Mycophenolate Mofetil-Induced Peripheral Neuropathy In The Treatment of Membranous Glomerulonephropathy: A Case Report

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Abstract:
Mycophenolate mofetil (MMF) as an immunosuppressive agent is widely used in the management of Membranous Glomerulonephropathy (MGN). In this report, we describe a 66-year-old male MGN case treated with MMF and revealed acquired sensory-motor axonal polyneuropathy, which is rare and has not been reported before.

Key Clinical Message:
Although mycophenolate mofetil is effective in the management of some immune-mediated neuromuscular disorders, it could inversely cause peripheral neuropathy as a rare side effect, which is hopefully reversible with drug discontinuation.

1. Introduction

Membranous Glomerulonephropathy (MGN) is an autoimmune progressive disorder in which deposition of immune complexes occurred in the subepithelial space. It is commonly associated with nephrotic syndrome and can cause end-stage renal disease (ESRD) in long term. It is usually seen as an idiopathic form (primary MGN) but the etiology can be diagnosable (secondary MGN). MGN typically presented with nephrotic syndrome (80%) or persisting nonnephrotic proteinuria (20%). Patients with asymptomatic nonnephrotic proteinuria usually only need conservative therapy.[1] Indications of immunosuppressive treatment in idiopathic MGN include increased creatinine level at presentation, progressive disease, severe symptomatic nephrotic syndrome, thromboembolism, persistent

nephrotic syndrome, persistent nephrotic syndrome, male sex, and age older than 50 years, increased IgG excretion, HLA-DR3 +/B8 +, white race, and elevation of urinary excretion of complement activation products, and tubulointerstitial changes or focal sclerosis. [2]

Immunosuppressive drugs that are commonly used to treat MGN include steroids, cyclophosphamide, chlorambucil, mycophenolate mofetil (MMF), cyclosporine, tacrolimus, and rituximab, an anti-CD20 antibody directed at B cells. [1]

According to The 2012 Kidney Disease Improving Global Outcomes guidelines, a 6-months course of alternating monthly cycles therapy with intravenous and oral glucocorticoids in combination with oral alkylating agents can reduce the progression of disease. [3] Remission and reduction in nephrotic-range proteinuria are eventuated with cyclosporine and tacrolimus, while relapses are frequent after discontinuation of the drug. [4] Just like the combination mentioned above, administration of MMF with steroids obtains remission in 70% of patients. [5] MMF may be considered in patients with contraindication for alkylating agents and those are at risk of renal damage associated with calcineurin inhibitors. [2]

- ***Pharmacology And Indications of MMF***

MMF is an ester prodrug that is converted to its active metabolite Mycophenolic acid with immunosuppressive properties. MMF blocks inosine monophosphate dehydrogenase, a key enzyme for guanosine nucleotides synthesis leading to inhibition of T and B lymphocyte proliferation. [6] It is widely used for the treatment of patients with a variety of collagen-vascular diseases like systemic lupus erythematosus (SLE). [7]

MMF also has been used in neuropathic conditions including polymyositis, chronic inflammatory demyelinating polyradiculoneuropathy, and multifocal motor neuropathy. Primarily it is used as an adjunctive therapy for steroid-sparing effect or reducing the administration frequency of IVIG. [8] It has an acceptable safety profile and also can be useful as monotherapy in some patients.

- ***Adverse Effects of MMF***

MMF affects multiple body organs including cardiovascular, endocrine, gastrointestinal, genitourinary, respiratory, neuromuscular & skeletal, hematologic and central nervous systems, skin, liver and kidney. Considering its immunosuppressive effects, the patient also becomes susceptible to bacterial, viral (cytomegalovirus), and fungal infections. [9]

2. Case Presentation

A 66 -year -old Iranian male was refered to the emergency room because of weakness, imbalance, lethargy, and tremor from 10 days ago. His past medical history revealed a 3-months MGN diagnosis and. His medical history consisted prednisolone 100 mg/day, MMF 1500mg/day, spironolactone 100mg/day, aspirin 80mg/day, chlordiazepoxide 5mg/day, and tamsulosin 0.8mg/day.

Physical examination showed a lethargic man with an oral temperature 37˚ C, blood pressure 100/60 mm Hg, pulse rate 74 beats/minute, respiratory rate 18 breaths/minute, and oxygen saturation 100% on room air. No abnormality on abdominal and pelvic ultrasonography was detected. Electromyogram (EMG) demonstrated reduced proximal force in upper and lower limbs [Table 1] and muscle enzymes were in the normal range. Neurology, infectious, cardiology, gastrointestinal, and hematology assesments did not show any problem that could be related to the patient's symptoms. Other causes of neurotoxicity were also ruled out. The patient's drug history were evaluated for contributing to these manifestations. Accordingly, prednisolone tapered down to a maintenance dose of 60 mg/day and then 45 mg/day concomitantly starting vitamin B1 300 mg/day and L-Carnitine 500 mg/day which were not effective.

3. Discussion

Peripheral neuropathy results from the dorsal route ganglia damage which is triggered by different etiologies. Medications are one of the common causes of peripheral neuropathy named as Drug-Induced Peripheral Neuropathy (DIPN). Covalent modification, organelle damage, intracellular inflammatory signaling, axonal transport defects, and channelopathies are the proposed mechanisms of DIPN.[10] DIPN involves sensory nerves resulting in paresthesia and is reversible if diagnosed before significant axonal damage. After weeks to months of

exposure, the signs and symptoms of peripheral neuropathy start in a dose-dependent manner. [11] Some antimicrobial, psychotropic, anticonvulsants, immunosuppressive, chemotherapeutic and cardiovascular agents are known causes of DIPN. Risk factors that are contributed to DIPN incidence are diabetes, metabolic diseases, preexisting neuropathy, and genetic predisposition. [12]

Despite MMF reveals beneficial effects in immune-mediated neuromuscular disorders, it inversely caused progressive neuropathy in our patient which has not been reported before.

Most DIPNs cause a mild sensory peripheral neuropathy, while our patient was also suffered from even significant neurogenic and motor (defecation, urination, and walking) impairments. Hopefully, DIPN usually needs no special intervention and improves only with dose reduction or drug discontinuation. In this case, no clinical improvement was achieved after the gradual elimination and discontinuation of any drug were expected to justify the patient's symptoms, including prednisolone. Subsequently, with dose reduction of MMF, and substitiution of cyclosporine, the patient gradually was able to stand on his feet and walk with a cane and perform his self-care activities such as defecation and urination after a week. EMG result was also confirmed these observed improvements. After one, three, six, and twelve months follow-up, the primary disease, MGN, was well controlled and he had no problem in walking. The capillary serum zone electrophoresis test was also revealed an ameliorative trend at the 3rd and the 6th months [Table 2].

4. **Conclusion**:

Although MMF is one of the effective drugs in the management of immune-mediated neuromuscular disorders, it could inversely cause progressive neuropathy as a rare side effect. Hopefully, it can be completely recovered by dose reduction or cessation of the treatment.

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Authorship:

All authors contributed to the preparation of this manuscript and have read and approved the final manuscript. Farhad Gholami was the patient's nephrologist who managed the peripheral neuropathy and was responsible for following up the patient. Minoo Moghimi and Zahra Nekoukar were involved in gathering patient's data and writing the manuscript.

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Table 1: EMG Findings

Clinical remarks: Weakness and paresthesia in all limbs.

A: NCS

Motor nerves	Amplitude (mv)	Distal latency (ms)	NCV (m/s,>48)	F-Wave latency (ms)	H-Reflex (ms)
Rt.Tibial	Unobtain				Unobtain
Rt.DPN	Unobtain				
Lt.Tibial	Unobtain				Unobtain
Lt.DPN	Unobtain				
Rt.Median	2.1	5.8			
Rt.Ulnar	1.4	6.0			
Lt.Median	1.7	5.9			
Lt.Ulnar	0.8	5.4			

NCS: Nerve Conduction Studies, NCV: Nerve Conduction Velocity, H-Reflex: Hoffmann Reflex

B: Needle EMG

Muscle	I	Spontaneous activity	MUAP

	A	Fib.	PSW	Fasc.	Others	Amplitude	Duration	Polyphasic	Pattern
Lt.Tib.Ant	inc	2+	2+	0	0	Inc	Inc	Inc	Single
Lt.Per.long	inc	2+	2+	0	0	Inc	Inc	Inc	Single
Lt.GCS	inc	2+	2+	0	0	Inc	Inc	Inc	Single
Lt.VMO	inc	0	0	0	0	Inc	Inc	Inc	Discrete
Lt.Add.Mag	inc	0	0	0	0	Inc	Inc	Inc	Discrete
Rt.Tib.Ant	inc	2+	2+	0	0	Inc	Inc	Inc	Single
Rt.Per.long	inc	2+	2+	0	0	Inc	Inc	Inc	Single
Lt.FCR	inc	0	0	0	0	Inc	Inc	Inc	Discrete
Lt.EDC	inc	0	0	0	0	Inc	Inc	Inc	Discrete
Lt.Biceps	inc	0	0	0	0	Inc	Inc	Inc	Discrete
Rt.EDC	inc	0	0	0	0	Inc	Inc	Inc	Discrete
Rt.FCR	inc	0	0	0	0	Inc	Inc	Inc	Discrete

IA: Insertion Activity, Fib: Fibrillation, PSW: Positive Sharp Waves Fasc: Fasciculation, MUAP: Motor Unit Action Potential,

1. Compound muscle action potentials and Sensory nerve action potentials are unobtainable or low amplitude.
2. Neurogenic defects are seen in some sampled muscle

Impression:

These finding are compatible with neurogenic progressive process. Acquired sensory motor axonal polyneuropathy would be the main impression.

Table 2: Capillary Serum Zone Electrophoresis

Date	Fraction	%	Ref.%	g/dl	Ref. g/dl
Baseline	Albumin	32.2 L	55.8 – 66.1	1.58	4.02 – 4.76
	Alpha 1	5.1 H	2.9 – 4.9	0.25	0.21 – 0.35
	Alpha 2	29.0 H	7.1 – 11.8	1.42	0.51 – 0.85
	Beta 1	4.8	4.7 – 7.2	0.24	0.34 – 0.52
	Beta 2	10.9 H	3.2 – 6.5	0.53	0.23 – 0.47
	Gamma	18.0	11.1 – 18.8	0.88	0.80 – 1.35
Comments	T.P.: 4.9			A/G - Ratio: 0.47	
First follow up (3rd month)	Albumin	53.9 L	55.8 – 66.1	3.18	4.02 – 4.76
	Alpha 1	5.8 H	2.9 – 4.9	0.34	0.21 – 0.35
	Alpha 2	21.3 H	7.1 – 11.8	1.26	0.51 – 0.85
	Beta 1	5.9	4.7 – 7.2	0.35	0.34 – 0.52
	Beta 2	4.3	3.2 – 6.5	0.25	0.23 – 0.47
	Gamma	8.8 L	11.1 – 18.8	0.52	0.80 – 1.35
Comments	T.P.: 5.9			A/G - Ratio: 1.17	
Second follow up (6th month)	Albumin	48.2 L	55.8 – 66.1	3.0	4.02 – 4.76
	Alpha 1	6.8 H	2.9 – 4.9	0.35	0.21 – 0.35
	Alpha 2	18.9 H	7.1 – 11.8	1.2	0.51 – 0.85
	Beta 1	7.1	4.7 – 7.2	0.4	0.34 – 0.52
	Beta 2	5.0	3.2 – 6.5	0.3	0.23 – 0.47
	Gamma	14.0	11.1 – 18.8	0.9	0.80 – 1.35

Comments	T.P.: 6.3	A/G - Ratio: 0.93

A/G: Albumin to glubolin, T.P.: Total Protein, L: Low, H: High

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