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Editorial

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DOUBLE POSITIVE ANTI-GBM AND ANCA-ASSOCIATED GLOMERULONEPHRITIS – A CASE REPORT

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ABSTRACT

Double-Positive Anti-Glomerular Basement Membrane (Anti-GBM) and Anti-Neutrophil Cytoplasm Antibody (ANCA)- Associated Glomerulonephritis is a rare disease. The disease is characterized by the concurrent presence of Anti-GBM antibodies and ANCA in a patient. The patient usually presents with rapidly progressive glomerulonephritis with or without pulmonary haemorrhage. We report a case of a middle-aged gentleman who presented with acute kidney injury with a serum creatinine level of 459umol/L. He tested positive for both Anti-GBM and ANCA with high titers. He underwent 8 cycles of plasma exchange, pulse IV cyclophosphamide, and high dose steroids. At the time of review at 6 months, a total of 6 doses IV cyclophosphamide had been given and his serum creatinine had recovered to 146 umol/L with the eGFR of 42ml/min. Although there is no published literature to date on the use of IV cyclophosphamide as compared to oral cyclophosphamide for the initial immunosupressive therapy, the encouraging response in this patient suggests that it could be an alternative to oral cyclophosphamide to reduce overall immunosuppressive load.

Keywords: ANCA, Anti-GBM, vasculitis

INTRODUCTION

Double-Positive Anti-Glomerular Basement Membrane (Anti-GBM) and Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Glomerulonephritis is a very rare disease with an incidence of less than one per million population. The disease is characterized by the concurrent presence of Anti-GBM antibodies and ANCA in a patient presenting with rapidly progressive glomerulonephritis with or without pulmonary haemorrhage. It has been previously reported that up to 50 per cent of patients with Double-Positive Anti-Glomerular Basement Membrane (Anti-GBM) and Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Glomerulonephritis became dialysis dependent (1).

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CASE REPORT

We report a case of Double-Positive Renal-Limited Anti-GBM disease in a 59-year-old gentleman. The patient, who was a smoker, presented with a history of dry cough and intermittent fever over one month. There was no history of haemoptysis or reduced urine output. The patient has underlying chronic obstructive airway disease in which he requires two types of inhalers for disease control. He also has type 2 diabetes mellitus currently controlled by tablet vildagliptin 50mg once daily. He worked as a truck driver. Physical examination showed the presence of moderate lower limb oedema but was otherwise unremarkable. His blood pressure on admission was 145/64, pulse rate was 67, and the temperature was 37-degree Celcius.

Initial blood investigations showed hemoglobin 8.7 g/dL (normal range 13.0 - 17.0 g/dL), total white blood cells 5.6 x109 /L (normal range 4.0 - 10.0 x109 /L), platelet 343 x 109 /L (normal range 150 – 410 x109 /L), urea 10.3 mmol/L (normal range 2.76-8.07 mmol/L), creatinine 256 µmol/L (normal range 62- 106 µmol/L). The full blood picture was not performed. Twenty-four-hour urine protein was 1.8g/day. His renal function deteriorated rapidly, with a rise in creatinine to 459 µmol/L on day 3 of presentation.

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Serology for autoimmune workup revealed Antinuclear Antibody (ANA) positive with a titre of 1:160, Anti-Double Stranded DNA was negative, p-ANCA positive with a titre of 1:320 and Anti-GBM antibody positive with a titre of >200 IU. Anti-Myeloperoxidase antibody (MPO) and Anti-Proteinase-3 (PR-3) antibodies were not performed. His serology testing for hepatitis B, hepatitis C and HIV were negative. Lung involvement was ruled out by the presence of clear lung fields on chest radiography and high resolution computed tomography of the thorax. Ultrasound of the abdomen showed normal echogenicity of the bilateral renal parenchyma. The size of the right kidney on ultrasound was 11.9cm and left kidney was 12cm. Urgent renal biopsy on day 3 of the presentation showed 22 glomeruli with 64% fibrinoid necrosis of the glomerular tufts and the presence of cellular crescents in 59 % (Figure 1 & 2). Immunofluorescent staining of the renal biopsy specimen revealed linear IgG (3+) positivity along the glomerular basement membrane (Figure 3).

The patient was given pulse intravenous methylprednisolone 500mg for 3 days followed by 8 cycles of plasma exchange at 1.5 times plasma volume replaced by FFP for 2 weeks. At 2 weeks, his serum creatinine improved to 300 µmol/L. The serum Anti-GBM antibody titre decreased to 84 IU/L. Proteinuria reduced to 0.5g/day. Repeated p-ANCA was negative. Subsequently, he was given monthly IV cyclophosphamide of 0.5g/m2 beginning at 3rd week of presentation for 5 doses to reach a total of 6 intravenous cyclophosphamide doses. Prednisolone was tapered to 10 mg a day. Serum creatinine further improved to 146 µmol/L over the following 6-month period.

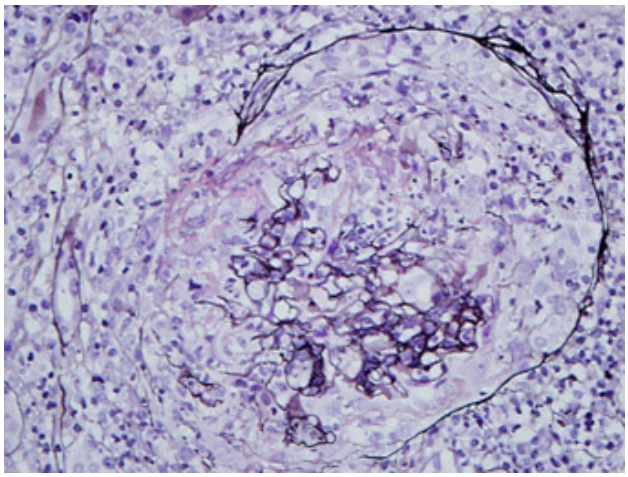

Figure 1: Methenamine silver x 400. A glomerulus with large cellular crescent and disruption of Bowman capsule

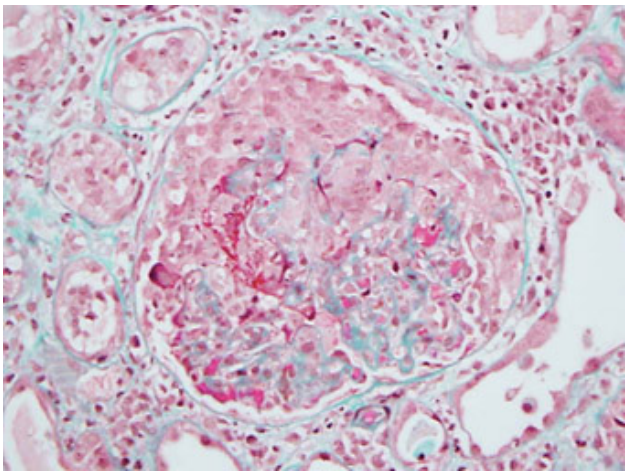

Figure 2: Masson trichrome x400. A glomerulus with fibrinoid necrosis and cellular crescent

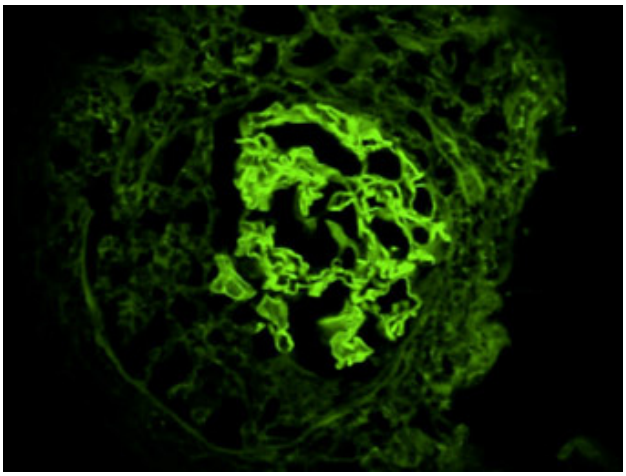

Figure 3: Immunofluorescent stain x400. Linear IgG positivity along the glomerular basement membrane

DISCUSSION

ANCA and anti-GBM are two antibody populations that are antigenically distinct (2). However, several case series reported that around fifty per cent of patients with the anti-GBM disease have the concurrence of circulating ANCA. This association is unknown. Suggested aetiology is the presence of ANCA causing glomerular injury and triggering the development of antiGBM antibodies by exposing the α-3(IV)NC1 antigen in the glomerular basement membrane (3). On light microscopy, 'Double-positive' disease often shows interstitial fibrosis, tubular atrophy and asynchronous crescents, which are the evidence of chronic injury compared to single positive anti-GBM disease, explaining the clinically longer prodrome of illness1. The finding of ANA positivity in this patient was unlikely to be significant given the patient do

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not achieve American College Rheumatology criteria for the diagnosis of Systemic Lupus Erythematosus (SLE).

Patients who have Double-Positive disease had an older age distribution similar to ANCA- associated glomerulonephritis which was 46 - 76 years old. In contrast, the age distribution is bimodal for patients with single positive anti-GBM disease. There is no significant difference in gender distribution for both diseases (1). It had been reported that patients who presented with dialysis-dependent renal failure secondary to Double-Positive disease have better renal survival at one year, which was 53 per cent compare to single positive anti-GBM disease, which was 44 per cent. It was also reported that 22 per cent of the patient with Double-Positive anti-GBM disease had relapse of their disease beyond 6 months follow up. No relapse of disease been reported for the patient with single positive anti-GBM disease. The median time of the first relapse for the patient who had double-positive disease was 4.4 years with a range of 1.1 to 7.9 years. Majority of these patients showed a rise in serum ANCA titres of more than 25% with the absence of serum anti-GBM antibodies. Therefore, maintenance immunosuppression therapies are mandatory for patients who have Double-Positive (1). To date, guidelines on the choices of immunosuppression therapies for patients with double-positive disease is not yet fully established. Several drugs like Azathioprine, Mycophenolate Mofetil, Cyclosporin had been tried with variable outcomes. In view of the possibility of relapse in double-positive disease, we planned to start this patient on azathioprine as the long-term maintenance immunosuppressive agent once the disease is in remission. The duration of maintenance immunosuppressive therapy will be at least 24 months.

Initial treatment of Double-Positive disease includes plasma exchange for 14 days or until serum anti-GBM antibody level is suppressed, combined with high dose steroid followed by oral cyclophosphamide at a dose of 2-3mg/kg daily for 3-6 months (4). Anticipating longer duration of immunosuppressive therapy after the initial 6 months because of the double-positive antibody status, we opted for IV cyclophosphamide 0.5 g/m2 monthly instead of oral cyclophosphamide to reduce the cumulative cyclophosphamide dose. Although no evidence as yet supports the use of IV, in preference of oral cyclophosphamide in double-positive disease, the marked improvement of renal function in our patient over the 6 months is encouraging. There is no proposed second-line agent for the initial treatment of the patient with the double-positive disease, only several case reports suggest that mycophenolate mofetil may be a reasonable option in the treatment of single positive anti-GBM disease (5).

CONCLUSION

Double-positive Anti-GBM and ANCA Associated Glomerulonephritis is a rare disease with better renal survival outcome in comparison with single positive Anti-GBM disease. However, the chance of relapse is higher in double-positive disease. IV cyclophosphamide could be a viable alternative to oral cyclophosphamide in such cases to reduce overall immunosuppressive load.

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