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CASE REPORT INTENSIVE CARE

The role of therapeutic plasma exchange using membrane plasma separation in the late onset myasthenic crisis: a case report

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune disease, in which antibodies bind to receptors in the neuromuscular junction (NMJ), causing muscle weakness. This disease is relatively challenging to diagnose due to its late onset and comorbidities. Several treatment options include therapeutic plasma exchange (TPE) with membrane plasma separation, that aims to remove large molecular-weight toxins such as pathogenic antibodies and lipoproteins. A 61-year-old male patient was admitted to the ICU post-sternotomy due to mediastinal tumor resection. Extubation failed, so we decided to undergo a tracheostomy. The lung pathology result showed lymphocyte-predominant thymoma, and along with symptoms of chest weakness and ptosis, the patient was suspected for MG. Electromyography results confirmed the occurrence of functional lesions in post-synaptic NMJ consistent with MG. We assessed patient with myasthenic crisis (MC), then gave pyridostigmine 60 mg 6x/day, and planned for TPE using membrane plasma separation. Plasma exchange was done by 1.5 of blood volume. The patient developed sepsis pneumonia and was administered levofloxacin based on his culture results. Patient still had weakness. We re-evaluated the drugs that might have exacerbated MG. Aztreonam in combination with co-trimoxazole was administered to combat *Stenotrophomonas maltophilia* pneumonia. The patient was eventually weaned from the ventilator and gradually recovered.

Keywords: Membrane Plasma Separation; Myasthenia Gravis Crisis; Therapeutic Plasma Exchange; TPE

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1. INTRODUCTION

Myasthenia gravis (MG) is a well-known autoimmune disease characterized by antibodies against postsynaptic nicotinic acetylcholine receptors and fluctuating weakness, which may sometimes be life-threatening.[1] MG has annual incidence of approximately 30 new cases per million, approximately 15–20% of these patients will go into myasthenic crisis (MC). It has been traditionally considered a disease of predominantly younger women and older men. However, recent epidemiologic and clinical studies suggest an increasing incidence of MG in the elderly of both genders, at least in part due to improved diagnostic methods and an aging population.[2]

Therapeutic Plasma Exchange (TPE) is blood purification technique designed for removal of large molecular weight toxins such as pathogenic antibodies and lipoproteins. Plasma exchange can be performed either by membrane separation or centrifugation. The membrane separation technique is similar to the

ultrafiltration procedures performed with a standard dialysis machine or CRRT systems in which the membrane's pores are large enough to allow removal of all circulating molecules while retaining the cellular components. Its efficiency in MG is due to removal of proteins of autoimmune biological activity, mainly antibodies to acetylcholine receptor, leading to short-term improvement of neuromuscular junction transmission, improved muscular strength and motor performance.[1]

This case study describes the membrane separation techniques using the PRISMAFLEX TPE system for treating late onset myasthenic crises which make it difficult to wean from mechanical ventilation.

2. CASE REPORT

A 61-years-old male patient was admitted to the ICU in Fatmawati Hospital post-sternotomy and fiberoptic bronchoscopy for mediastinal tumor resection. He also presented with pneumonia, hypertension, history of type-2 diabetes mellitus (T2DM) and ischemic stroke. Echocardiography was performed, which showed good cardiac function with 59% left ventricular ejection fraction (LVEF). The patient opened his eyes with adequate contact and obeyed to command to raise hands. Extubation was attempted on the third day of care, but patient became deteriorated, breathless and tachycardic. He was subsequently re-intubated and reconnected to the mechanical ventilator. The patient developed sepsis pneumonia with an increased production of yellowish sputum, thus bronchoscopy was performed showing thick mucoid phlegm in the bronchi and the branches. At this point, administration of ceftriaxone was stopped and changed to meropenem 2-gram TID due to instability of hemodynamic parameters, and levofloxacin 1 gram OD IV was continued. Fluconazole was also prescribed empirically. Bacterial culture of the bronchial lavage showed resistance towards multiple antibiotics. The bacteria were resistant towards amoxiclav, ceftazidime, imipenem, and phosphomycin; and sensitive towards levofloxacin and co-trimoxazole. In accordance to the culture results, oral co-trimoxazole 960 mg TID and levofloxacin 1 g IV were added to the patient's antibiotic regimen.

Due to unsuccessful weaning attempts and prolonged intubation, tracheostomy was performed on day 9. The lung pathology result showed lymphocyte-predominant thymoma along with symptoms of ptosis, persistent respiratory muscle weakness and breathing difficulties, so the patient was suspected for MG. The EMG result performed on day 13 confirmed the occurrence of functional lesions in post-synaptic neuromuscular junctions consistent with MG. The repetitive nerve stimulation with frequencies of 3 Hz, 5 Hz, and 7 Hz on the left orbicularis oculi muscle and left abductor digiti minimi muscle showed a decrease of amplitude with the compound muscle amplitude potential (CMAP) >10% (positive) on the left orbicularis oculi muscle. The patient was initially given mestinon (pyridostigmine) 60 mg IV TID, and the dose was increased to 6 times daily once the diagnosis of MC was established.

TPE was performed by 1.5 of blood volume on day; 17 with blood-flow 150 ml/min, replacement 1250 ml/h, total replacement volume 6200 ml, and TPE initiation with 24 bottles of 250 ml 5% albumin using the

PRISMAFLEX TPE system. During plasmapheresis, the patient developed hypoglycemia and hypotension, that

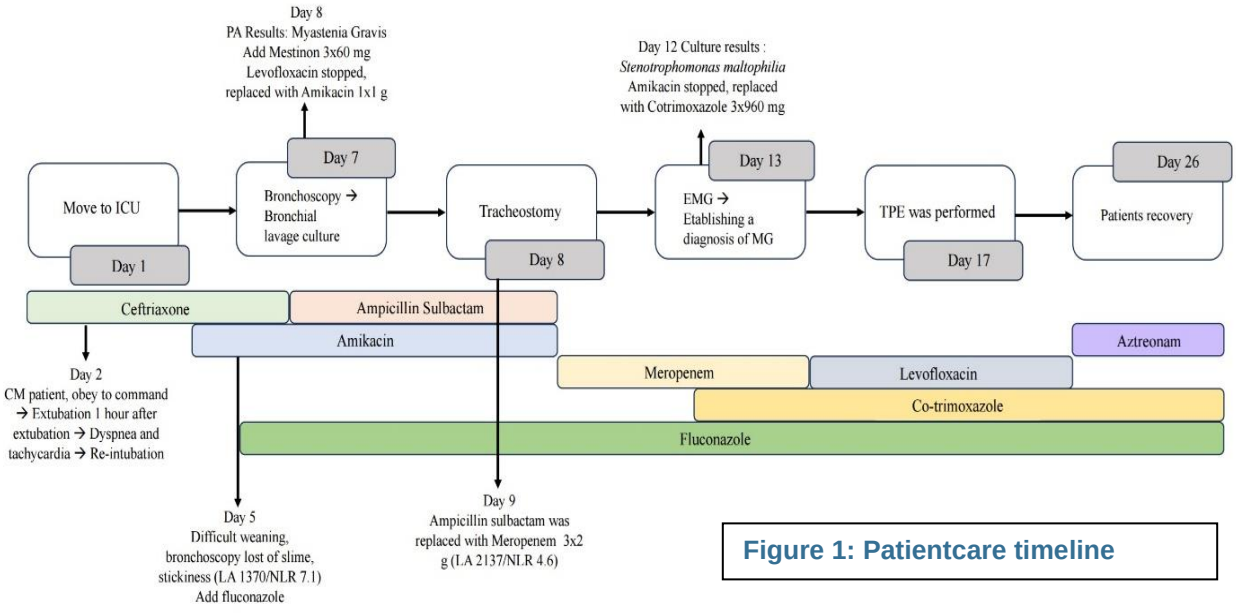

Figure 1: Patientcare timeline

was corrected with norepinephrine and then patient became stable.

Three day after the procedure, sepsis of the patient responded well with the antibiotic regimen but he was still weak and breathless. We re-evaluated the treatment to remove inadvertently prescribing drugs that may have exacerbated symptoms of MG such as levofloxacin. Levofloxacin was changed to Aztreonam at day 21, which is a synthetic monobactam antibiotic similar to aminoglycosides, mainly used to combat gram-negative and pseudomonas pathogens, with co-trimoxazole and fluconazole. The patient was eventually weaned from the ventilator, he started to show adequate response and obeyed commands, without complains of dyspnea. He was discharged from ICU at day 33. The patientcare timeline from beginning to end, is illustrated in Figure 1.

3. DISCUSSION

Myasthenia gravis (MG) is an autoimmune neuromuscular disease, in which the antibodies bind to postsynaptic acetylcholine receptors at the NMJ – or sometimes to muscle-specific tyrosine kinase (MuSK) receptors – resulting in fluctuating muscle weakness, especially in the ocular, bulbar, extremity, and respiratory muscles.[3,4] Meanwhile, the diagnosis of myasthenic crisis (MC) is established in MG patients with rapid deterioration, for example in patients with MG exacerbations that threaten/cause respiratory failure and require mechanical ventilation or non-invasive positive pressure ventilation.

The gold standard for diagnosis is by electrophysiological examination to assess NMJ function with repetitive nerve stimulation (RNS) and jitter analysis with single-fiber muscle electromyography (SFEMG).[4]

In this case, the patient underwent a sternotomy without prior history and was being monitored for MG. In the ICU post-surgery, the patient's hemodynamics were stable and respiratory effort was good, so we decided to extubate. However, one hour later, the patient developed tachypnea and desaturation, necessitating reintubation. The patient continued to experience respiratory muscle weakness, leading to repeated failed attempts to wean off the ventilator. The patient's eyelid ptosis worsened, and the anatomical pathology results identified a thymoma, raising suspicion of MG. An electromyography was performed, which confirmed the diagnosis of MG. This patient had pneumonia and thymoma tumor that was surgically removed, both of which might be risk factors for MG. Treatment of MC in this patient was TPE which exchanged 1.5 blood volumes.

The main principle of MG management is to maximize the activity of the remaining acetylcholine neurotransmitter in the NMJ by administering anti-acetylcholinesterase drugs (pyridostigmine). The second is to suppress the immunological attack on the motor endplate with immunosuppressants or immunomodulatory therapy.[4]

Therapeutic Plasma Exchange (TPE) or plasmapheresis is one of the immunological therapies of choice in MC. It is an extracorporeal blood purification technique which aims to separate plasma and remove pathogenic autoantibodies, immune complexes, cryoglobulins and toxins that accumulate in the plasma. In MG, TPE aims to remove Ach receptor antibodies so as to improve neuromuscular transmission, therefore patients can immediately show short-term improvements in muscle strength and motor function.[3,4] A retrospective study involving 36 patients with acute exacerbation of MG showed that nanomembrane-based TPE could reduce mechanical intubation rates, more non-invasive ventilation, lower tracheostomy rates, thereby reducing complications due to ventilator use.[5] Another study in West India involved 68 patients of MG who underwent TPE. also showed clinical improvement which was immediately visible after TPE.[3] To avoid rebound overproduction of autoantibodies, immunosuppressants such as steroids are recommended to be given simultaneously with TPE.

Side effects that may be caused by TPE include transfusion reactions, citrate toxicity (e.g., hypokalemia, hypomagnesemia, muscle spasm, tetany), and hypocoagulability.[4] Platelet loss is another patient safety concern during TPE. It has been previously reported that cTPE devices confer a greater risk of platelet loss than mTPE devices.[6] Another positive aspect of mTPE is the fact that the action completes in less than 24 h, preventing the development of any further antibodies during that time. This is in contrast to cTPE, which takes 3 treatments for 3 h/day, increasing the probability that new antibodies may develop during that period. In addition, mTPE costs less than cTPE, with prices ranging from $215 to $275 and $300 to $350, respectively.[7] In this case, we used mTPE using the PRISMAFLEX TPE system because this technique is simpler, less expensive, and more reliable.

On the PRISMAFLEX system, plasma exchange is accomplished by infusing a replacement solution concurrently with plasma filtration. During TPE, plasma is extracted and pushed through the plasma filter's large-pore membrane. To replace the extracted plasma, a colloid solution—such as albumin and/or plasma, or a combination of crystalloid and colloid solutions—is then fed into the post-plasma filter. Access Transmembrane Pressure (TMPa) and the filter pressure drop are computed during TPE by PRISMAFLEX software using observed pressure measurements.[7,8]

A previous case from Nigeria reported a 47-y old male patient with MG on ventilator and complications of sepsis due to Acute Respiratory Infection (ARI). He underwent TPE 6 times after being treated for 1 month in ICU without improvement. After the first TPE, there was significant clinical improvement, so that he could be extubated, but it only lasted 4 days and then the patient's condition worsened and he was put back on the ventilator. Another case report of a 78-year-old woman with post-thymectomy MC and complications of phrenic nerve injury and respiratory failure, reported a significant increase in aPTT after TPE (> 170 sec). It underscores the importance of dose adjustment of unfractionated heparin (UFH) and the importance of aPTT monitoring to prevent bleeding complications.[9] A retrospective study of 14 patients with refractory MG (not improved with conventional therapy) who underwent maintenance TPE for >12 months showed observed improvement in myasthenia gravis activities of daily living (MG-ADL) and myasthenia gravis composite (MGC) scores with reduced need for administration of immunosuppressants.[10] This patient underwent TPE once, with improvement in less than 2 weeks. Besides treating MG, selecting the right antibiotics for MG patients, who have comorbid sepsis as cause of pneumonia is also essential because certain antibiotics have been associated with MG exacerbations.

Our patient was evaluated for TPE and was expected to show improvement soon; however, the patient's respiratory condition did not improve significantly. We then considered replacing levofloxacin, which might exacerbate MG, with aztreonam. Several classes of antibiotics that can worsen MG or cause MG-like symptoms due to their direct action on NMJ include: macrolides (azithromycin, telithromycin, clarithromycin), fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, moxifloxacin), aminoglycosides (neomycin, amikacin, streptomycin, gentamycin), penicillins (ampicillin, amoxicillin).[11] In this case, the patient was given long-term levofloxacin, considering the blood culture results, which was S. maltophilia, a gram-negative bacteria, that is only sensitive to levofloxacin and co-trimoxazole. However, in the end levofloxacin was stopped and replaced with aztreonam, along with meropenem and co-trimoxazole (sulfonamide group). Aztreonam is a synthetic monobactam antibiotic that is similar to aminoglycosides and is effective against gram-negative anaerobic bacteria. A study reported the success of treating S. maltophilia infections with the combination of aztreonam-amoxicillin-clavulanate. It is assumed that β-lactamase inhibitors (avibactam, clavulanate, tazobactam) are able to restore sensitivity to aztreonam.[12]

4. CONCLUSION

In this case, TPE could be effective for myasthenic crisis therapy in MG, reflecting the patient's clinical improvement. This is in line with previous research recommendations, which state that TPE is faster, more effective, and less expensive than IV immunoglobulins. It is also important to re-evaluate antibiotic therapy in MG patients because there are several classes of antibiotics that can trigger MG exacerbations.

5. Conflict of interests

The authors declare there are no competing interests.

6. Ethical Considerations

Written informed consent was obtained from the patient to publish this report as well as the pictures.

7. Authors' contribution

DK: Planning and supervised the work, took the lead in writing the manuscript, follow-up patient, discussed the results and commented on the manuscript

SKM, VI: Writing the manuscript, helped supervise the work, discussed the results and commented on the manuscript

8. REFERENCES

1. Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis - autoantibody characteristics and their implications for therapy. Nat Rev Neurol. 2016;12(5):259-68. [PubMed] DOI: 10.1038/nrneurol.2016.44
2. Bubuioc AM, Kudebayeva A, Turuspekova S, Lisnic V, Leone MA. The epidemiology of myasthenia gravis. J Med Life. 2021;14(1):7-16. [PubMed] DOI: 10.25122/jml-2020-0145
3. Dogra A, Rana K, Rathod C, Prakash S. Outcome of therapeutic plasma exchange in Myasthenia gravis patients. J Fam Med Prim Care. 2020;9(12):5971-5. [PubMed] DOI: 10.4103/jfmpc.jfmpc_1026_20
4. Akingbola TS, Shonde-Adebola KB, Anyanwu-Yeiya CC, Ezekekwu CA, Adeoye OA, Odebiyi HA, et al. Therapeutic plasma exchange in the management of myasthenia crisis in a resource poor setting. Int J Healthc Med Sci. 2019;5(5):22-5. DOI: 10.32861/ijhms.55.22.25
5. Tonev D, Georgieva R, Vavrek E. Our clinical experience in the treatment of myasthenia gravis acute exacerbations with a novel nanomembrane-based therapeutic plasma exchange technology. J Clin Med. 2022;11(14):4021. [PubMed] DOI: 10.3390/jcm11144021
6. Janssens ME, Wakelin S. Centrifugal and membrane therapeutic plasma exchange – a mini-review. Eur Oncol Haematol. 2018;14(2):105. [FreeFullText]
7. Ahmed S, Kaplan A. Therapeutic plasma exchange using membrane plasma separation. Clin J Am Soc Nephrol. 2020;15(9):1364-70. [PubMed] DOI: 10.2215/CJN.12501019

8. Mateos-Dávila A, Betbesé Roig AJ, Santos Rodríguez JA, Guix-Comellas EM. Change in prefilter pressure as a key determinant in the decision to return blood in continuous renal replacement therapy: An observational study. Nurs Crit Care. 2023. [PubMed] DOI: 10.1111/nicc.12933

9. Alshehri SD, Al Sulaiman K, Aljuhani O, Al Harbi SA, Alalawi M, Alenazi AA, et al. Therapeutic plasma exchange and supratherapeutic levels of unfractionated heparin in the management of critically ill patient with myasthenia gravis: A case report. Am J Case Rep. 2022;23. [PubMed] DOI: 10.12659/AJCR.937617

10. Sheckley H, Malhotra K, Katyal N, Narula N, Govindarajan R. Clinical experience with maintenance therapeutic plasma exchange in refractory generalized myasthenia gravis. J Clin Apher. 2021;36(5):727-36. [PubMed] DOI: 10.1002/jca.21923

11. Sheikh S, Alvi U, Soliven B, Rezania K. Drugs that induce or cause deterioration of myasthenia gravis: An update. J Clin Med. 2021;10(7):1537. [PubMed] DOI: 10.3390/jcm10071537

12. Emeraud C, Escaut L, Boucly A, Fortineau N, Bonnin RA, Naas T, et al. Aztreonam plus clavulanate, tazobactam, or avibactam for treatment of infections caused by metallo-β-lactamase-producing gram-negative bacteria. Antimicrob Agents Chemother. 2019;63(5). [PubMed] DOI: 10.1128/AAC.00010-19

