



# Environmental triggers of dermatomyositis: a narrative review

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**Abstract:** Dermatomyositis (DM) is an autoimmune disease that affects the skin, lungs, and muscle. Although the pathogenesis of DM is not completely understood, several environmental triggers have been linked to DM onset or flare. This article specifically examines the effects of herbal supplements, drugs, infections, ultraviolet (UV) radiation, and environmental pollutants on the onset or exacerbation of DM. Herbal supplements such as *Spirulina platensis*, *Aphanizomenon flos-aquae*, *Chlorella*, *Echinacea*, and Alfalfa have been implicated and are frequently used in health foods. Medications such as hydroxyurea, TNF- $\alpha$  inhibitors, immune checkpoint inhibitors (ICI), and penicillamine, as well as certain viral infections, such as parvovirus B19, coxsackie virus, polyomavirus, Epstein-Barr virus (EBV), hepatitis, influenza, and human immunodeficiency viruses (HIV) have been associated with DM onset. Bacterial infections and vaccinations have also been linked to the development of DM. Additional environmental factors, including UV radiation and air pollutants, such as silica, biological/mineral dust, and particulate air matter from vehicle and industrial emissions, may also play a role in DM pathogenesis. Overall, there is general agreement that an autoimmune attack of the skin, muscle, and lungs in DM can be triggered by various environmental factors and warrants further investigation.

**Keywords:** Dermatomyositis (DM); triggers; herbal supplements; drugs; infections; ultraviolet irradiation (UV irradiation); air pollution

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## Introduction

Dermatomyositis (DM) is an autoimmune disease that affects the skin, lungs, and muscle, among other organs. The age of onset of DM has a bimodal distribution, with one peak occurring at ages 5–14 and the other at 45–64 years (1). While the exact etiology and pathogenesis of DM are yet to be determined, there is general agreement that DM results from an autoimmune attack on affected organs and can be triggered by environmental factors, such as drugs, infections, ultraviolet (UV) exposure, and pollutant exposure in genetically susceptible individuals (1).

The objective of this article is to critically review the literature on environmental triggers of DM, specifically herbal supplements, drugs, infections, UV radiation, and environmental pollutants (*Table 1*). Our goal is to provide dermatologists, rheumatologists, and general practitioners with a framework for understanding and recognizing the various environmental triggers of DM in order to use this knowledge for the diagnosis, treatment, and prevention of the disease. In this narrative review we collected published peer-reviewed papers and abstracts from all available years, languages, study designs, and databases of coverage that we

**Table 1** Environmental triggers of DM

## Herbal supplements

*Spirulina platensis* (2-4)*Aphanizomenon flos-aquae**Chlorella**Echinacea* (2)

Alfalfa (5)

## Drugs

Hydroxyurea (6-10)

TNF- $\alpha$  inhibitors (6,11-18)

PD-1 inhibitors (19-25)

CTLA-4 inhibitors (19,26,27)

Penicillamine (6,28-31)

Hydroxymethylglutaryl Co-A reductase inhibitors (32,33)

Lacosamide (34)

Additional drugs:

Phenylbutazone, Cyclophosphamide, Etoposide, Imatinib mesylate, Interferon- $\alpha$ 2b, Omeprazole, Phenytoin, Tegafur, Alfuzason, Etanercept, Gemfibrozil (6)

## Vaccinations

Smallpox, diphtheria and tetanus, Bacillus-Calmette-Guerin (BCG), diphtheria, inactivated polio, oral cold vaccine, influenza (35-45)

## Infections

## Viral

Parvovirus (46)

Coxsackie B virus (47-49)

Polyomavirus (50,51)

Epstein-Barr virus (52,53)

Hepatitis B and C virus (54-57)

Human immunodeficiency virus (58)

## Bacterial

Streptococcus pyogenes (59)

Mycobacterium tuberculosis (60)

Borrelia burgdorferi (61)

## Ultraviolet radiation (62-70)

## Environmental pollution

Silica (71-73)

Dust (biological, mineral, gases/fumes) (74)

Particulate matter (vehicle/industrial emissions) (75-78)

Cigarette smoking (79,80)

Maternal exposure (associated with JDM): Chalk dust, gasoline vapor, maternal smoking, carbon monoxide (81)

**Table 1** (continued)

Table 1 (continued)

Miscellaneous
Seasonal variation (82-86)
Pregnancy (87-93)
Liquid silicone filler rhinoplasty (94)
Silicone breast implants (95)

deemed essential for the goals of this review. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3719>).

### DM and herbal supplements

Various herbal supplements, including *Spirulina platensis*, *Aphanizomenon flos-aquae*, *Chlorella*, *Echinacea* and Alfalfa stimulate the immune system (96-102), and their use has been associated with autoimmune skin disease exacerbations and even disease onset (2-5,103,104). Many patients with autoimmune skin diseases consume herbal supplements, with 35% to 69% of dermatology patients reporting complementary and alternative medicine use (105). Our preliminary survey data of DM, bullous pemphigoid, pemphigus vulgaris, and cutaneous and/or systemic lupus erythematosus patients show that DM patients had the highest rate of herbal supplement use compared with cutaneous lupus erythematosus and healthy controls, with 21.5% of DM patients reporting usage, and 14.6% reporting *Spirulina* consumption (4). In this context, it is important to consider that many of these herbal supplements are included in commercially available vitamin products, protein powder and weight loss mixes, and food items, either packaged in health food snacks and drinks like *Naked Juices Green Machine shake* or used in food establishments that serve smoothies and other made-to-order drinks.

Two case reports and one case series suggest that herbal supplements may cause DM onset or flare in susceptible patients (2,3,5). In one report, a patient experienced acute new erythema of her face and hand knuckles one to two days after starting daily consumption of *You're My Everything*, a supplement containing *Spirulina platensis*, *Aphanizomenon flos-aquae*, organic cayenne pepper, and methylsulfonylmethane. After discontinuing the supplement and completing a 10-day course of 40 mg prednisone

daily, she re-started *You're My Everything* and upon re-challenge, her rash worsened acutely in conjunction with significant swelling of her face, eyes, and ears. Prior biopsy findings and clinical exam were consistent with DM; however, despite appropriate treatment, cutaneous symptoms did not resolve completely (2). The temporal relationship between consumption and symptom onset, improvement with withdrawal, and response to re-challenge suggest that the herbal supplement was the likely culprit drug. In another report, a woman developed a widespread rash several days after taking a *Spirulina* supplement. She subsequently developed neck flexor and left proximal upper extremity weakness in association with an elevated serum creatine kinase (1,268 IU/mL). Clinical presentation and muscle histopathology were consistent with DM (3). Zeidi *et al.* (5) reported on three patients who developed DM or had a DM flare after ingesting Isalean® weight loss shake, which contains alfalfa and a proprietary enzyme blend of *Aspergillus oryzae*, *Rhizopus oryzae*, *Trichoderma longibrachiatum*, *Saccharomyces cerevisiae*, *Bacillus subtilis*, *Ananas comosus*, and *Aspergillus niger*. *In vitro* testing showed that Isalean® dose-dependently stimulates peripheral blood mononuclear cell secretion of inflammatory cytokines TNF- $\alpha$ , IFN- $\alpha$ , and IFN- $\beta$ , primarily via toll-like receptor 4 activation (5). Practitioners should be aware of the potential immunostimulatory effects of herbal supplements on DM and specifically ask their patients about possible consumption.

### DM and drugs

Several drugs have been linked to DM onset or flare, including hydroxyurea, TNF- $\alpha$  inhibitors, ICI, and penicillamine (Table 1). Few controlled trials exist (11-13) and the majority of evidence is based on case reports. It is important to note that identifying culprit drugs and connecting them temporally with disease course is difficult for several reasons. First, many DM patients

have underlying malignancies or autoimmune disorders, predisposing them to or triggering DM (6,106). Second, patients are often on numerous drugs, and determining the offending agent can therefore be challenging. Third, the time course between beginning a drug and reported DM onset may be months to years, depending on the drug, making it difficult to link the two temporally (6). Thus, showing drug causality can be difficult or nearly impossible. For that reason, the World Health Organization (WHO) designed the Causality Assessment Algorithm to standardize the likelihood that a drug incited disease onset using four criteria: (I) temporal relationship; (II) no other attributable causes; (III) response to withdrawal; and (IV) response to re-challenge. Drugs are graded as certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable (107).

### *Hydroxyurea*

Hydroxyurea is a cytotoxic agent most commonly used to treat myeloproliferative disorders, such as chronic myeloid leukemia (CML), polycythemia rubra vera, and essential thrombocythemia (108). It works by inhibiting ribonucleotide reductase, resulting in S-phase arrest and thereby halting *de novo* DNA synthesis (108,109). Hydroxyurea has been frequently implicated in DM-like cutaneous eruptions (6-10); however, myopathy and new, DM-associated malignancy are typically not present (9,110,111). In a review of 70 cases by Seidler and Gottlieb (6), hydroxyurea was the most common cause of drug-induced DM, accounting for 51% of cases (n=36/70). The authors found that compared to the non-hydroxyurea-treated patients, hydroxyurea patients had no muscular weakness/myositis (*vs.* 79.4%) and had a median time from start of drug to DM onset of 60.0 *vs.* 2.0 months for non-hydroxyurea-treated patients (6). The suspected culprit drug was withdrawn in 83.3% of the cases and nearly all patients had clinical improvement after drug withdrawal. In Vassallo *et al.* (112), 7/158 patients (4.4%) on hydroxyurea for CML developed skin changes resembling Gottron's papules after long-term hydroxyurea use. The mechanism of action that causes DM-like manifestations is poorly understood. However, one possibility is that DM-like cutaneous eruptions arise due to the drug's cytotoxic effects from inhibiting both DNA repair and DNA synthesis (109,113). It is thought that hydroxyurea inhibits the ribonucleotide reductase enzyme system thereby inhibiting cell DNA

synthesis and reducing intracellular deoxyribonucleotide pools, ultimately leading to cell death (114). Another possibility is that the synergistic effects of hydroxyurea blocking DNA site repair and UV irradiation causing DNA strand breaks lead to DM manifestations (110,112,113,115).

### *TNF- $\alpha$ inhibitors*

TNF- $\alpha$  inhibitors, such as infliximab, adalimumab, and etanercept are frequently used for a wide range of autoimmune and rheumatological disorders, such as psoriasis, rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease (116-118). There are numerous cases reporting a temporal associations between anti-TNF- $\alpha$  therapy in autoimmune disease patients and new onset DM (6,14-18). Although TNF- $\alpha$  inhibitors have been tested as potential therapies to treat DM, results have been mixed with many patients experiencing worsening of their disease (11-13). These results are paradoxical as high TNF- $\alpha$  is implicated in DM pathogenesis. For instance, the proinflammatory cytokine and its receptor are upregulated in DM and likely contribute to muscle inflammation and catabolism (119). Polymorphisms in the TNF- $\alpha$  promoter have also been linked to a greater risk of acquiring DM and increased severity in juvenile DM (JDM) (120,121). The cytokine-shift hypothesis proposes one explanation for why pharmacologically blocking TNF- $\alpha$  counter-intuitively leads to DM onset or flare (16,122). TNF- $\alpha$  inhibition increases type 1 interferon production (12,119,121). The interferon signature plays a key role in DM pathogenesis by activating antigen presenting cells and stimulating autoantigen production, which in turn stimulates antibody production (119,123). In an open pilot study of infliximab in patients with refractory inflammatory myopathies, several patients' DM acutely worsened and these flares were associated with increased type 1 interferon activity in both the blood and muscle (12). An alternate hypothesis is that TNF- $\alpha$  blockade may decrease cell apoptosis, leading to increased autoantibody production (124). As the use of TNF- $\alpha$  inhibitors continues to increase, health care professionals must be aware of the paradoxical, deleterious effects that these drugs may have in patients.

### *ICI*

ICI, including PD-1 inhibitors such as pembrolizumab and nivolumab and CTLA-4 inhibitors such as ipilimumab, are

increasingly being used worldwide and are an innovative approach to treating both solid and hematological malignancies (19). ICI aim to enhance the immune system's ability to recognize and destroy malignant cells. However, autoimmune-related adverse events, including autoimmune skin diseases such as DM, are increasingly being associated with ICI due to the enhanced activation of anti-tumor T cells and non-specific blockage of self-tolerance (19-21,125-127). Specifically, several case reports have noted new onset DM after pembrolizumab (21-23), nivolumab (20,24,25), and ipilimumab (26,27) therapy. As the use of ICI to target malignancies continues to grow (128), it is important for physicians to be aware of and recognize ICI-induced DM.

### *Penicillamine*

Penicillamine, a copper chelating agent used primarily in the treatment of Wilson disease as well as previously in rheumatoid arthritis, has also been implicated in DM onset or flare. In a review of 70 reported cases involving drug-induced DM, penicillamine was found to be the second most frequent drug to induce DM onset or flare (10/70 cases) (6). Disease remission occurred in all cases once penicillamine therapy was stopped. The majority of case reports are from the 1970s–1980s when penicillamine was more commonly used for rheumatoid arthritis (28-31). Nevertheless, it's important to recognize that the drug has frequently been associated with DM exacerbations.

### *Additional drugs*

Hydroxymethylglutaryl Co-A reductase inhibitors are also drugs that have frequently been associated with DM (32,33). Other DM-inducing drugs cited in Seidler and Gottlieb's review of 70 cases include: phenylbutazone, cyclophosphamide, etoposide, imatinib mesylate, interferon- $\alpha$ 2b, omeprazole, phenytoin, tegafur, alfuzosin, etanercept, and gemfibrozil (6). Lacosamide (34) has also recently been associated with cases of new onset DM.

### *Vaccinations*

Although rare, multiple cases have reported instances in which vaccines, including smallpox, diphtheria and tetanus, Bacillus Calmette-Guerin (BCG), inactivated polio, oral cold vaccine, and influenza (35-45), may have triggered DM.

## **DM and infections**

In genetically susceptible individuals, viral, bacterial, and parasitic infections have been suspected to induce autoimmunity and even exacerbate existing autoimmune conditions (129). Epidemiological data shows that subsets of polymyositis (PM) and DM patients defined by various myositis-specific antibodies tend to develop disease at specific times of the year (82,130). This seasonal clustering of disease onset could be indicative of a common environmental trigger such as infection (82). The relationship of infection to DM onset has been better evaluated in children. Two studies evaluated the roles of infections prior to development of JDM. One study identified clinical signs of infection three months before JDM onset in 71% of the 110 patients (131). Another study involving 286 children with JDM found frequent complaints of respiratory (57%) and constitutional (56%) symptoms three months before diagnosis of JDM. The authors believed this to be a viral prodrome before JDM onset (132). Although infection as a trigger has been heavily studied in JDM, infections have also been shown to play a role in adult DM onset.

### *Parvovirus*

Parvovirus B19 (B19) is most known for causing disease in the pediatric population and is the classic cause of the childhood rash fifth disease or erythema infectiosum. B19 has been implicated in the pathogenesis of connective tissue diseases such as JDM (46). In one prospective study of seven patients who demonstrated clinical and/or serological signs supporting a diagnosis of connective tissue disease subsequent to B19 infection, five of the seven patients fulfilled the American College of Rheumatology's criteria for DM (46).

### *Coxsackie B virus*

Coxsackie viruses are enteroviruses of the family Picornaviridae. Coxsackie B contains six serotypes that trigger illnesses ranging from gastrointestinal symptoms to pericarditis and myocarditis (47). One study sought to determine whether human response to Coxsackie B virus could be implicated in the pathogenesis of DM (48). Viral complement-fixation antibodies to Coxsackie B1, B2, and B4 were found significantly more frequently in the sera

of 12 JDM patients, who were tested within four months of JDM onset, than in the sera of their matched juvenile rheumatoid arthritis controls and from pediatric controls hospitalized for viral syndromes (48). Except in the cases of persistent antigenic stimulation of latent virus infection, complement-fixation antibodies can only be detected for a few months after the onset of viral infection (48). Another study reported elevated antibody titers to Coxsackie B3 in adult DM patients without malignancy when compared to controls with rheumatoid arthritis and normal healthy controls (49).

### ***Polyomavirus***

Human polyomavirus (HPyV) 6 and HPyV7 are closely related polyomavirus species and are thought to infect the skin of many healthy individuals in a latent or subclinical manner (50). However, recent studies revealed that HPyV6 and HPyV7 could infect and actively replicate in immunosuppressed patients causing the formation of pruritic, scaly brown plaques that, when biopsied, show a characteristic parakeratotic pattern called a “peacock plumage” (50). Nyugen *et al.* (50) demonstrated that both HPyV6 and HPyV7 are associated with rare, pruritic skin eruptions that have a distinct dyskeratotic histologic pattern by performing polymerase chain reaction for HPyVs on biopsies showing this “peacock plumage”. They found high viral loads in lesional skin compared with normal-appearing skin and concluded that HPyV6 and HPyV7 are associated with these rare, pruritic skin eruptions (50). This entity was described by Nyugen *et al.* as HPyV6- and HPyV7-associated pruritic and dyskeratotic dermatoses and had been previously identified in Wong-type DM, a rare variant of DM characterized by tiered parakeratosis with dyskeratosis or “peacock plumage”. Matsumoto *et al.* (51) initially described the connection between Wong-type DM and Nyugen *et al.*'s finding of HPyV6- and HPyV7-associated pruritic and dyskeratotic dermatoses and suggested further investigation for the relationship between HPyV infection and Wong-type DM.

### ***Epstein-Barr virus (EBV)***

EBV is a human herpesvirus that resides in memory B cells in a latent form. EBV has been linked to the development of a number of autoimmune disorders (52). A case-control study showed higher frequencies of anti-Epstein-Barr

nuclear antigen 1 (EBNA1) antibodies at the onset of DM/PM and the EBV genome was detected at a higher frequency in DM/PM patients than in their matched healthy control counterparts (53). This study also showed that the concurrence of malignancies, such as nasopharyngeal carcinoma, further increased the development of idiopathic inflammatory myositis (IIM) (53).

### ***Hepatitis B virus (HBV) and Hepatitis C virus (HCV)***

HBV and HCV are viruses that can cause liver inflammation and damage. Both HBV and HCV can cause either acute or chronic illness. Occasionally, HBV infection has been reported to cause a variety of extrahepatic symptoms including PM and DM although the exact mechanism remains unknown (54). In certain cases of chronic hepatitis infection, hepatocellular carcinoma (HCC) develops and has been noted as the inciting factor for DM (55-57). In one 79-year-old female with HCV-associated HCC, DM developed 9 months after diagnosis with HCC and coincided with an enlargement of her tumor (55).

### ***Human immunodeficiency virus (HIV)***

The occurrence of DM has also been reported in the setting of HIV infection. With only four known cases, the development of DM in a patient with HIV is exceedingly rare, and occurred between 6–18 months after HIV diagnosis (58).

### ***Bacterial causes***

A case-control study (59) found increased frequency of streptococcal infection in those with JDM than in matched controls. A case series from Mexico (60) showed that of the 30 patients who developed systemic rheumatic disease after *Mycobacterium tuberculosis* infection, five were diagnosed with PM or DM. One case report (61) describes the development of DM subsequent to *Borrelia burgdorferi* infection, suggesting that this bacterial cause of Lyme disease may be an inducer of DM.

### **DM and UV radiation**

Cutaneous features of DM including persistent erythema, increased prevalence in sun-exposed areas, and photoaggravation all suggest that UV radiation plays a

strong role in disease pathogenesis (62,63). In fact, Quain *et al.* (64) suggest that recurrent photosensitive dermatoses may be an initial presenting sign of DM and should prompt consideration of the diagnosis. The prevalence of DM increases significantly with decreasing geographical latitude from northern Europe (Reykjavik, Iceland) to southern Europe (Athens, Greece), suggesting that UV exposure may be implicated in DM pathogenesis (65). One study surveyed and performed photoprovocation testing on 19 DM patients to further investigate the nature of photosensitivity in DM (66). Of these, seven patients reported increased photosensitivity and four reported aggravation of existing lesions or inducement of new lesions after photoprovocation (66). Formal UVB testing of these patients demonstrated a reduced minimal erythema dose in nine patients (66). This study proposes that UV exposure correlates significantly with DM pathogenesis as exposure caused induction of new lesions and exacerbation of pre-existing lesions. The anti-Mi-2 antibody has been associated with UV exposure and is more common in DM patients living in regions with higher UV exposure (67). Patients with anti-Mi-2 antibody have also been reported to have increased severity and activity of DM (68). Additionally, increases in the DM-specific anti-TIF1- $\gamma$  antibody have been reported with decreasing latitudes, further highlighting potential mechanisms explaining the increased prevalence of DM closer to the equator (69). One study examined 919 patients from 15 locations to determine how geoclimatic factors influence the frequency of DM and associated autoantibodies around the world (70). This study found UV radiation intensity to be the strongest multivariate predictor of DM, followed by latitude as the second strongest predictor (70). Furthermore, UV radiation intensity was the geoclimatic variable most strongly related to the proportion of DM patients positive for the anti-Mi-2 antibody (70). UV exposure should be recognized as a prevalent environmental trigger of DM.

### DM and air pollution

Occupational exposure has been linked to the onset of both adult DM and JDM. In one study of male construction workers in Sweden, occupational exposure to silica and inorganic dusts was associated with an increased risk of rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and DM (71) after accounting for age and smoking. Several other cases have also linked the

association of silicosis and DM and PM (72,73). In another study of 32 patients with antisynthetase syndrome patients, half of whom also had DM, patients with greater exposure to biological dust, mineral dust, or dust/gases/fumes had higher rates of interstitial lung disease than patients with low or no exposure, although it was not statistically significant (74). Such occupational exposure has also been linked with JDM. One study in Brazil analyzing pregnancy risk factors associated with a child developing JDM compared to healthy controls found that maternal exposure to chalk dust or gasoline vapor, maternal smoking, and carbon monoxide exposure (3.18–5.35 ppm) all increased the JDM risk (81).

It is well established that increased particulate matter in the air, such as from vehicle and industrial emissions, is associated with increased mortality (75,76). Particulate matter has been shown to trigger the release of pro-inflammatory cytokines, including TNF- $\alpha$ , IL-6, IL-1 $\beta$ , MIP-1 $\alpha$ , and GM-CSF (77). In a population study of Canadian patients, the likelihood of having a systemic autoimmune disease increased with the amount of fine particulate air pollution (76). Moreover, an analysis of the geospatial distribution of DM patients in the Philadelphia metropolitan area found that point sources of airborne pollutant matter, such as emissions from industrial and commercial sources, were associated with the presence of clinically amyopathic DM, but not classic DM (78).

Cigarette smoking is associated with varying phenotypic characteristics of DM. Schiffenbauer *et al.* (79) studied 465 patients with IIMs (58% PM, 42% DM), finding that smokers were more likely to have PM, antisynthetase antibody, and anti-Jo-1 antibody. However, smokers were less likely to have anti-p155/140 antibody (79). Another European case study found similar results; among 557 Caucasian IIM patients (50% PM, 38% DM, 12% overlap), smoking was associated with anti-Jo-1 antibody, which was more pronounced among patients with HLA-DRB1\*03 (80).

### Miscellaneous triggers of DM

Seasonal variations affect both the symptoms and the course of DM, with the most relapses occurring during the summer and spring (83,84). However, studies have yet to find a consistent link between seasonal variations and DM onset. Sarkar *et al.* (85) analyzed the dates of disease onset of 268 PM patients and 235 DM patients, finding no significant difference in seasonal variation between the two groups.

While seasonal variations have not correlated with DM as a whole, seasonal variations correlate with the presence of DM autoantibodies (84). For example, Sarkar *et al.* (85) observed the onset of myositis among non-black patients with antisynthetase antibodies to be around March-April, and patients that tested negative for myositis autoantibodies to be around June-July. Leff *et al.* (82) found that the onset of weakness for anti-Jo-1 patients was April, and anti-SRP patients was November.

Seasonal variation in maternal exposure may also play a role for a subset of juvenile DM patients. Vegosen *et al.* (86) analyzed the birth dates of 307 juvenile IIM and 668 adult IIM compared to controls and did not find any significant difference between birth dates in either group. However, among Hispanic juvenile IIM patients, a seasonal variation was observed compared to Hispanic controls (October *vs.* year-round) and non-Hispanic juvenile IIM (October *vs.* May). Additionally, JDM patients who were anti-p155-positive had a mean birthdate of February, while the mean birthdate of anti-p155 negative JDM patients was July (86).

Gestation also has effects on DM symptoms. In one study of 10 DM patients and 21 pregnancies, while all patients continued to have rashes during pregnancy, the majority experienced improvement of weakness, rash, and arthritis during pregnancy (87). In one rare case, gestation may have triggered DM, with the patient experiencing onset of symptoms during gestation, which abated after a spontaneous termination of the pregnancy (88). Two types of pregnancy-related DM have been proposed: (I) DM presenting during pregnancy and (II) DM developing during the postpartum period (89). Three cases of postpartum DM development have been reported; one woman developing symptoms five days after delivery, another experiencing symptoms one month after normal delivery, and the last being diagnosed 15 days after cesarean section (89-91). Additionally, women have experienced exacerbation of DM symptoms during the postpartum period (91,92). Overall, various factors during pregnancy such as exposure to fetal antigens, changes in maternal hormonal status, and the reactivation of certain viruses by pregnancy have been considered as triggers for the development of DM (93). Other miscellaneous triggers of DM include liquid silicone filler rhinoplasty and silicone breast implants (94,95).

## Conclusions

The factors that can cause disease and DM pathogenesis

are still not fully understood (119,133). However, herbal supplements and weight loss powders, drugs, infections, UV radiation, and pollution, are several environmental factors associated with DM onset and flares and may contribute to disease manifestation in genetically susceptible individuals. Physicians should consider possible inciting environmental factors, as in some cases, such as with herbal supplements and drugs, removal of the environmental factor may improve DM symptoms and clinical course. It is important to continue to investigate the association between environmental risk factors and DM onset or flare in order to better understand the disease and to guide patients in best practices, as well as to aid in developing better therapies.

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