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Successful treatment with intense immunosuppressive therapy in an initially 100% crescentic lesion of anti-GBM nephritis

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ABSTRACT

Anti-glomerular basement membrane (anti-GBM) nephritis is uncommon glomerular disease caused by autoantibodies targeting the capillary beds of the kidney. The clinical presentation of the disease is a variable nephritic syndrome, rapidly progressing to glomerulonephritis. Treatment outcomes are dependent on predictors at first diagnosis. We presented a case of 58-year-old man who did not have underlying disease presented with marked abdominal distension and acute kidney injury. He had no evidence of chronic renal disease before admission however, laboratory test showed microscopic haematuria (RBC 30-50 per high-powered field), proteinuria (2.9 g/d), and renal failure (serum creatinine 610 µmol/L) compatible with rapidly progressive glomerulonephritis; hence, a renal biopsy was conducted. The pathology showed 100% crescentic glomerulonephritis with IgG deposits in a linear pattern at the GBM. The initial serum anti-GBM titre was 105.59 RU/mL. This patient had poor renal prognosis factors for treatment response. After a discussion regarding treatment option with the patient, we decided to give intensive immunosuppressive therapy and plasmapheresis due to his good baseline functional status. The patient achieved partial remission and is not dialysis dependent. In conclusion, despite a poor renal prognosis with 100% crescents and serum creatinine ≥ 600 µmol/L, the treated patient had a good survival status and did not become dialysis-dependent. However, immunosuppressive treatment should be performed along with careful monitoring for infection to avoid infection-related morbidity and mortality.

Case Report

Implication for health policy/practice/research/medical education:
Anti-glomerular basement membrane nephritis is a rare glomerular disease characterized by IgG deposit at the glomerular basement membrane and crescentic lesion. The 100% crescentic lesion is related to unfavorable prognosis and is challenging to treat with the immunosuppressive drug. Here we reported the successful treatment with the intense immunosuppressive therapy in a 58-year-old male with 100%crescentic lesion of anti-GBM nephritis preventing to become dialysis-dependent status.

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Introduction

Anti-glomerular basement membrane (anti-GBM) nephritis is an autoimmune disorder characterised by circulating autoantibodies targeting the α3 chain of type IV collagen located in the GBM and the alveolar basement membrane. The incidence of disease is less than one per million population/year in the European population. Anti-GBM nephritis had been reported in bimodal age groups, commonly in young men in the third decade of life and in both genders in the sixth decades (1). In younger patients, Good pasture syndrome presents as pulmonary hemorrhage combined with anti-GBM nephritis. In contrast, isolated anti-GBM nephritis is more noted in the elderly. Patients can present with various clinical features such as acute nephritis syndrome, rapidly progressive glomerulonephritis, chronic glomerulonephritis, or concomitant with pulmonary hemorrhage (good pasture syndrome). Crescentic glomerulonephritis (with linear immunoglobulin G and C3 deposition along the glomerular membrane is the pathognomonic of kidney pathological features (2). The mainstay of treatment is immunosuppressive therapy and plasmapheresis.

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However, the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines suggest avoiding intense treatment of patients with 100% crescent or presentation of dialysis-dependence (3). Here, we report a case of anti-GBM nephritis with 100% crescentic lesions presenting with renal pathology in which we successfully achieved partial remission using steroid, cyclophosphamide, and plasmapheresis treatment.

Case Presentation

A 58-year-old British male was hospitalised at the Prince of Songkla University hospital, a tertiary hospital in southern of Thailand, on 18th February 2021 due to marked abdominal distension for one week. One month prior to admission, he complained of progressive anorexia, fatigue, and abdominal distension. He noticed that both legs were swollen, and his urine became frothy. He did not complain of dyspnoea, cough, or hemoptysis. He denied any medical or family history of hypertension, diabetes mellitus, cardiovascular disease, cirrhosis, or renal disease. He had history of heavy alcohol drinking (three bottles per day) and quit drinking for two weeks. He also had a surgical history of cholecystectomy four years prior. At first, he had presented to local hospital and was considered for dehydration. After intravenous fluid was given, his clinical condition was not improved. Hence, he was referred to the tertiary care hospital. On physical examination, he was presented with mild drowsiness. His body temperature was 37.0°C, his respiratory rate was 28 per minute, and his pulse was regular at 92 per minute. He also had new onset hypertension with evidence of his blood pressure rising to 178/87 mm Hg. Conjunctiva was pale and anicteric, and multiple spider nevi were found. Lung and heart were otherwise normal. There was marked abdominal distension with fluid thrill, and shifting dullness was positive. Peripheral oedema was also found upon leg examination. The urinary bladder could not be palpated.

Laboratory investigation

His complete blood count showed that the patient's haemoglobin was 13.9 g/dL, with a normal white blood cell count and no thrombocytopenia. Coagulation screening showed a normal range of prothrombin and activate prothrombin time. Urinary analysis showed microscopic haematuria (30-50 red blood cells per high-powered field) and proteinuria 3+ in the urine dipstick test. The urine examination under light microscopy found that red blood cells in urine were dysmorphic for 80% of the total count. Red blood cell casts and oval fat bodies were not present. The quantitative spot urine protein to creatinine ratio was 2.9 g/d. The patient's renal function was impaired with creatinine 610 µmol/L, urea 27.07 mmol/L, and estimated glomerular filtration rate 8 mL/min/1.73^2. The rest of the lipid profile was normal, including the cholesterol level. There were no abnormalities of the liver function test except for hypoalbuminemia (3.0 g/dL). However, abdominal ultrasound findings found cirrhosis with large ascites. Both kidneys were normal in size. Viral hepatitis serology was negative. Complement levels were normal. The ANA level was positive with low titre (1:80). The serology results were negative for anti-neutrophil cytoplasmic antibody (ANCA) and anti-double stranded DNA antibodies. His anti-GBM antibody findings were positive at a titre of 105.59 RU/mL (normal value 0-20 RU/mL). Planar chest X-ray was conducted and it showed unremarkable findings.

A kidney biopsy was performed. Light microscopy reviewed six glomeruli. The rest of them showed crescentic glomerulonephritis with cellular crescents (100% crescent) and mesangial expansion (Figure 1). Immunofluorescence analysis demonstrated linear IgG staining along the glomerular capillary basement membrane with intensity 3+ (Figure 2). IgA, IgM, C3c, and C1q were negative. There was weak linear staining for anti-lambda antibodies and intensity 2+ for anti-kappa antibodies along the GBM. Severely atrophic tubules and severe interstitial fibrosis with lymphocyte infiltration occupied 50% of the renal tissue. No vascular abnormalities were observed. Electron microscopy exhibited no immune complex deposits. Based on serology and pathology findings, the patient was diagnosed with anti-GBM nephritis.

Treatment and follow-up

Intense immunosuppressive drug therapy was

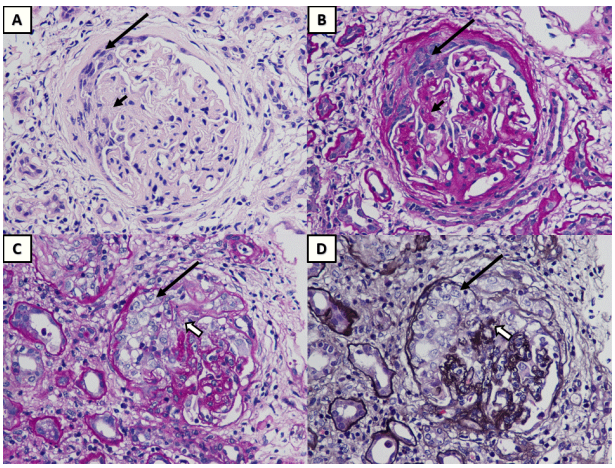

Figure 1. Light microscopic findings; (A and B) cellular crescentic glomerulonephritis indicated by the long arrow, mesangial expansion indicated by short arrow (HE ×400; PAS ×400). (C and D) Ruptured of GBM indicated by the white arrow and cellular crescentic glomerulonephritis indicated by the long arrow (PAS ×400; PASM ×400).

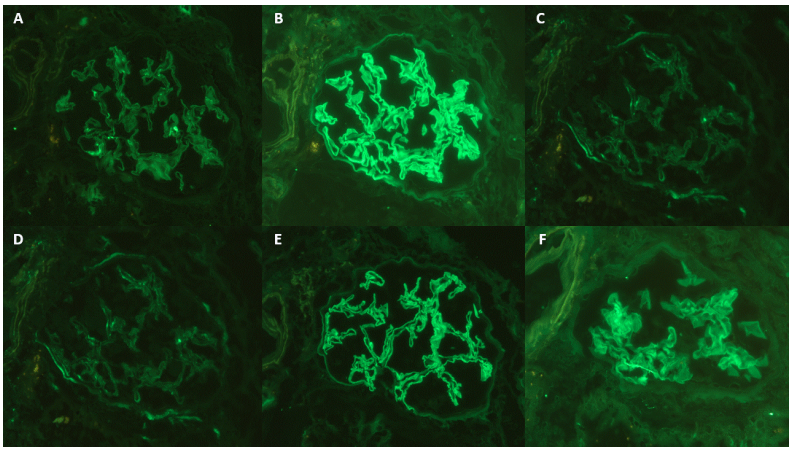

Figure 2. IF findings; IgA showed negative staining (A), strong positive 3+ linear pattern staining of the GBM for IgG (B), IgM (C), C3c (D) were negative, positive staining 2+ for kappa at the GBM (E) and weak staining 1+ for lambda at the GBM (F).

administered due to worsening renal function. Intravenous methylprednisolone 1000 mg was given for three days, then switched to oral prednisolone 40 mg/d on a weaning regimen. Therapeutic plasma exchange with exchange volume 3.5 L was started for seven consecutive days and then 4.5 L on alternate days until 18 days. Moreover, the patient received oral cyclophosphamide 2 mg/kg/d (150 mg/d) for three months. The patient achieved partial remission due to a reduced serum creatinine level to 353 µmol/L and reduced anti-GBM titre to 7.75 RU/m on day 14 (Figure 3). He was discharged on day 21 after admission.

He was re-hospitalised in the next month because of complete anuria and he developed alterations of consciousness without a focal neurological deficit for two days. The physical examination showed fever without organ-specific symptoms. The patient underwent computerised tomography of the brain. A normal brain parenchyma was observed, with no evidence of structural abnormalities. Blood test were then obtained. We found that his blood urea nitrogen and serum creatinine had risen to 64.64 mmol/L and 825 µmol/L. His sputum culture reported *Klebsiella pneumoniae*. Thus, the most likely diagnosis was septic acute kidney injury with uremic encephalopathy. After initial evaluation, acute hemodialysis was started due to the indication of uraemia. Antibiotics were given for 14 days and hemodialysis was performed for a total of four sessions. Subsequently, he demonstrated renal recovery due to spontaneous urine output at one litre/day and improved consciousness. The patient was then followed in the outpatient setting. Cyclophosphamide was discontinued after three months. He was doing well with serum creatinine 265 µmol/L and no signs of recurrent anti-GBM nephritis.

Discussion

Good pasture syndrome or anti-GBM glomerulonephritis, was first named by Ernest Good Pasture in 1919 (4). A little later, Lerner et al found that anti-GBM antibodies cause this abnormality (5). Anti-GBM nephritis is described as a vasculitis disorder characterised by autoantibody attack against the α3 chain of the type IV non-collagenous domain in the GBM and alveolar basement membrane. The prevalence is less than one per million population/

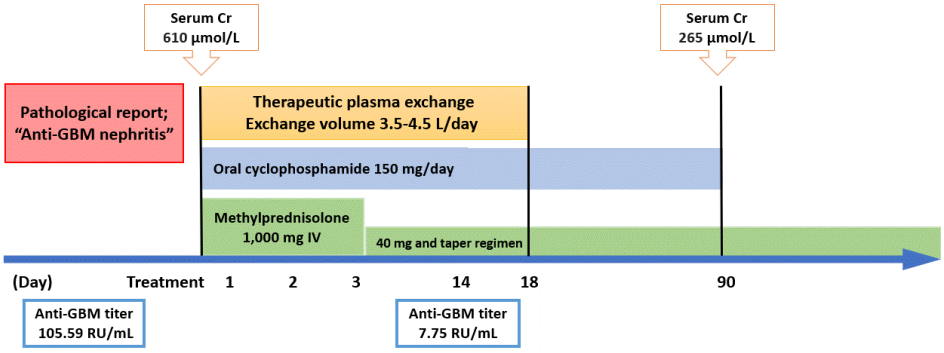

Figure 3. The course of treatment showed improvements in serum creatinine and anti-GBM antibody titres after intensive treatment.

year with two peak incidences in the third and six decades of life. It mostly affects young males more than females and is predominant in Caucasian populations (6).

The clinical features of kidney damage include nephritis and rapidly progressive glomerulonephritis, as typically found in our case. Anti-GBM antibodies in serum or kidney pathology are indicated for the definitive diagnosis. To assess serum anti-GBM antibodies, enzyme-linked immunosorbent assay (ELISA) is used. A negative test for circulatory antibodies cannot exclude this disease since patients might have atypical antigen epitope specificity (1). Detection of anti-GBM by histology is the second method used to perform the diagnosis. The pathognomonic is linear IgG staining along the GBM by direct immunofluorescence. However, a good substrate and a trained pathologist are needed (1).

Factors predicting poor renal outcomes in anti-GBM nephritis are a high titre of circulating anti-GBM antibodies, a high percentage of crescentic lesions involving glomeruli, the absence of normal glomeruli, oliguria-anuria at presentation, and initially rising serum creatinine above 600 µmol/L (7). As a reported by Levy et al (8), in patients who present with dialysis-dependent renal failure, patient and renal survival were 65% and 8% at one year. Additionally, all patients who required immediate dialysis and had 100% crescents on renal biopsy remained dialysis-dependent. Alchi et al (9), found that oligo-anuria is the strongest predictor of patient and renal survival, while a high percentage of glomerular crescents (>75%) was the only pathologic parameter associated with poor renal outcomes in anti-GBM disease. Our patient presented with a serum creatinine level of 610 µmol/L. The diagnosis was confirmed by the anti-GBM antibody titre (105.59 RU/mL) and IgG linear pattern on the GBM and 100% crescents in renal pathology. This indicated that the patient had a poor renal prognosis due to the high serum creatinine and high percentage of crescents.

At first admission, our patient was treated using the general treatment for glomerulonephritis, comprised of fluid management, blood pressure control, correction of acid-base and electrolyte abnormality, and standby for dialysis when indicated. After the diagnosis of anti-GBM nephritis was confirmed, the standard treatment included immunosuppressive drugs and plasmapheresis was discussed. Immunosuppressive drugs that have shown benefits in inhibiting autoantibody production and improving organ inflammation are corticosteroids and cyclophosphamide. Lockwood et al (10), reported the first use of this regimen in 1976, leading to suppression and eventual termination of antibody synthesis with improvement in renal function; then, it has become the recommendation in the KDIGO 2012 guidelines for treating anti-GBM nephritis (3). The use of plasmapheresis combined with immunosuppressants is supported by Johnson et al (11). They conducted a randomised trial to compare the effect of therapy with immunosuppression alone versus immunosuppression plus plasma exchange in 17 patients and found a higher rate of disappearance of anti-GBM antibodies and better serum creatinine levels in patients who received both immunosuppressants and plasmapheresis. In addition, they reported that patients with pulmonary haemorrhage and serum creatinine less than 500 µmol/L show a favourable response to this combination treatment. However, patients with creatinine ≥ 500 µmol/L had renal survival of only 50% at 5 years. Moreover, in patients presenting with an initial requirement for dialysis, renal recovery after treatment occurred in only 8% at one year. The KDIGO 2012 guidelines recommend against plasmapheresis treatment in poor prognosis patients such as those without pulmonary haemorrhage, 100% crescentic lesions or dialysis dependence at presentation because the risk of treatment outweighs the benefit (3).

In our case, the patient currently has an active status, and he can perform the activities of daily living. His performance status is good. We discussed the treatment options and made decisions with the patient. Despite the poor prognosis at first presentation, our decision was to actively treat with cytotoxic drugs combined with plasmapheresis. Although palliative options should be considered for patients in whom the risk outweighs the benefit, this patient did not present with dialysis dependence, so he might have a chance for renal recovery. After 14 days of treatment, we tested the anti-GBM antibody titre in the patient and showed a reduced titre, indicating a favourable outcome. Because the risk of relapse is very low, the patient completed a course of cyclophosphamide for approximately three months and then tapered the corticosteroid to the lowest dose for total treatment time about 6 months.

Data on severe infection after intensive treatment have been reported worldwide. Huart et al (12), found that 50% of anti-GBM nephritis patients in the first year of follow-up had died due to infection. A study in China reported that 74 of 140 patients with anti-GBM nephritis had at least one infectious episode (13). Our patient had pneumonia after one month of immunosuppressive drug usage. However, he survived and achieved partial remission of anti-GBM disease after the infection subsided.

Conclusion

In conclusion, this case report describes a patient with anti-GBM nephritis with an unfavourable prognosis initially. Despite a poor renal prognosis with 100% crescents and serum creatinine ≥ 600 µmol/L, the treated patient had a

good survival status. As a solution, our patient survived after intense treatment. Although his serum creatinine is not in the normal range, he has not become dialysis dependent. Immunosuppressive treatment should be performed along with careful monitoring for infection for the potential benefit of a good survival rate without infection-related morbidity and mortality.

Authors' contribution

AP and SP collected the data. AP designed and wrote the paper. UB and PD participated in the treatment of anti-GBM nephritis. PW performed histological diagnosis. SP and PD gave the idea for the paper. AP drafted the manuscript. AP, SP, PD, UB and PW reviewed and revised the manuscript. All authors read and signed the final manuscript.

Ethical issues

This case report received ethical approval from Prince of Songkla University Hospital (Approval No. REC.64-393-14-1). The patient provided written informed consent for publication of this case report and any accompanying images.

Conflicts of interest

The authors declare that there is no conflict interests.

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References

1. McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease. Clin J Am Soc Nephrol. 2017;12:1162. doi: 10.2215/CJN.01380217.
2. Segelmark M, Hellmark T. Anti-glomerular basement membrane disease: an update on subgroups, pathogenesis and therapies. Nephrol Dial Transplant. 2019;34:1826-1832. doi: 10.1093/ndt/gfy327.
3. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179-184. doi: 10.1159/000339789.
4. Henderson HM. Goodpasture's 1919 article on the etiology of influenza. Am J Med Sci. 2009;338:152-3. doi:10.1097/MAJ.0b013e3181acbd8e.
5. Okiro JO, Ebad CA, Khan AZ. Atypical presentation of anti-GBM nephritis in a 90-year-old patient. BMJ Case Rep. 2016;2016:bcr2016217990. doi: 10.1136/bcr-2016-217990
6. Salama AD, Levy JB, Lightstone L, Pusey CD. Goodpasture's disease. Lancet Lond Engl. 2001;358:917-920. doi:10.1016/S0140-6736(01)06077-9
7. Herody M, Bobrie G, Gouarin C, Grünfeld JP, Noel LH. Anti-GBM disease: predictive value of clinical, histological and serological data. Clin Nephrol. 1993;40:249-55.
8. Levy JB, Turner AN, Rees AJ, Pusey CD. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med. 2001;134:1033-42. doi: 10.7326/0003-4819-134-11-200106050-00009
9. Alchi B, Griffiths M, Sivalingam M, Jayne D, Farrington K. Predictors of renal and patient outcomes in anti-GBM disease: clinicopathologic analysis of a two-centre cohort. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2015;30:814-821. doi: 10.1093/ndt/gfu399
10. Lockwood CM, Rees AJ, Pearson TA, Evans DJ, Peters DK, Wilson CB. Immunosuppression and plasma-exchange in the treatment of Goodpasture's syndrome. Lancet Lond Engl. 1976;1:711-715. doi: 10.1016/s0140-6736(76)93089-0
11. Johnson JP, Moore JJ, Austin HA 3rd, Balow JE, Antonovych TT, Wilson CB. Therapy of anti-glomerular basement membrane antibody disease: analysis of prognostic significance of clinical, pathologic and treatment factors. Medicine (Baltimore). 1985;64:219-227. doi: 10.1097/00005792-198507000-00003
12. Huart A, Josse A-G, Chauveau D, et al. Outcomes of patients with Goodpasture syndrome: A nationwide cohort-based study from the French Society of Hemapheresis. J Autoimmun. 2016;73:24-9. doi:10.1016/j.jaut.2016.05.015.
13. Gu Q-H, Xie L-J, Jia X-Y, et al. Fever and prodromal infections in anti-glomerular basement membrane disease. Nephrol Carlton Vic. 2018;23:476-82. doi: 10.1111/nep.13040.