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Glomerulonephritis With Positive Anti-Glomerular Basement Membrane Antibodies Following Alemtuzumab Treatment

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Abstract

Presentation
A 28 year old female presented to the emergency department with a one week history of headache, vomiting and diaphoresis. Creatinine on admission was 492 and urinalysis revealed blood and protein. This was 5 months after a second infusion of Alemtuzumab, for treatment of highly active relapsing remitting multiple sclerosis.

Diagnosis
Anti-glomerular basement membrane disease was diagnosed after a vasculitic screen was sent for suspected glomerulonephritis.

Treatment
Unfortunately despite early diagnosis and immunosuppressive treatment, the patient progressed to end stage kidney failure.

Conclusion
It is important to maintain a high index of suspicion and test for anti-GBM disease in patients receiving alemtuzumab who develop acute renal failure.

Introduction

Alemtuzumab is a humanized monoclonal antibody directed against CD52 and has been shown in clinical trials to be an effective disease modifying treatment for active relapsing remitting multiple sclerosis (RRMS) [1].

We present a case of anti-GBM disease following two courses of alemtuzumab for the treatment of highly active RRMS.

Case Report

The patient received two infusions of Alemtuzumab 12 months apart. Baseline blood tests and urinalysis were normal.

12 months later she was admitted for a second course of alemtuzumab which was administered at a dose of 12mg daily over a three day period for a total cumulative dose of 96mg. Baseline bloods, urinalysis and urine microscopy were normal.

5 months after the second infusion she presented to emergency department with a one week history of headache, vomiting and diaphoresis. Creatinine on admission was 492 and urinalysis revealed blood and protein. A vasculitic screen was sent for suspected glomerulonephritis.

Anti-GBM antibody was positive at 463.0 U/ml. Renal biopsy subsequently showed necrotizing and crescentic glomerulonephritis with features typical of anti glomerular basement membrane disease. 39/41 glomeruli showed presence of extensive inflammation, crescent formation and fibrinoid necrosis. Immunofluorescence showed IgG pattern consistent with anti-GBM disease with positivity for kappa and lambda light chains.

Patient was commenced on haemodialysis. Anti-GBM treatment included 19 sessions of plasmapheresis, Rituximab at a cumulative dose of 1.35g (675mg x2), two doses of IV methylprednisolone 500mg which was changed to 60mg oral prednisolone and tapered slowly over the course of the following three months.

Unfortunately, despite early diagnosis and treatment, kidney function failed to recover and she remains dialysis dependent.

Discussion

Alemtuzumab is humanized monoclonal antibiody that selectively targets CD52, resulting in depletion of circulating T and B lymphocytes which susequently recover. Alemtuzumab has been evaluated in patients with RRMS in phase 2 and phase 3 studies and showed superior efficacy vs subcutaneous interferon beta-1a in patients with RRMS[2].

Adverese events of interest include autoimmune effects such as thyroid disorders, immune thrombocytopenia and glomerulonephritis including membranous nephropathy and anti-glomerular basement membrane disease.

Meyer et al describe a case of anti GBM disease following alemtuzumab treatment of an RRMS patient in the CAMMS223 trial[3]. Treatment included plasmapheresis, cyclophosphamide and prednisolone. 26 months after diagnosis the patient remained in remission with no clinical sequelae.

Two other cases of anti-GBM disease following alemtuzumab treatment have been reported by Clatworthy et al. Both progressed to chronic renal failure and became dialysis dependent despite appropriate treatment[4].

The first a 40 year old woman with RRMS who received a total dose of 100mg of alemtuzumab and nine months later was diagnosed with anti GBM disease. She was treated with plasmapharesis, pulsed cyclophosphamide and corticosteroids. She required dialysis and ultimately renal transplantation.

The second patient was a 43 year old male with refractory ANCA associated vasculitis who was treated with a total dose of 788mg of alemtuzumab. Ten months later he was diagnosed with acute renal failure with positive anti GBM antibodies. He became dialysis dependent and also underwent renal transplantation.

The time frame of both of these cases is consistent with our report, occuring after the second infusion of alemtuzumab.

Epidemiological studies have suggested that anti-GBM disease has an incdidence of 0.5 to 1 case per million population per year and may account for <7% of patients with end stage kidney disease[5]. The incidence of anti-GBM disease occuring after alemtuzumab treatment is estimated to be 0.13%.[6]

There is a strong association with the human leucocyte antigen (HLA) DR2, which is carried by approximately 85% of patients with anti GBM disease[7].

Most patients now survive the acute disease with 75 to 90% of patients surviving for > 1 year, however only about 40% of patients recover independent kidney function[8]. It has been reported that those who have a creatinine level greater than >600 umol/L or who are oliguric rarely recovered kidney function[9]. A single center study of 71 treated patients showed that almost all patients with a creatinine of <500 umol/L receovered kidney function at year 5 highlighting the importance of early identification and treatment[10].

Autoimmune renal disease can occur following treatment with alemtuzumab with varied outcomes from complete recovery to ESKD requiring dialysis and transplantation. We recommend close monitoring for potential side effects, together with monthly renal function and urine testing in patients receiving alemtuzumab.

Declaration of Conflicts of Interest:
There authors have no conflicts of interest to declare.

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