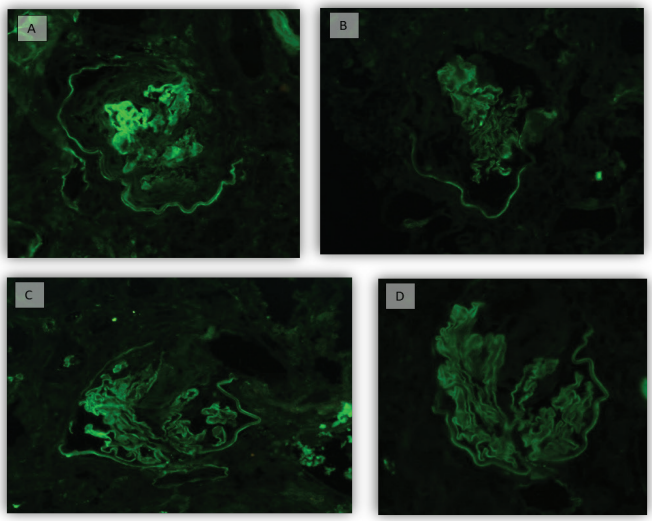

Figure 2: Immunofluorescence (IF) staining features of the renal biopsy. (A&B) showed linear staining of IgG (3+) and C3 (2-3+) respectively. (C&D) showed Kappa light chain (2-3+) and Lambda light chain (2-3+) respectively.

Oral cyclophosphamide was commenced and continued with oral prednisolone. However, there is no renal recovery, and the patient is dialysis dependent now. During subsequent clinic visits, the parents and the patient were counselled for long-term renal replacement therapy, including renal transplant. The mother agreed to be the donor.

DISCUSSION

Anti-GBM disease is a small vessel vasculitis. The circulating antibodies are directed against an antigen intrinsic to the GBM and alveolar basement membrane, causing RPGN and/or alveolar hemorrhage. The majority of patients present with RPGN (crescentic), if untreated, progresses rapidly to end-stage kidney disease (ESKD).

Early diagnosis and intervention determine the response to therapy and long-term prognosis. Kidney biopsy provides information regarding the disease activity and chronicity of kidney involvement [1] and may help in guiding the treatment. It also excludes the other possible causes of other GN. However, in this case, renal biopsy was delayed in view of the concurrent infection. The differential diagnosis at that point of time includes, linear antibody deposition: anti-glomerular basement membrane (GBM) disease; granular immune complex disorder: post infectious glomerulonephritis (PSGN), lupus nephritis, Ig A nephropathy; pauci-immune disorders. Nonetheless, AKI due to acute tubular injury, obstructive uropathy need to be ruled out. ASOT titer was the first marker to be positive, ANCA titer is negative, thus, the preliminary diagnosis was made as PSGN.

The association of anti-GBM disease with high ASOT titer is not known. There is a case report by Emma O'Hagan et. al. reported the patient has high ASOT titer and histologic feature shows anti-GBM disease. Elevated ASOT titer indicates that the body has been exposed to streptococcal bacteria, typically within the past few weeks. High ASOT levels can persist for some time after the infection has resolved. ASOT levels are particularly helpful in diagnosing post-streptococcal complications such as acute rheumatic fever, or PSGN, a type of kidney inflammation that occurs after an infection with certain strains of streptococcus bacteria, particularly after a throat or skin infection caused by these bacteria. It's an immune-mediated response to the streptococcal infection that affects the glomeruli of the kidneys. It associates with low complement levels. Anti-GBM disease, on the other hand, is an autoimmune disorder, has normal complement levels. While it's theoretically possible for someone to have both conditions simultaneously, it's extremely rare and not commonly reported. Both conditions have distinct triggers and mechanisms, so experiencing both at the same time would be unusual. However, if someone has a pre-existing kidney condition like PSGN and later develops anti-GBM disease due to autoimmune factors, it might complicate the kidney condition and worsen the overall kidney function.

With regards to the treatment, the patient received IV Methylprednisolone on the first admission, then oral prednisolone 1mg/kg initiated after the preliminary report of renal biopsy while waiting for the immunofluorescence from renal biopsy for the definite diagnosis. Unfortunately, there hasn't been any renal recovery following the treatment.
Hence, it comes to this common clinical question of whether to start treatment empirically in a patient with the suspected anti-GBM disease before the diagnosis is confirmed by serological or kidney biopsy; and whether to treat a patient who presents with dialysis-dependent kidney failure without pulmonary hemorrhage.

There is a review by Ruchi H. Naik, proposed to start empiric treatment before the definitive diagnosis is made, especially in the case where serology and kidney biopsy are delayed due to any reason, as untreated RPGN progress to rapid loss of renal function over weeks to months. The suggested empiric therapy includes pulse with IV methylprednisolone, either 500 mg or 1 gm, for a minimum of 3 doses. Plasmapheresis may be considered specifically if the patient has haemoptysis raising concern for the severe form of anti-GBM disease until one has the definitive diagnosis. Later more specific treatment is considered once the definitive diagnosis is made.

Some of the experts do not treat a patient who is dialysis dependent without pulmonary hemorrhage since there is a very low likelihood of kidney response. Some of them consider short trials of plasmapheresis and immunosuppressive therapy,

particularly among those patients with very acute disease, younger patients who are better able to tolerate aggressive immunosuppression, and patients whose renal biopsy shows focal crescentic glomerular damage associated with acute tubular injury [1]. In observational studies, the use of plasmapheresis has been associated with improved patient and kidney survival [2].

A trial of plasmapheresis is generally recommended for the treatment of patients with anti-GBM disease. Two factors are considered by many experts to justify this recommendation: Improved morbidity and mortality in the era of plasmapheresis compared with historic rates; rapid removal of anti-GBM antibody, compared with immunosuppressive agents alone with a slower reduction in levels. There is a case series by Michele H. Mokrzycki et al., suggested infusion of intravenous immune globulin (IVIG; 100 to 400 mg/kg) can be given after a plasmapheresis session to partially replenish immunoglobulin levels if there is a severe infection in the setting of plasmapheresis.

There is a direct correlation between the initial plasma creatinine concentration and the percent of glomeruli with crescents, and between anti-GBM antibody levels and the plasma creatinine at presentation for prognostication. When the plasma creatinine concentration is above 442 µmol/L, crescents are usually present in more than 75% of glomeruli [3]. In another words, a low proportion of preserved glomeruli and presence of oligoanuria may have poor prognosis for recovery.

There is a cohort of patients with creatinine <500 µmol/L, in which renal survival was 95% and 94% at one and five years, respectively. Compared with patients with creatinine >500 µmol/L at presentation but not requiring immediate dialysis, renal survival was 82% and 50% at the same respective time points. For patients who require dialysis at presentation, renal recovery occurred in 8% at 1 year. There are reports showing similarly poor renal recovery in patients with dialysis-dependent kidney failure at presentation, with the highest rate of approximately 20% recovery in one series [4].

For patients with the anti-GBM disease who progress to ESKD, require long-term renal replacement therapy, and opt for kidney transplantation, some experts suggested postponing until anti-GBM antibodies remain undetectable for six months or longer. Recurrence of anti-GBM disease may be as high as 50% after transplantation in patients with detectable anti-GBM antibodies at the time of transplantation. Rate of graft failure and overall patient and renal survival with anti-GBM disease after kidney transplantation is similar to that in patients with other causes of kidney failure [5].

CONCLUSION

Anti-GBM disease has poor prognostic value in untreated patients or the treatment is delayed. Renal recovery is less likely in patients requiring renal replacement therapy at presentation. Early diagnosis and intervention are crucial for achieving a good response to treatment. A trial high dose pulse of methylprednisolone for those patient who suspected anti-GBM disease if the serology or renal biopsy is delayed for some reasons, and trial of plasmapheresis plus immunosuppressive therapy can be considered for patients once the diagnosis of anti-GBM disease is confirmed, who require immediate dialysis at presentation but do not have a pulmonary haemorrhage. This is particularly important for patients with very acute disease, renal biopsy showing focal crescents and tubular damage.

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