Renal-Limited Antiglomerular Basement Membrane Disease Related To Alemtuzumab: A Case Report

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Abstract
Rationale: Alemtuzumab is a monoclonal antibody approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). Many autoimmune-mediated adverse events have been associated with alemtuzumab, including renal-limited anti-glomerular basement membrane (GBM) disease.

Presenting concern: A 52-year-old female with RRMS presented with acute kidney injury 39 months after receiving 1 cycle of alemtuzumab. She had a history of alemtuzumab-associated hypothyroidism and thrombocytopenia, urinary tract infections, and chronically abnormal urinalyses.

Diagnosis: A diagnosis of renal-limited anti-GBM disease was made based on renal biopsy and positive anti-GBM serology. Alemtuzumab was thought to be the trigger of the anti-GBM disease as there were no other exposures or serologic findings suggesting other causes.

Interventions: She was treated with corticosteroids, cyclophosphamide, and plasmapheresis. She required hemodialysis for acute renal failure.

Outcomes: Despite treatment, the patient’s renal function did not recover. She remained dialysis-dependent and anti-GBM antibody titers remained elevated 6 months after presentation.

Teaching points: Anti-GBM disease is a life-altering adverse event that can be associated with alemtuzumab. Our case highlights the limitations of monitoring urinalyses as a trigger for anti-GBM antibody testing in patients who have received alemtuzumab and have baseline abnormal urinalyses; such patients may require further protocolized anti-GBM antibody testing, although the optimal frequency of such antibody screening remains unclear.

Abridged
Justification: L’alemtuzumab est un anticorps monoclonal approuvé pour le traitement de la sclérose en plaque récurrente-rémittente (SPRR). De nombreux événements indésirables à médiation auto-immune ont été associés à ce traitement, notamment la glomérulonéphrite auto-immune (maladie anti-MBG).

Présentation du cas: Une femme de 52 ans atteinte de SPRR présentant une insuffisance rénale aiguë 39 mois après avoir reçu un cycle d’alemtuzumab. La patiente avait des antécédents d’hypothyroïdie et de thrombocytopenie liées à la prise d’alemtuzumab, en plus de présenter des tests urinaires anormaux et de souffrir d’infections des voies urinaires de façon chronique.

Diagnostique: Un diagnostic de glomérulonéphrite auto-immune a été établi sur la base d’une biopsie rénale et d’une sérologie anti-MBG positive. On a suspecté l’alemtuzumab d’être à l’origine de la glomérulonéphrite auto-immune puisqu’aucun résultat sérologique ou exposition ne suggérait d’autres causes.

Interventions: La patiente a été traitée aux corticostéroïdes, au cyclophosphamide et par plasmaphérèse. L’insuffisance rénale aiguë a requis un traitement d’hémodialyse.

Résultats: Malgré le traitement, la fonction rénale de la patiente n’est pas rétablie. La patiente a dû poursuivre les traitements de dialyse et ses titres d’anticorps demeuraient élevés six mois après la présentation des symptômes.

Leçons tirées: La glomérulonéphrite auto-immune est un événement indésirable aux conséquences dévastatrices et cette affection peut être associée à la prise d’alemtuzumab. Notre cas met en lumière les limites du suivi des analyses urinaires comme critère de dépistage des anticorps anti-MBG chez les patients ayant reçu de l’alemtuzumab et dont les analyses urinaires préalables sont anormales. Ces patients pourraient nécessiter des tests de détection des anticorps anti-MBG supplémentaires, bien que leur fréquence optimale demeure incertaine.
Keywords
alemtuzumab, anti-glomerular basement membrane disease, multiple sclerosis, case report

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Introduction

Anti-glomerular basement membrane (GBM) disease is a rare and often rapidly progressive form of glomerulonephritis that is caused by autoantibodies directed to a specific antigen on the GBM of the kidneys. Anti-GBM disease is estimated to affect about 0.5 to 1 patient per million. Triggers associated with anti-GBM disease include antineutrophil cytoplasmic antibodies–associated glomerulonephritis, infection, cigarette smoke, inhalation of hydrocarbons, and lithotripsy. Alemtuzumab, an approved therapy for relapsing-remitting multiple sclerosis (RRMS), has also been reported as a trigger for anti-GBM disease. Alemtuzumab is a humanized monoclonal antibody that targets cluster differentiation (CD)-52 expressing B and T lymphocytes, which contribute to the inflammatory cascade that results in focal demyelination of the central nervous system during flares of RRMS. Alemtuzumab leads to the selective depletion and repopulation of these lymphocytes and aims to restore the immune system’s self-tolerance networks. Significant secondary autoimmune adverse events (AEs) have been associated with alemtuzumab including hypo- and hyperthyroidism, immune thrombocytopenic purpura (ITP), and nephropathies such as acute interstitial nephritis, membranous glomerulonephritis, and anti-GBM disease. To help with early detection of these autoimmune AEs, there are published recommendations outlining monitoring parameters for individuals treated with alemtuzumab. However, there are limitations to these monitoring parameters. We aim to illustrate an example of these limitations by describing a case of anti-GBM disease in a patient with RRMS who received a course of alemtuzumab 39 months after receiving alemtuzumab, the patient presented to her family physician with symptoms of an LUTI and was prescribed amoxicillin for 5 days. Urinalysis via the indwelling urinary catheter was cloudy brown with specific gravity (SG) 1.020, proteinuria (1 g/L), positive leukocyte esterase (125 leukocytes/µL), 4+ blood, and negative for nitrite. Urine culture grew Escherichia coli sensitive to ampicillin. Two days after completing the antibiotics, the patient presented to a peripheral hospital’s emergency department (ED) with malaise, nausea, and low-grade fever.

Clinical Findings and Diagnostic Focus and Assessment

In the ED, the patient’s physical examination was unremarkable. Laboratory investigations were notable for acute kidney injury (AKI) (creatinine 316 µmol/L; urea 15.1 mmol/L), hyponatremia (sodium 128 mmol/L), and microcytic anemia (hemoglobin 94 g/L, mean corpuscular volume 76.8 fl). Serum creatinine was 46 µmol/L 2 months prior. Urinalysis from the urinary catheter was unchanged from previous
except for increased proteinuria (>3.0 g/L). The working diagnosis was UTI with AKI secondary to volume depletion. The patient was sent home with a prescription for oral ciprofloxacin and instructed to increase her fluid intake.

The patient returned to the ED 2 days later with decreased urine output. Physical examination was notable for new hypertension (148/90 mm Hg). Laboratory investigations showed an elevated serum creatinine (429 µmol/L) and low bicarbonate (19.9 mmol/L). Urinalysis was turbid yellow, SG 1.015, proteinuria 1 g/L, leukocyte esterase 500 leukocytes/µL, 4+ blood, and nitrite negative. Urine culture from 2 days earlier had no growth. An unenhanced computed tomographic scan of the abdomen and pelvis did not show a kidney stone or hydronephrosis.

She was admitted to the peripheral hospital and given a trial of intravenous fluids with monitoring of urine output and laboratory investigations. Over the next 48 hours, the patient produced minimal urine and creatinine increased to 695 µmol/L with hyperkalemia requiring oral sodium polystyrene sulfonate. Ultrasound showed no hydronephrosis. The right and left kidney measured 11.7 and 11 cm in sagittal length, respectively. She was transferred to the nephrology service at a tertiary care center. On arrival, the patient was euvolemic, weight 97.2 kg, hypertensive (150/88 mm Hg), and anuric. Serum creatinine was 687 µmol/L. A tunneled hemodialysis catheter was inserted and she was started on hemodialysis.

An ultrasound-guided percutaneous renal biopsy was performed. Light microscopy showed a core of cortex and medulla with 17 glomeruli, one of which was globally sclerosed, and the remainder (all) showed marked global necrosis with hypercellularity and cellular crescents (Figure 1A). There was a marked active interstitial lymphoid infiltrate with acute tubular injury in a background of mild interstitial fibrosis and tubular atrophy and marked arterio- and arteriolosclerosis (Figure 1A). Immunofluorescence showed 3+ peripheral linear positivity for IgG, C3, kappa and lambda, and 1+ for C1q (Figure 1B). Electron microscopy showed glomerular necrosis and hypercellularity without presence of electron dense deposits or fibrils (Figure 1C). These features were consistent with crescentic anti-GBM disease.

Serology showed an anti-GBM antibody titer with activity index (AI) greater than 8.0, where AI ≥ 1.0 indicates a positive result with an antibody cutoff concentration that corresponds to approximately the 99th percentile of values obtained from a nondiseased population. Other serologies were negative including antineutrophil cytoplasmic antibody, antinuclear antibody screen, anti-streptolysin O titer, human immunodeficiency virus, hepatitis C and B. Hemoglobin A1C was 5.1%. Chest x-ray was normal. The etiology of the anti-GBM disease was thought to be alemtuzumab, which the patient had received 39 months prior to presentation. There were no other exposures or procedures that are known to be associated with anti-GBM disease.

**Therapeutic Focus and Assessment**

The patient received methylprednisolone 1 g intravenous daily for 3 days followed by prednisone 50 mg orally daily, cyclophosphamide 125 mg orally daily plus 5 plasmapheresis treatments. She was transfused with packed red blood cells to maintain a hemoglobin above 70 g/L and was started on an erythropoiesis-stimulating agent. Hypertension was controlled with amlodipine. She continued on regular hemodialysis.

**Outcomes**

After 6 weeks, due to lack of response, cyclophosphamide was stopped and prednisone was slowly tapered to discontinuation. The patient remained anuric and dialysis dependent 6 months after diagnosis with persisting anti-GBM antibodies with an AI of 6.6 (Figure 2).

**Discussion**

Our case adds to the body of reports describing autoimmune nephropathies associated with alemtuzumab. The
incident of autoimmune nephropathy in post-alemtuzumab monitoring programs in clinical trials and in the postmarketing setting are estimated at 0.27% to 0.34% and 0.05% to 0.17%, respectively. While anti-GBM disease has been rarely reported in patients with RRMS in the absence of alemtuzumab therapy, anti-GBM disease is the best described and most common alemtuzumab-related autoimmune nephropathy. In a review by Phelps et al, they identified 7 cases of anti-GBM disease in patients with RRMS who had received alemtuzumab. There are many similarities between these cases and the present case. All cases presented with AKI 9 to 39 months following their last dose of alemtuzumab and almost all were female. Renal-limited anti-GBM disease was diagnosed by renal biopsy (5 cases) and/or positive anti-GBM antibodies serology (6 cases). They all received treatment with plasmapheresis and immunosuppression with corticosteroids and a cytotoxic agent, cyclophosphamide, or mycophenolate mofetil (1 case). Despite treatment, anti-GBM disease carries a poor prognosis for recovery of renal function. Clinical features associated with poor renal outcomes include markedly elevated serum creatinine, oligoanuria, or need for dialysis at presentation and renal biopsy showing a high proportion of crescentic glomeruli. Our patient had all of these features and remains on dialysis. Similarly, 5 of the other reported cases also remained dialysis dependent despite immunosuppressive therapy. Only 1 case recovered renal function after immunosuppressive treatment for anti-GBM disease; this patient did not have any of the above-mentioned poor prognostic features. Although there are a limited number of patients reported, it would appear that alemtuzumab-associated anti-GBM disease has a similar outcome to that seen with the more common idiopathic form.

It is unknown which patients with RRMS are most susceptible to the autoimmune AEs of alemtuzumab. As a result, there are published recommendations outlining parameters for monitoring of post-alemtuzumab autoimmune AEs. From a renal perspective, these include monthly urinalysis and serum creatinine measurements. Our patient’s indwelling urinary catheter and recurrent LUTIs resulted in persisting abnormal urinalyses, thereby confounding the interpretation of changes that might suggest glomerular disease. Serum creatinine was normal up to 8 weeks before presentation. In the Belgian consensus guidelines for the

| Date          | Event Description                                                                 |
|---------------|------------------------------------------------------------------------------------|
| October 2018  | - Migrated post-alemtuzumab monitoring                                            |
| November 21, 2018 | - Renal ultrasound                                                               |
| November 22-26, 2018 | - Admission to local hospital                                                          |
| November 28, 2018 | - Urology consult and cystoscopy                                                   |
| November 27-Dec 1, 2018 | - Plasmapheresis for treatment of anti-GBM disease                                   |
| December 2018 | - Nephrology consult and biopsy                                                   |
| January 2019  | - Second presentation to ED with symptoms in addition to decreased urine output    |
| February 2019 | - Urology consult with cystoscopy for intermittent hematuria on urinalysis         |
| March 2019    | - Nephrology consult and biopsy                                                   |
| April 2019    | - Urology consult and biopsy                                                   |
| May 2019      | - Hospitalization for trial IV fluids                                             |
| June 2019     | - First presentation to ED with nausea, generalized malaise and low-grade fever    |
| July 2019     | - Second presentation to ED with nausea, generalized malaise and low-grade fever    |
| August 2019   | - Post-alemtuzumab monitoring                                                    |
| September 2019| - Post presentation to ED with nausea, generalized malaise and low-grade fever    |
| October 2019  | - Hospitalization for trial IV fluids                                             |
| November 2019 | - Post-alemtuzumab monitoring                                                    |
| December 2019 | - Post-alemtuzumab monitoring                                                    |
monitoring and management of autoimmune AEs post-alemtuzumab, measurement of anti-GBM antibodies is recommended after detection of persistent hematuria. However, it is unclear how frequently anti-GBM antibodies should be measured in the presence of chronic hematuria.

Conclusions
Our case highlights an infrequent but life-altering AE associated with alemtuzumab and supports the recommendations for monthly monitoring of serum creatinine and urinalysis for these complications for 4 years postdrug exposure. Our case also highlights the limitations of using urinalysis as a trigger for anti-GBM antibody testing in patients with underlying abnormal urinalyses; such patients require protocolized anti-GBM antibody testing for up to 4 years post-alemtuzumab therapy, although the optimal frequency of such antibody screening remains unclear.

Patient Perspective
“Alemtuzumab seems to have been beneficial as I have not had a flare of RRMS since receiving the medication. The renal failure happened so quickly and unexpectedly, and the sequela of end-stage renal disease have been challenging. I often wonder if this could have been caught sooner and if so, would the outcome have been different? It is frustrating that a medication taken to help improve your quality of life can cause a different life-altering adverse event. I am now focusing on establishing a new normal. I am looking forward to my peritoneal dialysis teaching. Once I am able to do dialysis at home, I will no longer travel 1.5 hours every other day for hemodialysis.”

Ethics Approval and Consent to Participate
Due to this publication being a case report describing an anecdotal educational account, it does not fall within the definition of research requiring Research Ethics Board (REB) review at our institution as per the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans - TCPS 2 (2018).

Consent for Publication
In compliance with our institution’s Research and Ethics Board policy, written informed consent was obtained from the patient for the publication of her case in the medical literature.

Availability of Data and Materials
The original data presented in this case report are not available for public viewing.

Author Contributions
M.L.W. identified the case, obtained written informed consent for the case report and edited the manuscript. A.M.H. wrote the first draft of the manuscript and requested the patient perspective. P.P. supervised the case report, critically reviewed and edited the manuscript and provided more detail to the discussion and conclusion. L.G. provided the micrographs and descriptions of the renal biopsy. All authors read and approved the final manuscript.

Declaration of Conflicting Interests
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