Treatment-resistant CIDP in an IgG Tubulin Autoantibody Positive Patient: Case Report and Review of the Literature

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ABSTRACT

Objectives. To describe a case of rapidly relapsing chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in the setting of positive serum IgG tubulin autoantibodies.

Methods. We wrote a case report and performed a literature review of IgG tubulin autoantibodies and the use of rituximab in treatment resistant CIDP.

Results. Our case report describes a 29-year-old woman with CIDP that was resistant to treatment with steroids, intravenous immunoglobulin, and plasma exchange. An extensive workup of her rapidly relapsing CIDP was negative, with the exception of positive serum IgG tubulin autoantibodies. She ultimately stabilized on oral steroids, plasma exchange and rituximab, with a regular recurrence of weakness occurring approximately every month that led to rehospitalization.

Conclusions. Anti-tubulin antibodies could be a marker of a subtype of CIDP that is treatment resistant. We detail her clinical course to serve as an example for other cases of IgG tubulin autoantibody positive CIDP patients that could be described in the future.

Keywords: *CIDP, IgG tubulin autoantibodies, rituximab, demyelinating neuropathy.*

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a heterogeneous disease caused by autoimmune destruction of the peripheral nerve myelin sheaths. Numerous antibodies felt to play a role in the underlying pathophysiology of this disease have been isolated in an attempt to better understand it.

In the literature, there is disagreement about whether anti-tubulin antibodies are markers for a subset of patient's with CIDP. In 1993, Connolly et al published a paper on the detection of IgG and IgM tubulin autoantibodies in the sera of CIDP patients. Using ELISA, selective high-titer serum anti-B-tubulin antibodies occurred in up to 42% of patients with CIDP.[1] In 1995, Van Schaik et al questioned their diagnostic value when only 3 of their 43 patients had positive antibodies using Western Blot.[2] Manfredini et al found similar results using an immunoblot technique, with high serum tubulin IgM titers in only 10.5% of CIDP patients.[3] While the more recent studies indicate that anti-tubulin may not have good diagnostic value,[2,3] one could also infer that anti-tubulin CIDP may represent a rare form of the disease and could even warrant a different treatment approach.

Here we describe a patient with positive anti-tubulin antibodies, whose diagnosis followed a somewhat atypical clinical and electrodiagnostic pattern for CIDP; resistant to treatment with steroids and IVIG.

Case Presentation

A 29-year-old woman presented with two months of progressive upper and lower extremity weakness with inability to walk, as well as numbness and tingling in the hands. On examination, she had diffuse muscle weakness, most prominent in the proximal upper extremities. Bulbar and respiratory muscles were spared. She was areflexic. Nerve conduction studies (NCS) showed a severe generalized sensorimotor polyneuropathy with axonal and demyelinating features (Table 1). Needle-EMG showed active denervation in the proximal more than distal upper extremities, and to a lesser degree in the proximal and distal lower extremities. EMG suggested an acute to subacute process, with minimal chronic features. The working diagnosis was CIDP. She completed five days of intravenous immunoglobulin (IVIG) and was discharged with improved strength in all extremities, however she remained areflexic. Figure 1 shows her MRC sum scores and treatments for each admission.[4]

Four weeks later, she experienced worsening paresthesias and weakness in upper extremities and was readmitted. Cerebrospinal fluid (CSF) showed protein of 78 mg/dL and cell count of 17 WBCs/mcL with 100% lymphocytes. She received four days of IVIG but failed to respond to the treatment, and her examination at discharge was unchanged.

Five days after discharge, she returned with profound weakness in all extremities and continued areflexia. NCS showed a primary demyelinating polyneuropathy. EMG

Figure 1: MRC Sum Scores with Corresponding Treatments

Admissions and days between each admission	1	(30 days between)	2	(5 days between)	3	(18 days between)	4	(10 days between)	5
MRC admission	36		44		34		44		23
MRC discharge	48		44		46		32		54
Treatment	IVIG 2g/kg		IVIG 2g/kg		Plex x5 1 g Solumedrol		Plex x5 Prednisone 80mg QD		Plex x5 Rituximab 900 mg/m^2

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).

showed many muscles with markedly reduced recruitment, with absent or sparse active denervation, suggestive of interval reinnervation since the prior study (Table 1). Workup for reversible, infectious, paraproteinemic and common autoimmune conditions were unrevealing. Repeat lumbar puncture demonstrated elevated CSF protein (61 mg/dL) and cell count (30 WBCs/mcL, with 99% lymphocytes). CSF testing for neurotropic viruses were negative. CSF cytology and flow cytometry studies showed no evidence of malignancy. Pan-CT and transvaginal ultrasound were negative for malignancy. MRI brain and spine imaging showed only minimal enhancement in the upper cauda equina. A demyelinating polyneuropathy panel (Washington University in St. Louis) revealed elevated IgG anti-tubulin antibodies (20,000, ref range <2500). The IgM anti-tubulin titer was zero. Neurofascin 140 and 155, anti-ganglioside and contactin-1 antibodies were negative. She received three days of IV solumedrol and five days of plasma exchange (PLEX). She clinically improved, with only residual numbness and tingling of her hands.

Another relapse occurred eighteen days later. Her MRC sum score on admission was 44. On day three of admission, she worsened to an all-time low MRC sum of 8. She then received PLEX, was started on an oral course of high-dose prednisone, and clinically improved to an MRC score of 32, albeit still not back to her strength on admission.

She returned ten days later for recurring weakness, and the decision was made to administer IV rituximab 900mg (2nd dose 2 weeks later) in addition to PLEX. Upon discharge, she regained her strength and was discharged home on 80mg per day of prednisone. Over the next six months she presented monthly with weakness in her arms > legs which improved with PLEX sessions to roughly 5/5 strength everywhere. Rituximab was administered again six months after the last infusion.

Discussion

Our patient meets the EFNS/PNS clinical and electrodiagnostic criteria for typical CIDP, based on her recurrent symmetric proximal and distal muscle weakness, sensory impairment, and areflexia in all extremities for more than two months,[5] reduced motor nerve conduction velocities of >30% below the lower limit of normal in more than two nerves, increased motor distal latency of >50% above the upper limit of normal in two nerves, and absent F-waves in two nerves.

Based on the EFNS/PNS criteria, CSF with elevated protein and absent pleocytosis (leukocytes <10 cells/μL) is supportive of CIDP. Our patient had elevated lymphocytes in both lumbar punctures, which could be because she received IVIG prior to both as IVIG has been linked to CSF pleocytosis.[6] The CSF pleocytosis from IVIG is associated with symptomatic aseptic meningitis in the literature, which our patient did not have.[6] Additionally, prior studies suggest that a mild to moderate pleocytosis in the CSF does not exclude the diagnosis of CIDP. Lucke et al found that of 273 patients with CIDP based on the EFNS/PNS criteria, 14 of them had >10 leukocytes in the CSF. Most patients with CSF pleocyto-

Table 1: Serial NCS and Needle EMG Data

		1st Admission	3rd admission
R median	motor NCS: DML (ms)	**5.05**	
	CMAP amplitude (distal/proximal), μV	**5.3/3.6**	
	CV (m/s)	**33**	
	sensory NCS: amplitude (μV)	**12.9**	
	F wave latency (ms)	**NR**	
L median	Motor NCS: DML (ms)	**6.35**	**6.88**
	CMAP amplitude (distal/proximal), μV	**2.8/2.3**	**2.2/1.3**
	CV (m/s)	43	**32**
	Sensory NCS: amplitude (μV)	**4.9**	**NR**
	F wave latency (ms)	**NR**	**42.9**
R ulnar	Motor NCS: DML (ms)	4.43	
	CMAP amplitude (distal/proximal), μV	**2.1/1.5**	
	CV (m/s)	**34**	
	Sensory NCS: amplitude (μV)	**5.0**	
	F wave latency (ms)	31.3	
L ulnar	Motor NCS: DML (ms)	3.49	3.18
	CMAP amplitude (distal/proximal), μV	**5.1/4.3**	**4.4**/3.4
	CV (m/s)	**39**	**37**
	Sensory NCS: amplitude (μV)	23.7	**11.5**
	F wave latency (ms)	**NR**	
L tibial	Motor NCS: DML (ms)		**6.72**
	CMAP amplitude (distal/proximal), μV		**2.7**/2.8
	CV (m/s)		42
	F wave latency (ms)		**58.3**
R peroneal	Motor NCS: DML (ms)	5.89	
	CMAP amplitude (ankle/fib head/pop), μV	7.8/6.0/5.3	
	CV (fib head, pop) m/s	40/**26**	
	F wave latency (ms)	**NR**	
L peroneal	Motor NCS: DML (ms)		6.15
	CMAP amplitude (ankle/fib head/pop), μV		4.9/4.2/3.9
	CV (fib head, pop) m/s		41/**28**
	F wave latency (ms)		**60.5**

NCS = nerve conduction study, EMG = electromyography, NR = no response, L = left, R = right, fib head= fibular head, pop = popliteal fossa, blank rows = not done. Abnormal values are bolded.

sis had an acute to subacute presentation and responded to therapy with steroids and/or IVIG after six months.[7]

The assessment of this patient's response to therapy has been guided by the clinical picture and treatment time to efficacy as documented in the existing literature. However, there is subjectivity in our patient's examinations as they were performed by different neurologists. The findings were consistent with the patient's own subjective reports of wors-

ening muscle weakness on admission and improved muscle weakness upon discharge.

Additionally, we classified our patient's disease process as "treatment-resistant," because of her multiple relapses into recurrent inflammatory demyelinating disease despite standard therapies of corticosteroids, IVIG, and PLEX.

Our decision to start rituximab was based on a randomized controlled trial by Roux et al, which showed that rituximab administration in patients within a shorter duration of disease was associated with a better clinical response. The median time to response was six months, and 75% of the patients in that study responded to rituximab.[8] It is notable, that most of those patients had an associated hematologic or autoimmune condition, which were absent in our patient.

A second study of 13 patients with CIDP refractory to standard treatments found that on average, the response duration to rituximab was only two months. Of the five patients without a coexisting hematologic disease in this study, two responded to rituximab within two months and three did not respond at all. Three patients were able to stop their IVIG or plasmapheresis after starting rituximab.[9] Another study showed similar findings.[10]

In a study looking at treatment-resistant patients with antibodies against Node of Ranvier proteins, disease duration in both patients that responded was less than one year at the time of initiation of rituximab.[11]

Compared to IgM anti-tubulin antibodies, the spectrum of clinical disorders associated with IgG anti-tubulin antibodies is even less well-defined. In Connolly's original 1993 paper out of 70 CIDP patients, there were twice as many IgM protein positive patients than IgG protein positive patients.[1] This is different from van Schaik's study, where 2 of the 43 patients had detectable IgG anti-tubulin antibodies and 1 had IgM anti-tubulin antibodies.[2] Our patient would have been excluded from van Schaik's study because they only included patients with a CSF cell count of < 10/mm.[3] Our study also differs from van Schaik's study because our patient's IgG anti-tubulin antibodies were detected using ELISA, the same method used in Connolly's paper. In van Schaik's study they used Western Blot, which is not as sensitive but has greater specificity.

Of the 10 CIDP cases with anti-tubulin antibodies mentioned in the literature, the average age of onset was 60. The weakness pattern was variable (proximal, distal, symmetric, asymmetric) and only 2 of them had positive IgG anti-tubulin antibodies.[2,3,12,13] A case by Stubbs et al described an IgM anti- tubulin antibody positive patient with a sensory-predominant polyneuropathy.[12] No details about treatment outcome have been described in these cases.

This may be the first detailed case report of the clinical course of an IgG anti-tubulin positive patient with CIDP. With the paucity of prior data about this CIDP variant, we are unsure if the tubulin autoantibodies are associated with the treatment-resistant nature of this disease or if the positive antibodies are an incidental finding. We hope that this report will inspire more research that can lead to faster recognition and treatment of refractory CIDP patients.

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