

Case Report

Rapidly Progressive Glomerulonephritis with Anti-Gbm and Anti-Pla2r Antibodies after Alemtuzumab Treatment in a Multiple Sclerosis Patient

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Abstract

We present a patient with MacDonald criteria of relapsing remitting multiple sclerosis treated with Alemtuzumab, who showed a rapidly progressive glomerulonephritis with complete loss of renal function. Anti-Glomerular Basement Membrane antibodies (GBM) and anti M-type phospholipase A2 receptor (PLA2R) antibodies were detected. Nine days before acute kidney injury, serum creatinine was normal and urine analysis only detected proteinuria (+1). HLA DRB1*15:01, associated both to MS and anti GBM-disease was positive. These findings suggest that periodic antibodies determination may allow early detection and etiological treatment of autoimmune nephropathies associated with alemtuzumab, especially if HLA predisposition is detected.

Keywords: Glomerulonephritis; Multiple Sclerosis; Proteinuria and hematuria

Case Presentation

We describe a 43-year-old male fulfilling the Macdonald's criteria of relapsing-remitting Multiple Sclerosis (MS) initially staged at level 0/10 in the Expand Disability Status Scale (EDSS). He was initially treated with intramuscular interferon beta-1a and posteriorly with dimethyl fumarate 240 mg twice a day due to adverse effects. Despite the initial disease modifying therapy, He showed 3 relapsing episodes and showed a higher score in the EDSS (3/10) and also showed in the Cervical and Brain MRI new demyelinating active lesions, therefore Natalizumab infusions were prescribed for 2 years showing only 1 relapsing episode and keeping the same score at the EDSS (3.0) however a stratified JC index of 1.59 was determined whereby Alemtuzumab was prescribed in July 2018 (20 mg/day for accumulative dose of 100 mg), 8 months after the first Alemtuzumab infusion, he showed a sudden anuria and showing an acute renal failure. Anti-GBM antibodies titers were markedly raised (>680U/ml. Normal: <7) and tested positive for anti-PLA2R. Renal biopsy showed extensive necrotizing and crescentic lesions with IgG lineal deposition

(Figure 1), therefore an anti GBM disease was diagnosed and treated with plasmapheresis, pulsed cyclophosphamide and corticosteroids. Despite this treatment, he didn't recover the renal function and now he is dialysis-dependent waiting for renal transplantation. Urine analysis just only showed proteinuria 14 days before recognition of acute kidney failure nevertheless the serum creatinine level was still normal and showed not hematuria.

Discussion

Alemtuzumab (LEMTRADA®) has been approved in more than 70 countries for the treatment of adults with Relapsing-Remitting Active Forms of Multiple Sclerosis (RRMS) defined by clinical and imaging criteria.

The incidence of autoimmune nephropathies related to Alemtuzumab within the Clinical Development Program (CDP) was 0.34% (5 cases reported); one of them was an Anti-Glomerular Basement Membrane (anti-GBM) disease, two cases with membranous glomerulonephropathies, and two other cases with serum anti-GBM antibody without typical anti-GBM disease, these later cases responded to conventional therapy and had favorable outcomes. Three of 11 cases outside the CDP were detected following off-label Alemtuzumab use prior to approval for RRMS and were all anti-GBM disease. All anti-GBM disease cases with documented urinalysis demonstrated prior microscopic hematuria [1].

In our case, the pre-onset urinalysis showed no microscopic hematuria however once acute renal failure was diagnosed and the anti-PLA2R was tested positive. Approximately 70% to 80% of Membranous Glomerulonephritis (MGN) have circulating antibodies to the M-type receptor of phospholipase A2 (anti-PLA2R) and such antibody is not described in other glomerular diseases, these

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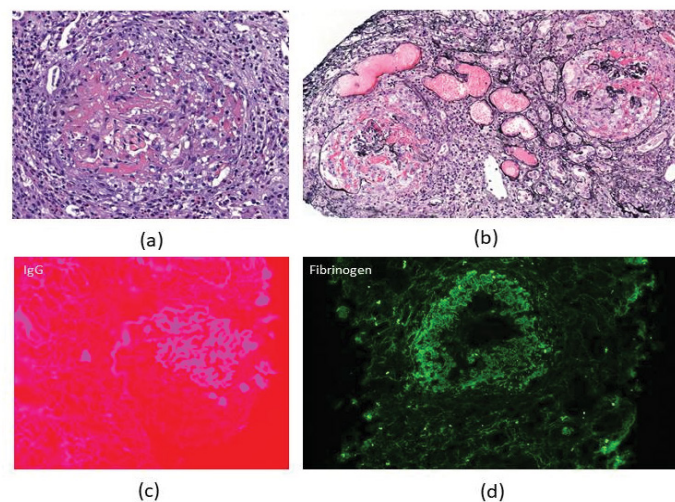


Figure 1: Histological findings and immunofluorescence from renal biopsy.

- (a) Glomerulus was involved by cellular crescents with associated fibrinoid necrosis stain brick red (Hematoxylin and eosin stain x 400)
 (b) Large cellular crescents occupy nearly every glomerulus with disruption of Bowman capsule. Interstitial inflammation and tubulitis were present (Jones silver stain x 200)
 (c) Diffuse, bright, linear staining of the GBM for IgG (+++).
 (d) Fibrinoid necrosis is highlighted by strong fibrinogen staining in the crescent in this glomerulus.

antibodies have diagnostic value for primary MGN nevertheless the renal biopsy of our patient showed anatomopathological criteria of membranous glomerulonephropathy.

The current monitoring of renal involvement includes serum creatinine, proteinuria and hematuria monthly as well as the detection of renal symptoms [2]. However, it may not identify patients with an explosive onset of rapidly progressive glomerulonephritis with a high risk of loss of renal function.

Based on the observation that autoimmune disorders in general and glomerular nephropathy and anti-GBM disease in particular usually occurred within 40 months after the last Alemtuzumab's dose, MS patients receiving this drug should be monitored monthly for 48 months following the last exposure [3]. Nowadays the routine renal safety monitoring include serum creatinine and urinalysis with microscopy monthly intervals thereafter until 48 months after the last infusion [4,5]. All cases reviewed by Phelps of anti-GBM disease with documented urinalysis demonstrated prior microscopic hematuria. In our case, the pre-onset urinalysis did not show microscopic hematuria.

Despite allele HLA DRB1*15:01 has been associated both to MS and anti GBM disease, the risk of developing anti-GBM disease in patients with MS treated with Alemtuzumab has not been established. Of all reported cases, HLA genotyping data were only available for one patient who was HLA DRB1*15*01 allele [6-8].

In view of the severity of rapidly progressive glomerulonephritis secondary to the treatment of MRSS with Alemtuzumab, we believe that monitoring levels of anti-GBM between 4 and 6 months after the start of treatment, and every 2 months until 24 months after the last infusion could help to detect and early treatment an imminent anti-GBM disease. On the other hand, the estimation of risk factors such as genetic predisposition HLA DR B1*15:01 could identify patients who could be monitored more closely.

References

1. Phelps R, Winston JA, Wynn D, Habek M, Hartung HP, Havrdová EK, et al. Incidence, management, and outcomes of autoimmune nephropathies following alemtuzumab treatment in patients with multiple sclerosis. *Mult Scler J*. 2019.
2. Sprangers B, Decoo D, Dive D, Lysandropoulos A, Vanopdenbosch L, Bovy C. Management of adverse renal events related to alemtuzumab treatment in multiple sclerosis: a Belgian consensus. *Acta Neurol Belg*. 2018;118(2):143-51.
3. Meyer D, Coles A, Oyuela P, Purvis A, Margolin DH. Case report of anti-glomerular basement membrane disease following alemtuzumab treatment of relapsing-remitting multiple sclerosis. *Mult Scler Relat Disord*. 2013;2(1):60-3.
4. Genzyme Therapeutics Ltd. Lemtrada™ (alemtuzumab 12 mg concentrate for solution for infusion). EU summary of product characteristics, <https://www.ema.europa.eu/en/documents/product-information/lemtrada-epar-product-information-en.pdf> (2018, accessed 12 February 2018).
5. Sanofi Genzyme. Prescribing information. Lemtrada™ (alemtuzumab), for intravenous injection. Cambridge, MA: Sanofi Genzyme, 2017.
6. Hollenbach JA, Oksenberg JR. The immunogenetics of multiple sclerosis: A comprehensive review. *J Autoimmun*. 2015;64:13-25.
7. Jones JL, Thompson SA, Loh P, Davies JL, Tuohy OC, Curry AJ, et al. Human autoimmunity after lymphocyte depletion is caused by homeostatic T-cell proliferation. *Proc Natl Acad Sci U S A*. 2013;110(50):20200-5.
8. Clatworthy MR, Wallin EF, Jayne DR. Antiglomerular basement membrane disease after alemtuzumab. *N Engl J Med*. 2008;359(7):768-9.