



# Anti-MDA-5 Dermatomyositis With Development of Drug-Mediated Necrolytic Skin Lesions

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## Abstract

A 59-year-old male presented with 1 month of progressive dyspnea, 30-lb weight loss, and skin changes on the digits of the hands. In the 4 weeks prior to admission, he was admitted and treated twice for pneumonia at another hospital and received intravenous (IV) vancomycin, ceftriaxone, and azithromycin for a total of 10 days. After admission, he underwent computed tomography imaging of chest, which revealed findings suggestive of interstitial lung disease but given the fact that infection was not ruled out, empiric antibiotics were initiated. The skin lesions on the fingers were felt to be consistent with Gottron's papules, and his overall constellation of findings were felt to be consistent with dermatomyositis (DM). Over the following 3 days, he developed diffuse, violaceous skin lesions, elevation of liver transaminases, and severe thrombocytopenia. The skin lesions progressed to epidermal necrosis. He developed erosions of the oral mucosa and scrotum. Before skin biopsy results were finalized, IV immunoglobulin and IV dexamethasone were started empirically for suspected DM and immune-mediated thrombocytopenia. His laboratory abnormalities normalized within a week. Biopsy results of the skin were consistent with Stevens-Johnson syndrome (SJS). Autoantibody test for anti-MDA5 were positive, confirming a diagnosis of anti-MDA5 associated DM. Subsequent development of SJS was likely due to antibiotic exposure in the preceding month. Simultaneous development of anti-MDA5 DM and SJS raises the question of a link between the 2 conditions. To our knowledge, this is the first reported association of these 2 conditions reported in the literature.

## Keywords

anti-MDA5 dermatomyositis, Stevens-Johnson syndrome, immune thrombocytopenia, transaminitis

## Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy classically characterized by muscle weakness, laboratory or histological evidence of muscle inflammation, skin lesions, and involvement of other organs.<sup>1,2</sup> In 2005, Sato et al described a new autoantibody directed against melanoma differentiation protein-5 (MDA-5) in Japanese DM patients who presented with rapidly progressive interstitial lung disease and absent muscle weakness.<sup>3</sup> In a recent cohort from the United States, anti-MDA-5 patients demonstrated unique skin findings compared with other groups of DM patients. These findings included cutaneous ulcerations (often over Gottron's papules) and oral ulcerations.<sup>4</sup>

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered to represent a drug-induced hypersensitivity.<sup>5</sup> The pathophysiology of SJS/TEN remains incompletely elucidated but appears to involve immune-mediated signaling that leads to apoptosis of epidermal

cells.<sup>5</sup> Skin manifestations typically evolve from areas of tender erythema or hemorrhagic erosions that progress to detachment of the epidermis. SJS/TEN characteristically also involves mucous membranes. A diagnosis of SJS is made in cases where 10% or less of the skin is involved. TEN is diagnosed when >30% of the epidermis is involved.<sup>5</sup> Many drugs have been associated with SJS/TEN, and certain genetic factors appear to predispose to development of SJS/TEN in response to certain drugs.<sup>5</sup> Recently, it has been noted that patients with systemic lupus erythematosus (SLE)

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**Figure 1.** Gottron's papules on hand at the time of presentation.

appear to be at increased risk for development of SJS.<sup>6</sup> It is unclear if patients with other autoimmune conditions have a predisposition to development of SJS.

We describe a patient who presented with acute development of anti-MDA-5 DM who developed necrotizing skin lesions, which were histologically consistent with SJS.

## Case Presentation

A 59-year-old male was admitted to the medical intensive care unit (ICU) for acute respiratory failure. He complained of 4 weeks of progressive dyspnea, skin changes on his hands consistent with Gottron's papules, and 30-lb weight loss. His medical history was significant only for hypertension, which was managed with amlodipine. He had no prior history of autoimmune disease. He was admitted to a local hospital twice in the preceding month for dyspnea and treated for presumed bacterial pneumonia. He received azithromycin, vancomycin, and ceftriaxone during those hospitalizations for approximately 10 days. His symptoms improved minimally during those hospital stays and so he was admitted to our hospital 1 day after his most recent discharge. Computed tomography scan of the chest showed extensive reticular opacities largely sparing the periphery, scattered areas of ground-glass changes, and traction bronchiectasis. High-flow nasal cannula and noninvasive positive-pressure ventilation were required for respiratory support. Empiric vancomycin and cefepime were started for presumed pneumonia until it could be ruled out. He underwent bronchoscopy after admission, which did not reveal any infectious causes for his respiratory disease so the antibiotics were discontinued.

The patient reported that about a month before admission, he had noticed skin changes on his hands. On examination, he had small papules on the metacarpophalangeal and proximal interphalangeal joints of the fingers, consistent with



**Figure 2.** Scattered circular skin lesions on back and an area of full-thickness skin separation on the right shoulder.

Gottron's papules (Figure 1). He did not have muscle weakness on physical examination. The Rheumatology service evaluated the patient and felt that his clinical findings were highly suspicious for undiagnosed amyopathic DM, favoring a diagnosis of anti-MDA5-associated DM.

The patient had noticed new skin lesions that began to develop just 2 to 3 days before presenting to our hospital. On initial evaluation, the lesions were violaceous, flat, and scattered on his trunk and extremities without a clear pattern. After admission, these skin lesions began to increase in number and size. Over the following 3 days, the skin lesions evolved to separation, suggestive of epidermal necrosis (Figure 2). He also developed erosions on the oral mucosa and on his scrotum. During this same time frame, he developed significant laboratory abnormalities. Laboratory results were available from a week prior to arrival at our hospital. Those laboratory results showed a platelet count of 250 000/mm<sup>3</sup> and mildly elevated liver enzymes to 166 IU/L for aspartate aminotransferase (AST) and to 172 IU/L for alanine aminotransferase (ALT). On arrival to our hospital, the platelet count had decreased to 16 000/mm<sup>3</sup>, then decreased to 8000/mm<sup>3</sup> after receiving 2 units of platelets in preparation for bronchoscopy. The liver function tests increased exponentially after admission, in synchrony with worsening of the skin lesions. The AST peaked at 2081 IU/L and ALT at 1427 IU/L. The total bilirubin was initially normal but increased to 6.2 mg/dL by day 4 at its peak.

Dermatology evaluated the patient and performed skin biopsies. While waiting to confirm the cause of the skin lesions, rheumatology advised initiating immunosuppression for suspected DM. Hematology evaluated him for his thrombocytopenia and favored an immune-mediated mechanism. For this, they advised providing IV dexamethasone at 40 mg, and this was continued for 4 doses. He was started on IV immunoglobulin at the same time and received 400 mg/kg daily for 3 days. His laboratory abnormalities improved by the following day and were nearly normal by a week later.

His respiratory failure also improved after starting immunosuppressive therapy.

Days later, the skin biopsies returned and revealed epidermal apoptosis and areas of full-thickness epidermal necrosis, findings that were consistent with SJS. Intravenous antibiotics, either vancomycin or cefepime, were favored to be the cause. He was taken off IV antibiotics after 2 days in the hospital. His laboratory testing revealed a positive result for the anti-MDA5 autoantibody. Rheumatology began treatment with cyclophosphamide infusions and oral tacrolimus therapy, with a plan to continue this therapy in the outpatient setting for his anti-MDA5 DM. After approximately 2 weeks, we re-evaluated his skin lesions and they had all healed with hyperpigmentation at previous areas of skin loss.

## Discussion

The manifestations in this case are best explained as development of a necrolytic, likely drug-mediated skin syndrome, in a patient with untreated anti-MDA5 DM. It is our best estimation that the skin lesions, favored to be SJS clinically and histologically, were provoked by IV vancomycin or cefepime, which he had been receiving at the outside hospital on and off in the preceding 4 weeks. In our review of the literature, we did not identify an association between DM and SJS. In this patient, we found it intriguing that he developed SJS within a month of developing rapidly progressive symptoms related to his anti-MDA5 DM. Interestingly, an association between SLE and development of SJS has been reported in the literature. In patients with SLE, disease involvement of the skin when severe can histologically resemble SJS/TEN.<sup>6</sup> However, most reported cases of SJS in patients with a history of SLE are thought to reflect separate clinical processes.<sup>6</sup> Though by different underlying mechanisms, it can be stated that both DM and SJS are related to dysregulation of the immune system.<sup>5</sup> Additionally, patients with the anti-MDA5 variant of DM have been shown to have prominent skin manifestations, including patterns of skin involvement that are unique among subtypes of DM.<sup>4</sup> Based on this, we were intrigued by the possibility of an association between anti-MDA5 DM and SJS. If additional examples are reported, a more clear association may be appreciated.

Dermatomyositis of any variant is a relatively rare disease and has been reported to occur in 2 per 100 000 people annually in the United States.<sup>7</sup> Anti-MDA-5 variant of DM is a relatively recently described subset among people with DM. In 2 cohorts from US tertiary care centers, 10 of 77 and 11 of 160 DM patients were found to have the anti-MDA-5 antibody.<sup>4,7</sup> Compared with the initial reported cohorts from Japan where the anti-MDA5 antibody was associated with a high mortality, early results from the cohort from Hall et al suggest that patients have a good response to immunosuppressive therapy.<sup>3,8,9</sup> Although in a review of ICU patients diagnosed with anti-synthetase or anti-MDA-5 DM by Vuillard et al, MDA-5 patients had a mortality rate of 84% in

the ICU compared with 18% for anti-synthetase patients, highlighting the morbid prognosis related to the interstitial lung disease associated with anti-MDA-5 DM.<sup>10</sup> Interestingly, anti-MDA-5 DM patients have been shown to frequently present with prominent and diverse skin manifestations.<sup>4,10</sup> Examples include classical DM-associated changes, such as Gottron's papules and mechanic's hands, and also additional reported findings of skin ulcerations, facial erythema, and rash on the trunk. Skin ulcerations have been noted to occur around nail beds or within Gottron's papules, in particular. On histology of cutaneous ulcerations, they found vasculopathy with varying degrees of inflammation.<sup>4</sup> For our case, we reviewed the skin biopsy histology with our pathologist, who could not identify any features suggestive of a role from DM. Rather, the findings were hallmark for SJS.

Both the clinical progression of the skin lesions and histological findings were highly consistent with SJS in this case. Among causes of SJS, we identified both cephalosporin drugs and vancomycin as associated triggers for the condition.<sup>11</sup> In a review of antibiotic-mediated cutaneous reactions and 25 cases of SJS, there were 5 cases associated with cephalosporins and 3 associated with vancomycin.<sup>11</sup> In another retrospective study involving 41 cases of SJS, 3% of cases were due  $\beta$ -lactam antibiotics and 10% related to vancomycin.<sup>12</sup> Treatment for SJS is often focused on withdraw of the offending agent and supportive care.<sup>5</sup> Our patient sustained complete resolution of his skin lesions in less than a month. Both agents he received in the hospital, IV immunoglobulin and steroid, have been studied in SJS patients, but data are limited to case reports and case series, largely due to the rarity of the condition.<sup>13</sup> In a case series spanning multiple hospitals, 48 patients were treated with IV immunoglobulin and the treatment was associated with more rapid healing of skin lesions.<sup>14</sup> Steroids remain controversial in the management of SJS.<sup>15</sup> High-dose steroids were reported to be associated with improvement in skin lesions in 5 cases of SJS, according to one study.<sup>16</sup> Our case adds information in favor of a positive treatment response for both therapies in a case of SJS.

The thrombocytopenia seen in our case has a broad differential diagnosis. Marrow suppression was deemed unlikely due to the rapid drop in platelet count. The severity of thrombocytopenia at  $<20\,000/\text{mm}^3$  argued against heparin-induced thrombocytopenia.<sup>17</sup> An immune-mediated mechanism for thrombocytopenia was favored by our team clinically. This was supported by spontaneous normalization of the platelet count quickly after initiating corticosteroids and worsening of the thrombocytopenia with platelet transfusion. The patient also had a normal platelet count a week before at the other hospital and a rapid reduction. Development of immune thrombocytopenia among patients with autoimmune conditions is a known association, but is not common with DM. In a review by Liu et al of 104 cases of immune thrombocytopenia in patients with multiple autoimmune conditions, only 2.3% of cases were DM.<sup>18,19</sup> Primary SLE and Sjogren's

syndrome accounted for 56% of the cases in their review. We identified one other report of DM-associated idiopathic thrombocytopenia in our literature review.<sup>20</sup> We suspect that a more plausible trigger for immune-mediated thrombocytopenia in this case is the drug that also triggered SJS. This is supported by the time course of development of thrombocytopenia in this case as well. Both cephalosporin antibiotics and vancomycin are associated with drug-induced thrombocytopenia.<sup>21</sup> Thrombocytopenia is also reported among patients with SJS but the mechanism behind the drop in platelets is not clear. In a review by Yang et al, among 41 cases of SJS, 25% had thrombocytopenia and the lowest level reported was 19 000/mm<sup>3</sup>.<sup>12</sup> In our review, it is not completely clear if the thrombocytopenia was a primary drug-mediated reaction or a part of the constellation of findings related to SJS.

When considering the elevated transaminase levels in our case, it is more likely that it was related to the ongoing drug-mediated skin syndrome. Transaminase elevation in patients with DM is relatively common. However, when studied, it has been shown that most patients only have a mild elevation and it is referable to the ongoing myopathy and release from skeletal muscle.<sup>22</sup> In such instances, the transaminase level is often misinterpreted as being a liver abnormality. Regarding SJS, there were 2 retrospective studies that commented on severity of liver enzyme elevation in this population. In the first by Jeung et al, 17 out of 20 cases of SJS were associated with elevated liver enzymes, but the severity was not reported.<sup>23</sup> More compelling, in the review by Yang et al, the average ALT level among 41 cases of SJS was elevated to 207 IU/L and the peak level in their group was elevated to 1582, which is nearly the same as in our case.<sup>12</sup>

## Summary

This is the first report of a possible association between anti-MDA DM and development of SJS. The cutaneous reaction was likely driven by either vancomycin or a cephalosporin antibiotic. The development of immune thrombocytopenia and transaminitis appeared to coincide with onset of his cutaneous lesions. The patient had a positive clinical response to steroids and immunoglobulin therapy.

## Declaration of Conflicting Interests

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## Ethics Approval

At the University of Florida, institutional review board or ethic board approval is not required for publication of case reports that do not disclose identifiable patient information.

## Informed Consent

Written informed consent and verbal consent was obtained from the patient for their anonymized information to be published in this article.

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