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Treatment option intravenous immunoglobulins

Assist. Prof. Jan Ehrchen, M.D., Ph.D.
Head, Autoimmune Diseases

Nina Magnolo, M.D., Ph.D.
Head, ZID Study Center

Department of Dermatology
Münster University Medical Center

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Introduction

Dermatomyositis is a rare systemic autoimmune disease.[1] The eponymous involvement of the skin and muscles is characteristic; in addition, many patients exhibit specific autoantibodies, the identification of which has an important prognostic impact.[2] Other organs such as the joints, heart, and lungs may also be affected and have a profound bearing on the prognosis of the disease. In addition, dermatomyositis may be paraneoplastic, specifically if certain autoantibodies are present.

Clinical presentation and diagnosis

The cardinal symptoms of dermatomyositis are weakness and sometimes pain of the proximal limb muscles along with typical skin lesions. When muscle involvement is pronounced, patients find it difficult to rise from a sitting position and/or to raise their arms above the shoulders. In cases of particularly severe symptoms of the leg muscles, patients may become dependent on a wheelchair. Often, the muscles for swallowing and breathing will also be affected. Magnetic resonance imaging and targeted muscle biopsy are recommended to assess muscle involvement. In addition, cardiac symptoms, such as pericarditis and dilated cardiomyopathy, are frequently reported in dermatomyositis. Pulmonary involvement, manifesting as interstitial lung disease, is particularly feared, and in some cases may progress quite rapidly. The latter is particularly likely if certain autoantibodies, e.g., MDA5 and anti-synthetase antibodies such as Jo-1, are present.[3]

Characteristic skin lesions include lilac-colored (livid) papules on the extensor aspects of the small finger joints (Gottron papules), livid erythema around the eyelids (heliotrope erythema), and partly macular, partly papular livid skin lesions around the cleavage and neck (V sign and scarf sign) and on the lateral proximal thighs (holster sign). Involvement of the hairy head is equally characteristic, often accompanied by marked pruritus, especially there.[1,4]

Skin biopsy is recommended. Dermatomyositis exhibits characteristic histologic changes, although these cannot be reliably differentiated from lupus erythematosus. Differential diagnosis should consider this, as pathophysiologically and clinically, lupus erythematosus resembles dermatomyositis.

Amyopathic dermatomyositis may also present without demonstrated musculoskeletal involvement. Again, in addition to the skin, internal organs may also be involved and there may be tumor association as well. Appropriate thorough diagnostic organ workup is therefore urgently indicated in these cases, too.

Marked pathologies, especially capillary ectasia and hemorrhage, are often seen around the nail fold capillaries of the fingers. These changes can often be seen with the naked eye, but are best assessed by capillary microscopy.

Diagnostic lab panels typically reveal elevated muscle enzymes (creatine kinase, AST, LDH), but may be absent in active myositis. A key diagnostic factor is the finding of myositis-specific autoantibodies (e. g., anti-Mi2, anti-Jo-1, anti-TIF-1-gamma, anti-NXP2, anti-MDA5, anti-SRP). In addition to myositis-specific autoantibodies, myositis-associated autoantibodies (e. g., anti-Ro 52 antibodies) are also found, but their diagnostic significance is more limited. Myositis-specific autoantibodies have important prognostic significance (e. g., tumor association when TIF-1-gamma antibodies are present, risk of pulmonary fibrosis when MDA5 antibodies and anti-synthetase antibodies are found, and calcinosis when NXP2 antibodies are detected).[5] When dermatomyositis is suspected, a comprehensive diagnostic autoantibody workup should always be performed (e. g., myositis blot).[2]

If dermatomyositis is diagnosed or suspected, contacting a specialized rheumatology, neurology, or dermatology center is recommended for this rare condition.

Case 1

Figure 1 shows the skin lesions of a 50-year-old female patient in the fall of 2017 who had been undergoing our treatment since 2012. The patient had the typical cutaneous symptoms of dermatomyositis, and histology confirmed this suspected diagnosis. Over the course of the patient's disease, the myositis-specific autoantibody TIF-1-gamma was identified. Due to the tumor association of this antibody, appropriate screening was performed which did not reveal any evidence of malignancy. In addition to the cutaneous symptoms, the patient complained of myofascial pain and temporary weakness of the proximal limb muscles, but neither imaging nor muscle biopsy could unequivocally confirm muscle involvement. The patient was treated with hydroxychloroquine 5 mg/kg body weight, azathioprine 2–2.5 mg/kg body weight, and local and internal corticosteroids. Even with high-dose systemic steroids (short-term up to 1 mg/kg body weight oral prednisolone as well as intrave-

nous steroid pulse therapy with 100 mg dexamethasone), the skin condition did not improve significantly. Therefore, in the fall of 2017, the patient decided to enroll in the ProDerm trial studying additive administration of intravenous immunoglobulins (IVIG, octagam® 10 %, 2 g/kg body weight every 4 weeks for 16 weeks) in patients with active dermatomyositis. The skin findings improved markedly under IVIG therapy (Figure 1 D), as did the myofascial pain symptoms.

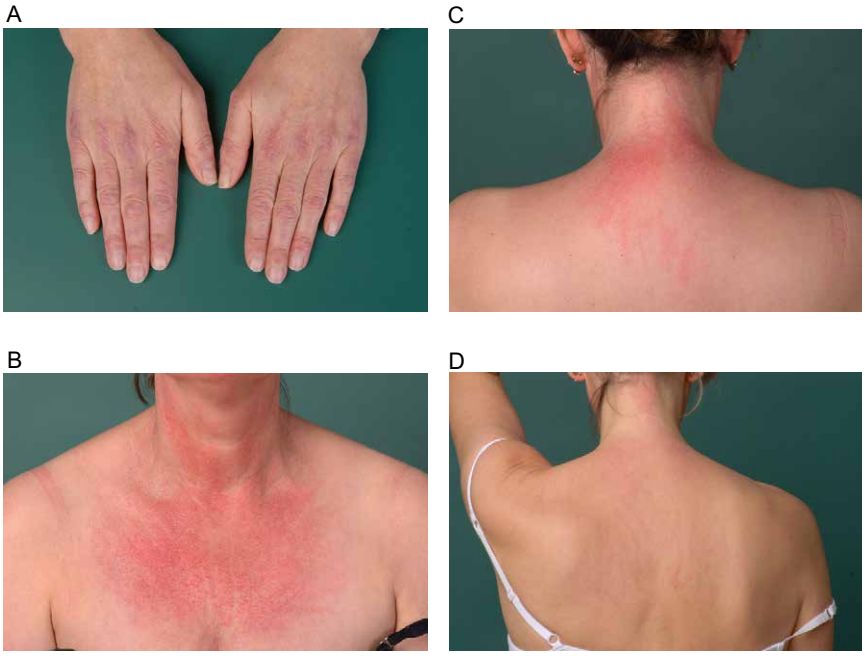
Case 2

In July 2009, a 56-year-old male patient presented at our clinic with painful, marked swelling of the right leg (Figure 2 B). Ultrasonography has already ruled out potential deep venous thrombosis of the leg. Further clinical workup revealed livid scalp erythema (Figure 2 A), and lab panels showed marked CK elevation (1300 mg/dl) and finely speckled low-titer ANA (1:80) without evidence of specific autoantibodies. Workup also included a skin biopsy, which was consistent with dermatomyositis and concomitant lobular panniculitis. Magnetic resonance imaging demonstrated muscle edema of the upper and lower leg, consistent with active myositis. No specific changes were seen in the muscle biopsy performed. An extensive follow-up examination revealed no evidence of malignancy. We diagnosed dermatomyositis with skin and muscle involvement and and marked fatty tissue involvement in unusual locations.

High-dose steroid therapy was initiated, but despite repetitive i.v. administration of 1000 mg prednisolone, progressive muscle weakness with loss of ambulation, additional dysphagia, and massively elevated CK levels up to 20,000 U/l developed. For this reason, an initial single-shot regimen of 1000 mg cyclophosphamide was administered, followed by an additive regimen of IVIG (2 g/kg body weight distributed over 5 days). Within a few weeks, this treatment resulted in marked improvement and eventual normalization of the muscle enzymes, notable recovery of the muscle weakness, and almost complete healing of the cutaneous lesions (Figure 2 C). For 11 years, the disease remained stable under immunomodulation with methotrexate subsequently switched to ciclosporin due to intolerance. The patient reports that his muscle strength has returned to approximately 95% of baseline.

Summarizing assessment

The cases presented here show the broad clinical spectrum of dermatomyositis, which ranges from symptoms largely confined to the skin to massive muscle involvement. Moreover, it also requires extensive diagnostic workup to rule out involvement of other organs, such as the heart and lungs, as well as malignancy. In order to avoid irreversible damage, particularly in patients with pronounced muscle involvement, it is crucial to achieve fast control of disease activity by rapidly effective initial treatment. In addition to high-dose cortisone, an IVIG preparation (octagam® 10 %) has also been approved since May 2021 for active dermatomyositis treated with immunosuppressants.

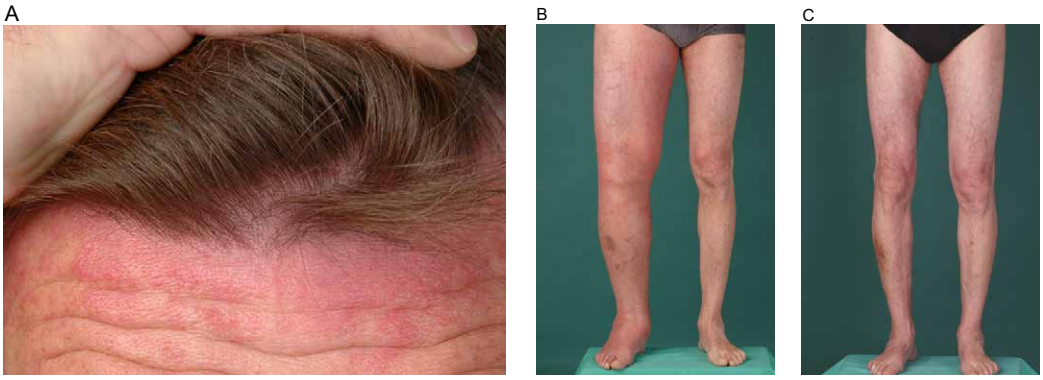


1. Characteristic skin lesions in dermatomyositis
Gottron papules (A), V sign (B), scarf sign (C), and therapeutic response after 4 months (D).

Treatment

Treatment with immunomodulatory drugs is mostly empirical.[4] Initial first-line treatment to achieve disease control is with systemic steroids. Typical dosing here are 1–2 mg/kg body weight oral prednisolone or 500–1000 mg intravenous methylprednisolone for 3 days. Initial oral steroid therapy is maintained for 2–4 weeks or until clinical symptoms improve and then cautiously tapered down. Depending on the response, intravenous pulse therapy may be repeated after 2–4 weeks.

Glucocorticoids should be dosed below the Cushing threshold after 6 months at the latest. The German guideline recommends additional basic medication if it becomes evident after 3 months at the latest that glucocorticoid therapy alone will not be successful.[4] Given the markedly delayed onset of action of steroid-sparing baseline therapeutics, some experts, including the authors of this paper, prefer to initiate baseline treatment concurrently with the initiation of steroid therapy. The most common baseline medication used is azathioprine dosed at 2–3 mg/kg body weight. Thiopurine methyltransferase (TPMT) activity should be measured prior to treatment in order to best tailor the azathioprine dose. In any case, regular lab panels are needed because the hepatic side effects are independent of the TPMT activity. From the dermatological perspective, consistent sun protection is mandatory as there is a markedly increased risk of skin tumors. Concomitant medication with azathioprine and allopurinol must be avoided.



2. Dermatomyositis-associated panniculitis (A, typical lilac-shaped erythema at the hairline) and massive swelling of the right leg in a 56-year-old patient (B); therapeutic response after 6 months (C).

The prime therapeutic alternatives besides azathioprine are methotrexate and mycophenolate mofetil. Since there are no comparison studies on the efficacy of these therapeutics, the choice depends on the individual risk factors of the patients.

If this course of treatment does not control the disease, the German guideline recommends the additive administration of IVIGs. An IVIG approved for the treatment of this disease (octagam® 10%) has been available since May 2021. The approval was based on the pivotal international multicenter ProDerm trial (GAM10-08, EUDRA CT 2016-002902-37), in which 95 adult patients with active dermatomyositis on at least 4 weeks of stable baseline immunomodulatory therapy were randomized 1:1 to IVIG (2 g/kg body weight) or placebo.[6] The achieved primary objective of the study was an improvement in the total improvement score (TIS) by at least 20 points after 16 weeks. The TIS represents response according to the ACR/EULA (American College of Rheumatology/European League Against Rheumatism) criteria published in 2016. Outcomes of the trial (NCT02728752) were presented at the annual meetings of the American and European specialty societies ACR 2020 and EULAR 2021. After 16 weeks, 78.8% of patients on IVIG experienced a treatment response compared with 43.8% of controls. This difference was statistically highly significant (p = 0.0008). Safety and tolerance of IVIG therapy were consistent with the treatment profile known from other indications.

Other third-line options in the initial treatment of dermatomyositis include individualized curative regimens with cyclophosphamide, B-cell-depleting antibodies, or, especially in associated rapidly progressive interstitial lung disease[3], Janus kinase inhibitors.

Long-term treatment of the disease generally aims for the lowest possible dose of the immunomodulatory medication administered.

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Contact

■ **Assist. Prof. Jan Ehrchen, M.D., Ph.D.**
Head, Autoimmune Diseases
Nina Magnolo, M.D., Ph.D.
Head, ZID Study Center
Department of Dermatology
Münster University Medical Center
Von-Esmarch Straße 58
48149 Münster, Germany
www.ukm.de

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