Gottron Papules and Gottron Sign with Ulceration: A Distinctive Cutaneous Feature in a Subset of Patients with Classic Dermatomyositis and Clinically Amyopathic Dermatomyositis

Hua Cao, Qunli Xia, Meng Pan, Xiaoqing Zhao, Xia Li, Ruofei Shi, Min Zhou, Xiaoyi Ding, Masataka Kuwana, and Jie Zheng

ABSTRACT. ***Objective.*** Gottron papules and Gottron sign are characteristic and possibly pathognomonic cutaneous features of classic dermatomyositis and clinically amyopathic dermatomyositis (DM/CADM). However, the Gottron papules/Gottron sign with cutaneous ulceration (ulcerative Gottron papules/Gottron sign) are less common. We aimed to clarify the clinical characteristics of patients with DM/CADM who have ulcerative Gottron papules/Gottron sign.

Methods. Clinical features, laboratory findings, and prognosis of patients with DM/CADM who had Gottron papules/Gottron sign with or without ulceration were analyzed and compared.

Results. Occurrences of acute interstitial pneumonia/subacute interstitial pneumonia (AIP/SIP) were significantly higher in patients with ulcerative Gottron papules/Gottron sign (19/26) versus patients with Gottron papules/Gottron sign without ulceration (2/66, $p < 0.001$). We also observed that the white blood cell counts (mean ± SD 4.2 ± 1.6 vs 6.9 ± 2.9; $p < 0.001$) and creatine kinase (CK) levels (198.0 ± 377.7 vs 1364.0 ± 2477.0; $p = 0.019$) were significantly lower, whereas the positive rate of antimelanoma differentiation-associated gene 5 antibody (anti-MDA5; 88.5% vs 6.1%, $p < 0.001$) and serum ferritin levels (665.2 ± 433.5 vs 256.2 ± 279.0, $p < 0.001$) were significantly higher in the patients with ulcerative Gottron papules/Gottron sign. Moreover, the cumulative survival rate of the group with ulcerative Gottron papules/Gottron sign was significantly lower ($p < 0.001$).

Conclusion. Patients with DM/CADM who have ulcerative Gottron papules/Gottron sign, positive anti-MDA5 antibody, and significantly lower baseline CK level are at increased risk of interstitial lung disease, especially AIP/SIP. A new designation for this subgroup of patients should be established to draw more attention to this clinical entity. (First Release June 15 2016; J Rheumatol 2016;43:1735–42; doi:10.3899/jrheum.160024)

Key Indexing Terms:
DERMATOMYOSITIS
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The idiopathic inflammatory dermatomyopathies form a spectrum of clinical disease with expression ranging from cutaneous-only disease to cutaneous and/or systemic disease, including clinically amyopathic dermatomyositis (CADM), classic dermatomyositis (DM), and polymyositis/inclusion body myositis[1]. Clinical manifestations of this clinical entity

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are diverse, involving various degrees of muscle, skin, and lung impairments. Among these, the exclusively cutaneous or predominantly cutaneous form of DM or CADM showed the lowest survival rates[2,3,4,5].

Hallmark clinical cutaneous manifestations of DM and CADM include Gottron papules, Gottron sign, periorbital heliotrope erythema, periungual telangectasias, and photodistributed erythema or poikiloderma. Gottron papules and Gottron sign are characteristic and possibly pathognomonic cutaneous features of DM and CADM, and appear to be the most frequent presentation, with 54%-91% occurrence[6,7]. Gottron papules refer to a violaceous hue located at the dorsal-lateral interphalangeal (IP) and/or metacarpophalangeal (MCP) joints. When fully formed, these papules become slightly depressed at the center, showing a white atrophic appearance. Associated telangiectasia can be present. Gottron sign refers to symmetric confluent macular violaceous erythema with or without edema at the dorsal aspect of the IP/MCP joints, olecranon processes, patellae, and medial malleoli[8,9]. According to the definition, Gottron papules/Gottron sign with cutaneous ulceration or combined with necrosis are not included.

The rash of DM is heterogeneous with a diverse range of skin impairments, some of which may be used to predict the likelihood of concurrent or development of systemic disease, such as interstitial lung disease (ILD) or internal malignancy[10,11,12,13]. Gottron papules has been consistently shown to be unassociated or even negatively correlated with ILD[14,15]. The goal of our study is to provide a more comprehensive perspective on the clinical features and prognosis of DM/CADM patients with Gottron papules/Gottron sign with cutaneous ulceration (ulcerative Gottron papules/Gottron sign).

MATERIALS AND METHODS

Patient population. This retrospective study included 112 Chinese adult patients with DM or CADM who were admitted to the Department of Dermatology at Shanghai Rui Jin Hospital from January 2008 to June 2014. DM or CADM was diagnosed based on the criteria of Bohan and Peter[16], or followed the modified Euwer and Sontheimer definitions[17]. The study excluded the patients who were diagnosed with polymyositis or had symptoms similar to those in systemic lupus erythematosus and systemic sclerosis or other connective tissue diseases. Clinical data including medical history and physical examination results were collected upon admission and during followup. Management and complications were all documented.

Diagnosis of ILD. All patients received high-resolution computed tomography (HRCT) upon admission and during followup. The diagnosis of ILD was made according to the respiratory symptoms and the presence of bibasilar infiltrates on HRCT. A rapidly progressive ILD leading to respiratory function failure within 3 months is defined as acute interstitial pneumonia/subacute interstitial pneumonia (AIP/SIP). On the other hand, an asymptomatic or slowly progressive ILD with respiratory function failure presented later than 3 months after initial respiratory dysfunction is defined as chronic interstitial pneumonia. Definition was made following the regulations by International Consensus Statement of Idiopathic Pulmonary Fibrosis of the American Thoracic Society and the European Respiratory Society[18]. Informed consent was obtained from study participants. The institutional review board approved the study.

Laboratory tests. The anti-MDA5 (melanoma differentiation-associated gene 5) antibody was detected by ELISA using recombinant MDA5 antigen as described[19]. Additionally, blood tests including erythrocyte sedimentation rate (ESR), albumin, creatine kinase (CK), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and antibodies to nuclear antigen (ANA) levels and extractable nuclear antigen (ENA) were performed by standard protocols. The HRCT findings were scored independently by 2 thoracic radiologists who did not know the patients' diagnosis or clinical course, with more than 10 years of experience in CT interpretation[20,21].

Statistical analysis. Statistical analysis was performed using the Fisher's exact test for the comparison of frequencies, the t test for the comparisons of mean values, and the Mann-Whitney U test for the comparisons of median values. Data management and analysis were performed using SPSS 13.0 software. P values < 0.05 indicated statistical significance.

RESULTS

Clinical characteristics associated with patients with DM/CADM. Our consecutive cohort of patients consisted of 45 (12 male, 33 female) with classic DM and 67 (26 male, 41 female) with CADM. The average onset age of DM and CADM was 50.40 ± 2.27 years and 46.03 ± 1.64 years, respectively.

In our study, 28 cases (25%) had cutaneous ulcerations widely distributed over the body, including auricle, digital pulp/lateral nailfolds, anterior portion V area, and trunk as well as the dorsal-lateral knuckles, a preferential location (26/28, 92.9%) of Gottron papules and/or Gottron sign.

Among 92 patients, including 36 with classic DM and 56 with CADM, Gottron papules/Gottron sign without ulceration was detected in 31 of DM and 35 of CADM, while ulcerative Gottron papules/Gottron sign was detected in 5 of DM and 21 of CADM patients. No significant difference in the incidence of Gottron papules/Gottron sign without ulceration between DM and CADM (68.9% vs 52.2%) was observed, while the occurrence of ulcerative Gottron papules/Gottron sign was significantly higher in CADM than in DM (31.3% vs 11.1%, $p = 0.013$).

Of the 26 patients with ulcerative Gottron papules/Gottron sign, 10 (38.5%) who were diagnosed as CADM had deep ulceration with or without necrotic crust (Figure 1A and Figure 1B). Eleven patients (42.3%) who had ulcers over both the Gottron papules/Gottron sign and elsewhere (auricle, digital pulp/lateral nailfolds, anterior portion V area, trunk) were detected in 3 patients with DM and 8 with CADM.

In 3 of 26 cases with ulcerative Gottron papules/Gottron sign, skin biopsies were performed on the site of ulceration. The results revealed vasculopathy. One biopsy showed epidermal necrosis and multiple venule emboli with sparse inflammatory infiltration and rare interface change (Figure 2A), whereas the other 2 showed mild interface change, thickening of the vascular walls, and intravascular thrombus involving small vessels (Figure 2B). Supplementary Figure 1 shows that the interface change, a main histopathologic feature of Gottron papules, was adjacent to the vasculopathy in nonulcerated areas (available online at jrheum.org).

Characterization of ILD in DM/CADM patients with ulcer-

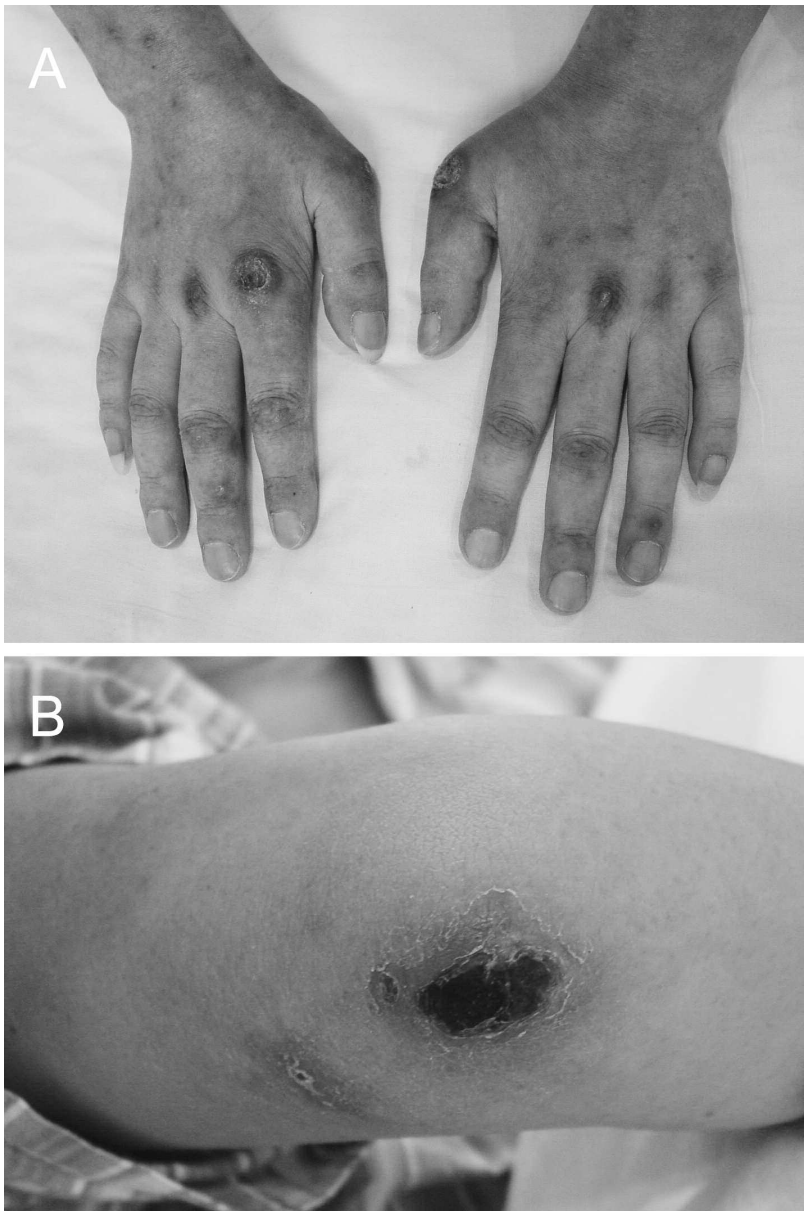

Figure 1. Patients with ulcerative Gottron papules/Gottron sign. A. Patient with clinically amyopathic dermatomyositis and Gottron sign with deep ulceration at the metacarpophalangeal joint area. B. Necrotic crust at the elbow joint.

ative Gottron papules/Gottron sign. The DM/CADM patients with ulcerative Gottron papules/Gottron sign showed higher prevalence of ILD (26/26, 100%). In most patients (92.3%), ILD onset was concomitant with a diagnosis of DM/CADM. By contrast, a lower occurrence of ILD was observed in patients with Gottron papules/Gottron sign without ulceration (35/66, 53.0%; Table 1).

The occurrence of AIP/SIP in the patients with ulcerative Gottron papules/Gottron sign was significantly higher than in the group of Gottron papules/Gottron sign without ulceration (19/26 vs 2/66, $p < 0.001$). Moreover, 10 patients with deep or necrosis ulcerative Gottron papules/Gottron sign were all complicated with AIP/SIP.

We analyzed HRCT scores in DM/CADM–ILD patients with Gottron papules/Gottron sign. HRCT scores in patients with ulcerative Gottron papules/Gottron sign were higher than in those without ulceration (mean ± SD, 98.4 ± 79.6 vs 31.1 ± 46.7; $p < 0.001$).

Characterization of other clinical manifestations with ulcerative Gottron papules/Gottron sign. Our data also showed that extrapulmonary symptoms, including fever (21/26 vs 2/66, $p < 0.001$) and arthralgia (21/26 vs 30/66, $p = 0.002$),

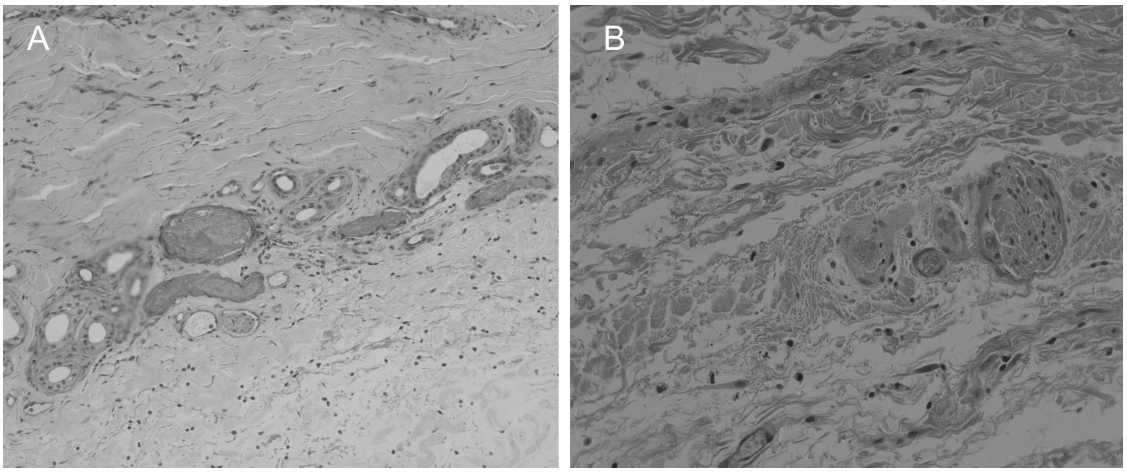

Figure 2. The biopsy results of the patients with ulcerative Gottron papules/Gottron sign revealed vasculitis or vasculopathy. A. One biopsy showed epidermal necrosis and multiple venule emboli with sparse inflammatory infiltration. B. Another biopsy showed mild interface change, thickening of the vascular walls, and intravascular thrombus involving small vessels.

Table 1. Clinical characteristics of the patients with DM/CADM who had Gottron papules/Gottron sign, with or without ulceration. Data are n (%) unless otherwise indicated.

Characteristics	Gottron Papules/Gottron Sign without Ulceration, n = 66	Ulcerative Gottron Papules/Gottron Sign, n = 26	p
Age at onset, yrs, mean ± SD	45.9 ± 13.5	50.4 ± 15.0	0.101
CADM	35 (53.0)	21 (80.8)	0.031
Periorbital heliotrope erythema	65 (98.5)	25 (96.2)	1.000
Fever	2 (3.0)	21 (80.8)	< 0.001
Arthralgia	30 (45.5)	21 (80.8)	0.002
ILD	35 (53.0)	26 (100)	< 0.001
AIP/SIP	2 (3.0)	19 (73.1)	< 0.001
Internal malignancy	7 (10.6)	0	0.185

DM: dermatomyositis; CADM: clinically amyopathic DM; ILD: interstitial lung disease; AIP/SIP: acute interstitial pneumonia/subacute interstitial pneumonia.

were more common in DM/CADM patients with ulcerative Gottron papules/Gottron sign than in those without ulceration (Table 1).

We next analyzed cancer locations and histological types among the patients having Gottron papules/Gottron sign without ulceration. We found breast cancer (2), nasopharyngeal carcinoma (2), lung cancer (1), ovarian cancer (1), and metastatic cancer of the liver (1). In those malignant patients, only 2 had cutaneous ulceration (superficial, painless erosions on the chest and arms). No patient with ulcerative Gottron papules/Gottron sign had cancer.

Laboratory findings of the DM/CADM patients with ulcerative Gottron papules/Gottron sign. We also focused on the laboratory results of 92 patients who had Gottron papules/Gottron sign with or without cutaneous ulcerations. No significant differences were detected in the 2 groups in the levels of LDH (mean ± SD, 288.4 ± 105.2 vs 297.5 ± 179.1; p = 0.808) and AST (mean ± SD 107.5 ± 149.2 vs 75.0 ± 89.0; p = 0.201; Table 2).

In the patients with ulcerative Gottron papules/Gottron sign, the white blood cell counts (4.2 ± 1.6 vs 6.9 ± 2.9; p < 0.001) and CK levels (198.0 ± 377.7 vs 1364.0 ± 2477.0; p = 0.019) were significantly lower, while the ESR (25.7 ± 16.1 vs 15.3 ± 13.6; p = 0.004) and serum ferritin were significantly higher (665.2 ± 433.5 vs 256.2 ± 279.0; p < 0.001) compared to the Gottron papules/Gottron sign without ulceration (Table 2).

The positive rate of anti-MDA5 antibody was significantly higher in the group with ulcerative Gottron papules/Gottron sign than in those without ulceration (88.5% vs 6.1%;

Table 2. Laboratory findings of the patients with DM/CADM and Gottron papules/Gottron sign with or without ulceration. Data are mean ± SD, unless otherwise indicated.

	Gottron Papules/Gottron Sign without Ulceration, n = 66	Ulcerative Gottron Papules/Gottron Sign, n = 26	p
CK, IU/l	1364.0 ± 2477.0	198.0 ± 377.7	0.019
LDH, IU/l	297.5 ± 179.1	288.4 ± 105.2	0.808
AST, IU/l	75.0 ± 89.0	107.5 ± 149.2	0.201
WBC, × 10^9	6.9 ± 2.9	4.2 ± 1.6	< 0.001
ESR, mm/h	15.3 ± 13.6	25.7 ± 16.1	0.004
Ferritin, μg/l	256.2 ± 279.0	665.2 ± 433.5	< 0.001
Anti-MDA5 antibody, n (%)	4 (6.1)	23 (88.5)	< 0.001
ANA, n (%)	19 (28.8)	3 (11.5)	0.106

DM: dermatomyositis; CADM: clinically amyopathic DM; CK: creatine kinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; WBC: white blood cell count; ESR: erythrocyte sedimentation rate; MDA5: melanoma differentiation-associated gene 5; ANA: antinuclear antibodies.

$p < 0.001$; Table 2). In contrast, there was no significant difference in the positive rate of ANA between the 2 groups (11.5% in ulcerative Gottron papules/Gottron sign vs 28.8% in Gottron papules/Gottron sign without ulceration; $p = 0.106$). The same was true for the rate of ENA between the 2 groups.

Prognosis of the patients with DM/CADM with ulcerative Gottron papules/Gottron sign. During the followup, 8 (30.8%) of the 26 patients with DM/CADM having ulcerative Gottron papules/Gottron sign were dead. The direct causes of death included ILD and its complications, i.e., respiratory failure, pneumomediastinum, or secondary infection. In the DM/CADM group who had Gottron papules/Gottron sign without ulceration, 1 of the 66 (1.5%) patients died, of nasopharyngeal carcinoma.

The cumulative survival rate of the subsets with ulcerative Gottron papules/Gottron sign was significantly lower than that of the subsets without ulceration ($p < 0.001$; Figure 3).

DISCUSSION

Heinrich Gottron, in 1931, was one of the first to describe the cutaneous manifestations of DM in detail, including the hallmark atrophic violaceous papules located at the dorsal-lateral knuckles, later called Gottron papules. Previous studies indicated that various subtle skin impairments may provide clinicians and patients with important diagnostic and prognostic information[7,14,22,23,24]. However, Gottron papules or Gottron sign do not include cutaneous ulcerations. In our study, 112 Chinese adult patients with DM or CADM were evaluated for ILD upon admission and during followup, and we observed that DM/CADM patients with ulcerative Gottron papules/Gottron sign had a high incidence of ILD and mortality. A question therefore remained whether the ulcerative Gottron papules/Gottron sign can be classified into a new category because we did observe clinical symptoms, laboratory findings, and prognosis in the patients with DM/CADM who had the exclusive rash.

Loss of dermis and epidermis, often combined with loss of the underlying tissues, is a typical manifestation of cutaneous ulceration[25]. Many factors can lead to the occurrence of cutaneous ulceration in patients with DM such as vasculitis[26], vasculitis secondary to calcinosis[27], or scratching caused by pruritus and ischemia. Narang, *et al*[28] recently reported that 28% of the patients with DM had cutaneous ulcers. Of them, 56% had ulcers over the Gottron papules and extensor surface. In agreement with previous reports[26,29], we also found that the ulceration is widely distributed all over the body, including auricle, digital pulp/lateral nailfolds, trunk, anterior portion V area, trunk, as well as the dorsal-lateral knuckles, a preferential location of Gottron papules and/or Gottron sign.

We reviewed the history of the patients with ulcerative Gottron papules and Gottron sign. The Gottron papules and Gottron sign were preceded by the ulcers (Supplementary Figure 2, available online at jrheum.org), or appeared simultaneously. Skin biopsy of ulcerative Gottron papules and Gottron sign showed that interface change in nonulcerated areas was adjacent to the vasculopathy (Supplementary Figure 1, available online at jrheum.org).

Vasculitis is considered a major cause of the cutaneous ulcerations in DM/CADM. However, true vasculitis with fibrinoid necrosis of vessel walls and leukocytoclastic figures was observed in only 3% of the patients with skin necrosis or ulcers. Most of these cases showed obliterative microvasculopathy, such as thickening of vascular wall obstruction or narrowing of vascular lumen or perivascular lymphocytic infiltration[26,28]. In our study, skin biopsy of ulcerative Gottron papules/Gottron sign confirmed the presence of vasculopathy and intraluminal thrombosis. The lesions were often painful, especially the cutaneous necrosis, and healed slowly after skin biopsy. In fact, results from skin biopsy are valuable but are not a gold standard for diagnosis. Recently, a general population-based study demonstrated an increased

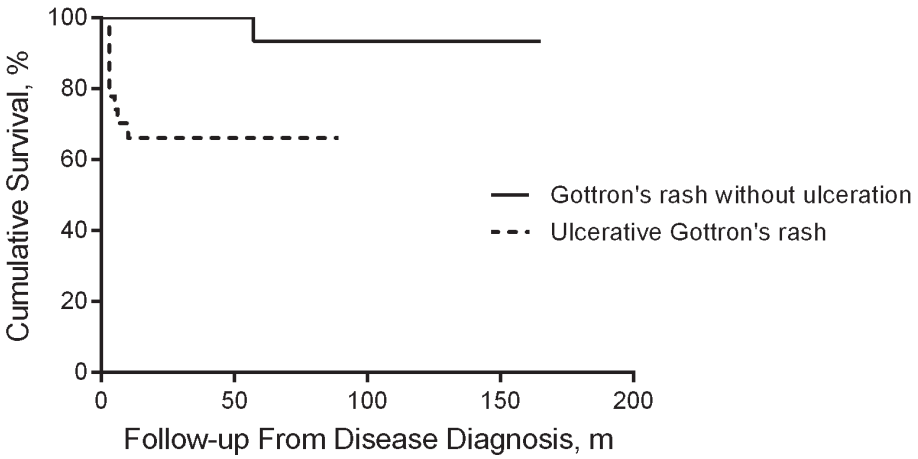

Figure 3. The cumulative survival rate of the subsets with ulcerative Gottron papules/Gottron sign was significantly lower than that of the patients with Gottron papules/Gottron sign without ulceration.

risk of venous thromboembolism (VTE) in patients with inflammatory myopathies, especially within the initial years of diagnosis[30]. This calls for increased vigilance in monitoring VTE, a potentially preventable complication in individuals with inflammatory myopathies. Reports suggest that certain skin impairments (vesiculo-bullous change, chronic cutaneous ulceration, and malignant erythema) could be cutaneous features that are associated with a higher risk of internal malignancy[31,32,33]. The distribution and severity of cutaneous ulcerations related with Gottron papules/Gottron sign are probably different from those that occur in patients with malignancy. Truncal cutaneous necrosis and cutaneous leukocytoclastic vasculitis would be risk factors for malignancy in DM/CADM[33,34]. Our study showed that ulcerative Gottron papules/Gottron sign were detected in 5 of DM and 21 of CADM patients and even to be necrosis in 38.4% of them. None of the patients with ulcerative Gottron papules/Gottron sign had cancer. Two patients with malignancy had skin ulceration in the form of superficial, painless erosions on the chest and arms. Unfortunately, the patients with malignancy did not undergo the skin biopsy at the location of ulceration. Our patient numbers might be too small to further demonstrate the difference of pathology and mechanism between ulcerative Gottron papules/Gottron sign and ulceration related to malignancy.

DM/CADM is often associated with ILD and is known to cause significant organ damage, adversely affecting the prognosis of patients with ILD. Thus, early diagnosis and treatment is critically important. Reports of Asian populations have defined an association with CADM and a high incidence of ILD; the latter was often rapidly progressive and fatal, and related to the frequency of anti-MDA5 antibody positivity. This is not the experience in white populations[35]. Anti-MDA5 antibody is even more intriguing because there are ethnic and/or geographic differences in the clinical features of patients with DM and CADM[36]. Several studies report that anti-MDA5 antibody was strongly associated with ILD-related early death and poor prognosis[37,38,39]. A Japanese dermatomyositis cohort showed that skin ulcers are associated with reduced survival, and that the majority of these patients died of ILD[29]. A study has confirmed the strong association between anti-MDA5 antibodies and cutaneous ulcers[28], and that ulcers are associated with the presence of ILD primarily in anti-MDA5–positive patients.

In our study, DM/CADM with ulcerative Gottron papules/Gottron sign were reported to be complicated by AIP/SIP, especially in those patients with deep ulceration or cutaneous necrosis. The positive rate of anti-MDA5 antibody was significantly higher in the group with ulcerative Gottron papules/Gottron sign than in those without ulceration. Our previous studies found that adult patients with circulating antibodies to MDA5 have a high incidence of cutaneous ulceration[38]. In addition, not only is the anti-MDA5 antibody–positive rate associated with the incidence of cutaneous ulcerations, but the antibody level is well correlated with the severity of the cutaneous ulcerations. Several studies demonstrated that the similar obliterative microvasculopathy may be involved in the pathogenesis of ILD in the MDA5-positive patients, and have also postulated a role for endothelial injury in the development of ILD and cutaneous ulcers[28,39,40]. Chaisson, *et al* suggested that the link between all of these clinical findings was autoimmunity to MDA5[36]. It is possible that blood vessel exposure to local interferon might induce mild endothelial cell injury that leads to overexpression and/or modification of MDA5, resulting in loss of tolerance and immune response under a corresponding genetic background. It is possible that unique patterns of skin disease expression might be partly explained by characteristic distribution(s) of antigen expression in target cells of the skin, but this hypothesis needs to be tested[26,41]. One study supported aggressive screening for ILD in anti-MDA5–positive patients with cutaneous ulceration[28].

The prevalence of CADM is higher than reported in the past, because clinicians have become increasingly familiar with the condition. Klein, *et al* reported the number of patients with CADM seen in dermatology practices [56 of 83 (68%)] differed significantly from the subsets seen in rheumatology [3 of 27 (3%)][42]. In our cohort, a majority of the study subjects had clinically amyopathic DM rather than classic DM. The patients who presented exclusively or predominantly with cutaneous conditions were seen in dermatology practices versus other medical disciplines, potentially contributing to bias.

Patients with DM/CADM who have ulcerative Gottron papules/Gottron sign and who exhibit fever and arthralgia and present with anti-MDA5 antibody and baseline lower CK level are at increased risk of ILD, especially with AIP/SIP. The patients with DM/CADM who have Gottron papules/Gottron sign combined with cutaneous ulceration need to be distinguished from the typical rash without ulcerations. We suggest a new designation for this subgroup of patients, to draw attention to this clinical entity.

Because ILD can be rapidly fatal in this setting, it is important to understand the relationships that exist between ulcerative Gottron papules/Gottron sign, anti-MDA5 antibody, and ILD in patients with DM/CADM. Exploring the characteristics of early cutaneous manifestation (ulcerative Gottron papules and Gottron sign) might be useful for the early diagnosis of ILD.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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