Long-term Treatment With Rituximab of Autoimmune Autonomic Ganglionopathy in a Patient With Lymphoma

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Objective: To report on the response to therapy in a patient with autoimmune autonomic ganglionopathy with a high titer of an autoantibody directed against the α-3 subunit of the nicotinic acetylcholine receptor (nAChR) of the autonomic ganglia.

Design: Case report.

Setting: University-based referral center for autonomic dysfunction.

Patient: Patient with prior indolent B-cell lymphoma who presented with symptomatic orthostatic hypotension and autonomic failure and was found to have a high titer of nAChR antibody.

Intervention: Plasma exchange and rituximab therapy (both initial 4-week therapy and maintenance therapy).

Main Outcome Measures: Autonomic ganglionic antibody titer; the autonomic assessments were the presence of orthostatic hypotension, the concentration of plasma norepinephrine, and quantitative sweat testing.

Results: Treatment with rituximab followed by plasma exchange significantly decreased the nAChR antibody titers for a short time, and then the titers increased. The titers suppressed to almost undetectable levels once regular maintenance therapy with rituximab was initiated. Reduction in nAChR antibody titer resulted in a decrease in orthostatic hypotension, an increased concentration of upright plasma norepinephrine, improvement in some sweat function, and improvement in symptoms.

Conclusions: Long-term rituximab therapy suppressed autoantibody production to undetectable levels over the course of 2 years and resulted in sustained clinical improvement in this patient with debilitating autoimmune autonomic ganglionopathy. More data are needed before rituximab therapy can be recommended as routine therapy for this disorder.


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AUTOIMMUNE AUTONOMIC ganglionopathy (AAG) is a rare, acquired immunoglobulin-mediated disorder of autonomic failure associated with autoantibodies to the nicotinic acetylcholine receptor (nAChR) of the autonomic ganglia. The clinical picture manifests as pandysautonomia, with patients presenting with the following symptoms: orthostatic hypotension, recurrent syncope, anhidrosis, sicca syndrome (xerostomia and xerophthalmia), bowel and bladder hypomotility, and pupillary dysfunction; however, not all of these symptoms are present in every patient with pandysautonomia. Although this constellation of symptoms overlaps with pure autonomic failure or other causes of pandysautonomia, the presence of nAChR autoantibodies suggests disrupted cholinergic synaptic transmission in the autonomic ganglia leading to autonomic failure.

The optimal therapy for AAG remains uncertain. No randomized controlled trials are available, and there are only limited case reports of successful treatment of AAG. Standard treatments for orthostatic hypotension (including the use of volume expansion, vasoconstrictors, compression stockings, and abdominal binders) rarely provide adequate symptomatic relief in AAG. Previous case reports have described successful treatment of AAG using plasma exchange (PLEX) with and without immunosuppressive therapies. On the basis of animal models and prior case reports, the early use of immunomodulatory therapy directed at eliminating IgG and decreasing ongoing autoantibody production may be effective in patients with AAG. Herein, we report a case of AAG in a pa-
A 65-year-old woman presented to the Vanderbilt Autonomic Dysfunction Center in December 2005 for evaluation of syncope. The patient had been healthy until January 2004 when she was diagnosed with small lymphocytic lymphoma (defined as expressing both CD5 and CD20 antigen). She had minimal disease and did not require therapy. In July 2004, she developed light-headedness and presyncope. She became severely disabled with multiple episodes of syncope and presyncope. She reported an unintentional 20-lb weight loss over 2 years, constipation, anhidrosis, and xerostomia. Treatment with midodrine and fludrocortisone did not significantly improve her symptoms.

Physical examination showed a pleasant woman in a wheelchair. She was noted to be profoundly orthostatic on examination. While supine, she had a heart rate of 66 beats/min and a blood pressure of 151/77 mm Hg, and after 1 minute of standing, she had a heart rate of 67 beats/min and a blood pressure of 56/29 mm Hg. She became light-headed during her respiratory examination at a time when she was hyperventilating, likely as a result of hyperventilation-induced hypotension.1 Her pupils were noted to be reactive to light, although formal measurements were not obtained. Her hands were dry. The remainder of her examination was unremarkable.

Formal autonomic function testing6 demonstrated a blunted sinus arrhythmia ratio of 1.01. The cold pressor test (ie, a hand in ice water for 60 seconds) showed that there was no sympathetic vasopressor response. There was a lack of blood pressure recovery during the later part of phase 2 of the Valsalva maneuver and no blood pressure overshoot during phase 4. The results of the quantitative sudomotor axon reflex test were abnormal (ie, no sweat response in the 3 leg sites, consistent with severe postganglionic sudomotor deficit). Her plasma norepinephrine levels were very low (23 pg/mL while in the supine position and 96 pg/mL while in the upright position [to convert to nanomoles per liter, multiply by 0.00591]). In total, the results of her autonomic function test were consistent with severely impaired autonomic function involving both the sympathetic and parasympathetic limbs. An autoantibody panel showed a high titer of nAChR antibody directed against the α-3 subunit of the nicotinic ganglionic acetylcholine receptor (2.63 nmol/L). She received a diagnosis of AAG.

She was still severely disabled when her condition was reassessed 2 months later. Her lymphoma was restaged and showed no progression. Given the presence of an antibody possibly related to her lymphoma, she was treated with a 4-week cycle of rituximab in March 2006. Shortly after rituximab treatment, she had perforated sigmoid diverticula requiring emergent hemicolecotomy and colostomy. She recovered well and showed significant improvement in her autonomic symptoms. In June 2006, she no longer required a wheelchair. She was able to walk 1 block and could independently cook and bathe. Despite these positive signs, she had persistent severe orthostatic hypotension with limited ability to stand.

Her symptoms had worsened by March 2007. She reported experiencing debilitating light-headedness whenever she tried standing and received a diagnosis of progressive xerostomia. Her nAChR antibody level was 1.02 nmol/L. She completed a 5-day course of PLEX with subjective improvement in her symptoms. By the final day of treatment, her xerostomia had resolved and she was able to walk for more than 10 minutes, although she remained significantly orthostatic. While supine, she had a heart rate of 61 beats/min and a blood pressure of 145/66 mm Hg, and after 1 minute of standing, she had a heart rate of 73 beats/min and a blood pressure of 86/43 mm Hg. One week after PLEX, her nAChR antibody titer was 0.62 nmol/L.

By September 2007, her nAChR titer had increased to 1.87 nmol/L. She underwent another 4-week course of rituximab. The patient was concerned about the benefits of therapy waning over time; therefore, she elected maintenance therapy with rituximab every 2 months. Serial nAChR antibody titers (Figure) decreased and remained low, eventually reaching undetectable levels. She showed great clinical improvement. Her standing time improved to greater than 10 minutes (which is the maximal duration of our standing test), and her orthostatic hypotension decreased. She gave away her wheelchair. She has had residual sweat abnormalities in her foot, although the sweating in her hands normalized. Her clinical sweat function suddenly improved after therapy.

This case highlights the dramatic clinical improvement and successful antibody clearance that were associated with the use of both PLEX and long-term rituximab therapy for a patient with debilitating AAG. Ganglionic AChRs are expressed peripherally in sympathetic, parasympathetic, and enteric ganglia. Vernino et al10 first described a population of patients with AAG by the detection of serum autoantibodies to neuronal nAChRs of autonomic ganglia. Subsequently, mice injected with rabbit IgG–ganglionic AChR antibodies developed transient gastrointestinal dysmotility, urinary retention, mydriasis, and autonomic failure.10

The significant but transient improvement associated with using PLEX in this case is in agreement with prior reports. Schroeder et al13 described a patient with AAG who was successfully treated with PLEX. They observed that orthostatic hypotension was markedly reduced with decreased plasma antibody concentration after PLEX. Gibbons et al14 reported on a series of 3 patients for whom immunosuppressive medications (prednisone and mycophenolate mofetil) plus PLEX resulted in sustained clinical improvements that were superior to either treatment modality alone. Interestingly, PLEX monotherapy and intravenous immunoglobulin monotherapy did not result in sustained clinical improvement or improved autonomic function testing results in any of these 3 patients. The ap-
parent consistent relapse of symptoms in a patient with AAG after PLEX suggests that the problem of ongoing autoantibody production may need to be addressed before we can begin to see sustained clinical improvement.

We demonstrate that long-term CD20⁺ B-cell depletion using rituximab results in suppressed antibody production with concurrent sustained clinical improvement. Rituximab is a chimeric murine or human monoclonal antibody directed against the CD20 surface antigen of B cells.¹¹ It is approved for the treatment of refractory or relapsed non–Hodgkin B-cell lymphoma and rheumatoid arthritis in poorly responding patients. Rituximab has been used successfully for other paraneoplastic disorders.¹² ¹³ Rituximab may function as a nonspecific intravenous immunoglobulin, rituximab-induced B-cell depletion may inhibit production of disease-specific autoantibodies, or rituximab may reduce or eliminate the autoantibody-independent roles played by circulating B cells.¹¹ We demo-

Figure. Clinical parameters and antibody levels over time. A, Nicotinic acetylcholine receptor antibody (nACHr Ab) titer in response to standard rituximab therapy (R × 4), plasma exchange (PLEX), and maintenance rituximab therapy (R maintenance). B–F, Autonomic parameters tracked over time: Change in systolic blood pressure (Δ SBP) from lying supine to standing upright (B); standing plasma norepinephrine (NE) levels (C); standing time before having to sit down as a result of orthostatic symptoms (D); sinus arrhythmia (SA) ratio (E); and quantitative sweat volumes in the forearm and foot (F).
onstrated that there was sustained clinical improvement and autoantibody suppression to undetectable levels associated with long-term rituximab therapy. These findings suggest that rituximab was effective in this patient because of the suppression of disease-specific autoantibody production, although the role of other mechanisms cannot be evaluated or excluded. Our patient’s low-grade lymphoma did not warrant treatment. She was treated only because of the nAChR antibody and its clinical sequelae.

Clinical improvement associated with declining autoantibody titers has been described in other autoimmune and paraneoplastic diseases. Gibbons and Freeman have described a correlation between AAG clinical severity and antibody titer. They found severe, widespread dysautonomia at higher titers with clinically significant orthostatic hypotension appearing at a threshold of greater than 1.0 mmol/L. The patient described in our case had disabling orthostatic hypotension, which resolved at a nAChR antibody titer of 1.0 mmol/L or less.

Despite antibody clearance and significant clinical improvement, persistent objective autonomic function abnormalities remain in our patient. Orthostatic hypotension persists, although the symptoms have improved enough from initial presentation that they are tolerable. Some sweating abnormalities (as measured by use of the quantitative sudomotor axon reflex test) have improved (eg, in the forearms), whereas as others (eg, leg sites) have persisted (Figure). Iodice et al reported improvement in the results of quantitative sudomotor axon reflex testing with regard to sweating in 4 of 6 patients after sequential intravenous immunoglobulin monotherapy, PLEX, and immunomodulator therapy. Persistent autonomic dysfunction despite autoantibody clearance raises the question of whether there is permanent damage as a result of the nAChR antibody. One possibility is that sweat abnormalities relate initially to acute decreases in autonomic ganglionic traffic but that, over time, Wallerian degeneration occurs (starting with the longer nerves). This hypothesis could explain the persistent decrease in sweat function in the foot and suggests that, if the antibody were not cleared, eventually the forearm damage would also become permanent. Sweat function has been shown to improve with treatment in other types of peripheral neuropathy, which suggests that nerve regeneration may account for some of the recovery. Although rituximab may be promising for the treatment of AAG, the following factors are significant barriers to frequent treatment with rituximab: the high cost, an immune response to rituximab that limits effectiveness, and progressive multifocal leukoencephalopathy (which can be fatal).

In conclusion, the use of PLEX followed by long-term rituximab therapy suppressed autoantibody production to undetectable levels over the course of 2 years and resulted in sustained clinical improvement in this patient with debilitating AAG. Further data are needed before rituximab can be recommended as routine therapy for this disorder.

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REFERENCES