

Intravenous Immune Globulin in Amyopathic Dermatomyositis - Report of Two Cases and Review of the Literature

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Abstract: Amyopathic dermatomyositis (ADM) is a rare subtype of dermatomyositis which is often recalcitrant to immune suppressing treatments. Intravenous immunoglobulin (IVIG) has been used in the treatment of refractory dermatomyositis. We present two patients with severe ADM, who were treated with IVIG at 2 g/kg every four weeks. Both patients had a successful response and were able to taper the dosage of prednisone. We present both cases in describing IVIG as a rescue and maintenance steroid-sparing agent in the treatment of severe refractory ADM. We also review the treatment of refractory ADM with IVIg in the English literature.

Keywords: Intravenous immunoglobulin, treatment, amyopathic dermatomyositis, direct immunofluorescence.

INTRODUCTION

Amyopathic dermatomyositis is a rare but well described subset of dermatomyositis in which patients develop the characteristic cutaneous lesions of dermatomyositis but clinical or laboratory evidence of muscle disease is absent. As muscle disease in dermatomyositis is typically more responsive to immunomodulatory therapy than cutaneous disease, effective treatments are limited. Here we discuss two cases of refractory ADM (dermatomyositis *sine* myositis) that responded to IVIG as adjuvant therapy. We briefly review the evidence for the use of IVIG in adult patients with ADM and implications for therapy in the future. Search of the literature was performed with use of PubMed/MEDLINE and Google Scholar, with use of the search terms “amyopathic dermatomyositis”, “immune globulin dermatomyositis”, “IVIG dermatomyositis” and “IVIG amyopathic dermatomyositis”. The bibliography of articles found in the search was also reviewed and included if appropriate. This retrospective study was conducted after obtaining approval from the University of Alabama Institutional Review Board.

CASE #1

A 60 y/o woman with a past medical history significant for hypertension presented for evaluation history of pruritus and a blistering rash. A skin biopsy was performed and demonstrated subepidermal blisters with eosinophilic infiltration. Direct immunofluorescence (DIF) was weakly positive along the base while the indirect immunofluorescence (IIF) was positive for a net-like pemphigus pattern. The main differential diagnoses were blistering drug eruption and paraneoplastic pemphigus.

A comprehensive evaluation for occult malignancy was unremarkable, as were laboratory studies, apart from a mild eosinophilia and a positive anti-nuclear antibody (ANA), with titer 1:1280. Further autoantibody studies, including anti-SSA, anti-SSB and anti-Sm were negative and the patient was diagnosed with bullous drug eruption. Anti-hypertensive therapy was changed and a prednisone taper was initiated. The rash relapsed whenever the prednisone dose fell below 20 mg daily and dapsone (150 mg/d) was prescribed for at least eight weeks, without benefit.

She presented one year later with worsening severe pruritus and diffuse erythema over her face, back, chest, eyelids and arms, as well as plaques over the meta-carpal phalangeal (MCP), proximal intra-phalangeal (PIP) and distal intra-phalangeal (DIP) joints of both hands. She denied any other symptoms, specifically weakness, dysphagia, arthralgia or dyspnea. A skin biopsy at this time showed changes consistent with dermatomyositis. Additional laboratory evaluation was unremarkable, apart from a persistently positive ANA that remained positive. Laboratory tests including complete blood count (CBC), metabolic profile, creatinine kinase, serum protein electrophoresis (SPEP) and serum immunofixation (IFE) did not reveal any abnormalities. Tests for autoantibodies to Smith, Sjögren's-syndrome-related antigen A and B (SSA, SSB), Jo1, Mi2 and P140 (anti-MJ) were negative.

Based on the clinical course, laboratory studies and pathology results, the patient was diagnosed with amyopathic dermatomyositis and corticosteroid sparing was begun, with an attempt to taper off prednisone. She was on each of the following systemic medications for three months without any success: mycophenolate mofetil (MMF- 2 g/d), methotrexate (15 mg/wk), and sirolimus (2 mg/d), and hydroxychloroquine (400 mg/d). Various topical corticosteroids used as adjuvant treatment provided brief temporary relief with pruritus. At this time, therapy with IVIG at a total dosage of 120 grams (2 g/kg over 3 days

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every 4 weeks) was initiated. Eighteen months following initiation of IVIG therapy, prednisone was tapered to 10 mg daily without a flare. Attempt to reduce the frequency of IVIG infusions to every 6 weeks resulted in a flare of skin disease that required an increase in the corticosteroid doses. At this time, her skin disease remains quiescent with IVIG infusions every 4 weeks.

CASE #2

A 51 year-old man presented for evaluation of intensely pruritic, erythematous plaques on both hands (MCP and PIP joints), and diffuse erythema of his chest, back and arms. He denied any systemic symptoms, including weakness, dysphagia and dyspnea. Laboratory evaluation, including CBC, metabolic profile, aldolase, creatinine kinase, ANA, SPEP, and serum IFE were within reference ranges. Autoantibodies to Smith, SSA, SSB, Jo1, Mi2, Scl70, perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), cytoplasmic anti-neutrophil cytoplasmic antibodies (cANCA), anti-proteinase 3 (anti-PR3), anti-myeloperoxidase (anti-MPO) were negative. A workup for occult malignancy, including whole-body computed tomography (CT), was unremarkable. A skin biopsy was consistent with dermatomyositis.

Following this evaluation, therapy with prednisone 60mg daily was initiated. Attempts to taper the prednisone below 40 mg/day were unsuccessful, despite the use of azathioprine 150 mg/day and hydroxychloroquine 400 mg/day. In addition to the erythematous plaques described above, he developed several painful, draining non-healing ulcers on his feet and buttocks. Treatment with IVIG at total dosage of 160 grams (2g/kg over 4 days every 4 weeks) was initiated and within 12 weeks, improvements were noted in the rash and ulcers. The prednisone was tapered to 20 mg/day without any flare in his skin disease.

Following the prednisone taper, he developed severe Raynaud's phenomenon that did not respond to treatment with oral nifedipine and pentoxifylline as well as topical nitroglycerine. He did have a good response to local botulinum toxin in all digits except his index finger, which required partial amputation due to persistent ischemia.

After eight months, the IVIG dose interval was increased to every 6 weeks since his cutaneous disease was well controlled. Shortly after the IVIG interval was increased, he developed spontaneous pneumomediastinum and was diagnosed with interstitial lung disease. The IVIG dose interval was decreased to every 4 weeks and 4 doses of rituximab at 375 mg/m² were given.

At follow-up one year after the rituximab and IVIG dose-adjustment, he has had resolution of his cutaneous disease (rash and ulcers) and improvement of his ILD. He has had no further pneumomediastinum or flares of Raynaud's. He is currently stable on prednisone 5 mg/day, azathioprine 150 mg/day and hydroxychloroquine 400mg/ day.

DISCUSSION

Dermatomyositis is a humoral inflammatory disease, with an antibody and complement mediated necrotizing

vasculopathy though it is thought that Toll-like receptors (TLR) and type 1 interferon also are involved in pathogenesis [1, 2]. This is in contrast with polymyositis, which is generally understood to be that of a cellular inflammatory process, primarily mediated by CD8⁺ T lymphocytes [1].

Dermatomyositis can occur as an idiopathic process, as an association with malignancy, as a drug reaction or in association with another connective tissue disease [3]. Additionally, dermatomyositis can be complicated by ulcerated skin lesions [4] or interstitial lung disease, which is often associated with poor prognosis [5].

The therapeutic approach in dermatomyositis is based on the presence or absence of muscular involvement. Since our patients did not report or demonstrate any clinical symptoms or signs of muscle disease on physical examination and creatine kinase assay was within normal limits, further involvement of muscle disease was not tested. In classical DM, initial therapy consists of 1mg/kg prednisone (or equivalent) daily that is continued for at least 6 weeks after clinical and biochemical remission is achieved. Steroid therapy will result in remission of muscle disease in 75% of patients. The remaining patients require the addition of an additional immunosuppressive agent such as azathioprine, mycophenolate or methotrexate [6]. The cutaneous findings are often more refractory to therapy and frequently do not respond to corticosteroids [6]. As such, an alternative approach to immunosuppressive therapy such as intravenous immune globulin is often required.

In Tables 1 and 2, we summarize the published English-language literature regarding IVIG in amyopathic dermatomyositis from Japan, Spain, France, and the United States which were between the years 2009-2013. Table 2 is separate because of a different degree of detail in the reported cases. In Table 2, the treatment course of IVIG was 2gm/kg, given as 1gm/kg every two days and was repeated every three to four weeks. Cases of paraneoplastic amyopathic dermatomyositis were not included.

The cases reviewed show that IVIG in adults is effective as in amyopathic dermatomyositis refractory to standard immunosuppressive regimens. In our review of IVIG as salvage therapy, 35 of 43 patients with amyopathic DM had at least a partial response and 26 of 43 had a significant (complete or nearly complete) response. Additionally, 2 of 6 with concomitant interstitial lung disease had a good clinical response. We believe this is significant, as all had failed to respond to previous intensive immunosuppressive regimens, including systemic glucocorticoids, calcineurin inhibitors and antimetabolites such as azathioprine, mycophenolate and cyclophosphamide. Although the small numbers of patients and the significant population heterogeneity does not allow us to draw definitive conclusions, we believe that the use of IVIG can be considered as adjuvant therapy in amyopathic DM refractory to conventional oral treatments.

Immune globulin therapy has the additional benefit of acting as an immunomodulatory agent rather than an immunosuppressive agent. The mechanism of action is incompletely understood, but is believed to include inhibition of antibody activity and suppression of

Table 1. Demographics, Clinical response and follow-up to IVIg treatment.

Age/Gender	Associated Findings	Duration of IVIG Therapy	Therapy Prior to IVIG	Therapy After IVIG	Response [#]
45 Female [7]	ILD	5 day course (400 mg/kg/day) total 2gm/kg Two Courses, one month apart	PSL 60/day CSA 250/day	PSL taper (60 to 20 - 4 months) CSA 250/day	Survived (Condition not otherwise described)
72 Male [7]	ILD	5 day course (400 mg/kg/day) total 2gm/kg One Course	MPD* PSL 60/day CSA* CYC*	PSL* CSA* Polymyxin B Hemoperfusion	Died (46 days after onset of illness)
75 Female [7]	ILD	5 day course (400 mg/kg/day) total 2gm/kg One Course	MPD* PSL 50/day CSA*	PSL* CSA* CYC*	Died (47 days after onset of illness)
55 Female [7]	ILD	5 day course (400 mg/kg/day) total 2gm/kg One Course	MPD* PSL 50/day CSA*	PSL* CSA* CYC*	Died (29 days after onset of illness)
24 Male [7] [†]	ILD	5 day course (400 mg/kg/day) total 2gm/kg Two Courses, one month apart	MPD 3g PSL 60/day	CSA 150 mg/day PSL taper (60 to 10 mg)	Survival, with resolution of pulmonary and cutaneous findings
55 Female [8]	Calcinosis Cutis	5 day course (400 mg/kg/day) total 2gm/kg Five Courses one month apart, then one course yearly for 5 years	Pred 60/day HCQ 400/day CLQ 250/day MTX 7.5/week AZA 100/day CSA 200/day MMF 1500/day	No immunomodulatory therapy	Complete resolution
54 Male [9]	ILD	5 day course (400 mg/kg/day) total 2gm/kg One Course	PRED taper (30 mg over 12 days) MPD 3 g PRED 75/day	PRED 75/day	Died
61 Female [10] [§]	None Noted	2 day course (1gm/kg/day) Total 2gm/kg 7 courses, one month apart	HCQ* PRED 40/day	No immunomodulatory therapy	Complete resolution
29 Female [10]	None Noted	2 day course (1gm/kg/day) Total 2gm/kg 28 courses, one month apart	HCQ* MMF* MTX*	HCQ*	Complete Resolution
36 Female [10]	None Noted	2 day course (1gm/kg/day) Total 2gm/kg 22 courses, one month apart	HCQ* MTX*	No immunomodulatory therapy	Complete Resolution
22 Female [10] [§]	None Noted	2 day course (1gm/kg/day) Total 2gm/kg 6 courses, one month apart	HCQ*	HCQ*	Complete Resolution
53 Female [10] [§]	None Noted	2 day course (1gm/kg/day) Total 2gm/kg 4 courses, one month apart	HCQ* MTX*	No immunomodulatory Therapy	Complete Resolution
93 Female [10]	None Noted	2 day course (1gm/kg/day) Total 2gm/kg 4 courses, one month apart	HCQ* PRED 10/daily	No immunomodulatory Therapy	>75% resolution
56 Female [10]	None Noted	2 day course (1gm/kg/day) Total 2gm/kg 11 courses, one month apart	HCQ* MMF* MTX*	HCQ* (summer months only)	>75% resolution
87 Female [10]	None Noted	2 day course (1gm/kg/day) Total 2gm/kg 9 courses, one month apart	HCQ*	None	<75% resolution
58 Male [10]	None Noted	2 day course (1gm/kg/day) Total 2gm/kg 7 courses, one month apart	HCQ* THAL* MTX* PRED 40/day	PRED 20/day	<75% resolution

Key:

[#] Clinical Response, as described by the authors. When percentages are given, they represent the Cutaneous Dermatomyositis Disease Activity and Severity Index (CDASI)

* Drug dosage, route and/or schedule not given in text

[†] This patient was classified by the authors as amyopathic dermatomyositis, He had no clinical muscular symptoms and normal EMG. This patient did, however, have small elevations in CK and aldolase at initial presentation, which normalized with initial glucocorticoid therapy and remained within normal limits throughout the remainder of his described course

[§] Diagnosis described by authors as “provisional” amyopathic dermatomyositis, which is not defined in the text

Drug Abbreviations:

AZA – Azathioprine; CLQ – Chloroquine; CSA – Cyclosporine A; CYC – Cyclophosphamide; HCQ – Hydroxychloroquine; MMF – Mycophenolate Mofetil; MPD – Methylprednisolone; MTX – Methotrexate; PRED – Prednisone; PSL – Prednisolone; THAL – Thalidomide.

Table 2. Baseline characteristics of this population are summarized below: All data are from Bonfour *et al.* [11].

Gender Distribution	Age (y) Mean [Range]	Classification	Associated Malignancy	ILD	Therapy Prior To IVIG	Time Until Initiation of Glucocorticoids (Mean/Range - Months)
3 M 24 F	52 (25-90)	ADM: 10 (37%) hDM: 6 (22%) pDM: 5 (19%) CR-CDM: 6 (22%)	5 (19%)	3 (11%)	TGC: 11 (41%) TAC: 2(7%) SGC: 11(41%) HCQ: 14(52%) MTX: 3(11%) AZA: 1(4%)	34 (4-240)

Clinical response and follow-up treatment are summarized below:

IVIG Courses (Mean/Range, in Months)	Response to IVIG (N - %)	Therapy Concurrent with IVIG	Additional Therapy if NR/PR	Relapse Among SR	IVIG Treatment of Relapse in SR	Clinical Course After IVIG Treatment of Relapse	Progression to CDM
All: 4.8 (1-15) SR: 5.3 (3-15)	NR: 4(15%) PR: 4(15%) SR: 19(70%)	All: 17(63%) TAC: 2(7%) CLQ: 1(4%) HCQ: 9(33%) SGC: 6(22%)	SGC: 7(26%) MTX: 1(4%) MMF: 1(4%) HCQ: 2(7%)	10 (53%)	6 (60%)	Required Multiple courses of IVIG: 3/6 Treatment following IVIG Retreatment SGC=2, MTX=2 TGC=2	6/27 (22%) 0/9 non-relapsed SR 2/10 relapsed SR 4/8 NR or PR

Key:

ADM: Amyopathic Dermatomyositis: Cutaneous findings for at least 6 months, without clinical or laboratory evidence of muscle disease

hDM: Hypomyopathic Dermatomyositis: Cutaneous findings with subclinical muscle disease (i.e. asymptomatic and normal exam with abnormal muscle enzymes and/or abnormal EMG)

pDM: Premyopathic Dermatomyositis: Cutaneous findings for less than 6 months, without clinical or laboratory evidence of muscle disease

CR-CDM: Cutaneous relapse of Classical Dermatomyositis (relapse involving only cutaneous manifestations, with previous muscle involvement)

ILD: Interstitial Lung Disease; TGC: topical glucocorticoids; TAC: topical tacrolimus; SGC: Systemic Glucocorticoids; CLQ: Chloroquine; HCQ: Hydroxychloroquine; MTX: Methotrexate; MMF: Mycophenolate Mofetil; AZA: Azathioprine; SR: significant response, defined by the investigators as a complete or near-complete response; NR: no response; PR: Partial Response.

inflammatory cytokine secretion [12]. Of particular interest, IVIG has been noted to have efficacy in steroid-resistant cases and has demonstrated efficacy in treatment of dermatomyositis [13]. Although expensive, its costs should be balanced with the long-term adverse effects of steroids, antimetabolites and calcineurin inhibitors. Additional adverse effects of IVIG include nephrotoxicity with high or repeated doses, however newer formulations appear to have a reduced incidence of renal toxicity, which make this a more appealing option [14].

CONCLUSION

Both our cases support the use of IVIG for ADM that is refractory to standard therapy, both with and without interstitial lung disease. Further data is needed to better understand the role and timing of IVIG in therapy of ADM.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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