CASE REPORT

Refractory Thymoma associated Myasthenia Gravis Successfully Treated with Cyclical Intravenous Immunoglobulins: Case-Based Review.

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Abstract

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disease characterized by easy fatigability of skeletal muscles. Thymoma associated myasthenia gravis (T-MG) is defined as MG occurring with a concurrent thymoma. T-MG is associated with more severe generalised and bulbar disease. T-MG is also a risk factor for developing MG refractory to standard immunosuppression therapy.

We report a case of T-MG with multiple relapses despite undergoing a thymectomy. Her relapses were also refractory to escalated immunosuppressive therapy (azathioprine and mycophenolate mofetil). Her disease dramatically stabilised on cyclical intravenous immunoglobulin therapy combined with maintenance oral corticosteroids.

We also discuss newer therapeutic options for refractory myasthenia gravis including monoclonal antibodies against C20 (rituximab) and C5 complement component (eculizumab).

Keywords: *myasthenia gravis, thymoma, autoimmune, intravenous immunoglobulins, treatment-refractory myasthenia gravis.*

Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disease characterized by fatigable skeletal muscle weakness (exacerbated with repetitive movements and towards the days end). MG can be classified clinically into ocular MG (involving only extraocular and eyelid muscles) and generalised MG (ocular plus weakness involving other skeletal muscle groups which may include the diaphragm). MG can also be classified according to their serological antibody status (seropositive or seronegative). The standard antibody tested is anti-Acetylcholine receptor (AchR)-antibodies. Increasingly, anti-muscle-specific kinase (MuSK)-antibodies are also measured by some clinical laboratories. Other autoimmune antibodies have been identified but are not routinely measured.

Thymoma-associated MG (T-MG) is defined as MG concurrently occurring with a thymoma. This constitute 10-20% of all MG patients [1]. T-MG can be considered as a paraneoplastic phenomenon secondary to a thymoma where a neo-antigen expressed on thymoma cells shares a homology to skeletal muscle proteins, thus provoking an auto-immune response [2]. However, there is increasing evidence indicating loss of central immune tolerance as the predominant driver for autoimmunity in T-MG [3]. This is supported by the myriad of other auto-immune diseases associated with a thymoma [4].

T-MG is associated with more severe generalised and bulbar disease [5]. Furthermore, an American retrospective study identified thymoma as one of the risk factors for developing MG refractory to standard immunosuppressive therapy [6]. Here, we discuss a case of T-MG post thymectomy with multiple clinical relapses not responding to conventional immunosuppression.

Case presentation

A 35- year old lady with a diagnosis of T-MG (Osserman stage IIB) with a long-term tracheostomy post-thymectomy and hyperthyroidism (Grave's disease) presented with a three day history of left eye ptosis associated with increased production of purulent respiratory secretions and dyspnoea. These were accompanied by worsening of neck extensor weakness. She is seropositive for anti-acetylcholine receptor (AChR) antibodies.

Upon examination, she was tachypnoeic and was persistently tachycardic (pulse ranging from 115-130 per minute) with a blood pressure of 124/80 mmHg. Her initial oxygen saturation was 96% on high-flow oxygen and chest auscultation revealed widespread crackles. She was electively placed under sedation and mechanical ventilation upon reduced consciousness and a drop in her oxygen saturation to 90 % on high-flow oxygen. There were no evidence of lower limb swelling or abdominal masses. Apart from the pre-sedation neurological findings of left eye ptosis, weak bulbar speech and neck extensor weakness, the rest of her physical examination was unremarkable.

Her electrocardiograph (ECG) revealed sinus tachycardia with no evidence of right ventricular strain and her chest X-ray revealed bilateral lower zone consolidation. Her laboratory tests revealed leukocytosis with neutrophilia (13.0×10^9/L and 11.47×10^9/L respectively) while the rest of her blood investigations including thyroid function test were unremarkable. Her Covid-19 polymerase chain reaction test returned negative. Her blood cultures were negative but sputum cultures (tracheal aspirates) repeatedly grew *Pseudomonas aeruginosa* with intermittent growth of *Proteus mirabilis* and *Citrobacter loseri*.

She was diagnosed with myasthenic crisis secondary to bronchopneumonia. Her immunosuppression (mycophenolate mofetil 500mg twice daily) was withheld and she was given a 5-day course of intravenous immunoglobulins (IVIG) (total dose: 2 g/kg), pyridostigmine and intravenous Tazocin (tazobactam/piperacillin).

Unfortunately, we repeatedly failed to wean her off mechanical ventilation and she remained tachycardic. This led to a suspicion of a probable pulmonary embolism causing this clinical picture. A CT pulmonary angiogram was performed which revealed no evidence of pulmonary embolism. However, it revealed multi-lobar pulmonary collapse bilaterally with copious secretions obliterating even the tracheal lumen. Her pyridostigmine was intensified to 60mg every four hourly and she underwent intensive chest physiotherapy with bronchoscopic sputum clearance. A second course of IVIG (total dose: 2g/kg) was also administered and her Tazocin was switched to intravenous ceftazidime (due to high MIC, total duration for 2 weeks for airway decolonization of pseudomonas aeruginosa). Her tracheostomy was also changed to eliminate the pseudomonal antigenic burden. She gradually improved over a course of a week and was successfully weaned off positive airway ventilation.

Prior to this presentation, this lady has had an illustrious past history. This lady was originally diagnosed with MG in 2015 in a tertiary centre and at the time was treated with pyridostigmine four times daily, prednisolone and azathioprine. A CT scan (Figure 1), revealed an anterior mediastinal mass which is likely to represent a thymoma. However, she declined surgical resection. She was then transferred under our care in 2017. Since July 2017, she has been plagued with multiple relapses mainly presenting with respiratory insufficiency, requiring intravenous steroids and antibiotics.

In March 2020 (21 months prior to this current admission), she underwent a thymectomy in a tertiary centre. At the time, histopathalogical examination of the thymic tissue revealed a type B2 thymoma with no lymph node involvement. She was induced with IVIG pre-operatively and had another course post-operatively for a myasthenic crisis. Unfortunately, since her thymectomy, she remained dependent on a tracheostomy airway due to multiple factors including laryngeal muscle weakness and probable laryngeal nerve injury. At this point, her azathioprine was deemed inefficient in stabilizing her disease and was discontinued. She was commenced on mycophenolate mofetil (MMF), aiming to achieve better disease control.

She continued to have relapses of her MG post-thymectomy and institution of MMF, albeit at a lesser frequency (4.5 episodes per year) which were mainly triggered by respiratory infections. Additionally, she had an episode of herpes zoster (thoracic) in January 2021. It was thought that these infective episodes were due to the heightened immunosuppression provided by the combination of oral corticosteroids and MMF. She had her MMF withheld during exacerbations and also for a more prolonged period between April to June 2021. Due to this current severe myasthenic crisis which was also triggered by an infective element, a decision was made to stop her MMF altogether. Upon discharge, she was planned for cyclical IVIG combined with maintenance oral corticosteroids (prednisolone 20mg daily).

She had two courses of IVIG (total dose: 2g/kg each course) at 1-month and 6-months post discharge. She remains well nearly nine months post-discharge with only one episode of relapse secondary to acute gastroenteritis (0.75 episodes per year). Her prednisolone has been successfully weaned down to 10mg daily. Her swallowing function, anti-gravity neck extensors and speech has improved. She is still dependent on a tracheostomy but is under continuous assessment, aiming for stoma extubation once deemed safe.

Discussion

Described above is a case of a T-MG seropositive for AChR antibodies failing to achieve significant clinical improvement post thymectomy, refractory to conventional immunosuppression. Refractory MG occurs in 10-30% MG patients and is often secondary to underlying thymoma with AChR antibodies or serologically positive for anti-MuSK antibodies [7]. Refractory patients with T-MG and AChR antibodies positive such as

our patient, often benefit from undergoing a thymectomy.

In a retrospective Mexican case series, 68% of patients undergoing thymectomy demonstrated a positive response (40% achieved remission and 28% clinical improvement) [8]. However, patients who responded well were patients with less severe symptoms at presentation (Osserman stage II or less and not requiring high doses of maintenance pyridostigmine) and having pre-operative symptoms of less than 2 years. Our patient, did not achieve a positive response post-thymectomy. A possible explanation for this was the delay between symptom onset of MG and thymectomy (five years). Thymic auto-reactive memory T cells has been detected in peripheral blood from patients developing MG post-thymectomy for thymoma [9],[10]. Similarly, the presence of autoreactive memory B cells has been demonstrated in peripheral blood (by DNA sequencing) in post-thymectomy patients [11]. These evidences, combined with the occurrence of persistent auto-antibody titres post thymectomy indicates migration of adaptive immune cells out of the thymus leading to persistent MG post thymectomy via resulting long-lived plasma cells (secreting auto-antibodies). Long-lived plasma cells often homes to the bone marrow and indeed, myelo-ablation with high-dose cyclophosphamide and rescue autologous stem cell transplantation has been successfully employed as a salvage therapy for refractory MG. It will be interesting to study if delay in thymectomy is proportionally related to persistent disease and if there is an inflection point in time when this occur.

MG is conventionally treated with remission induction using corticosteroids. Alternative induction agents includes IVIG (for septic patients) and plasma exchange (patients with end-stage renal failure where corticosteroids needs to be avoided). Once achieved, remission is maintained with the lowest possible dose of oral corticosteroids (usually prednisolone) with or without a steroid sparing agent. Traditional steroid sparing agents are generally anti-metabolites (azathioprine, methotrexate and MMF). Other forms of traditional therapy employed in MG include calcineurin inhibitors (ciclosporin and tacrolimus) and alkylating agents (cyclophosphamide). However, these agents are not commonly utilized as they carry a heavier toxicity profile. Table 1 compares the features of different traditional agents used in MG.

Refractory MG is defined as patients not clinically controlled on conventional immunosuppressive therapy, patients experiencing clinical relapses during immunosuppressive taper or patients developing severe toxicity from immunosuppressive therapy for at least a 1 year duration [13]. Newer therapy has been developed and trialled in refractory MG patients. These newer agents include monoclonal antibody biologics antagonizing CD20 (e.g rituximab) , complement component 5 (eculizumab) and cyclical immunoglobulins therapy.

IVIG utilization has long been established in remission induction for MG crisis but has been increasingly utilized periodically for remission maintenance in refractory patients with good evidence of response [14]. In fact, periodic subcutaneous immunoglobulin (SCIG) therapy which was traditionally used for hypogammaglobulinaemia, has also been utilized in MG [15]. However, the utility of periodic immunoglobulins are still considered as 'off label'. This strategy was employed in our patient and has dramatically improved her clinical outcomes, consistent with numerous case reports in the literature.

Rituximab has been the most widely used biological agent in refractory MG patients. Evidence for utility was based upon multiple retrospective studies demonstrating good response for refractory MG patients with positive anti-AChR and anti-MuSK antibodies. The 'BeatMG' multi-centric randomized Phase II clinical trial (NCT02110706) did not reveal statistically significant clinical improvement comparing 'rituximab with corticosteroid' versus

'corticosteroid and placebo' groups [16]. Hence, the use of rituximab in refractory MG is still considered 'off label', although there is class IV evidence that rituximab has a favourable outcome in refractory anti-MuSK MG patients [17].

Eculizumab is a recombinant monoclonal antibody that inhibits complement component C5 which is the terminal component of the complement activation pathway. Significant AChR destruction is mediated by the complement 'membrane attack complex' lending the rationale into the utility of this agent in MG. Eculizumab received FDA approval for use in refractory MG patients with positive anti-AChR antibody positive serology in 2007. Despite this, a phase 3 randomised controlled trial (REGAIN study: NCT01997229) did not reveal statistical difference in clinical efficacy comparing eculizumab to placebo therapy [18]. Furthermore, its cost implications would preclude usage of eculizumab is most developing countries. Table 2 compares the features of newer agents used in refractory MG.

Other novel agents are currently being developed and may be further ammunition to combat refractory MG in the future including neonatal Fc receptor inhibitors and alternative terminal complement inhibitors, however, discussion of these experimental therapy is beyond the scope of this paper.

Conclusion

The pathophysiology of T-MG is complicated and it may present as MG refractory to conventional immunosuppression. In some cases, disease control is not achieved post-thymectomy. Newer immune-modulators such as monoclonal antibodies and immunoglobulin therapy can be utilized for such patients. There are no head-to-head comparison studies between these newer agents available to guide clinical recommendations. Hence, the choice of therapy would depend on individualized clinical assessment and availability of the agent. There is ongoing research into novel therapeutic compounds which may hold promise into increased therapeutic efficacy in the future.

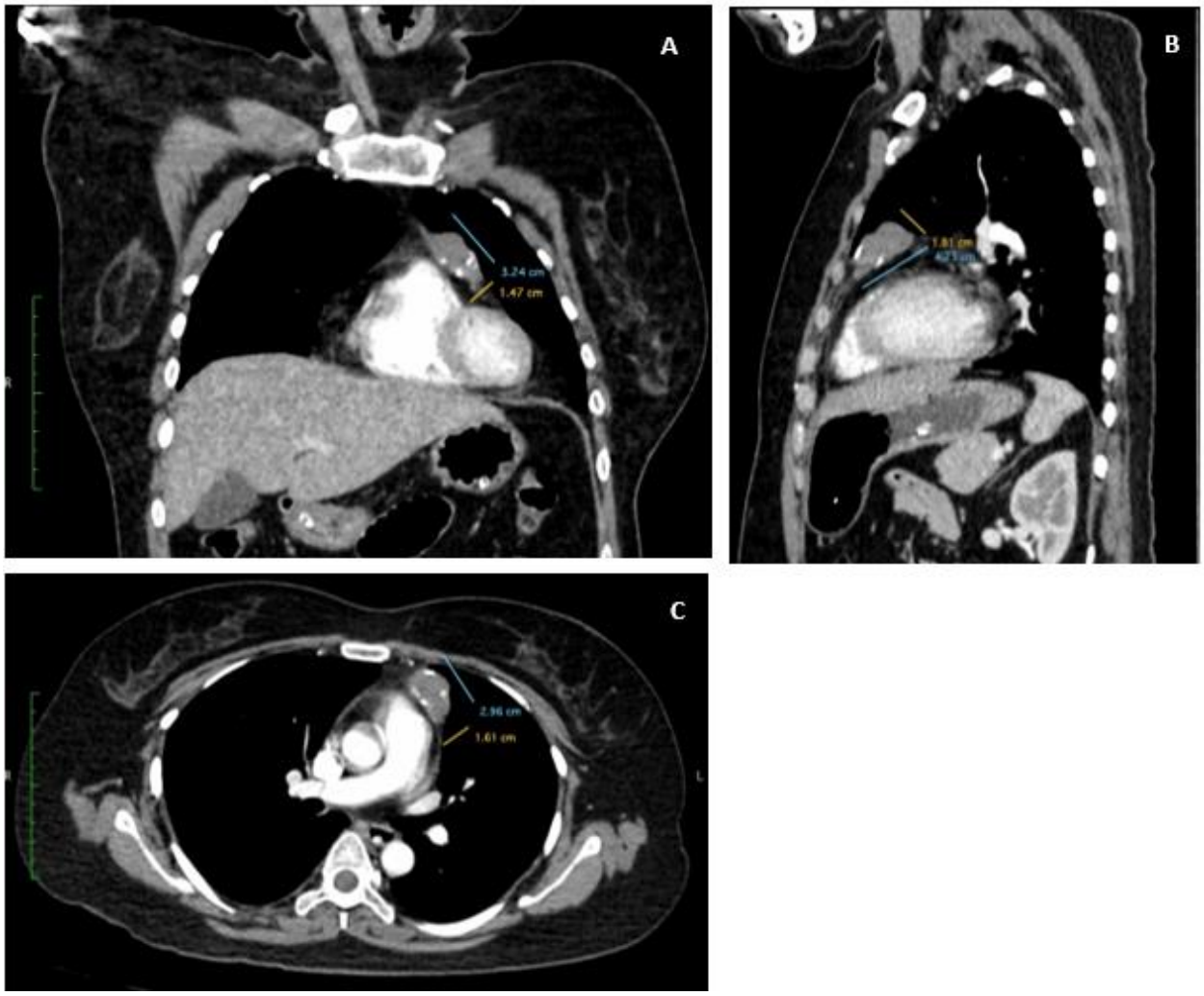

Figure 1. A (coronal view) B (sagittal view) C (axial view): Contrasted CT scan of the neck and thorax demonstrating a calcified lobulated soft tissue mass occupying the anterior mediastinum (representing the thymoma). There are no fatty infiltration or intra-thoracic lymphadenopathies.

Table 1. Traditional drugs used for remission maintenance in MG.

Therapy	Mechanism	Onset of action (months)	Toxicity (other than immunosuppression)	Comments
Prednisolone	Glucocorticoid (downregulates expression of pro-inflammatory genes)	0.5-1	Adrenal insufficiency, gastritis, glaucoma, metabolic (weight gain, hyperglycaemia, hypertension, osteopenia, hypokalaemia)	Mainstay therapy (affects both innate and adaptive immune system)
Azathioprine	Anti-metabolite (purine analogue)	6-12 (peak: 24)	hepatotoxicity, pancreatitis, myelosuppression	Commonest steroid sparing agent used, safe in pregnancy
Methotrexate	Anti-metabolite (DHFR inhibitor)*	3-12	Hepatotoxicity, Pulmonary fibrosis, mucositis, myelosuppression, infertility, teratogenic	Weekly administration, teratogenic, avoid in background liver disease
Mycophenolate mofetil (MMF)	Anti-metabolite (IMPDH inhibitor)**	2-12	Diarrhoea, nausea, cramps, myelosuppression, teratogenic	Easy administration, teratogenic
Cyclosporine	Calcineurin-inhibitor	1-3	Nephrotoxic, hypertension, tremor, gingival hypertrophy, hirsutism, teratogenic	Requires drug trough level and renal monitoring.
Cyclophosphamide	DNA alkylating agent	2-6	Myelosuppresion, infertility, haemorrhagic cystitis, bladder cancer, teratogenic	Requires full blood count, urinalysis and metabolic profile monitoring.

Abbreviations: DHFR* (dehydrofolate reductase), IMPDH* (inosine-5′-monophosphate dehydrogenase). Adapted from Farmakidis C *et al* [12].

Table 2. Newer drugs used for remission maintenance in MG.

Therapy	Mechanism	Onset of action (weeks)	Toxicity (other than immunosuppression)	Comments
Intravenous immunoglobulins	Interfering Fc receptor function and neutralizes the activation of complements/pro-inflammatory cytokines.	1-2	Infusion reaction, anaphylaxis, nephrotoxicity, thromboembolism	Safe in pregnancy
Rituximab	Anti-CD20 antibody (depletion of B-cell lineage from pre-B cell that mature peripheral B-cells)	4-12	Infusion reaction, anaphylaxis, mucositis, myelosuppression, PML*, hepatitis B reactivation.	B-cell depletion (immunize prior commencing) long-lasting plasma cells unaffected ($CD20^-$).
Eculizumab	Anti-C5 molecule antibody (inhibits cleavage of C5, thus preventing formation of MAC**.	2-4	Meningococcal infection, mild infusion reaction	Mandatory meningococcal vaccination (ACYW conjugate and serovar B) prior commencing.

Abbreviations: PML (progressive multifocal leukoencephalopathy), MAC (membrane-attack complex). Adapted from Farmakidis C *et al* [19].

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