A Second Case of Treatment-resistant CIDP in an IgG Tubulin Autoantibody Positive Patient

Alaina Giacobbe MD, Tawfiq Al-lahham MD, Ajitesh Ojha MD, Sasha A. Živković MD, PhD

Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA

Introduction

In this case report, we describe the second case of treatment-refractory chronic immune demyelinating polyradiculoneuropathy found to have high titers of positive IgG anti-tubulin antibodies. As described previously,[1] the clinical significance of anti-tubulin antibodies found in the serum of CIDP patients is still uncertain.

IgG anti-tubulin antibodies can be found generally in low titers of human sera. It has been shown that an epitope on beta-tubulin has some sequence homology to several human viruses. However, the role of these antibodies in the pathogenesis of acquired demyelinating neuropathy remains unclear.[2] An association between anti-tubulin autoantibodies and CIDP was first hypothesized in a 1993 study by Connolly et al. when analysis of the serum of 70 patients with CIDP showed that 57% had high-titer IgG or IgM anti-tubulin reactivity compared to 3% on controls determined by ELISA.[3] However, later studies using immunoblot techniques could not replicate these results.[4,5]

In a previous report, a patient with typical CIDP had a quickly relapsing disease requiring monthly hospitalizations despite treatment with IVIG, glucocorticoids, and PLEX. She underwent extensive workup, which was only notable for positive serum IgG tubulin autoantibodies at 20,000 (ref range 2500). Subsequently, the patient remained stable off steroids and PLEX therapy for the last two years on rituximab monotherapy every six months without further hospitalizations.[1] This report is meant to support the possibility that tubulin autoantibodies are related to a rare subset of CIDP that is more resistant to typical treatment for CIDP with IVIG, PLEX, and glucocorticoids.

Case Presentation

A 57-year-old female with a history of idiopathic transverse myelitis 16 years prior, hypothyroidism, and autoimmune hemolytic anemia presented to an outside hospital with one week of muscle soreness and proximal lower extremity weakness. The patient had no preceding illness and received a second Moderna covid vaccine three months earlier. On exam, the patient had symmetric lower extremity weakness, proximal>distal, and preserved upper extremity strength. Bulbar and respiratory muscles were spared. She was areflexic. Given her remote history of transverse myelitis, which presented with lower extremity numbness, weakness, and urinary retention that improved with IV steroids, MRIs of her brain and whole spine with and without contrast were ordered and were unremarkable. Still, she was treated with IV 1g Methylprednisolone for five days for presumed central nervous system disease with improvement and was discharged home with physical therapy. She was discharged on a short steroid taper but started to worsen after completing the taper, so prednisone was restarted at 80 mg daily.

Despite this intervention, she continued to decline and presented to our hospital again a month later with a fall. The initial exam was like prior except for new proximal upper extremity weakness and decreased sensation to pinprick in bilateral feet. Medical Research Council-sum score (MRC) of six muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsiflexion) was 50. Initial workup for serum autoimmune, infectious, and metabolic etiologies of polyneuropathy was unremarkable apart from mildly elevated Gad-65 antibodies (0.16 nmol/L, ref <0.02) on the serum autoimmune panel. Lumbar puncture (LP) was performed on admission with 58 protein (ref 15-45 mg/dL), WBC 1 (ref 0-5/cu mm) and mildly increased IgG index 0.7 (ref <0.70) in the cerebrospinal fluid (CSF). CSF GAD antibodies were negative. EMG showed prolonged distal latencies, abnormal temporal dispersion with decreased conduction velocity, absent F waves, and partial motor conduction block consistent with demyelinating polyneuropathy. Given EMG findings, home prednisone 80mg daily was tapered, and 2g/kg intravenous immunoglobulin (IVIG) over five days was started. The patient worsened after being treated with IVIG. She was then treated with another five days of IV 1g Methylprednisolone with some improvement. However, she worsened again upon completion despite starting maintenance pulse therapy with prednisone 600mg weekly. Due to continued progressive weakness, plasma exchange (PLEX) was started and did not prove effective. See Table 1 for MRC scores before and after treatments.

The repeat EMG while the patient received PLEX showed a non-length-dependent demyelinating radiculoneuropathy with some ongoing denervation and active axon loss (likely secondary). Compared to the prior study, there was evidence of some interval worsening.

Also, while receiving PLEX, the patient developed cranial nerve involvement (VII, R > L V1, L V2-V3, XII). Workup included repeat Brain MRI with and without contrast and an unremarkable ophthalmology evaluation.

Table 1: Treatments with corresponding MRC Sum scores

	1	2	3	4	5
Treatment	IVIG 2g/kg	1g Solumedrol	Plex x5	1g Solumedrol	Rituximab 1000 mg/m^{2}x2
		Pulse steroids 600mg weekly started after 1st solumedrol round			
MRC pre-tx	50	41	40	12	20
MRC post-tx	41	44	38	16	44 (4 months post d/c)

MRC= Medical Research Council sum score (grades the sum of motor strength from 0 to 5 in bilateral deltoid, biceps, wrist extensor, iliopsoas, quadriceps femoris, and tibialis anterior for total score of 60 in patients with normal strength). Tx = treatment

AchR antibodies were negative. She also had involvement of respiratory muscles with NIF/VC as low as -20/1100. Given that cranial nerve involvement is less common in CIDP, there was an increased concern for CIDP mimics. Serum VEGF was negative. Further investigation for malignancy included pan-CT scans, which revealed a left renal mass concerning paraneoplastic polyradiculoneuropathy. She underwent a left radical nephrectomy which returned only to be an angiomyolipoma. Transvaginal ultrasound showed an ovarian dermoid cyst. Her physical exam reached a nadir (MRC 12). She was started on another course of IV methylprednisolone with mild improved strength and resolution of bulbar and respiratory symptoms.

Given the patient's temporary responsiveness to steroids with subsequent disease progression and lack of response to IVIG/PLEX, there was a concern for lymphoma. Her steroids were stopped to increase the sensitivity of LP for lymphoma versus an infiltrative process. LP was repeated twice. Both CSF studies had negative cytology and flow cytometry with elevated protein (57,47 mg/dL). Bone marrow biopsy without signs of lymphoma. Of note, the patient's hospital course was also complicated by worsening anemia with workup consistent with a hemolytic process such as autoimmune hemolytic anemia; however, her coombs test was negative three times.

Additional laboratory testing included anti-MAG antibodies, which were negative. The demyelinating neuropathy panel from Washington University in St. Louis returned positive for IgG B-Tubulin at 14,000 (ref range <2500). IgM tubulin, neurofascin, and contactin antibody titers were negative. CIDP was the most likely diagnosis due to peak disability occurring >2 months since the onset of symptoms. The patient was started on rituximab infusions, 1000mg, administered two weeks apart. She was discharged to inpatient rehabilitation and continued on pulse prednisone 600mg weekly with plans to taper as an outpatient. MRC on discharge was 20. She stayed at inpatient rehab for two months.

At outpatient follow-up four months after discharge, the patient reported gradual improvement in her strength with physical therapy (MRC 44). She was able to walk 10 feet after previously being paraplegic. Her repeat EMG/NCS showed improvement in upper extremity latencies and amplitudes. There was some interval worsening in lower extremity sensory amplitudes and motor conduction velocities, with mild ongoing denervation in her right gastrocnemius.

Discussion

Our patient meets the EFNS/PNS clinical and electrodiagnostic criteria for typical CIDP, based on progressive proximal and distal muscle weakness for >2 months, sensory involvement in bilateral feet, absent reflexes, distal motor latencies >50% above ULN in two nerves, motor conduction velocity >30% below LLN in two nerves, absence of F waves in two nerves, conduction block and abnormal temporal dispersion in >2 nerves.[6]

Cranial nerve involvement is atypical of CIDP; however, in a recent case series, it was shown that bilateral cranial neuropathies were seen in 11% of typical CIDP cases and were associated with more severe limb muscle weakness.[7] Respiratory insufficiency is also uncommon in CIDP; however, there are at least 20 reported cases of ventilatory failure in the literature that improved with typical treatment of CIDP,[8] and one study documented respiratory muscle weakness in 20% of patients with acute-onset CIDP.[9] Interestingly, prospective studies of CIDP patients found abnormal phrenic nerve conductions in 80-92%, which could suggest respiratory insufficiency is more common than traditionally thought and should be regularly evaluated in hospitalized patients.[10,11]

The fact that the third EMG showed worsening NCS in the lower extremities despite clinical improvement of symptoms reflects the gradual evolution of CIDP electrodiagnostically. In support of this theory is that she had improvement in the median and ulnar distal motor

latencies and compound motor action potentials.

Our patient's development of AIHA in parallel with CIDP supports prior case reports suggesting a possible association between the two autoimmune diseases.[12] Notably, a negative coombs test does not exclude a diagnosis of AIHA.[13] There have also been prior research linking polyclonal IgG tubulin autoantibodies in serum to acquired thyroid disease, which our patient has a history of.[14] Additionally, her history of transverse myelitis supports the association of CIDP with polyautoimmunity.[15]

Extensive workup for underlying autoimmune, inflammatory, neoplastic, and infectious etiologies was only notable for high-titer positive beta-tubulin antibodies. This case report suggests the role of high-titer beta-tubulin autoantibodies in refractory CIDP as previously described.[1] In both cases, patients were considered to have refractory disease based on failure to respond to or only partial response to typical immunotherapies for CIDP, including IVIG, glucocorticoids, and plasma exchange.

Based on the initial worsening of symptoms on daily steroid therapy and evidence that pulsed steroids may be effective in treating CIDP and reducing steroid-related adverse effects, we decided to treat our patient with pulsed steroids.[16]

Rituximab has been demonstrated to be more effective in treating nodal and paranodopathies that are less responsive to IVIG, glucocorticoids, and PLEX.[17] There is currently no known mechanism of action of anti-tubulin antibodies in CIDP,[2] but based on similar responses to treatment, it may be hypothesized that anti-tubulin antibodies act similarly to antibodies direct against the Node of Ranvier.

Conclusion

This case report describes the second case of a patient with treatment-refractory CIDP who was found to have a high titer of IgG tubulin autoantibodies. In both cases, patients were refractory to treatment with IVIG, glucocorticoids, and PLEX and responded to rituximab infusions, which suggests the use of rituximab treatment may improve outcomes in future cases. Increased testing for tubulin autoantibodies in CIDP is needed to determine their significance. Compared to the last case, this case is unique because of respiratory and cranial nerve involvement and existing past medical history of other autoimmune diseases.

References

1. Giacobbe A, Patel M, Heller S, Chuquilin M. Treatment-resistant CIDP in an IgG Tubulin Autoantibody Positive Patient: case report and review of the literature. *RRNMF Neuromuscular Journal*. 2020 Nov 30;1(5):20-4.

2. Connolly AM, Pestronk A. Anti-tubulin autoantibodies in acquired demyelinating polyneuropathies. *Journal of Infectious Diseases*. 1997 Dec 1;176(Supplement_2):S157-9. DOI: 10.1086/513801_PMID: 9396702

3. Connolly AM, Pestronk A, Trotter JL, Feldman EL, Cornblath DR, Olney RK. High-titer selective serum anti-tubulin antibodies in chronic inflammatory demyelinating polyneuropathy. *Neurology* 1993;43(3, Part 1):557-557. doi:10.1212/wnl.43.3_part_1.557. PMID 8451001

4. Schaik IN, Vermeulen M, Doom PA, Brand A. Anti-tubulin antibodies have no diagnostic value in patients with chronic inflammatory demyelinating polyneuropathy. *Journal of Neurology* 1995;242(9):599-603. doi:10.1007/bf00868814. PMID 8551323

5. Manfredini E, Nobile-Orazio E, Allaria S, Scarlato G. Anti-alpha- and beta-tubulin IgM antibodies in dysimmune neuropathies. *Journal of the Neurological Sciences*. 1995;133(1-2):79-84. doi:10.1016/0022-510x(95)00149-v. PMID 8583236

6. Van den Bergh PY, van Doorn PA, Hadden RD, Avau B, Vankrunkelsven P, Allen JA, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision. *Journal of the Peripheral Nervous System*. 2021 Sep;26(3):242-68. DOI: 10.1111/jns.12455 PMID: 34085743

7. Shibuya K, Tsuneyama A, Misawa S, Suichi T, Suzuki Y, Kojima Y, et al. Cranial nerve involvement in typical and atypical chronic inflammatory demyelinating polyneuropathies. *European Journal of Neurology*. 2020 Dec;27(12):2658-61. DOI: 10.1111/ene.14497. PMID: **32876980**

8. Živković SA, Peltier AC, Iacob T, Lacomis D. Chronic inflammatory demyelinating polyneuropathy and ventilatory failure: report of seven new cases and review of the literature. *Acta Neurologica Scandinavica*. 2011 Jul;124(1):59-63. DOI: 10.1111/j.1600-0404.2010.01431.x. PMID: **21649602**

9. Dionne A, Nicolle MW, Hahn AF. Clinical and electrophysiological parameters distinguishing acute-onset chronic inflammatory demyelinating polyneuropathy from acute inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2010;41:202–7. DOI: 10.1002/mus.21480. PMID: **19882646**

10. Macia F, Le Masson G, Rouanet-Larriviere M, Habonimana D, Ferrer X, Marthan R, et al. A prospective evaluation of phrenic nerve conduction in multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2003;28:319–23. DOI: 10.1002/mus.10430. PMID: **12929191**

11. Cocito D, Ciaramitaro P, Rota E, Isoardo G, Cannizzo

S, Poglio F, et al. Subclinical electrophysiological alterations of phrenic nerve in chronic inflammatory demyelinating polyneuropathy. *J Neurol* 2005;252:916–20. DOI: 10.1007/s00415-005-0780-5. PMID: **15772737**

12. Netherton SJ, Owen CJ, Zochodne DW. Monophasic CIDP Associated with Autoimmune Hemolytic Anemia. *Canadian Journal of Neurological Sciences*. 2014 Mar;41(2):290-2. DOI: 10.1017/s0317167100016772. PMID: **24534050**

13. Kamesaki T, Oyamada T, Omine M, Ozawa K, Kajii E. Cut-off value of red-blood-cell-bound IgG for the diagnosis of Coombs-negative autoimmune hemolytic anemia. *Am J Hematol*. 2009 Feb;84(2):98-101. doi: 10.1002/ajh.21336. PMID: 19105232.

14. Rousset B, Bernier-Valentin F, Poncet C, Orgiazzi J, Madec AM, Monier JC, et al. Anti-tubulin antibodies in autoimmune thyroid disorders. *Clin Exp Immunol*. 1983 May;52(2):325-32. PMID: 6688044; PMCID: PMC1535862.

15. Rodríguez Y, Vatti N, Ramírez-Santana C, Chang C, Mancera-Páez O, Gershwin ME, et al. Chronic inflammatory demyelinating polyneuropathy as an autoimmune disease. *Journal of autoimmunity*. 2019 Aug 1;102:8-37. DOI: 10.1016/j.jaut.2019.04.021. PMID: **31072742**

16. Muley SA, Kelkar P, Parry GJ. Treatment of Chronic Inflammatory Demyelinating Polyneuropathy With Pulsed Oral Steroids. *Arch Neurol*. 2008;65(11):1460–1464. doi:10.1001/archneur.65.11.1460. PMID: 19001164.

17. Querol L, Siles AM, Alba-Rovira R, Jauregui A, Devaux J, Faivre-Sarrailh C, et al. Antibodies against peripheral nerve antigens in chronic inflammatory demyelinating polyradiculoneuropathy. *Sci Rep*. 2017;7(1):14411. DOI: 10.1038/s41598-017-14853-4. PMID: **29089585**