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CASE REPORT

Alemtuzumab-induced antineutrophil cytoplasmic antibody-associated nephritis in a patient with multiple sclerosis

Furkan Sarıdaş[1], Saide Elif Güllülü Boz[2], Belkıs Nihan Coşkun[3], Emine Rabia Koç[1], Abdulmecit Yıldız[2], Berna Aytaç Vuruşkan[4], Ömer Faruk Turan[1]

[1]Department of Neurology, Bursa Uludağ University Faculty of Medicine, Bursa, Türkiye
[2]Department of Nephrology, Bursa Uludağ University Faculty of Medicine, Bursa, Türkiye
[3]Department of Rheumatology, Bursa Uludağ University Faculty of Medicine, Bursa, Türkiye
[4]Department of Pathology, Bursa Uludağ University Faculty of Medicine, Bursa, Türkiye

ABSTRACT

Alemtuzumab (ATZ), a potent disease-modifying drug used to treat relapsing-remitting multiple sclerosis, is a humanized anti-CD52 monoclonal antibody that causes profound depletion of B and T lymphocytes. Despite its potent immunosuppressive effect, paradoxically secondary autoimmune disorders, notably thyroid disease, were reported following ATZ treatment. There were few reports of ATZ-associated renal disease in the form of membranous glomerulonephritis and anti-glomerular basement membrane disease. In this article, we reported a 45-year-old female patient with relapsing-remitting multiple sclerosis with ANCA (antineutrophil cytoplasmic antibody)-associated vasculitis resulting in rapidly progressive glomerulonephritis limited to the kidney after ATZ treatment.

Keywords: Alemtuzumab, ANCA-associated vasculitis, multiple sclerosis, renal failure.

Alemtuzumab (ATZ), a potent disease-modifying therapy used in the treatment of relapsing-remitting multiple sclerosis (RRMS), is a humanized anti-CD52 monoclonal antibody that causes profound depletion of lymphocytes. It has strong immunosuppressive activity. On the other hand, paradoxically secondary autoimmune disorders have been reported following ATZ treatment. There are very few reports of ATZ-associated renal disease in the form of membranous glomerulonephritis and anti-GBM disease.[1]

CASE REPORT

A 45-year-old female patient, an active smoker with a six-year history of relapsing-remitting multiple sclerosis (MS), treated with dimethyl fumarate and ocrelizumab for three years each, received her first course of alemtuzumab (ATZ) at a cumulative dose of 60 mg. Until the 12th month, the patient was stable regarding the neurologic examination and radiologic findings for MS. Follow-up routine investigations, including creatinine and urinalysis, were normal. The patient was referred to our center due to elevated C-reactive protein and ANCA (antineutrophil cytoplasmic antibody) positivity before the second course of treatment. There was a decrease in glomerular filtration rate from 98 to 25 mL/min/1.73 m^2 and an increase in serum creatinine level from 0.74 to 2.3 mg/dL within two weeks. There were no predisposing factors (e.g., contrast enhancement and nonsteroidal anti-inflammatory drugs) that could cause nephropathy. Urinalysis revealed microscopic

Correspondence: Furkan Sarıdaş, MD. Bursa Uludağ Üniversitesi Tıp Fakültesi Nöroloji Anabilim Dalı, 16059 Görükle, Bursa, Türkiye.
E-mail: furkansaridas@uludag.edu.tr
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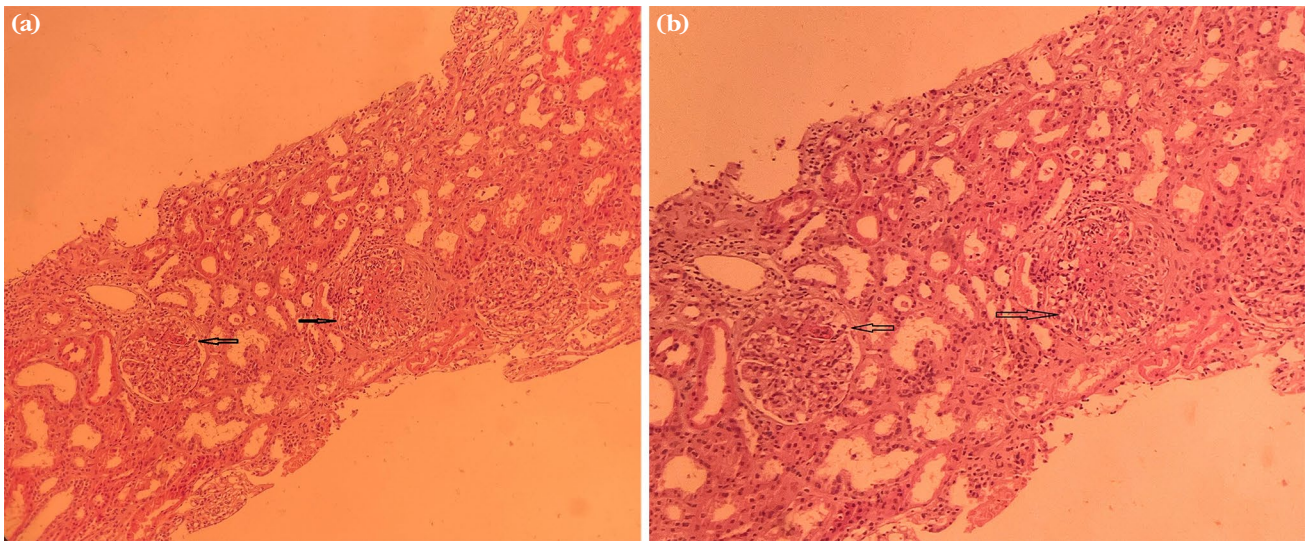

Figure 1. (a) (Hematoxylin-eosin, ×100) and **(b)** (Hematoxylin-eosin, ×200); cellular crescent formation and fibrinoid necrosis in glomeruli, less than 10% fibrosis and mild diffuse mononuclear inflammatory cell infiltration, less than 10% tubular atrophy and degenerative changes in epithelial cells, and intimal fibrosis less than medial thickness. On the histologic examination of the biopsy specimen, three of 10 glomeruli had cellular crescents, and two glomeruli had segmental fibrinoid necrosis. Tubulointerstitial changes, including mild interstitial fibrosis and inflammation with mild tubular atrophy, were observed, indicating necrotizing crescentic glomerulonephritis.

hematuria, and spot urine protein was 0.6 g/day. The infectious workup and autoimmune thyroid disease markers [anti-TPO (thyroid peroxidase), anti-TG (thyroglobulin), and TRAb (TSH receptor antibodies)] were negative. Serum ANCA testing revealed c-ANCA positivity by indirect immunofluorescence and myeloperoxidase positivity by enzyme-linked immunosorbent assay. Written informed consent was obtained from the patient. On renal Doppler ultrasonography, increased bilateral parenchymal echogenicity of Grade 1 was observed, and the mean resistive index value of the right kidney was 0.69, which approached the upper limit of normal. A renal biopsy was performed with the preliminary diagnosis of ANCA-associated vasculitis due to ATZ treatment, as creatinine continued to increase during follow-up (Figure 1a, b). The histopathologic diagnosis was necrotizing crescentic glomerulonephritis without immune complexes (pauci-immune glomerulonephritis). Other systems were not involved. The clinical diagnosis was ANCA-associated vasculitis limited to the kidney. The second course of ATZ was canceled, and it was decided to continue with rituximab treatment for both MS and vasculitis. After intravenous methylprednisolone therapy (1000 mg/day for three days), rituximab was administered at an induction dose of 1000 mg, given by two intravenous infusions two weeks apart. Subsequently, dosing was planned at six-month intervals for maintenance treatment. During this period, 7.5 mg/day oral prednisolone was added to the treatment, and no disease exacerbation was observed. Seven months after the start of treatment (after maintenance dose), the creatinine level improved from 2.29 to 0.89 mg/dL, and the glomerular filtration rate improved from 25 to 78 mL/min/1.73 m^2.

DISCUSSION

A previous study reported ANCA-associated systemic vasculitis after ATZ in a patient with MS.[2] This MS case illustrated ANCA-associated vasculitis limited to the kidney after ATZ treatment. Alemtuzumab causes rapid and prolonged lymphocyte depletion. B cell repopulation tends to precede T cells and returns to baseline within six months.[3] The mechanisms underlying ATZ-induced autoimmunity development are poorly understood.[4] Levels of CD4+ T cells can remain low for years, but data suggest that this depletion does not induce autoimmunity.[5] The autoimmunity response to B cell-depleting therapies indicates that it is predominantly antibody-mediated.[4] Since autoreactive B cells can function without T cell assistance, the appearance of autoreactive B cells during lymphocyte repopulation may be causing autoimmunity.[6] Furthermore, relative

memory and regulatory T cell levels increase during immune reconstitution, resulting in a shift in pro-/anti-inflammatory cytokine profiles.[7] The most common autoimmune adverse events were thyroid disease (most common in the third year after ATZ), with 42% (severe adverse event rate of 4 to 5%), followed by immune thrombocytopenia (2 to 3%).[8,9] Family history of autoimmune disease and current or past smoking are both risk factors for secondary immunity in MS patients treated with ATZ.[10] Regarding renal involvement, few cases of autoimmune nephropathy between the ages of 25 to 58 years were reported in the literature.[11-13] The two most common conditions for nephropathy are anti-glomerular basement membrane disease or antibody positivity. There is no association between nephropathy and MS exacerbation.

In conclusion, this case highlighted a subacute, progressive, and isolated ANCA-associated glomerulonephritis after ATZ treatment in MS. A high index of suspicion should be applied to every patient with MS receiving ATZ therapy, and close periodic monitoring of creatinine and urinalysis should be performed to protect thyroid function, as well as renal function. An early nephrology consultation should be urgently performed in case of any abnormalities. Active smokers, patients with a family history of autoimmune disease, and those who may be at increased risk of secondary autoimmunity should be strictly followed.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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