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REVIEW ARTICLE

Dermatomyositis: An Update on Diagnosis and Treatment

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Abstract
Dermatomyositis is a rare inflammatory disease with characteristic cutaneous findings and varying amounts of systemic involvement. Patients may present with skin disease alone, have concomitant muscle disease, or have extracutaneous manifestations such as pulmonary disease or an associated malignancy. Given such diverse presentations, dermatomyositis is both a diagnostic and therapeutic challenge. However, a prompt diagnosis is of utmost importance to institute adequate therapy and screen patients for an associated malignancy. Dermatologists should play a crucial role in the diagnosis and management of patients with dermatomyositis as cutaneous disease tends to be chronic, negatively impact quality of life, and be more recalcitrant to therapy. In this review, we discuss diagnosis, with a focus on myositis-specific antibodies and their associated phenotypes. We also review therapies available for this often refractory skin disease.

Key Points

Myositis-specific autoantibodies are associated with characteristic clinical features and can alert physicians to potentially associated systemic manifestations.

The skin disease of dermatomyositis can be particularly challenging to manage.

Treatment must be personalized depending on patient comorbidities and preference, risk–benefit ratio, and the presence of any associated internal manifestations.

1 Introduction

Dermatomyositis (DM) is an idiopathic multi-system inflammatory condition. Adult DM, which affects women more than men, remains a rare disease with an annual incidence of 1 per 100,000 persons, though incidence may be increasing [1–4]. While the exact pathogenesis of DM is still not fully elucidated, studies have shown abnormal and upregulated signaling through the interferon pathway [5, 6].

Classic DM (CDM) presents with pathognomonic cutaneous findings and progressive, symmetric proximal muscle weakness. Cutaneous disease precedes the appearance of myositis by 3–6 months in 30–50% of patients, while 10% of patients present with muscle symptoms prior to the development of skin findings [7, 8]. There is a subset of patients with DM (approximately 20%) who have a skin-predominant phenotype and are classified as clinically amyopathic DM (CADM) [1, 4, 9, 10]. Of note, the diagnosis of CADM is provisional at 6 months and confirmed at 2 years [10], and encompasses both amyopathic DM and hypomyopathic DM. In a large review of 291 patients with CADM, 70% had amyopathic DM and 13% had hypomyopathic DM [11]. Although both of these subtypes have no clinical evidence of muscle involvement, there is subclinical evidence of muscle involvement demonstrated on laboratory, electrophysiologic, or radiologic evaluations in the hypomyopathic variant [1, 9, 12]. Both patients with CDM and patients with CADM have an elevated risk of developing interstitial lung disease and occult malignancy [11, 13, 14]. Post-myopathic DM refers

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to a subset of patients who have resolution of their muscle involvement with therapy, but have persistent cutaneous disease [8, 11].

Dermatologists should play an integral role in the diagnosis and management of patients with DM as cutaneous involvement is evident in all DM subtypes, often persists after successful treatment of muscle disease, and can greatly impact quality of life [8, 15]. The course of cutaneous disease tends to be chronic and prolonged. A prospective cohort of 74 patients with DM receiving various systemic regimens found that only 38% had achieved remission of skin disease in a 3-year follow-up period [16]. With regard to CADM specifically, the role of dermatologists is crucial as many providers have difficulty recognizing DM in the absence of muscle involvement, which often leads to misdiagnosis and contributes to delays in treatment and an appropriate initial workup [11, 13, 17]. Da Silva et al. found the median delay to correct diagnosis was 17.1 months in patients with CADM, which was significantly higher than patients with CDM (12.2 months) [17]. This delay is clinically relevant, particularly with regard to adequately screening patients for malignancy given that the risk is highest in the first 2 years after symptom onset [14, 18, 19].

2 Diagnosis

Given DM's protean manifestations, a detailed physical exam is at the cornerstone of making the correct diagnosis. The cutaneous features of DM include the pathognomonic findings of Gottron's papules (pink-violaceous papules on the dorsal hands, with a predilection for the skin overlying the metacarpophalangeal and interphalangeal joints) and heliotrope eruption (pink-violaceous erythema involving the upper eyelids, at times accompanied with edema) [7]. Other characteristic findings are Gottron's sign (macular erythema or pink-violaceous papules overlying joints), photodistributed pink-violaceous erythema or poikiloderma of the upper back ("shawl" sign) and anterior neck and upper chest ("V" sign), and nailfold abnormalities (periungual erythema, dilated capillary nail bed loops with alternating areas of drop out, and cuticular hypertrophy) [3, 7]. Patients often also have midfacial erythema involving the nasolabial folds, unlike the malar erythema of acute cutaneous lupus erythematosus, which spares the nasolabial folds. Additional cutaneous findings of DM include pink-violaceous scaly erythema or poikiloderma of lateral thighs ("holster sign") and scalp involvement (erythema and psoriasiform scaling, often with associated non-scarring alopecia), amongst others. Of note, scalp involvement can be extremely symptomatic and scalp dysesthesia may occur in patients without evidence of an eruption [7].

Expert clinicians can usually arrive at a correct diagnosis of DM with a physical exam alone. However, a skin biopsy may be helpful if findings on exam are subtle or atypical. Skin biopsy demonstrates a vacuolar interface dermatitis with dermal mucin deposition. Physicians should be aware that these findings are also seen in lupus erythematosus. Hence, these two entities are difficult to distinguish on histology alone [20].

When evaluating muscle disease, a detailed history with pointed questions (difficulty combing hair, getting out of a seated position, difficulty swallowing, change in voice) and strength testing of muscle groups should be performed at each clinic visit. Muscle enzymes should be trended periodically for the first 2 years. When the clinical diagnosis is in question, or when the patient has normal muscle enzymes in the presence of clinical weakness, additional investigations may be warranted, including magnetic resonance imaging or ultrasound of proximal muscles, electromyography, or muscle biopsy [3, 21].

Patients should be screened regularly for pulmonary symptoms given the prevalence of interstitial lung disease (ILD) in 5–35% of patients with DM [22–27]. A thorough review of symptoms (cough, shortness of breath, dyspnea on exertion) is necessary at each clinic visit. Evaluation with pulmonary function tests with a diffusion capacity for carbon monoxide are warranted at baseline [28, 29]. If the pulmonary function tests demonstrate abnormal findings, a high-resolution chest computed tomography scan with an ILD protocol should be performed. Pulmonary function tests should be repeated every 3–12 months, depending on the initial findings and the risk of ILD in a particular patient (e.g., high-risk subtype) [30].

Myositis-specific autoantibodies (MSAs) are found only in patients with idiopathic inflammatory myopathies (DM, polymyositis, inclusion body myositis, and necrotizing myopathies). In recent years, more studies have focused on identifying MSAs in DM and describing their associated phenotype. The majority of patients with DM only have one MSA [31, 32], and only approximately 20% of patients with DM have a known MSA [33]. The gold standard for detection of MSAs is the immunoprecipitation assay, which is not widely available and lacks standardization, currently limiting the practical use of these antibodies [26].

It is important for clinicians to recognize the specific MSA-associated phenotypes as these can help with prognostication, alerting the clinician of systemic manifestations that are more likely in a patient. Despite the usefulness of the MSA-associated phenotypes, there is a considerable overlap of clinical features amongst some of the MSA groups [31].

- Mi-2 antibody: The prevalence of Mi-2 antibodies in adult patients with DM ranges from 2 to 38% [33, 34]. Patients present with classic skin findings and myositis

and have a decreased incidence of both ILD and malignancy compared with other patients with DM [33–36]. Overall, patients have a favorable prognosis and respond well to therapy [33, 37]. Longitudinal clinical monitoring is warranted as patients often have recurrence of disease with cessation of therapy [33].

- Anti-SAE1/2 antibody: The prevalence of anti-SAE1/2 autoantibodies ranges from 1 to 10% [26, 31, 32, 38]. These patients tend to have classic cutaneous findings, myositis, and dysphagia [22, 25, 39–41]. Several cohorts have reported a novel diffuse red-violaceous exanthem, which may ulcerate [22, 39–42]. An increased risk of mild ILD and malignancy in patients with anti-SAE1/2 antibodies has been reported, but only in small cohorts to date, warranting further investigation [22, 25, 40, 41]. Interestingly, four patients with anti-SAE antibodies in Asian cohorts have had pulmonary arterial hypertension that could not be attributed simply to the degree of ILD [40, 41]. This also warrants additional investigation.
- Anti-aminoacyl-transfer RNA synthetase (ARS) antibodies: Eight anti-ARS autoantibodies (anti-Jo-1, anti-OJ, anti-EJ, anti-KS, anti-Zo, anti-Ha/YRS, anti-PL-12, and anti-PL-1) have been associated with the anti-synthetase syndrome. Anti-Jo-1is the most common, with prevalence as high as 20% [31, 43]. The clinical presentation of anti-synthetase syndrome is quite heterogeneous and varies by anti-ARS antibody [44]. The "classic" clinical triad consists of ILD, myositis, and arthritis. Other associated features include fever, Raynaud's phenomenon, and mechanic's hands (dry, fissured, hyperkeratotic skin on the lateral and palmar hands and fingers). A Japanese cohort noted that the majority of their patients with the anti-ARS antibody who initially presented with only myositis later developed ILD, emphasizing that longitudinal monitoring is necessary [43]. For patients who develop ILD, the overall prognosis is favorable, with a 5-year-survival rate of 96% [45].
- Anti-melanoma differentiation antigen 5 (MDA-5) antibody: These autoantibodies, which are more prevalent in Asian (11–57%) compared with Caucasian (0–13%) cohorts [31, 46], convey an increased risk of developing ILD, including a rapidly progressive variant with high mortality [26, 27, 47]. One group reported a 90-day survival rate of only 66% for MDA-5-positive patients with ILD. In contrast, patients with ILD and anti-ARS antibodies had a survival rate of 100% [45]. Patients with MDA-5 DM have a higher prevalence of amyopathic disease (50–77%), fevers, and inflammatory arthritis [24, 27, 31, 33, 48]. Fiorentino et al. described a characteristic cutaneous phenotype in patients with MDA-5-positive DM, including painful erythematous palmar papules and macules (Fig. 1), cutaneous ulcerations of the digital pulp, nailfolds, and over the Gottron's papules and sign, oral erosions, prominent non-scarring alopecia, and mechanic's hands [24, 27]. These patients tend to have severe skin disease that is less likely to achieve clinical remission despite systemic therapy [16].

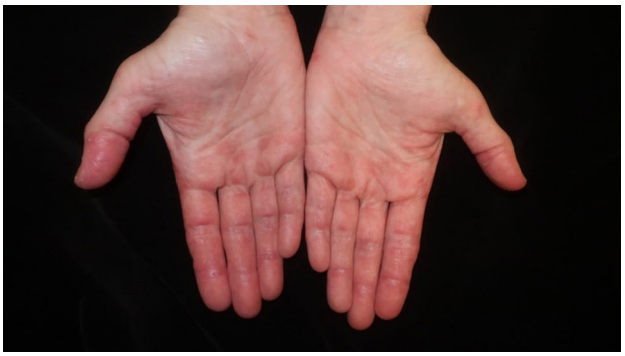

Fig. 1 Patient with MDA-5 dermatomyositis with tender erythematous papules and macules on palms and interphalangeal creases

- Anti-TIF-1γ antibody: These autoantibodies are more prevalent in Caucasian (41%) compared with Asian (17%) cohorts [32, 49–52]. Although there is a well-established association of malignancy in patients with anti-TIF-1γ antibodies, the risk may be influenced by several factors including male sex, older age, and smoking [26, 33, 49, 53–55]. Ethnicity may also be a factor, but more studies are necessary to validate this observation [49]. Patients with anti-TIF-1γ antibodies tend to have clinical evidence of myositis and lower prevalence of ILD, Raynaud's phenomenon, and arthralgias [33, 49]. Patients tend to have severe cutaneous disease, albeit with a decreased risk of calcinosis cutis [49, 53]. In addition to the classic photodistributed eruptions, these patients may also have asymptomatic hyperkeratotic papules on the palms, psoriasiform lesions (Fig. 2), hyperkeratotic Gottron's papules, red-on-white lesions (hypopigmented patches admixed with focal, often follicular, telangiectatic macules), and an ovoid palatal patch [49, 56].
- Anti-NXP2 (MJ) antibody: The prevalence of anti-NXP2 autoantibodies in adult patients with DM ranges from 2 to 30% [57]. Patients with anti-NXP2 antibodies often present with severe recurrent myalgias, both proximal and distal weakness, and severe dysphagia [57, 58]. Although patients have milder cutaneous findings, unique to their presentation is increased peripheral edema and calcinosis cutis [57–59]. Patients with NXP2-positive DM are also at an increased risk of developing malignancy, while the prevalence of ILD in this population is decreased compared with other patients with DM [31, 39, 58, 60, 61].

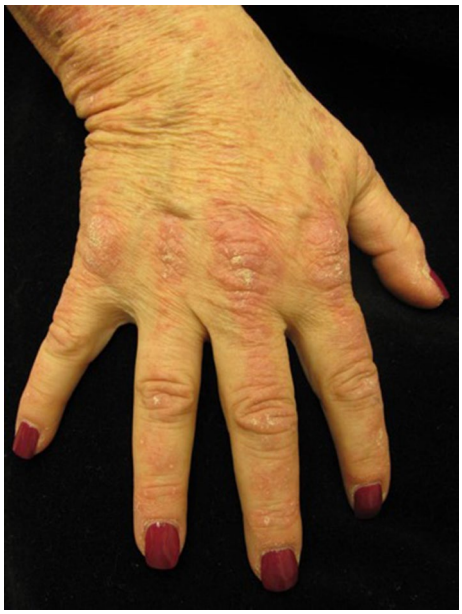

Fig. 2 Patient with TIF-1γ dermatomyositis with Gottron's papules with psoriasiform scale on the metacarpophalangeal, proximal, and distal interphalangeal joints

Importantly, MSAs are currently used to phenotype and stratify patients with DM rather than to make the diagnosis, given that they are only present in approximately 20% of patients with DM. When present, MSAs can serve to help confirm a diagnosis of DM. Presently, there are insufficient data to make formal guidelines regarding how to use MSAs to guide clinical management. However, with data from larger prospective cohorts and a standardized method of detection, there is potential to use MSAs to optimize management strategies in patients with DM.

Once DM is diagnosed, a thorough screening for internal malignancy is warranted. Multiple studies have substantiated that adult patients with DM have an elevated risk of malignancy, although the frequency (9–42%) and type of malignancy vary greatly in different studies [14, 18, 61–65]. A retrospective study of a US cohort of 400 patients with DM reported the risk of malignancy to be 12%, with no significant difference between CDM and CADM subtypes [14]. A meta-analysis found that several factors (older age, male sex, cutaneous necrosis, cutaneous vasculitis, dysphagia, elevated Erythrocyte sedimentation rate (ESR), and rapid onset of myositis) were associated with an increased malignancy risk and also found the presence of interstitial lung disease, arthralgia, and Raynaud's phenomenon to be protective [66]. As noted above, both anti-TIF-1γ and anti-NXP2 antibodies convey an increased risk of malignancy [66, 67]. Further studies are needed to determine whether these clinical factors and antibodies can be used to stratify patients with DM based on their malignancy risk, but at present, malignancy screening is recommended for all adult patients diagnosed with DM [14].

3 Management

Each patient with DM requires an individualized therapeutic plan that takes into account the cutaneous disease severity, presence of concomitant muscle disease, systemic involvement, other comorbidities, including underlying malignancy, and the overall impact of disease on a patient's quality of life. With regard to skin disease specifically, the treatment goal is to obtain control of cutaneous disease with the safest combination of therapeutics.

The treatment of skin disease in DM can be particularly challenging, given that cutaneous DM is often more recalcitrant to treatment than the muscle involvement in DM [2, 68]. Despite this challenge, clinicians should strive to optimize the treatment of cutaneous disease as the associated pruritus, photosensitivity, and appearance of skin lesions can significantly impact quality of life [12, 15, 69].

The majority of data for the treatment of cutaneous DM comes from expert opinion, case series, retrospective reviews, and open-label studies. There is a paucity of randomized controlled trials. Additionally, interpretation of the available literature is difficult owing to several factors in existing studies including: pooling of various inflammatory myopathies (i.e., polymyositis and DM), lack of use of a standardized measure (i.e., Cutaneous Dermatomyositis Disease Area and Severity Index [CDASI] or Dermatomyositis Skin Severity Index [DSSI]) to assess cutaneous response to therapy, primary focus on resolution of myositis, and concomitant administration of immunosuppressive therapies for muscle disease [70–72]. Despite these limitations, several management principles can be established.

3.1 Initial Management

First-line therapy should include aggressive photoprotection, antipruritic agents, and topical anti-inflammatory medications (corticosteroids and calcineurin inhibitors). A minority of patients can achieve remission of their cutaneous disease with these interventions alone. In the vast majority of patients with DM, these therapies should be used as adjunctive therapies to systemic agents given the refractory nature of DM skin disease.

3.2 Photoprotection

It is well established that ultraviolet light can induce or flare cutaneous DM; therefore, strict photoprotection is necessary [12, 68, 73, 74]. Patients should be counseled on the need to practice sun protection on a year-round basis, not only

during the summer months. A broad-spectrum sunscreen (with a sun protective factor of at least 50) should be used daily and reapplied every 2 h [2, 68, 75]. Sun avoidance, wide-brimmed hats, and sun-protective clothing should also be strongly encouraged. Given the level of photoprotection recommended, clinicians should consider the assessment of vitamin D levels and provide supplementation if needed.

3.3 Antipruritic Agents

Pruritus is often a debilitating feature of DM that can negatively impact a patient's quality of life, alter sleep patterns, and interfere with activities of daily living [15, 69, 76]. Aggressive management with a combination of proper skin care with bland emollients to minimize xerosis, oral antihistamines, and other anti-pruritic agents such as amitriptyline or gabapentin may be used [68, 74]. Immunosuppressive therapy may be warranted for intractable pruritus, even in the case of what may appear to be mild skin disease [74]. Elevated levels of interleukin-31 have been implicated in DM-associated itch, and lenabasum (JBT-101) is a non-psychoactive cannabinoid that suppresses interleukin-31 levels [77]. In a phase II study and open-label extension of patients with DM with skin-predominant refractory disease, lenabasum-treated subjects had a clinically significant decrease in CDASI activity scores and improvement in multiple patient-reported outcomes [78, 79].

3.4 Topical Therapy: Corticosteroids and Calcineurin Inhibitors

Topical therapy can serve as adjunctive treatment, but very rarely controls cutaneous disease as monotherapy [68]. Topical corticosteroids can be used to decrease erythema and pruritus. The strength and vehicle selected for topical corticosteroids depend on the site of application and patient preference. Stronger topical corticosteroids (group I and II) are generally reserved for areas with thicker skin such as the scalp, hands, and extensor surfaces, while lower potency topical corticosteroids (group VI and VII) can be used on thinner areas more prone to atrophy, such as the face. Use of high-potency corticosteroids under occlusion can increase efficacy, particularly for the dorsal hands [8].

Topical calcineurin inhibitors include tacrolimus and pimecrolimus. While data are mixed regarding their efficacy for cutaneous DM, most studies have found a positive effect [80–85]. An advantage of topical calcineurin inhibitors is that they can be used on areas with thinner skin without the risk of atrophy. Patients should be warned regarding the local side effect of burning with initial application, although these symptoms usually abate with repeated use [86, 87].

4 Systemic Therapy

As noted above, most patients with cutaneous DM require systemic medications. The choice of systemic agent should be tailored for each patient and is dependent on the presence of other manifestations of DM, predominantly myositis or lung involvement. Here, we focus on the therapies used most commonly in clinical practice for cutaneous DM in adult patients.

4.1 Antimalarials

For many years, antimalarials [hydroxychloroquine (HCQ), chloroquine (CQ), and quinacrine] have been the preferred initial treatment for cutaneous DM given their long history of use and overall tolerability. Although their exact mechanism of action is unknown, antimalarials have an anti-inflammatory effect and are photoprotective [88]. In Europe, CQ is favored as it is thought to be more effective; however, in the USA, HCQ is preferred owing to the greater risk of irreversible retinopathy associated with CQ [8].

Multiple case series, retrospective reviews, and open-label studies have found antimalarials to be beneficial for skin manifestations of DM, but not for myositis [88–93]. Although one series of seven patients demonstrated a complete clinical response in 43% of patients with cutaneous DM [89], a more recent retrospective review of 115 patients at four tertiary care centers demonstrated that only 11% of patients with cutaneous DM responded adequately to antimalarial therapy without requiring escalation to additional agents [94]. Furthermore, up to one-third of patients with DM develop a cutaneous drug reaction, typically a morbilliform eruption, with initiation of HCQ [94, 95]. Some patients that develop a drug reaction to HCQ may progress to tolerating CQ [96]. One retrospective cohort study found that patients with anti-SAE-1/2 autoantibodies were at a higher risk of developing a drug eruption to HCQ, while no patients with anti-MDA-5 autoantibodies had a drug reaction [52].

If cutaneous disease is not adequately controlled with HCQ, combining it with quinacrine (100 mg daily), owing to a possible synergistic effect, or switching to CQ are options [8, 75]. A small retrospective study found that 7/17 patients (41%) had near clearance of cutaneous symptoms with use of antimalarial therapy alone (three were controlled with HCQ alone and four required a combination of either HCQ and quinacrine or CQ and quinacrine) [97]. Hydroxychloroquine and CQ should never be combined because of the additive ocular toxicity. Of note, for patients with severe cutaneous disease, the authors favor

adding methotrexate (MTX) to HCQ, rather than combining antimalarials or switching to CQ. In our experience, this provides a more robust response in patients with severe skin disease.

Based on recently updated guidelines from the American Academy of Ophthalmology, the total dose of HCQ should be less than or equal to 5 mg/kg/day based on actual body weight, while the total dose of CQ should be less than or equal to 2.3 mg/kg/day based on actual body weight [98]. The response to antimalarials is usually not evident until 6–8 weeks after initiation of therapy [8], or even up to 12 weeks. Hydroxychloroquine and CQ are usually well tolerated but can cause a gastrointestinal upset, hypersensitivity reactions, and blue-gray dyspigmentation [68, 88]. Rarer adverse effects include: transaminitis, bone marrow toxicity, neuropathy, myopathy, and cardiomyopathy [12, 88, 99]. Their most feared side effect is irreversible retinopathy; thus, patients taking HCQ or CQ need a baseline fundus examination and regular follow-up with ophthalmology [98]. Quinacrine does not cause ocular toxicity, but can cause a reversible yellow discoloration of the skin and, rarely, aplastic anemia [68]. In the USA, quinacrine is only available at compounding pharmacies.

4.2 Methotrexate

Methotrexate is an antimetabolite with both anti-proliferative (through inhibition of dihydrofolate reductase, which ultimately leads to inhibition of cell division) and anti-inflammatory (through inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase) properties. Inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase leads to increased levels of adenosine, which is a purine with potent anti-inflammatory effects [100].

Methotrexate is often considered a first-line systemic therapy for cutaneous DM, particularly in those patients who are recalcitrant to or intolerant of antimalarial therapy. Importantly, it is effective for both cutaneous and muscle disease, making it an excellent corticosteroid-sparing agent for CDM [101]. It also may help in patients with associated joint symptoms. The majority of data supporting the use of MTX for cutaneous DM originates from case series and retrospective reviews [102–107]. Most recently, Hornung et al. conducted a retrospective analysis of 11 patients with systemic corticosteroid-resistant cutaneous DM and found a 73% response rate to MTX as evident by a mean decrease in the CDASI score from 14.1 to 5.5 ($p < 0.1$) [107].

Although the side-effect profile (including nausea, fatigue, malaise, hepatotoxicity, bone marrow toxicity, pneumonitis, mucositis, teratogenicity, and reversible oligospermia) of MTX is well established, the incidence of adverse events (AEs) in patients with DM taking MTX is quite variable in the literature. For example, one series of 13 patients with DM had no reported AEs, but in a different series of ten patients with DM, 70% had AEs attributed to MTX and 50% required drug discontinuation [104, 105]. This can be at least partially explained by the lack of standardization pertaining to MTX administration (route, dosing schedule), different folic acid supplementation practices, and the comorbidities of patients included [106]. Thus, patients must be carefully selected, and several factors should be assessed when considering MTX, including the presence of metabolic syndrome, alcohol consumption, non-alcoholic fatty liver disease, use of hepatotoxic medications, liver and renal function, concomitant pulmonary disease, and family planning. Because MTX can rarely cause pulmonary toxicity, its use is typically avoided in patients with DM with lung involvement [108].

At the authors' institution, MTX is considered the first-line systemic agent considered for patients with CDM, patients with CADM intolerant of or recalcitrant to antimalarials, and patients with CADM with severe cutaneous disease at initial presentation. Patients are carefully screened and baseline laboratory studies (complete blood count with differential, blood urea nitrogen/creatinine, liver function tests, hepatitis serologies) are obtained. Methotrexate is often given in doses of 25 mg weekly for DM, with folic acid supplementation of 1 mg daily. At the authors' institutions, MTX is started at a dose of 10 mg/week, with follow-up laboratory studies drawn at 2 weeks. If results are normal, the dose is typically escalated to 25 mg/week. As absorption of MTX is decreased at doses higher than 15 mg/week, we often split the dose (12.5 mg twice daily) [109]. Subsequent laboratory monitoring is conducted in 4–6 weeks and then every 2–3 months if the MTX dose remains stable. Patients are made aware that similar to antimalarials, MTX takes at least 6–12 weeks of continuous therapy to have a noticeable effect [74].

4.3 Systemic Corticosteroids

Systemic corticosteroids (SCS) have remained the cornerstone of initial therapy for patients with DM with active muscle disease [101]. Prednisone is typically started at doses of 0.5–1 mg/kg/day, but if the muscle involvement is severe or life threatening, intravenous methylprednisolone may be necessary [110, 111]. Corticosteroids are maintained at higher doses until muscle disease is quiescent and then are slowly tapered over several months. Some dermatologists use corticosteroids as initial treatment for cutaneous disease when it is severe, as a bridge until the effect of other systemic medication is evident [8, 96].

The myriad of AEs associated with prolonged SCS use are well established. Additionally, cutaneous and muscle disease tend to have a discordant response to therapy and skin disease is often more recalcitrant [75, 93]. While SCS

may be necessary for DM-associated lung or muscle disease, their efficacy in cutaneous disease is more variable [12, 75, 112]. Therefore, the authors do not routinely use SCS as therapy for cutaneous disease unless there are concomitant extracutaneous DM manifestations that require their use.

4.4 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a lymphocyte-selective immunosuppressive agent that inhibits inosine monophosphate dehydrogenase, an enzyme necessary for de novo purine synthesis. It exerts its immunosuppressive properties mainly through its potent cytostatic effect on lymphocytes, but also suppresses antibody formation and inhibits the recruitment of leukocytes into areas of inflammation [113, 114].

Mycophenolate mofetil is an effective agent for cutaneous disease, myositis, and DM-associated interstitial lung disease [113, 115–122]. The evidence for its efficacy in cutaneous disease comes from case series and uncontrolled studies. In 2006, Edge et al. conducted a review of 12 patients with DM with either refractory cutaneous disease or intolerance to more traditional agents, who were treated with MMF (dose range 1–4 g/day), and reported improvement in 83% of patients within 4–8 weeks [117]. A more recent prospective cohort study of 74 patients with moderate-to-severe cutaneous disease (CDASI activity score ≥ 12) found that treatment with MMF was significantly associated with achieving clinical remission [16]. The majority of patients who achieved clinical remission with MMF were treated with higher doses (3 g daily) [16]. Of note, in patients who have pulmonary involvement at presentation or are at increased risk (i.e., positive for the MDA-5 antibody or anti-synthetase syndrome) of developing DM-associated lung disease, MMF is the preferred first-line agent as it has been shown to allow for improvement in pulmonary function and have a corticosteroid-sparing effect [28, 123].

Mycophenolate mofetil is generally well tolerated. The most common AE is dose-dependent gastrointestinal distress (most commonly nausea, abdominal pain, diarrhea, and vomiting) [113]. Additionally, genitourinary symptoms may occur more commonly during the first year of therapy. It is teratogenic and can cause reversible cytopenias, and, as with any immunosuppressive agent, there is an increased risk of infection. There is a potential increased risk of malignancy with MMF, albeit the majority of malignancies reported with its use have been in the transplant population [113, 118].

Prior to starting MMF, required baseline laboratory studies include complete blood count with differential, blood urea nitrogen/creatinine, liver function tests, hepatitis serologies, and tuberculosis screening. We start MMF at 500 mg twice daily and recheck laboratory studies in 2 weeks. The dose is then titrated up to 1 g twice daily and in many patients subsequently increased to 1.5 g twice daily. Therapeutic effect from MMF is not seen until 6–12 weeks of therapy.

4.5 Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) is derived from pooled plasma from numerous donors. Although not entirely understood, proposed mechanisms of action in DM are neutralization of autoantibodies, downregulation of proinflammatory cytokines, binding of complement, and decreased formation and deposition of the membrane attack complex [124].

Intravenous immunoglobulin is effective for both refractory cutaneous disease and myositis. A double-blind placebo-controlled trial of 15 patients with DM refractory to various immunosuppressive agents showed significant improvements in muscle strength and neuromuscular symptoms in 9/12 (75%) patients. Additionally, 8/12 (67%) patients had marked improvement in their cutaneous disease as assessed by clinical photographs. Improvement was evident 15 days after the first infusion but peaked between the second and third month [125].

In a retrospective study, IVIg was added to the treatment regimen of 13 patients with DM with refractory cutaneous disease. All patients included were receiving antimalarial therapy, and 11/13 patients were taking at least one immunosuppressive agent. All patients had improvement, and a complete clinical response was seen in eight (62%) patients. Notably, IVIg had a corticosteroid-sparing effect and allowed for discontinuation of immunosuppressive agents in eight patients [126]. In another retrospective study of 27 patients with refractory cutaneous DM, IVIg was beneficial in 85% of the patients [127].

Intravenous immunoglobulin is typically well tolerated, with the most common AE being headache. Other rarer AEs include hypersensitivity reactions, aseptic meningitis, renal failure, myocardial infarction, and thrombosis. Given its expense, the authors typically reserve IVIg for patients with refractory cutaneous DM who have not responded to or are intolerant of first-line agents. Given its efficacy, however, we traditionally move quickly to IVIg for patients with very severe disease with poor quality of life as a result of their cutaneous DM. We use it both as monotherapy and as an adjunctive agent. Patients are usually treated with 2 g/kg of IVIg divided over 2 consecutive days every 4 weeks. Once clinical remission has been achieved, we typically increase the interval between treatments to every 5 weeks, then every 6 weeks, etc.

4.6 Rituximab

Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen protein on B cells. It is an effective treatment

for the extracutaneous manifestations of DM, particularly DM-associated interstitial lung disease and refractory myositis [28, 128–130]. For cutaneous disease, however, studies thus far have shown conflicting results.

In an open-label pilot study of seven patients with DM who received rituximab (RTX) [100 or 375 mg/m^2 weekly for 4 weeks], all had improvement in strength and three patients with impaired pulmonary function at baseline had improvement in their forced vital capacity. At the beginning of the study, cutaneous disease, albeit with a limited description and listed only as "rash", was documented in five patients and improved with treatment. Interpreting these results is challenging as a validated skin outcome measure was not utilized, and it is unclear what constituted improvement. Additionally, hair regrowth was noted in two patients with alopecia secondary to DM. Patients began relapsing around 24–36 weeks, which coincides with a return of B cells [131].

In contrast, an open-label study examined the effect of RTX (two 1-g doses separated by 2 weeks) added to the regimen of eight patients with DM with moderate-to-severe cutaneous disease, assessed by baseline DSSI scores. At week 24, three patients had achieved partial remission, which was defined as at least a 50% reduction in muscle strength deficit. However, the mean percentage of change in DSSI at week 24 was only 9.5%, which was not statistically significant. When evaluating specific cutaneous features through photographs, periungual telangiectasias and Gottron's papules remain unchanged. The heliotrope eruption remained unchanged in six subjects, worsened in one, and improved in one. Poikiloderma was present in six subjects and either remained unchanged or worsened in three subjects [132]. In sum, the authors concluded that RTX could be useful in the treatment of muscle disease but has a minimal effect on skin disease.

A large prospective, multi-center, randomized, double-blind, placebo-controlled trial (RIM trial) of 200 patients with myositis, including 76 with adult DM and 48 with juvenile DM, who were refractory to SCS in addition to at least three other immunosuppressive agents, did not reach its primary outcome [128]. This may have been because of the trial design, given that all patients received RTX (either at weeks 0 and 1 or at weeks 8 and 9) in a randomized placebo-phase design. Despite not reaching its primary outcomes, a majority of patients in the study did experience improved muscle disease and a corticosteroid-sparing effect [128]. While the original trial did not assess the effect of RTX on cutaneous disease, a recent post hoc analysis on the RIM trial data found a beneficial effect. Lack of use of a validated skin outcomes measure and assessment of skin disease by non-dermatologists make it difficult to draw definitive conclusions [38]. At this time, given the limited evidence of efficacy for cutaneous DM specifically, the authors rarely use RTX as treatment for DM skin disease, and generally reserve it for our patients with refractory myositis or DM-associated pulmonary disease.

4.7 Janus Kinase Inhibitors

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) is an intracellular signaling pathway utilized by cytokines (including interleukins and interferons) and other molecules to transmit signals from the cell membrane to the nucleus. In recent years, its role in many inflammatory dermatoses has been better elucidated, and JAK inhibitors have been used successfully to treat various dermatologic conditions [133, 134].

In 2014, Hornung et al. reported a case of an elderly woman with CDM refractory to SCS, IVIg, MMF, and azathioprine, who received ruxolitinib, a JAK 1/2 inhibitor, for the treatment of post-polycythemia vera myelofibrosis. Her muscle strength improved, and cutaneous disease resolved completely while taking ruxolitinib [135].

In a subsequent series, one patient with CADM and two patients with CDM with refractory cutaneous disease were treated with tofacitinib, a JAK 1/3 inhibitor, 5 or 10 mg twice daily. All patients had improvement by week 4, as evidenced by a decrease in their CDASI activity score, and all reported a decrease in pruritus. The two subjects with CDM also reported improvement in strength and fatigue [136].

In the authors' clinical experience, JAK inhibition can be an effective option for refractory cutaneous DM. Adverse events include an increased risk of infections, particularly herpes virus reactivation, gastrointestinal symptoms, laboratory abnormalities (dose-dependent increase in creatine phosphokinase, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol; dose-dependent decrease in hemoglobin and neutrophil counts), and a potential increased risk of malignancy [133]. More recently, an increased risk of pulmonary embolism and overall mortality has been reported in a study of tofacitinib 10 mg twice daily in patients with rheumatoid arthritis [137]. It is unclear whether this association will be found in patients with other autoimmune conditions taking tofacitinib at 10 mg twice daily.

4.8 Other Therapies

Immunosuppressive agents such as cyclophosphamide, tacrolimus, sirolimus, cyclosporine, azathioprine, and chlorambucil have been used in treatment of refractory myositis and DM-associated lung disease [138–148]. However, evidence for efficacy in the management of cutaneous disease is limited and in the form of case reports and series [143, 149–153].

A few case reports have demonstrated an improvement in cutaneous DM with dapsone, leflunomide, and thalidomide [91, 154–162]. In a series of two patients with refractory cutaneous DM, dapsone was added to their regimen and both had a rapid response. Additionally, cutaneous disease flared when dapsone was stopped and improved with re-initiation [156]. Thalidomide can be effective in recalcitrant patients, but its use may be limited by the development of peripheral neuropathy [161].

The evidence for tumor necrosis factor-α antagonists is contradictory regarding their benefit in cutaneous and muscle disease [163–167]. Most importantly, several reports note inciting or worsening of DM, both skin and muscle disease, with their use [168–182]. For this reason, myositis experts typically consider anti-tumor necrosis factor therapies contraindicated in patients with DM.

5 Conclusions

Dermatomyositis is a rare idiopathic inflammatory disease with diverse presentations that can have varying degrees of cutaneous and systemic involvement. This heterogeneity in phenotype makes DM both a diagnostic and therapeutic challenge. Diagnosis relies heavily on a comprehensive physical exam. Dermatologists should be aware of specific MSA-associated phenotypes that can help them anticipate the most likely systemic associations in a particular patient. Overall, cutaneous DM tends to be chronic, debilitating, and often recalcitrant to therapy. Although treatment may be challenging, dermatologists should play an active role in the management of patients with cutaneous DM. Randomized controlled trials, which use validated skin outcomes measures, are needed to develop an evidence-based treatment algorithm for this frequently refractory skin disease.

Compliance with Ethical Standards

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