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Plasmapheresis for Anti-Melanoma Differentiation-Associated Gene 5 Antibody Dermatomyositis with Rapidly Progressive Interstitial Lung Disease

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Abstract

This case report describes a patient with anti-melanoma differentiation-associated gene 5 antibody dermatomyositis with rapidly progressive interstitial lung disease who reported that his respiratory status improved remarkably after three plasmapheresis procedures and who had no need for supplemental oxygen on the day after the third plasmapheresis.

Keywords: *Plasmapheresis, plasma exchange, anti-melanoma differentiation-associated gene 5 antibody, dermatomyositis, rapidly progressive interstitial lung disease.*

Introduction

Idiopathic inflammatory myopathies (IIMs) are rare, chronic autoimmune diseases that affect primarily the skeletal muscle but can involve multiple organs **[**1**]**. They include different clinical subtypes of diseases such as dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), overlap myositis (OM), and inclusion body myositis (IBM) **[**1**]**.

Dermatomyositis (DM) which is an autoimmune inflammatory myopathy has a characteristic cutaneous involvement such as Gottron's papules (tender red or purple papules), a heliotrope rash, and/or an erythematous eruption around the neck and shoulders **[**1**]**. A subtype of DM, clinically amyopathic DM (CADM), is characterized by typical skin lesion of DM with no or subclinical muscular manifestations. Interstitial lung disease is a major cause of morbidity and mortality in dermatomyositis and polymyositis and has been recognized as the complication impacting on the prognosis **[**2**]**.

Anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody is associated with rapidly progressive interstitial lung disease (RP-ILD) in patients with clinically amyopathic dermatomyositis or dermatomyositis **[**3**]**. Measurement of anti-MDA5 antibody and an intensive immunosuppressive regimen might rescue these patients from RP-ILD. High serum titer of anti-MDA5-Ab (≥100 IU/mL) is associated with acute death via the development of RP-ILD, outcomes in the chronic phase for patients with a low titer of anti-MDA5-Ab (<100 IU/mL) were similar to those of patients without anti-MDA-Ab **[**4**]**.

Case Presentation

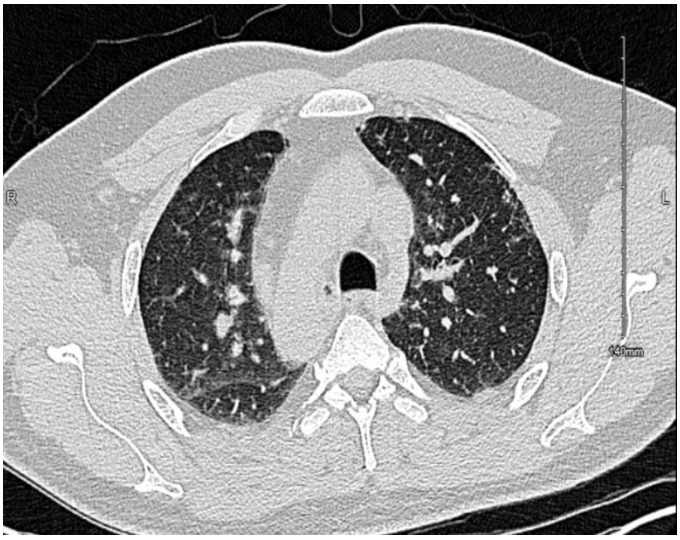
Our patient is a man in his forties with anti-MDA5 dermatomyositis complicated by RP-ILD. Initially, the patient presented for shortness of breath and mild myalgia that subsequently developed into a rash on his elbows, knees, ankles, back, and chest. The rash started slightly erythematous and pruritic but gradually worsened into second degree burns on his face, dorsal hands, and abdomen. Diagnostic workup confirmed serum anti-MDA5 antibody and RP-ILD diagnosed by radiology report of computed X-ray tomography imaging (Figure 1). Several trials of prednisone with taper failed to improve his symptoms (Figure 2). The patient began a trial of cyclophosphamide infusion and tacrolimus with no improvement. Over the next two months, the patient's myalgias and shortness of breath worsened until he was wheelchair bound. His skin had no improvement.

On day 92, he developed a deep venous thrombosis (DVT) and stopped tacrolimus. He received apixaban 10 mg BID. Over the next few days, he had worsening shortness of breath, a productive cough, and severe night sweats. Diagnostic workup showed acute ILD exacerbation and multifocal acute bilateral pulmonary embolism. He was given a course of methylprednisolone and restarted tacrolimus. Dyspnea immediately improved after reinitiation of tacrolimus, and hydroxychloroquine was initiated for joint pain.

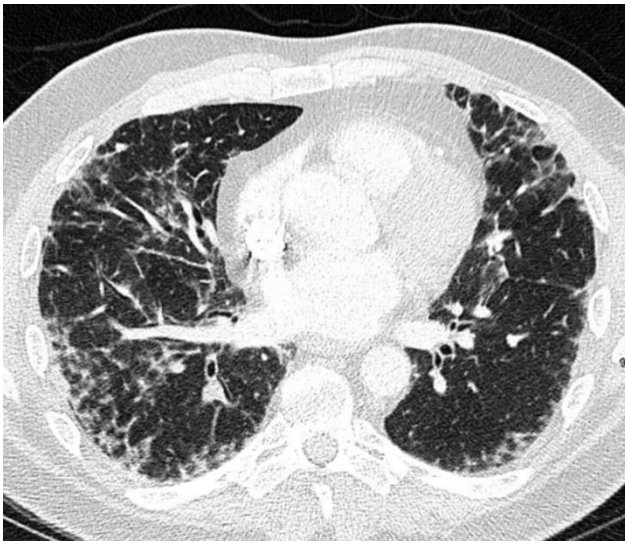
On day 3 of methylprednisolone, he started therapeutic plasma exchange (TPE) that was performed via centrifugal plasmapheresis with 5% albumin as the replacement fluid. The TPE series was performed in addition to tacrolimus, methylprednisolone, cyclophosphamide, and hydroxychloroquine.

After TPE #1 on day 101, he reported minimal improvement of arthralgias, and no new rashes were noted. After TPE #2 on day 104, he reported that his arthralgias, myalgias, shortness of breath, and exercise tolerance were significantly improved. No new rashes were noted. After TPE #3 on day 106, he reported that felt remarkably better and also slept without oxygen therapy. A day after TPE #3 and thereafter, he required no supplemental oxygen.

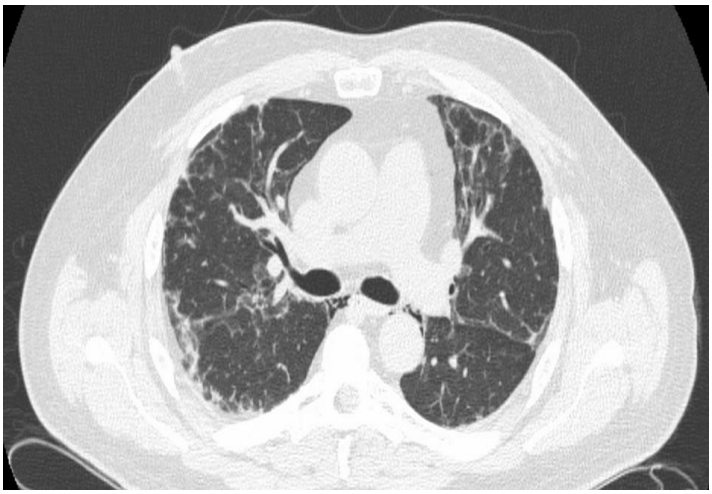
Later that same day (one day after TPE #3), he also received an EUA approved for PF-06823859, which is a humanized-antibody against interferon-beta-1 fibroblast (IFNB1). He was able to walk with a cane within a month. His rashes slowly improved over several weeks, largely resolved, but remained on his elbows and knuckles. His respiratory status and lung imaging remained unchanged. Other than the initial diagnostic anti-MDA5 serology, no follow up serologies were performed. A summary of his clinical course is described in Table 1.



CT Image (A)

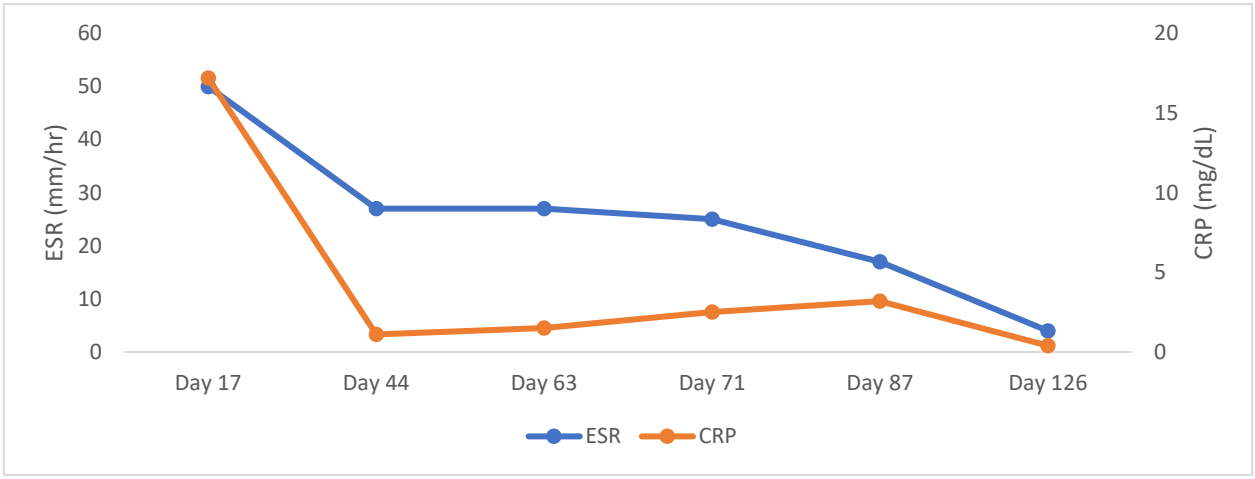


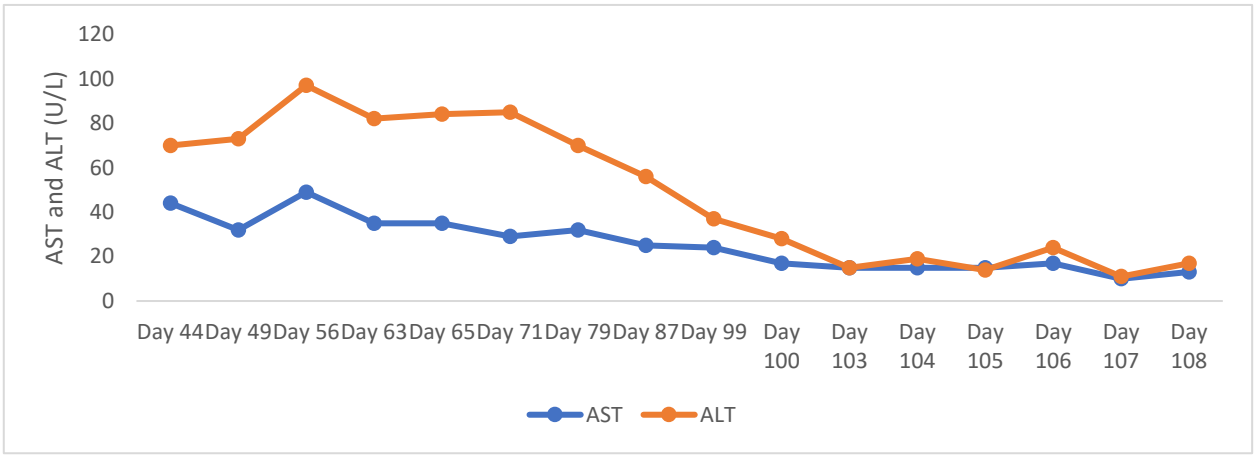
CT Image (B)

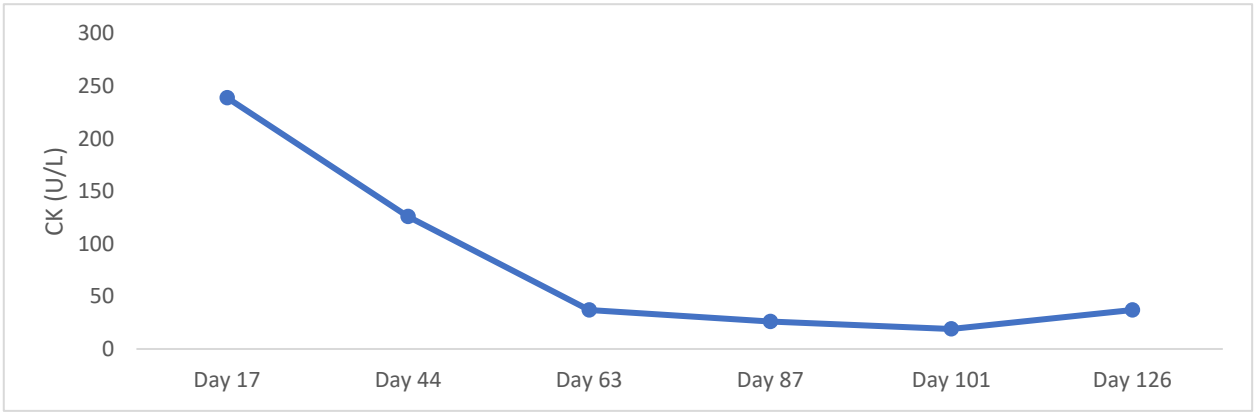


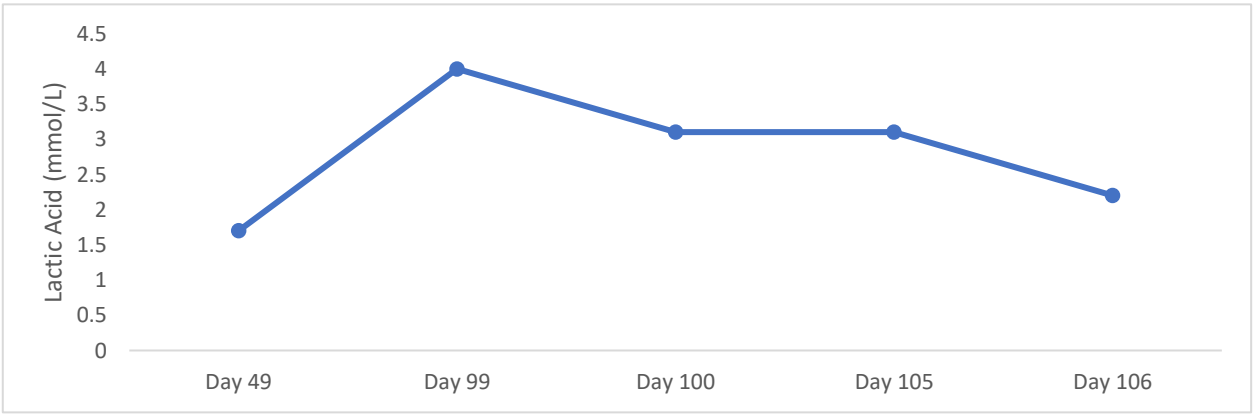
CT Image (C)

Figure 1: Chest CT Images (A) On day 27, multiple small bilateral ground glass opacities seen suggestive of pneumonitis superimposed on chronic interstitial scarring. (B) On day 101 prior to TPE #1, similar diffuse bronchiectasis, peripheral reticular opacities, and parenchymal bands seen. (C) 23 days after TPE #3, peripheral and perilobular reticular opacities remained, but improved. In addition, central airways are clear.


ESR (mm/hr)
CRP (mg/dL)
60
50
40
30
20
10
0
20
15
10
5
0
Day 17
Day 44
Day 63
Day 71
Day 87
Day 126
ESR
CRP


AST and ALT (U/L)
120
100
80
60
40
20
0
Day 44
Day 49
Day 56
Day 63
Day 65
Day 71
Day 79
Day 87
Day 99
Day 100
Day 103
Day 104
Day 105
Day 106
Day 107
Day 108
AST
ALT


CK (U/L)
300
250
200
150
100
50
0
Day 17
Day 44
Day 63
Day 87
Day 101
Day 126


Lactic Acid (mmol/L)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Day 49
Day 99
Day 100
Day 105
Day 106

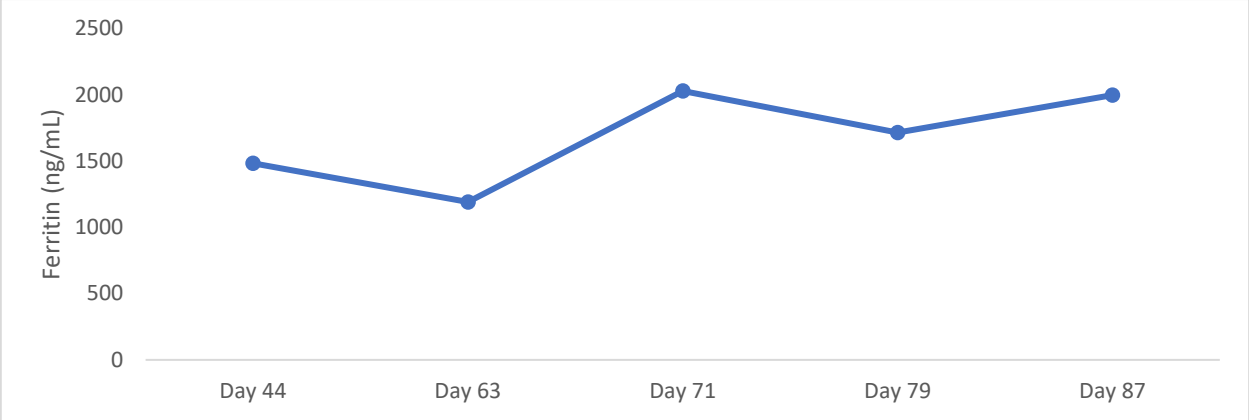


Figure 2: Laboratory Parameters Laboratory parameters of our patient during treatment course, including ferritin, creatine kinase (CK), aldolase, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic acid. TPEs occured on day 101, 104, and 106.

Drug Taken	Dosage and Duration	Patient Improvement
Clobetasol	Unknown dosage and duration	No rash improvement
Hydrocortisone	Unknown dosage and duration	No rash improvement
Prednisone	20mg/day x 3 days: Day 1 – Day 3	No rash improvement
	40mg/day and taper until improvement: Day 19 – Day 38	Developed painful, burning pruritus after tapering to lower dose
	40mg BID and taper until improvement: Day 38 – Day 63	Minimal improvement with higher dose Joint pain and pruritus worsened after tapering to a lower dose
	50mg/day: Day 63 – Day 70	Relief of symptoms from taper
	40mg/day: Day 70 – Day 110	Continued stabilizing symptoms
Vitamin D supplements	50mcg/day: 1/8/21 – Day 110	N/A
Calcium supplements	600mg BID: 1/8/21 – Day 110	N/A

Cyclophosphamide	1100mg IV infusion: Day 50	No improvement
	1100mg IV infusion: Day 66	No improvement
	1350mg IV infusion: Day 80	No improvement
	1672mg IV infusion: Day 103	No improvement
Tacrolimus	0.1% ointment BID PRN: Day 52 – Day 63	No relief
	3mg BID: Day 63 – Day 92	No improvement
	3mg BID: Day 99 – Day 110	Improvement in shortness of breath
Methylprednisolone	1000mg/day: Day 99 – Day 101	No improvement
	250mg/day: Day 102	No improvement
	125mg BID: Day 103	No improvement
	100mg/day: Day 104	No improvement
Hydroxychloroquine	200mg BID: Day 101 – Day 110	No improvement

Table 1: Summary of Clinical Course Description and duration of our patient's treatment including any clinical improvements.

Discussion

Myositis specific autoantibodies (MSAs), including anti-TIF-1γ, anti-NXP2, anti-Mi-2, anti-MDA5, and anti-SAE, have been found to be associated with DM in the past decade with different autoantibodies correlated with different clinical phenotypes. In DM, anti-MDA5 is a specific subtype that has been identified to be associated with RP-ILD **[**4,5**]**.

MDA5 belongs to the family of retinoic acid-inducible gene I-(RIG-I) like receptors (RLRs) and plays a crucial role in inducing an innate immune response against viral infection and is recognized as the specific autoantigen in DM, where upregulation of MDA5 in the innate immune system subsequently promotes anti-MDA5-Ab production **[**4,2**]**. In terms of mortality, anti-MDA5-Ab has been identified as a more severe DM subtype than other types of myositis.

Elevated levels of many kinds of cytokines/chemokines were reported to be related to the activity of ILD associated with PM/DM patients **[**6**]**. IL-6, IL-8, IL-10 and serum ferritin levels were significantly higher in PM/DM patients with RP-ILD compared with non- or chronic- ILD. Thus, excessive

monocyte/macrophage activation is suggested to be involved in the pathophysiology of PM/DM with RP-ILD, especially those with anti-MDA5 [6].

Glucocorticoids are the mainstay of treatment for all IIMs. Among the immunosuppressive agents, mycophenolate mofetil has been reported as an effective therapeutic tool for autoimmune myopathies [1]. We do not know why this agent was not used for this patient. Given the magnitude of immunosuppression, the physicians wanted to be vigilant about preventing infection. IVIG use is only recommended in the refractory forms [1]. However, in our current patient the Rheumatologist wanted to avoid IVIG due to an increase in the risk of thrombosis.

Rituximab (RTX), a chimeric monoclonal antibody depletes B cells for showing CD20 protein, seems effective for the treatment of a refractory skin and lung disease in IIMs [1]. Subsequent reduction of anti-MDA5-Ab after starting the treatment predicts a successful outcome. Rheumatologist also proposed that Rituximab could be considered for this patient but the onset of action would be more than 3 months and maybe some what risky given his fragile status at the time of consideration. Even after with combined therapy, some patients remain resistant to all the above therapeutic agents. Predictive factors for resistance to immunosuppressive therapy and poor prognosis includes elderly age, respiratory dysfunction, high HRCT scores of airspace consolidation and high ferritin levels at baseline [5].

While evidence is sparse and controlled trials are lacking, TPE may be an effective adjuvant treatment in anti-MDA5 positive DM with RP-ILD [7]. The mechanism is thought to be the adsorption and elimination of excessive inflammatory cytokines/mediators and activated leukocytes in addition to direct antibody removal [6].

In the context of this sparse data, we share our experience of a patient with anti-MDA5 positive DM with RP-ILD who reported that his respiratory status improved remarkably after three TPEs and who had no need for supplemental oxygen by the day after TPE #3.

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