

Successful therapeutic plasma exchange in post-operative myasthenic crisis in elderly woman

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Received - 22 December 2019

Initial Review - 07 January 2020

Accepted - 15 February 2020

ABSTRACT

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disorder that causes weakness of skeletal muscles responsible for breathing and moving parts of the body such as arms and legs. Surgical removal of thymoma may be associated with post-operative myasthenic crisis (POMC). Here, we report the case of a 70-year-old woman treated for squamous cell carcinoma of the uterine cervix, after a span of 11 years, presented with clinical features suggestive of MG. Investigations revealed type AB thymoma. The patient developed POMC, 3 days after the surgical excision procedure. The patient was subsequently treated with therapeutic plasma exchange (TPE), anticholinesterases, and steroids. The TPE in this elderly woman was not associated with any complications and was discharged in complete stable remission. Earlier studies show that many cases have immediate benefits from plasma exchange in MG, particularly MG crisis. TPE is a disease-modifying therapy for MG crisis.

Key words: *Elderly woman, Myasthenia gravis, Myasthenic crisis, Therapeutic plasma exchange*

Thymoma is the most common mediastinal tumor in adults and the most common tumor of the thymus [1]. They are associated with paraneoplastic syndromes (PNS) in 50–70% of cases [2]. Myasthenia gravis (MG) is the most common PNS concomitant with thymoma. One of the common disorders of the neuromuscular junction is MG which is a chronic autoimmune disorder with an annual incidence of 0.25–2 patients/100,000. Females are affected more than males at young age and there is an absence of gender bias with increasing age [3]. Approximately 15% of all MG cases may be associated with thymoma [4]. Antibodies against acetylcholine receptors (AChRs) in the post-synaptic motor endplate are seen in 85–90% of MG patients including the elderly [5].

The main modality of the treatment of thymoma is surgery, either by the trans-sternal approach or by video-assisted thoracoscopic surgery (VATS). Patients suffer from MG even after surgery and 12–18% of patients are affected with post-operative myasthenic crisis (POMC) [6]. POMC accounts for 6% of the complications related to thymectomy [7].

Myasthenia crisis (MC) is a life-threatening complication of acquired and autoimmune MG characterized by worsening skeletal muscle weakness, resulting in respiratory failure which requires intubation and mechanical ventilation. MC is more common in MG patients associated with thymoma [8]. About 15–20% of the patients with MG are affected by MC at least once in their lifetime [9] and 3–8% of all patients who enter MC may die [3]. The death rate of MC has decreased gradually from 80% to <5% with the advancement in treatment modality [10]. We

present a case of thymoma with a POMC attack in elderly woman treated with therapeutic plasma exchange (TPE).

CASE REPORT

A 70-year-old woman treated for squamous cell carcinoma of uterine cervix 1B2 in 2008, was on follow-up and presented in February 2019 with complaints of ptosis of both eyelids, weakness with fever for 1 week, and was suspected to have MG. The patient also complained of giddiness, breathing difficulty, swallowing difficulty to solid foods, poor oral intake, vomiting, blurring of vision, and jitteriness for 1 week. The patient was admitted for supportive care as clinical features were suggestive of MG.

The cardiorespiratory systems were within normal limits. The abdomen was soft on palpation and bladder habits were normal. There was no focal neurological deficit. The vitals were within normal limits. The patient was on treatment for hypertension.

Imaging studies like chest X-ray revealed mediastinal widening and computed tomography chest showed mediastinal mass probably a thymoma. Excision biopsy confirmed thymoma type AB. VATS was converted to open thoracotomy and thymoma excision was done under general anesthesia with a loss of 200 ml blood.

MC evolved 3 days after surgery. The patient was already in intensive care unit (ICU) and mechanically ventilated and intubated. The patient was referred for TPE on alternate days for 5 days. The procedure was carried out with Haemonetics MCS+ multicomponent collection system using a 12F dialysis catheter

in the right internal jugular vein that was maintained with heparin lock. The amount of plasma to be exchanged was determined in relation to the estimated plasma volume. (EPV) was calculated from the patients weight and hematocrit (HCT) with the formula $EPV = \{0.65 * wt (kg) * (1 - HCT)\}$. Nearly one plasma volume (1514–1616 ml) was exchanged per sitting per day with an equal volume of fluids comprising an equal combination of 0.9% normal saline and fresh frozen plasma (FFP). The ratio for the anticoagulant citrate dextrose solution and solution A (ACD-A) was 1:12 whole blood.

The procedures lasted for 118–130 min requiring 14–16 cycles. The anticoagulant volume used during the procedures ranged from 293 to 309 ml. The serum electrolytes, albumin, calcium, and coagulation profile were monitored. The pre- and post-procedure counts are depicted in Tables 1 and 2. The TPE procedure was not associated with any citrate related, cardiac or pulmonary complications. The patient was pre and postoperatively maintained with anticholinesterase and steroid therapy. The patient improved clinically with every procedure. She was weaned off the ventilator on day 14. She was shifted out of ICU after 16 days. She was discharged on day 25 when the clinical status observed was completely stable. She is doing all her routine activities at home.

DISCUSSION

Patients above 50 years of age are at greater risk of developing MC that increased when there was an associated thymoma.

Table 1: Hematological and biochemical parameters

Parameters (Units)	Pre-TPE	Post-TPE
Hemoglobin (g%)	10.6	11.0
Total leukocyte count (cells/cmm)	11,100	9400
Platelet count (cells/cmm)	302,000	303,000
Blood urea (mg/dl)	14.0	35.0
Serum creatinine (mg/dl)	0.7	0.7
SGOT (IU/L)	29	31
SGPT (IU/L)	17	20
Serum sodium (mEq/L)	138	140
Serum potassium (mEq/L)	3.0	3.3
Serum chloride (mEq/L)	100	103
Serum magnesium (mg/ dl)	1.3	1.6
Serum calcium (mg/dl)	8.3	9.0
Serum albumin (mg/dl)	2.5	3.0
Serum total protein (mg/dl)	5.3	5.5
Serum total bilirubin (mg/dl)	0.7	0.8

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, TPE: Therapeutic plasma exchange

Table 2: Coagulation parameters

Coagulation profile	Pre-TPE	Post-TPE
PT	0.13	0.12
APTT	0.21	0.22
INR	1.06	1.08

PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio. TPE: Therapeutic plasma exchange

Thymoma has been associated with poor prognosis in MC. MG persists despite the removal of thymus glands (the source of autoimmunization) as the primed B-cell and helper T-cells theoretically remain in circulation for a prolonged period.

The World Health Organization (WHO) classification system categorizes thymoma as type A, AB, B1, B2, and B3 according to the morphology of epithelial cells and the lymphocyte-to-epithelial cell ratio. The incidence of MG in thymoma patients was highest in the WHO type B2 [11]. Independent predictors of POMC in thymoma patients with MG who underwent surgery include WHO type B2-B3 thymomas. Vincent and Newson–Davis developed a radioimmunoassay test to detect the antibodies that bind to AChRs. This is now considered the diagnostic gold standard [12]. These antibodies are not detected in the bloodstream normally.

The various modalities of the treatment for MC are early mechanical ventilation, admission to ICU, recognition and treatment of precipitating factors, use of anticholinesterase drugs, steroid treatment, immunosuppression, plasma exchange, and intravenous immunoglobulin (IVIG). The first-line management for MC is IVIG and TPE. A better response may be seen with immunomodulation through TPE and IVIG. IVIG is a biological product derived from the fractionation of pooled blood donated from 2000 to 16,000 healthy people. TPE is an apheresis technique where the diseased plasma is removed and replaced with fluids.

IVIG and TPE were compared in terms of myasthenia muscle score as the outcome and no particular regime was superior. The patients, who received IVIG or TPE, improve by 16 points on an average on myasthenia muscle score. TPE is a better option as the next line of treatment modality in older patients not benefitted with thymectomy and medications [13]. In a different study, the authors concluded that TPE might be a more effective therapy than immunoglobulin for MC [14]. There were few randomized controlled treatment trials in MC and both the modalities were comparable in terms of clinical efficacy; however, more prospective studies are required.

The mechanism of action of IVIG is less clear and it may take as long as 4–5 days for it to reach its beneficial effect. The immediate benefits of TPE are seen in 1–2 days and include the removal of the pathological substances as autoantibodies. The long-term immune-modulatory effects of TPE are mediated by T-cell with a shift toward Th 2 (T helper cell type 2) balance and suppression of IL-2 and INF production [15,16]. The abnormal humoral immune response may be seen in patients treated with TPE for neurological disorders.

One may be cautious during infusion of FFP as a replacement solution during TPE as FFP contains 17–21 mmol of citrate per liter solution [17]. There is no consensus regarding the ideal replacement solution for TPE. Prospective studies are required to plan a combination of replacement fluids that include normal saline, FFP, and human serum albumin keeping in account their benefits, adverse effects, and pre-procedure values.

IVIG is preferred due to the ease of administration compared to plasma exchange. Heatwole *et al.* compared the short-term financial costs of treating a patient in MGC with IVIG and

TPE [18]. The difference in total cost favored IVIG over TPE taking into account the required number of plasma exchanges, the time required for the patient to be in ICU, and IVIG dosing. Many cases reported in India have used FFP as replacement fluid rather than human serum albumin, and thus, TPE was cost effective compared to IVIG.

Elderly onset MG has been reported among patients ≥ 65 years of age and an increase in the incidence of an elderly onset MG has been reported recently. TPE is seldom used in elderly patient population due to the risk of cardiovascular events. TPE, when performed by an experienced team, is a safe and effective procedure that may considerably improve the outcome in elderly patients affected with MC.

The binding AChR antibodies decreased from 23 nmol/L to 11.23 nmol/L. The antibody level seems to be high in elderly onset MG. The titer does not correspond with the disease severity varies from individual to an individual and a decrease of the titer means favorable outcome to the treatment. At many centers, 0.4–1.0 times, the plasma volume of the patient was exchanged. Sharma *et al.* reported an overall exchange volume as low as 2097 ± 916 ml [19]. The average body weight of a patient might be 40 kg with a low hematocrit of 35% to enable this to be a sufficient TPE dose. The total removal of pathogenic antibodies is almost impossible. The efficacy of TPE depends on the plasma protein binding affinity of the substance to be removed, the volume of distribution of the substance, the volume of plasma removed relative to the patient, total plasma volume, and the number of procedures. The patient was discharged in complete stable remission according to the De Filippi's classification. The patient was able to perform routine activities.

CONCLUSION

Despite the wide number of diseases currently present or previously treated with plasma exchange, the clinical effectiveness of these treatments has been established by large controlled clinical trials only in few clinical conditions. It is required for MC as well. The combination of thymectomy followed by the first-line TPE with anticholinesterase and steroid therapy has achieved complete stable remission in elderly woman. An apheresis registry will enable sharing the experiences and help in devising a consensus that may be intended as a guide for the clinician.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Yalamanchili S, Narmadha B. Successful therapeutic plasma exchange in post-operative myasthenic crisis in elderly woman. *Indian J Case Reports*. 2020;6(2):87-89.

<https://doi.org/10.32677/IJCR.2020.v06.i02.015>