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RESEARCH ARTICLE

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Therapeutic plasma exchange for the treatment of refractory necrotizing autoimmune myopathy

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Abstract

Introduction: Necrotizing autoimmune myopathy (NAM) is strongly associated with pathognomonic autoantibodies targeting 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) or signal recognition particle (SRP), whose levels in turn are correlated with serum creatine kinase (CK) and necrosis. Thus, NAM may be amenable to therapeutic plasma exchange (TPE) to remove pathogenic antibodies and improve patient symptoms.

Methods: A retrospective case series and literature review of patients presenting with NAM and undergoing treatment with TPE was performed. Clinical data including patient demographics, symptoms, physical exam findings, muscle biopsy, lower extremity imaging, prior therapy, and duration from diagnosis to TPE initiation were collected retrospectively for adult patients with NAM treated with TPE after failing to respond to immunomodulatory therapy. Laboratory data including change in CK levels and myositis-specific antibody titers from baseline were measured in some patients.

Results: Six patients (median age at diagnosis 52.5 years, interquartile range [IQR] 35.8-64.5 years, four male/two female) underwent a median of 7.5 (IQR: 5-10) TPE procedures with 5% albumin as replacement. All patients exhibited a statistically significant reduction in CK level from pre-TPE baseline (range: 43.0%-58.7% reduction). Responses in this cohort were best in patients with antibodies targeting HMGCR and SRP, which are most strongly associated with NAM. These results compare favorably to a literature review of NAM patients (n = 19) treated with TPE, who also exhibited positive clinical and laboratory responses across varying treatment lengths.

Conclusion: TPE can play a role in the management of NAM, particularly in patients with HMGCR or SRP antibodies who are refractory to pharmacologic immunosuppression.

KEYWORDS
anti-HMGCR, anti-SRP, apheresis, idiopathic inflammatory myopathy

1 | INTRODUCTION

Necrotizing autoimmune myopathy (NAM) (also referred to as immune-mediated necrotizing myopathy [IMNM]) is a subgroup of idiopathic inflammatory myopathy that presents with subacute, symmetric, proximal muscle weakness, and elevated creatine kinase (CK).[1] In contrast to the more commonly recognized entities of dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM), NAM is characterized by pauci-immune necrosis on muscle biopsy and the absence of extramuscular manifestations.[2,3] In addition, NAM is strongly associated with autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)[4] and signal recognition particle (SRP) suggesting that these antibodies play a role in the pathogenesis of the disease.[5] In addition, HMGCR antibody levels correlate with disease severity, while treatment and symptomatic improvement are associated with a decrease in HMGCR antibodies.[6] Similarly, SRP antibody levels correlate with CK levels in NAM patients.[5]

Steroids, intravenous immunoglobulin (IVIG) and other immunosuppressants such as methotrexate are among the different therapies that are used to treat inflammatory myopathies. While therapeutic plasma exchange (TPE) has been empirically attempted in refractory patients with DM and PM, and case reports have described positive clinical outcomes with TPE,[7] a randomized controlled trial failed to show any benefit.[8] The American Society for Apheresis (ASFA) has categorized DM, PM, and IBM as category IV indications for TPE, suggesting that TPE is ineffective and could promote harm in certain situations.[9] Although DM, PM, and IBM are no longer included in the most recent ASFA guidelines,[10,11] NAM is not contraindicated (category IV), rather no recommendation exists either way.

NAM has been treated with many of the same immunosuppressants as other myopathies; however, some patients are resistant to treatment, and almost all patients require two or more immunosuppressants.[12] Given the association of disease severity with pathogenic antibodies in NAM, TPE could play a role in treatment through removal of these antibodies. Furthermore, the efficacy of rituximab in SRP and HMGCR-associated NAM support the hypothesis of a primarily antibody-mediated disease.[13,14] Here, we present a case series of six NAM patients treated with TPE at our hospital. We also present a review of the literature in an effort to contextualize the role of TPE against current practices for management of NAM.

2 | MATERIALS AND METHODS

2.1 | Identification of Johns Hopkins Patients

The study was reviewed by Institutional Review Board at the Johns Hopkins University (IRB00223496) and deemed exempt. Patients with the diagnosis of "myositis" or "myopathy" were selected by review of apheresis case logs at Johns Hopkins Hospital (JHH), a large academic medical center providing tertiary care in Baltimore, Maryland, USA. Patients were eligible for inclusion if they had (a) a documented muscle biopsy consistent with a diagnosis of NAM or IMNM, (b) the presence of an identifiable myopathy-related autoantibody, and (c) underwent at least one TPE procedure at JHH.

An extensive review of the electronic medical record was undertaken to identify demographic, clinical, and laboratory characteristics including initial presenting symptoms, prior therapies, electromyography (EMG), lower extremity magnetic resonance imaging (MRI), apheresis course, biomarker responses, and long-term outcomes. Physical exam findings including assessments of proximal muscle strength (arm abductor and hip flexor) quantified according to the Medical Research Council scale were obtained from the most recent clinical documentation within 1 month prior to TPE onset and 3 months after TPE course was completed. Concerning TPE procedures, data were collected from the electronic medical record on the replacement fluid, complications, anticoagulation, and number of procedures conducted. When patients underwent >1 TPE series, CK levels and antibody titers (when tested) from before and after the patient's initial TPE course of five procedures were included in the analysis.

2.2 | TPE procedure

All patients were subjected to similar apheresis procedures using the Spectra Optia apheresis device (Terumo BCT, Lakewood, Colorado). The Optia Software version V11.3 was employed for the first five patients, whereas Optia Software version V12 was used for patient

6. Anticoagulant citrate dextrose solution, solution A was used as the anticoagulant during TPE with an AC ratio of 10:1. Briefly, individual procedures were performed with 1.0 plasma volume exchange and 5% human serum albumin as the replacement solution. The schedule varied as specified in the results section for each patient, but a typical course of TPE comprised five sessions on alternating days. No significant apheresis-related adverse events were reported. For five patients, apheresis procedures were initiated in the inpatient setting, while one patient had outpatient procedures only.

2.3 | Statistical analyses

Statistical analyses were performed using GraphPad Prism software version 7.00 (GraphPad Software, Inc., San Diego, California). Clinical and laboratory data are expressed as medians (range or interquartile range [IQR]), as appropriate. For comparing CK changes pre- and post-TPE, Wilcoxon matched-pairs signed rank test was performed. Analysis was two-sided and $P \leq .05$ was considered statistically significant.

2.4 | Literature review of patients

Previous reports were identified by searching the PubMed database with search terms for "plasmapheresis" or "plasma exchange" and for disease terms of "necrotizing," and "myopathy" or "myositis." The search terms were used alone and/or in combination. There were no limits on time period evaluated or language. Cases with highly-associated comorbid conditions (eg, interstitial lung disease [ILD]) were included in the analysis, although only the myopathy-related response to TPE was assessed.

3 | RESULTS

3.1 | Study population

The baseline demographics and clinical characteristics of six NAM patients are presented (Table 1). The median age at diagnosis was 52.5 years (IQR: 35.8-64.5 years) and 67% (4/6) were male. All patients demonstrated a myositis-specific or myositis-associated antibody (HMGCR, SRP, RNP [anti-U1-ribonucleoprotein], Ro, OJ [anti-isoleucyl-tRNA synthetase]) and evidence of irritable myopathy on EMG, whereas proximal weakness on physical exam and abnormalities on lower extremity MRI consistent with myositis/myopathy were documented for 83% (5/6) of patients. All patients with antibodies to HMGCR (n = 3) had confirmed exposure to statin therapy. ILD was definitively diagnosed in one patient, whereas an additional 33% (2/6) of patients had evidence of restrictive lung disease on pulmonary function testing. Patients were treated with a median of 6 (range: 4-8) immunosuppressants including azathioprine, cyclophosphamide, cyclosporine, glucocorticoids, IVIG, methotrexate, mycophenolate mofetil, rituximab, tacrolimus, and/or tofacitinib prior to TPE onset and continued with median 3.5 (range: 3-5) therapies post-TPE.

3.2 | Patient clinical courses

The pre- and posttreatment TPE treatment clinical courses of NAM patients at JHH are summarized in Tables 1 and 2, respectively. Variability exists with regard to the time from diagnosis to TPE onset (median: 37.5 months, IQR: 14.5-89.75 months), strength and functional status at TPE onset, and biomarker responses (Table 2). All patients had acute declines in functional status and strength that were refractory to multiple immunosuppressants. Patients underwent a median of 7.5 (IQR: 5-10) TPE procedures from June 2016 to September 2020. Procedures were performed in 50% (3/6) of patients exclusively as inpatients. Two patients had relapses and second TPE courses, while a 3-week TPE taper was attempted in one patient. No major TPE-related adverse events were reported; however, 33% (2/6) of patients experienced problems with vascular access. Peripheral access became inadequate in one patient while another patient experienced significant oozing at the catheter insertion site requiring multiple dressing changes during a procedure. Short-term clinical and laboratory responses to TPE are summarized in Table 2, which when tested achieved reductions in CK levels (median: 1338 IU/L, IQR: 847-5881 IU/L, n = 6, $P = .0313$) compared with pre-TPE baseline (median: 3197 IU/L, IQR: 1896-11 403 IU/L, n = 6) (range: 43.0%-58.7% reduction). Autoantibody titers pre and post-TPE were tested in 33% (2/6) of patients. Both these patients had HMGCR antibodies, and titers decreased post-TPE, reflective of the TPE mechanism of action. Titers were not available for 67% (4/6) of patients.

Patients were followed for median 19.5 months (IQR: 7.5-34.5 months) from the most recent TPE to the most recent myositis-related follow-up visit or death. Concerning long-term outcomes, Patient 1 had an initial response followed by relapse 5 months later and a second round of TPE. Despite acute improvement, the patient's clinical symptoms slowly returned to her pre-TPE baseline. The patient continued to decline and eventually died

TABLE 1 Summary of patient characteristics

Patient	1	2	3	4	5	6
Sex	F	M	F	M	M	M
Age at diagnosis (years)	64	66	58	36	35	47
Race	Asian	White	Asian	Black	Black	Black
Comorbidities	Hyperlipidemia, hypertension, hypothyroidism	Hyperlipidemia, ischemic cardiomyopathy, T2DM, recurrent DVT	Hyperlipidemia, hypothyroidism, T2DM	Hypertension	Myasthenia gravis	Hyperlipidemia, hypertension, stroke, T2DM
Statin exposure	+	+	+	−	−	+
Antibody	RNP	HMGCR	HMGCR	SRP, Ro	Ro, OJ	HMGCR
Muscle biopsy	Moderate necrotizing myopathy	Necrotizing myopathy	Moderate chronic necrotizing myopathy	Increased central nuclei, no significant fiber regeneration, no endomysial, perimysial, or perivascular inflammatory infiltrates, no vasculitis	Mild necrotizing myopathy	Mild to moderate necrotizing myopathy
EMG	Abnormal; mild irritable myopathy	Abnormal; irritable myopathy	Abnormal; irritable myopathy	Abnormal; irritable myopathy	Abnormal; irritable myopathy	Abnormal; irritable myopathy
Lower extremity MRI	Abnormal	N/A	Abnormal	Abnormal	Abnormal	Abnormal
Associated malignancy	−	−	−	−	−	−
Interstitial lung disease	+/− mild restrictive lung disease on PFT	N/A	−	+/− restrictive lung disease on PFT	+	−
Dysphagia	+	−	+	−	−	+
Pre-TPE strength hip flexor	2/5	2/5	2/5	2/5	4/5	N/A[a]
Pre-TPE strength arm abductor	2/5	Left 4−/5[b]	3/5	2/5	4/5	N/A[a]
Prior immunosuppression						
Azathioprine	+	+	+	+	+	−
Cyclophosphamide	+	−	−	+	+	−
Glucocorticoids	+	+	+	+	+	+
IVIG	+	+	+	+	+	+
Methotrexate	+	+	+	+	+	−
Mycophenolate mofetil	+	−	+	−	−	+
Rituximab	+	+	+	+	+	+
Tacrolimus	+	+	+	−	−	−
Tofacitinib	−	−	+	−	−	−

Abbreviations: +, present; −, absent; DVT, deep venous thrombosis; F, female; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IVIG, intravenous immune globulin; M, male; N/A, not available; PFT, pulmonary function testing; RNP, anti-U1-ribonucleoprotein; SRP, antisignal recognition particle; T2DM, type 2 diabetes mellitus.

[a]Physical exam not performed within 1 month prior to TPE onset, patient ambulatory to the apheresis clinic.

[b]Previous trauma to right arm with inability to abduct/flex before disease onset.

TABLE 2 Summary of apheresis treatment course and biomarker responses

Patient	1	2	3	4	5	6
Time from diagnosis to TPE onset (months)	25	17	50	92	7	89
Number of TPE procedures	10 (5 q.o.d.; 5 months later, 5 q.o.d.)	5	11	5	10 (5 q.o.d.; 3 months later, 5 q.o.d.)	5
Setting	Inpatient (5) Outpatient (5)	Inpatient	Inpatient (5) Outpatient taper (6)	Inpatient	Inpatient	Outpatient
TPE-related adverse event	Oozing at catheter insertion site	–	–	–	–	Difficulty with peripheral IV access
Pre-TPE CK (U/L)	3753	1896	2641	1147	11 403	15 137
Post-TPE CK (U/L)	1585	847	1090[a]	654	5881	8133
Reduction CK (%)	57.8	55.4	58.7	43.0	48.4	46.3
Change antibody titer	N/A	Pre: >200 Post: 33	Pre: >200 Post input: <20 (negative)	N/A	N/A	N/A
Strength hip flexor(post-TPE)	3/5	1/5	2+/5	1+/5	4/5	3−/5
Strength arm abductor (post-TPE)	3/5	Left 4+/5[b]	3+/5	3+/5	4/5	4+/5
Follow-up duration (months)	9	30	36	34	3	9
Outcome	Deceased; persistent decline to pre-TPE baseline	Alive; stable, continued ambulatory difficulty	Alive; sustained improvement with rituximab, independent with ADLs	Alive; continued wheelchair use, independent with most ADLs	Alive; sustained improvement, in strength and pulmonary function, independent with ADLs	Alive; sustained improvement in strength, able to jog, independent with ADLs
Immunosuppression post-TPE						
Cyclosporine	+	–	–	–	–	–
Glucocorticoids	+	–	–	+	+	–
IVIG	+	–	+	+	+	+
Methotrexate	–	+	+	–	–	+
Mycophenolate mofetil	–	–	–	–	–	+
Rituximab	–	+	+	+	+	+
Tacrolimus	+	+	–	–	+	–
Tofacitinib	+	–	–	–	–	+

Abbreviations: +, present; –, absent; ADLs, activities of daily living; CK, creatine kinase; IV, intravenous; IVIG, intravenous immune globulin; N/A, not available; q.o.d., every other day; TPE, therapeutic plasma exchange.

[a]CK level after inpatient intensive course, CK level returned to baseline at end of prolonged outpatient taper.

[b]Previous trauma to right arm with inability to abduct/flex.

TABLE 3 Summary of previous literature reports

Patient (age [years], gender, country)	Antibody	Clinical symptoms	Peak CK values (U/L)	Prior meds	TPE regimen concurrent immunosuppression	Clinical improvement post-TPE	Year
66, F, Australia	HMGCR	Proximal lower limb weakness and fatigue, initial treatment and stabilization; severe relapse with weaning resulting in functional quadriplegia, dysphagia, and respiratory failure	5700	High-dose prednisone	TPE x months (unspecified frequency), prednisone, cyclosporine	Improvement in shoulder abduction strength; relapse treated with cyclophosphamide and methotrexate; maintenance with prednisone and IVIG	2015[15]
77, M, Australia	HMGCR	Severe proximal weakness	4300	Cyclophosphamide, IVIG, methotrexate, prednisone, rituximab	TPE x months (unspecified frequency) & prior medications	Improved shoulder abduction strength; maintenance with prednisone and IVIG	2015[15]
47, M, USA	HMGCR	Myalgia, dysarthria, dysphagia, and generalized weakness; rash	37 527	IVIG, methylprednisolone	TPE x 5, then TPE 2x per month, mycophenolate mofetil, prednisone	Muscle strength returned to normal in almost all groups; rash resolved, post-CK 1427	2018[16]
15, F, Japan	SRP	Unable to turn over in bed, hold up her head, and accomplish antigravity movements, while the only conserved motility was of the limb extremities	20 375	Methylprednisolone	TPE (unspecified frequency), methylprednisolone, cyclophosphamide	Dramatic strength improvement, difficulties swallowing and holding head in place improved at 1 month; maintenance with prednisolone and azathioprine, able to jog at 1 year	2014[17]
35, M, France	SRP	Severe muscle weakness (2/5) in proximal arms and legs and inability to rise from a bed	4700	Cyclophosphamide, cyclosporine A, IVIG, mycophenolate mofetil, prednisone	TPE 3 x per week, then tapered to 1 procedure every 3 months (unknown duration) with sirolimus and prednisone TPE x 15 (3x per week over 5 weeks) followed by rituximab	Improved proximal arm strength (3/5); CK 1000; 6 months later, 4/5 muscle strength; CK 800	2006[18]
29, F, France	SRP	Severe (2/5) proximal muscle weakness, inability to walk	8000	Azathioprine, cyclophosphamide, IVIG, prednisone, methotrexate	TPE x 9 over 3 weeks in setting of prednisone dose increase, followed by rituximab	Reduced fatigue, proximal arm and leg strength improved (4/5), with ability to walk, CK 270	2006[18]
45, F, France	SRP	Proximal weakness, walk with walker	~9000	IVIG, methotrexate, prednisone	TPE x 3, then rituximab and azathioprine	Slight improvement, ability to walk with cane	2011[5]
62, F, France	SRP	Progressive difficulty walking; proximal strength (1/5) over 2 months	2262	corticosteroids	TPE x 6 over 3 weeks (x 3, x2, x1); 4 rituximab infusions post-TPE TPE x 3 for relapse	Muscle strength recovered (4/5), CK 200-250; maintenance with prednisone, rituximab, methotrexate	2012[19]
52, M, Ireland	SRP	Bilateral lower limb cramping pains, myalgia and increasing weakness of proximal muscles; later developed lupus nephritis	20 000	Methylprednisolone, mycophenolate mofetil prednisolone, rituximab	TPE x 3 per week for 3 weeks; previous meds	Proximal muscle strength (4/5), CK 1247; azathioprine added from long-term maintenance	2015[20]

TABLE 3 (Continued)

Patient (age [years], gender, country)	Antibody	Clinical symptoms	Peak CK values (U/L)	Prior meds	TPE regimen concurrent immunosuppression	Clinical improvement post-TPE	Year
65, M, Switzerland	HMGCR	Rapidly progressive symmetrical muscle weakness and myalgia of the proximal lower limbs, weight loss and erythrosquamous skin lesions	12 036	Methylprednisolone, IVIG, cyclophosmide, rituximab	TPE, 3 daily during acute decompensation, and prior medications	Dysphagia resolved at 1 week after TPE onset, and muscle strength gradually improved over the following 2 weeks. CK levels and HMGCR antibody levels normalized at 78 days post-TPE	2020[21]
63, F, China	SRP	Proximal muscle weakness (2/5), dysphagia, mechanic's hands, interstitial lung disease	8642	Glucocorticoids, IVIG	TPE x 1	Death from heart and respiratory failure at 33 days after diagnosis, CK reduced by 94.2%	2021[22]
28, F, China	SRP	Proximal muscle weakness (3/5)	2082	Glucocorticoids, IVIG	TPE x 1 complicated by allergic reaction	Improvement in strength (4+/5), reduction in CK by 80.8% by 3 weeks	2021[22]
52, F, China	SRP	Proximal muscle weakness (4/5), rash, interstitial lung disease	7220	Glucocorticoids, IVIG	TPE x 3 q.o.d.	improvement in strength (5/5) and reduction in CK by 78.4% by 3 weeks, improvement in chest CT	2021[22]
61, F, China	SRP	Proximal muscle weakness (3/5), dysphagia, myalgia, interstitial lung disease	5381	Glucocorticoids, tacrolimus	TPE x 3 approximately q.o.d.	Improvement in strength (5/5) and reduction in CK by 96.1% by 3 weeks, improvement in chest CT	2021[22]
32, F, China	SRP	Proximal muscle weakness (4/5), Raynaud's phenomenon	2606	Glucocorticoids, IVIG, tacrolimus	TPE x 2 q.o.d.	Improvement in strength (5/5) and reduction in CK by 60.7% by 3 weeks	2021[22]
53, M, China	SRP	Muscle weakness (MMT8 72/80), mechanic's hands, myalgia, interstitial lung disease	1656	Glucocorticoids, tacrolimus	TPE x 2 q.o.d.	Improvement in strength (MMT8 80/80) and reduction in CK by 88.6% by 3 weeks, improvement in chest CT	2021[22]
49, M, China	SRP	Muscle weakness (MMT8 72/80), Raynaud's phenomenon	1519	Glucocorticoids, IVIG	TPE x 2 q.o.d.	Improvement in strength (MMT8 80/80) and reduction in CK by 41.5% by 3 weeks	2021[22]
23, M, China	SRP	Proximal muscle weakness (3/5), mechanic's hands, myalgia, interstitial lung disease	11 647	Cyclophosphamide, glucocorticoids	TPE x 2	Improvement in strength (4+/5) and reduction in CK by 84.7% by 3 weeks; improvement in chest CT	2021[22]
56, M, China	SRP	Proximal muscle weakness (4/5), mechanic's hands	9630	Glucocorticoids, IVIG, tacrolimus	TPE x 2	Improvement in strength (5/5) and reduction in CK by 89.2% at 3 weeks	2021[22]

Abbreviations: CT, computed tomography; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IVIG, intravenous immune globulin; MMT8, manual muscle testing abbreviated score; q.o.d., every other day; SRP, antisignal recognition particle; TPE, therapeutic plasma exchange.

at 9 months post-TPE. The remaining 83% (5/6) of patients are alive at most recent follow-up and exhibited long-term gains, either in symptomatic improvement and/or biomarkers when placed on new immunosuppressants.

4 | REVIEW OF PREVIOUS LITERATURE

Nine reports from seven countries involving 19 patients are summarized (Table 3).[5,15-22] While all patients had an identifiable myopathy-related autoantibody either HMGCR (n = 4) or SRP (n = 15), only 53% (10/19) of patients had a documented muscle biopsy. All patients were treated with multiple immunosuppressants before TPE.

TPE protocols were heterogeneous, but 42% (8/19) included 2 weeks or more of treatment.[15,16,18-20] On the extreme, patients in Australia were treated for several months of TPE in addition to other immunosuppressive drugs.[15] In other cases, the regimen was most often TPE treatments over 3 weeks, either in a tapering series or in a series of three TPE procedures a week. In one of the short-term cases, TPE was principally used to treat a rapidly decompensating inpatient as a bridge to rituximab and cyclophosphamide.[21] Antibody titers and CK levels were measured in 5% (1/19) and 79% (15/19) of patients, respectively, and were found to decrease with TPE. Clinically, all patients noted improvement in strength, and in some cases recovered the ability to walk and/or the ability to perform other activities of daily living.

5 | DISCUSSION

We present a single-center, retrospective case series using TPE for chronic, refractory NAM. Despite multiple immunosuppressants, all patients had precipitous declines in strength and quality of life, which led to a trial of at least five TPE procedures. After TPE, all patients demonstrated at least temporary, subjective improvement in strength, ability to perform activities of daily living, and reductions in CK. While concurrent physical therapy and optimization of immunosuppression also play a role, TPE allowed an acute improvement in symptoms. Regarding serum CK as a biomarker in NAM, median peak levels reportedly range from approximately 3400 to 5000 IU/L.[3,23,24] An increase in CK precedes weakness onset and levels rise exponentially with disease activity; however, in the context of therapy, CK levels decline first before strength recovery.[3] Whether the decrease in CK observed with TPE reflects simple removal from the systemic circulation (mechanism of TPE) vs reduced synthesis due to a true therapeutic effect remains to be determined and is likely confounded by concurrent immunosuppressants.

Four patients with either HMGCR or SRP antibodies had the best responses in our cohort, consistent with previous reports from other countries.[5,15-22] Titers of these antibodies correlate with disease activity, and contribute to disease progression through impaired muscle regeneration, complement-dependent myofiber necrosis, and promotion of myofiber atrophy.[25-27] Beyond the removal of pathogenic antibodies, other mechanisms of action including removal of circulating cytokines, adhesion molecules, and complement components may contribute to the effectiveness of TPE for NAM.

While SRP and HMGCR antibodies are seen in 39% and 26% of NAM patients, respectively, it is likely that other pathologic antibodies exist in the remaining 35% of patients.[28] Two patients without pathognomonic antibodies for NAM (eg, RNP or Ro, instead of HMGCR or SRP) relapsed requiring another TPE series. Patients without HMGCR or SRP antibodies may be less responsive to therapy, have more severe disease, or more frequent extramuscular manifestations[29]; however, additional patients in this population will need to be assessed.

The optimal protocol and timing for introduction of TPE therapy in the context of NAM disease course remain uncertain. The duration of TPE treatment varied in our series compared with the previous reports, from intensive short-term courses (1-5 procedures) to extended outpatient tapers. The patients in our study were referred for TPE relatively late in their disease course, when there were no other options for therapy. There are no robust data regarding TPE in earlier stages of NAM disease progression. Based on the accumulated case reports, TPE offers benefits in the context of refractory disease, but the effects may be transient. Overall, poorer outcomes are associated with a greater extent of muscle damage in NAM.[30] Muscle atrophy and fatty replacement correlate with disease duration.[24] Although there is no consensus protocol for TPE in NAM, we suggest that an initial trial of five procedures every other day should be considered.

Given the close association of NAM with antibody-mediated pathogenesis, rituximab to suppress antibody production may be complementary to TPE.[13] We saw this type of favorable response with a few of our patients. We also suggest the importance of using available titer assays for HMCGR and SRP antibodies, which may be able to track the efficacy of TPE treatments. This would allow a more objective outcome measure to guide therapy.[5] The time for muscle recovery is uncertain, therefore, initial clinical improvement post-TPE may not be dramatic, unlike other conditions, such as acute myasthenia crisis.[31]

Our study has several limitations. This is a single-center, retrospective analysis with few patients. Heterogeneity

with regard to underlying antibody, as well as prior and concurrent treatments makes attribution of clinical benefit to TPE uncertain. Furthermore, response to myopathy treatments is largely subjective having been based on patients' reporting of clinical benefit whereby CK was the only available biomarker used to assess response. Compared with other reports using TPE to treat NAM, our study is also limited by its retrospective nature and short trials of TPE for NAM treatment. The impact of longer duration of treatment was not assessed. Another mitigating factor is the time from diagnosis to initial treatment with TPE, as well as the duration of acute decline in strength, both of which may mark more extensive muscle damage that may not be reversible by removing a pathologic antibody. Patients with shorter overall duration of NAM disease were not included in our study.

The reported findings on six NAM patients at our institution and 19 NAM patients in the literature refractory to other immunosuppressants suggests that TPE is well-tolerated and can at least lead to subjective improvements in muscle strength and mobility.[5,15-22] While this is only low quality evidence (GRADE 2C by ASFA standards), the results suggest that TPE can play a role in management of NAM especially in the context of refractory disease. Formal inclusion of NAM as a new fact sheet in the ASFA guidelines would allow broader implementation of TPE and consideration of this therapy earlier in the disease course. Future studies are necessary to evaluate effectiveness of TPE for NAM more systematically, which may include establishing a registry of NAM patient cases and prospective studies to assess clinical outcomes using a standardized approach with defined biomarkers and validated clinical endpoints.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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