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Authors
Manudhane, Albert P
Schrom, Kory P
Ezaldein, Harib H
et al.

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Low-dose naltrexone: a unique treatment for amyopathic dermatomyositis

Albert P Manudhane1 MD, Kory P Schrom2 MD, Harib H Ezaldein2,3 MD, James A Armile4 DO

Introduction
Amyopathic dermatomyositis (ADM) is a variant of dermatomyositis (DM) and occurs in approximately 20% of cases [1]. Amyopathic dermatomyositis is an autoimmune process that presents with typical cutaneous signs (Gottron papules, heliotrope rash) and symptoms (pruritus, fatigue), but lacks the pathognomonic proximal muscle weakness of typical DM [2]. Treatments range from topical corticosteroids to oral immunosuppressants and immunomodulators. These treatments, however, come with many adverse side effects and are not uniformly effective [3]. Recently, several case reports have demonstrated the efficacy of low-dose naltrexone in multiple autoimmune, dermatologic conditions (Hailey-Hailey disease, alopecia areata, lichen planopilaris) including dermatomyositis. Herein we report the use and efficacy of low-dose naltrexone in the treatment of ADM in one patient [4-7].

Case Synopsis
A 56-year-old man presented with Gottron papules, a heliotrope rash, periungual changes, holster sign, scalp erythema, and generalized pruritus. Past medical and social histories were non-contributory. Pertinent negatives included the absence of clinically significant proximal muscle weakness and pain. A punch biopsy of lesional forearm skin was performed and treatment was initiated with clobetasol shampoo for the scalp and hydrocortisone 2.5% ointment for other affected areas.

Two weeks after initial evaluation, there was no noticeable improvement in his condition. Blood tests showed positive (1:640) speckled pattern ANA and elevated lactate dehydrogenase (LDH), (258 IU/L, normal range 121-224 IU/L). Creatine kinase and aldolase were within normal limits. An extractable nuclear antigen assay was negative for all components — SSA, SSB Sm, nRNP, Scl-70, and Jo-1. Laboratory evaluation for anti-MDA5, anti-TIF1γ, and anti-NXP2 antibodies was not performed owing to high cost and lack of local availability. The skin biopsy demonstrated interface dermatitis and mucin
deposition highly suggestive of connective tissue disease (Figure 1). Given current diagnostic recommendations, a clinical diagnosis of ADM was made based on the clinical picture and the corresponding laboratory and pathologic findings. The differential diagnosis included lichenoid drug eruption or photoeruption, but were less likely given the clinical presentation and lack of offending medications. Lung cancer screening completed via chest X-ray was deemed negative. Topical treatment was discontinued and prednisone 50mg by mouth was initiated.

Symptoms improved initially; however, flaring occurred with steroid tapering. Therefore, at his two-month follow up, the patient was started on oral hydroxychloroquine 200mg daily and prednisone was discontinued. Hydroxychloroquine was started at a lower dose because the patient was an optometrist and was nervous about visual side effects. Weekly methotrexate, 20mg subcutaneously, was then added to the treatment regimen four weeks later in an effort to enhance and hasten therapeutic success. During this time, the lesions became more prominent and symptoms worsened. Increased severity of symptoms despite treatment with hydroxychloroquine and methotrexate prompted the search for additional treatment options.

Our patient eventually brought to our attention low-dose naltrexone as a potential therapeutic option. He had learned of low-dose naltrexone through reports of its use in other autoimmune, dermatologic disorders [4-6]. Notably, there have been two cases reported of successful DM treatment with low-dose naltrexone [7]. Because of his finding and his interest in adding it to his therapeutic regimen, low-dose naltrexone was added.

The patient was started on 1.5mg/day of low-dose naltrexone and methotrexate was stopped. Within a month, the scalp pruritus and burning sensation resolved and facial erythema became less apparent. The low-dose naltrexone dose was gradually titrated to 4.5mg/day and hydroxychloroquine was stopped. Lesions on his elbows, hands, and knees continued to improve in the months thereafter. At this time, the patient is maintained on 4.5mg of daily low-dose naltrexone and now has mild erythema of the hands and knuckles that continues to improve. Figure 2 demonstrates our patient’s response to therapy.

**Figure 1. Amyopathic dermatomyositis. Sections from a punch biopsy specimen show A) subacute interface dermatitis with squamotization of the epidermal basal layer, intrabasal lymphocytes and occasional necrotic keratinocytes. (H&E; 20×) B) There is a marked increase in reticular dermal mucin. (H&E; 20×).**

**Case Discussion**

Amyopathic dermatomyositis is an uncommon variant of DM that occurs in approximately 20% of DM cases [1]. Dermatomyositis and ADM are connective tissue diseases that classically present with Gottron papules,shawl sign, facial erythema, periorbital swelling, periungual telangiectasias, photosensitivity, arthralgia, and Raynaud phenomenon [2]. Amyopathic dermatomyositis,
however, lacks the clinically relevant muscle involvement and weakness of traditional DM. If muscle involvement develops, it typically will happen within the first decade after diagnosis and is identified because of symptom presentation and/or elevated muscle enzymes. Amyopathic dermatomyositis may be idiopathic but may also be a sign of an underlying malignancy. A Swedish study based on population data determined that DM has an associated malignancy rate of 15% [1]. In addition to malignancy, DM has also been associated with pulmonary fibrosis [2].

Insight into disease pathogenesis remains elusive; however, certain disease markers have been identified. The proteins Jo-1, Mi-2, and TIF1 may be elevated and are associated with developing autoimmunity following environmental triggers. Specific autoantibodies are also associated with ADM: anti-CADM-140 and anti-p155. Anti-CADM-140 inhibits MDA5 RNA helicase, a protein offering protection against viral infection, implicating a link between viral infection and ADM. The autoantibody anti-p155 inhibits TIF1 and has been detected in up to 58% of individuals with ADM and concurrent cancer [8]. The gold standard to detect these antibodies is an immunoprecipitation assay; however, it can be cost-prohibitive and not suitable for routine use in a clinical setting [9].

Once diagnosed, ADM treatment is variable. Topical therapies can be used for cutaneous lesions, but a systemic approach with corticosteroids, methotrexate, cyclosporine, azathioprine, rituximab, and/or hydroxychloroquine is often required [3]. Two cases of DM treated with low-dose naltrexone have been reported in the literature [7]. Likewise, the efficacy of low-dose naltrexone has been reported in other autoimmune, dermatologic diseases (alopecia areata, Hailey-Hailey disease, and lichen planopilaris), [4-6]. Traditionally, low-dose naltrexone dosing ranges from 1-4.5mg/day, whereas standard naltrexone dosing ranges from 50-100mg/day and is used for the treatment of opioid and alcohol dependency, initial FDA indications for naltrexone [4].

Mechanistic insight into the efficacy of low-dose naltrexone is still limited, but a few mechanisms have been proposed. Low-dose naltrexone administration increases beta endorphin (BE) levels and high levels of BE are associated with lower erythrocyte sedimentation rates, implying a reduced systemic inflammatory state [10]. Low-dose naltrexone may also work through its blockade of toll-like receptor 4 (TLR4). When blocked, TLR4 cannot stimulate the release of inflammatory cytokines and other mediators (substance P, nitric oxide, and excitatory amino acids) by astrocytes, macrophages, and microglia [11]. This lack of TLR4-mediated cytokine and mediator release results in anti-inflammatory effects [12].

The importance of this case lies in its support for the treatment efficacy of low-dose naltrexone in autoimmune dermatologic disease. Seeing efficacy in more than one disease state, whether dermatologic or not, adds validity to the idea that low-dose naltrexone is actually having an effect and that the recent reports are not simply a coincidence. Additionally, low-dose naltrexone adds a possible low-cost, limited-side-effect treatment option for our patients, which should be considered. Further research is clearly required to understand why low-dose naltrexone may be effective; however, the rarity of many autoimmune, dermatologic diseases creates a major challenge for researchers.

**Conclusion**

Patients with amyopathic dermatomyositis require treatment for their debilitating signs and symptoms, but current treatments have many adverse side effects, which make them inadvisable or undesirable...
to patients and practitioners. Low-dose naltrexone has emerged as an alternative treatment option for patients owing to its efficacy and limited toxicity as seen in the treatment of several autoimmune dermatologic conditions including our case of ADM [4-7]. The evidence for safety and efficacy, however, is still limited and further evaluation through well-designed research is required. Before starting a patient on low-dose naltrexone, a robust discussion of risks and benefits between patient and provider should be performed.

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Potential conflicts of interest
The authors declare no conflicts of interests.

References