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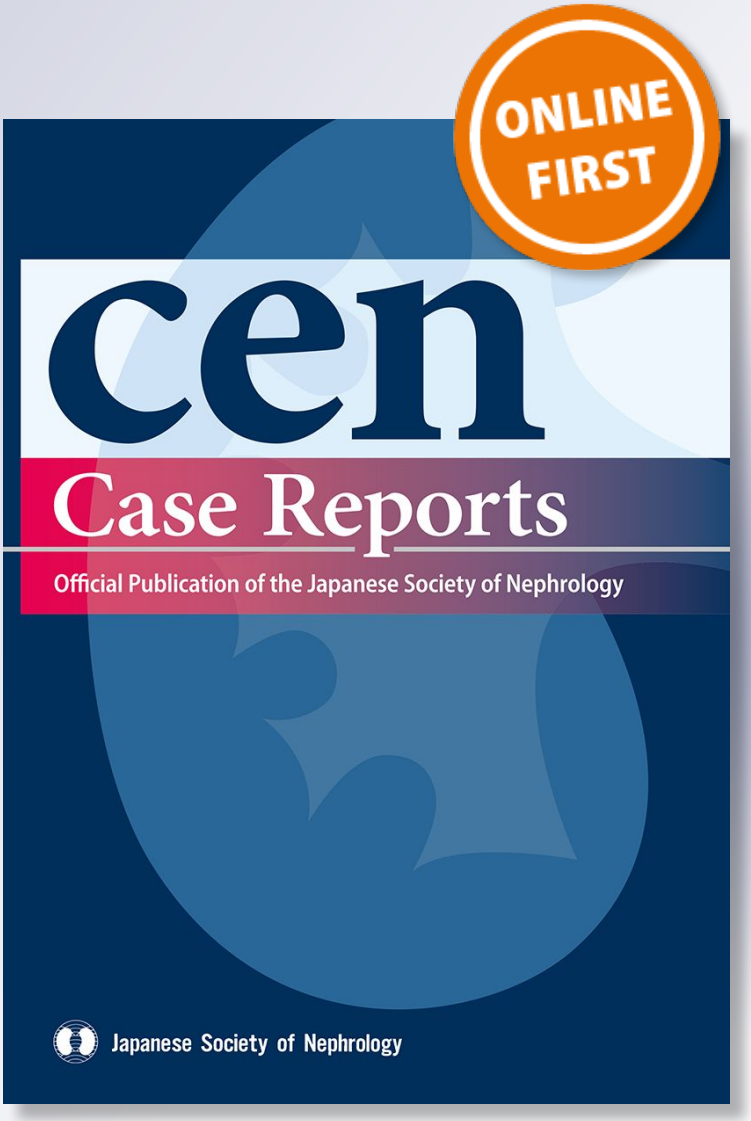

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LETTER TO THE EDITOR

Acute demyelinating neuropathy associated with rituximab treatment in a patient with relapsing nephrotic syndrome

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To the Editor,

Rituximab, the monoclonal antibody directed against CD20, represents ideal treatment of both membranous nephropathy (MN) and demyelinating neuropathy associated with antibodies to myelin-associated glycoprotein (MAG) [1, 2]. Clinical efficacy, safety, and modulating effects on normal and malignant pre-B and mature B cells have been reported [1, 2]. We encountered a 63-year-old woman who experienced acute onset of demyelinating polyneuropathy (AIDP) after rituximab infusions to treat her nephrotic syndrome (NS) [1]. This patient presented 5 month history of peripheral swelling and microscopic haematuria. Laboratory tests showed normal creatinine (0.8 mg/dl), heavy proteinuria (6 g/daily), and negative screening for secondary causes of MN [1]. Renal biopsy showed diffuse thickening of glomerular capillary basement membrane with basement membrane spikes and subepithelial granular deposits of IgG and C_3 on immunofluorescence. She had circulating anti-phospholipase A_2 receptor (PLA_2R) antibodies [1]. Patient received intravenous methylprednisolone (10 mg/kg of bw daily for 3 days) followed by tapering oral prednisone and cyclophosphamide (100 mg daily). Due to proteinuria exceeding 5 g/daily, 5 months later, patient was started on 6 month infusions of rituximab (375 mg/m^2) with clinical improvement. Five years later, because of NS relapse, a course of rituximab was started in a dosage of 375 mg/m^2. Ten days after fourth infusion, patient exhibited acute arthralgias, burning numbness in feet, which involved both legs and fingertips, and gait imbalance. After few hours, she developed hand and lower extremity distal muscle weakness, graded 3/5 on Medical Research Council Scale (MRC). Electrophysiology showed dispersed tibial and peroneal F-waves. Normal laboratory studies included rheumatological, virological, microbiological, neoplastic tests, and searches for anti-ganglioside antibodies in serum [3, 4]. Clinical signs spontaneously regressed within 2 weeks. In the following 6 years, patient had no neurological symptoms. In February 2016, due to relapse of her NS, a rituximab course was planed. Seven days after a single infusion of 375 mg/m^2, patient acutely developed ascending numbness and paraesthesias in hands and feet. On examination, cranial nerves and sensory testing were intact; there were 3/5 MRC weakness in upper extremities, 2/5 in the lower, deep areflexia, ataxic gait. Electrophysiology showed motor demyelinating neuropathy with slowed velocity (within 38 and 40 m/s) in all tested nerves, tibial, ulnar motor conduction blocks (CBs) [2], and normal sensory responses. Spinal tap was denied. Rituximab was halted. At 8 week follow-up, there was no residual weakness neither detectable CBs.

Our patient exhibited acute onset of demyelinating motor neuropathy (AIDP) that presented 6 years after NS due to MN. The long time interval between NS and our patient AIDP raised the possibility of coincidental association or of worsening of a pre-existing subclinical chronic neuropathy. This possibility was excluded as our patient had no prior neurological symptoms or signs. Furthermore, she denied antecedent infections. We know that AIDP are caused by aberrant autoimmune response damaging

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peripheral nerves and nerve roots by molecular mimicry mechanism, which may trigger, after infections, production of cross-reactive autoantibodies to gangliosides found in serum of half of AIDP patients. Such autoantibodies were absent in our subject. Moreover, AIDP rarely develops in patients who suffer from other autoimmune conditions [5]. We believe that the neuropathy of this patient should be classified as drug induced because of temporal association, lack of alternative explanation, and regression after interruption of rituximab without additional specific therapies. No other medications could be incriminated. The recurrence of neurological status after rituximab is strong argument for relation between neuropathy and treatment administered [3–5]. Rituximab induced Guillain–Barré syndrome in patient with idiopathic thrombocytopenic purpura [3] and a paradoxical worsening of anti-MAG polyneuropathy [4, 5]. Rituximab might rarely produce precipitous onset of reversible demyelination, as documented in our case by serial studies [3, 5]; nevertheless, it represents promising treatment for neuropathies associated with B-cell dyscrasias [2]. Rituximab specifically eliminates CD20 and their precursors; however, despite inhibition of CD20 cells, other pathogenic antibodies might be produced, either by CD20 cells at maturative stages or by different B-cell sub populations [2–4]. Some authors speculated that worsening could be the result of a specific autoimmune response induced by rituximab due to disruption of idiotype–anti-idiotype network and promotion of autoantibodies by proinflammatory cytokine interleukin-6, which demonstrated to be significantly elevated [5]. It is not clear how best to avoid or clinically predict this rare complication; measures might include pretreatment with corticosteroids, as has been proposed in Waldenström disease patients to prevent hyperviscosity [3, 5].

Given that one does not condemn a potentially important therapy based on isolated reports [1, 2, 5]. The current case provides emphasis that new therapies require close clinical monitoring and strict indications.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Human and animal rights statement This article does not contain any studies with human participants performed by any of the authors.

Informed consent No identifying information about individuals is included in the paper.

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