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Anti–Glomerular Basement Membrane Disease after Alemtuzumab

TO THE EDITOR: Alemtuzumab (Campath-1H) is a humanized anti-CD52 monoclonal antibody, the administration of which causes profound B- and T-lymphocyte depletion. It is licensed for use in the treatment of chronic lymphocytic leukemia, and it is increasingly used in the treatment of autoimmune diseases (particularly multiple sclerosis) and as an induction agent in renal transplantation. Although alemtuzumab is a potent immunosuppressant, several groups have described the paradoxical occurrence of autoimmune disease after

its use, including thyroid disease and cytopenias. We describe two patients in whom anti–glomerular basement membrane disease developed after treatment with alemtuzumab.

Patient 1 was a 40-year-old white woman with relapsing–remitting multiple sclerosis who received a total dose of 100 mg of alemtuzumab. Nine months after treatment, she received the diagnosis of acute renal failure secondary to anti–glomerular basement membrane disease (Table 1). Patient 2 was a 43-year-old white man with a re-

Table 1. Characteristics of the Patients.*

Variable	Patient 1	Patient 2
Age (yr)	40	43
Sex	Female	Male
Indication for alemtuzumab	Multiple sclerosis	ANCA-associated vasculitis (without renal involvement)
Duration of disease before alemtuzumab therapy (mo)	12	18
Previous immunosuppressive drugs	Methylprednisolone	Prednisolone, azathioprine, cyclophosphamide
Total dose of alemtuzumab (mg)	100	788
Time to development of anti-GBM disease (mo)	9	10
Renal-biopsy findings	Crescentic glomerulonephritis (95% crescents), linear deposition of IgG	Crescentic glomerulonephritis with fibrinoid necrosis (60% crescents), strong linear IgG staining
Results of autoantibody screening at onset of anti-GBM disease	Anti-GBM–positive, ANCA-negative, antinuclear antibody–negative	Anti-GBM–positive, ANCA-negative, antinuclear antibody–negative
C3 and C4 complement	Normal	Normal
Lymphocyte count at presentation (cells/mm ³)		
CD4 (normal range, 300–1400)	190	110
CD8 (normal range, 200–900)	190	80
CD19 (normal range, 100–500)	100	100

* ANCA denotes antineutrophil cytoplasmic antibody, and GBM glomerular basement membrane.

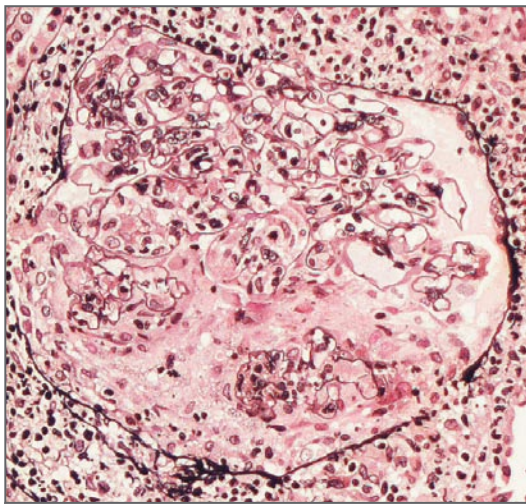


Figure 1. Photomicrograph of a Renal-Biopsy Specimen from Patient 2, Showing Crescentic Glomerulonephritis.

A cellular crescent occupies the lower half of the glomerulus, compressing the capillary tuft (silver stain).

fractory antineutrophil cytoplasmic antibody-associated vasculitis who was subsequently treated with a total dose of 788 mg of alemtuzumab. Ten months later, he was found to have acute renal failure with elevated titers of anti-glomerular basement membrane antibodies and renal-biopsy findings that were consistent with anti-glomerular basement membrane disease (Table 1 and Fig. 1). Despite appropriate treatment, both patients became dialysis-dependent and eventually underwent renal transplantation, with no recurrence of anti-glomerular basement membrane disease. At the time of presentation with anti-glomerular basement membrane disease, the levels of CD4+ T cells were reduced in both patients, whereas the levels of CD19+ B cells were within the normal range (Table 1). Both patients also carried the anti-

glomerular basement membrane susceptibility allele HLA-DRB1-15.

The anti-CD52 antibody alemtuzumab causes rapid and prolonged lymphocyte depletion; the levels of CD4+ T cells may remain depressed for many years, but the data show that it is not the depletion of CD4+ regulatory T cells by alemtuzumab that induces autoimmunity.^{1,2} After the administration of alemtuzumab, B-cell recovery tends to precede T-cell recovery² (Table 1), and the number of B cells may exceed baseline values in some patients.² The autoimmune diseases observed after the administration of alemtuzumab are predominantly antibody-mediated, and they respond to B-cell depletion.³ Autoreactive B cells can function without T-cell help⁴; thus, the emergence of autoreactive B cells during the reconstitution of lymphocytes may cause autoimmunity after treatment with alemtuzumab.

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