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Acute onset/flares of dermatomyositis following ingestion of IsaLean herbal supplement: Clinical and immunostimulatory findings

To the Editor: The use of complementary and alternative medicine has gained popularity over the past few decades.[1] Herbal and dietary supplements—the most common form of complementary and alternative medicine—are known to have various adverse medical and dermatologic[2] effects. Previous literature has reported the acute onset/flare of autoimmune cutaneous disease, including pemphigus vulgaris,[3] dermatomyositis,[3] and systemic lupus erythematosus, with the ingestion of known immunostimulatory herbal supplements. Although tumor necrosis factor-α (TNF-α) is thought to be a mediator[4] in the pathogenesis of autoimmune cutaneous disease, the exact mechanism by which herbal supplements cause the clinical precipitation or exacerbation of these diseases has never been described.

We observed 3 patients with an acute onset (2 cases) or flare (1 case) of their dermatomyositis after ingestion of the widely popular herb-based weight loss product IsaLean (Isagenix, Gilbert, AZ) (Fig 1). Patient 1 had classic dermatomyositis (positive for PM-scl 100 antibody), patient 2 had amyopathic dermatomyositis (negative for Jo-1 antibody), and patient 3 had undifferentiated connective tissue disease with features of amyopathic dermatomyositis and lupus pernio (positive for ANA [titer, 1:320], positive for SS-A (>8), negative for Scl-70, and negative for a myositis panel). The purpose of this study was to investigate and characterize the pathophysiologic mechanism of IsaLean underlying the acute onset or flare of dermatomyositis that was witnessed in all 3 patients.

Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples obtained from 5 patients with dermatomyositis and 5 control subjects. The PBMCs were stimulated with increasing concentrations of IsaLean (0, 0.05, 0.5, and 5 μg/mL) to measure the levels of key pathogenic cytokines (TNF-α, interferon-α [IFN-α], and interferon beta [IFN-β]) secreted. In addition, the effect of anti–Toll-like receptor 4 (TLR4) and 2 antimalarials used in the treatment of dermatomyositis—quinacrine and hydroxychloroquine—on cytokine production was examined after incubation of PBMCs with either lipopolysaccharide (LPS) or IsaLean alone.

Our results showed that IsaLean-treated cells secrete significantly higher levels of TNF-α, IFN-α, and IFN-β. IsaLean significantly increased TNF-α

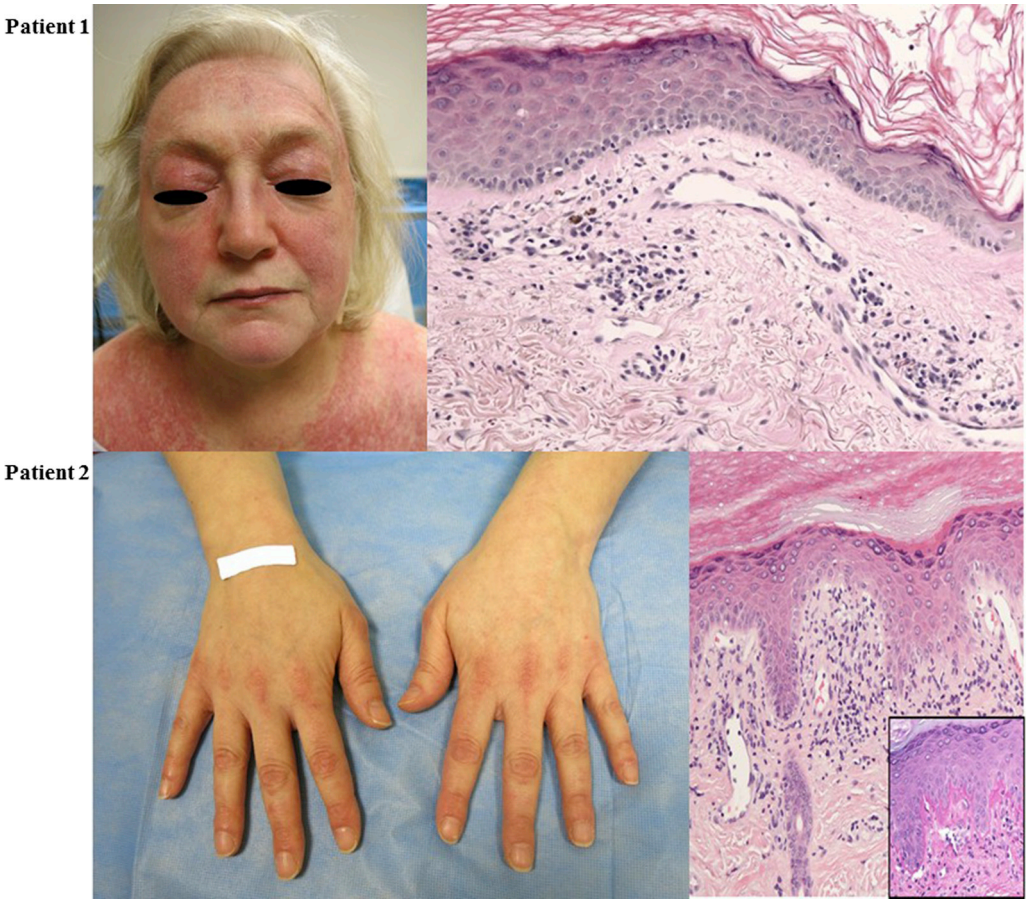

Fig 1. Photograph of patient 1 showing facial erythema, heliotrope rash, and V sign. Skin biopsy specimen of patient 1 (hematoxylin-eosin stain; original magnification: ×20) showing subtle vacuolar changes within the basal keratinocytes, dilated blood vessels, and sparse superficial lymphocytic infiltrates. Photograph of patient 2 showing the Gottron sign on the dorsal aspect of the hands. Skin biopsy specimen of patient 2 (hematoxylin-eosin stain; original magnification: ×20) with dermatomyositis showing interface dermatitis with vacuolization of basal keratinocytes, dilated blood vessels, and sparse superficial lymphocytic infiltrates (poikilodermatous changes); a thickened basement membrane is seen in the insert (periodic acid–Schiff stain; original magnification: ×40).

secretion from cells of patients with dermatomyositis and control subjects at concentrations of 0.5 μg/mL ($P < .001$) and 5 μg/mL ($P < .001$) but not at 0.05 μg/mL ($P = .0711$) compared with cells not incubated with IsaLean. IsaLean significantly increased secretion of IFN-α and IFN-β from cells of patients with dermatomyositis and control subjects at all of the tested concentrations of IsaLean ($P < .001$). Anti-TLR4 and quinacrine suppressed secretion of TNF-α from IsaLean- ($P < .001$ and $P < .001$, respectively) and LPS-stimulated cells ($P < .01$ and $P < .05$, respectively), but the same effect was not seen with hydroxychloroquine (Fig 2).

The results of our study confirmed the immunostimulatory properties of IsaLean in vitro by demonstrating a statistically significant dose-response elevation of all 3 cytokines. Although both LPS and IsaLean produce an increase in TNF-α concentration, they each have different immunostimulatory properties. The proinflammatory effect of LPS is mediated by both TLR4 and Toll-like receptor 2 receptors, which explains why there is only partial suppression of TNF-α with the addition of anti-TLR4 to LPS-treated cells. When PBMCs were incubated with IsaLean, on the other hand, there was a nearly undetectable TNF-α concentration after suppression with anti-TLR4, suggesting that the proinflammatory effect of IsaLean is largely mediated by TLR4 receptor agonism. Our results also confirm the therapeutic effect of quinacrine, which significantly reduced TNF-α production by IsaLean-stimulated PBMCs.

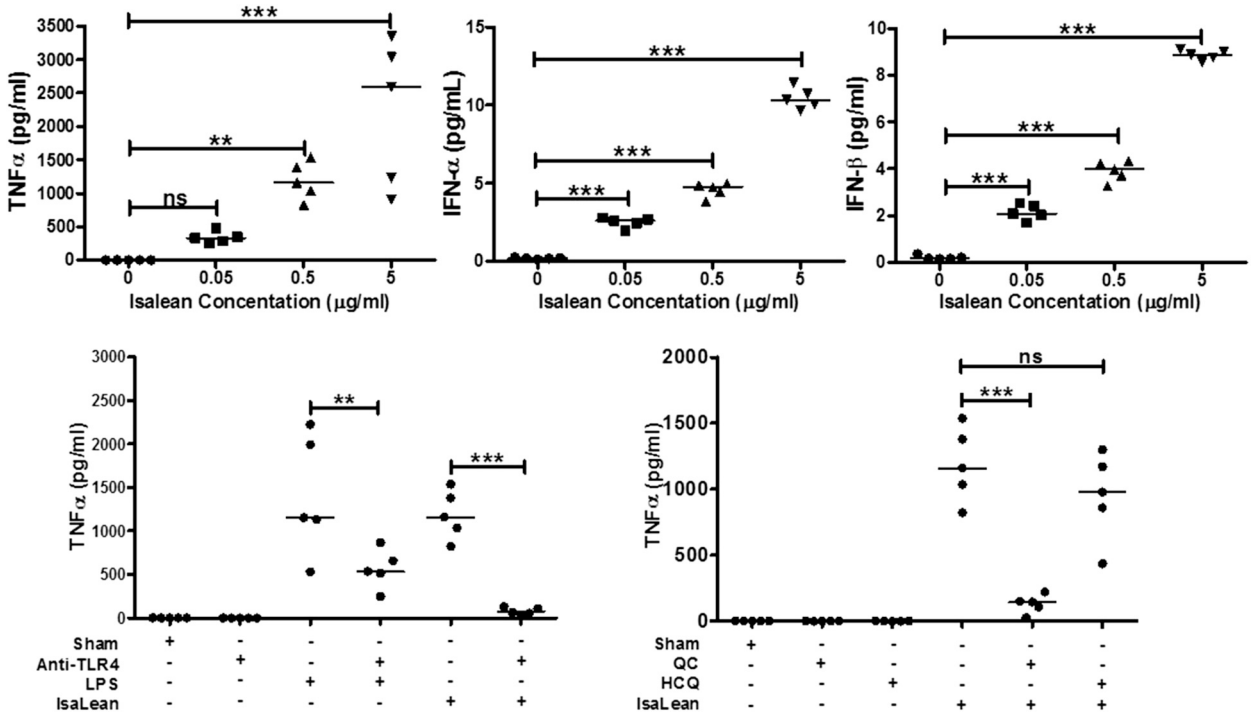

Fig 2. Secretion of tumor necrosis factor-α (TNF-α), interferon-α (IFN-α), and interferon beta (IFN-β) from unstimulated peripheral blood mononuclear cells (PBMCs) of patients with dermatomyositis and from PBMCs of the same patients that have been stimulated with different concentrations of IsaLean. Effects of anti−Toll-like receptor (TLR4) antibody versus sham on secretion of TNF-α from the unstimulated and lipopolysaccharide (LPS)- and IsaLean-stimulated PBMCs of patients with dermatomyositis. Effects of quinacrine (QC) and hydroxychloroquine (HCQ) versus sham on secretion of TNF-α from the unstimulated and IsaLean-stimulated PBMCs of patients with dermatomyositis (n = 5). *ns*, Not significant.

These findings are consistent with the prior hypothesis that quinacrine provides clinical benefit through effects on the TLR4 receptor.[5]

In conclusion, ingestion of IsaLean is associated with clinical onset or flare of dermatomyositis that is best explained by TLR4 receptor agonism, with significant elevation of proinflammatory cytokines.

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Possible long-term sequelae in hand, foot, and mouth disease caused by Coxsackievirus A6

To the Editor: We read with interest a paper disclosing the enterovirus (EV) types responsible for hand, foot, and mouth disease (HFMD) in Chinese children.[1] Among 2571 EV-positive cases, three quarters were attributed to 3 predominant types: Coxsackievirus (CV)-A16, CV-A6, and EV-A71. However, the report did not deal with EV-related atypical exanthems[2] nor with the possible long-term consequences of these infections.

We studied the clinical and virologic features of patients with skin/mucosal lesions seen at the Dermatology Department of the San Martino Hospital (Genoa, Italy) between November 2014 and March 2016. Clinical data and pictures of skin/mucosal lesions were acquired. To corroborate the diagnosis, blood was drawn for serology and polymerase chain reaction for viral genomes (all members of the EV genus[2] and other exanthem-inducing agents: cytomegalovirus, Epstein–Barr virus, human herpesviruses-6, -7, and -8, and parvovirus B19 [PVB19]). Fourteen cases with serology suggestive of recent enteroviral infection were selected.

Ten of the 14 cases had enterovirus RNA in plasma: sequencing identified the infecting pathogen as CV-A6. Cases 1 and 10 were also positive for PVB19. Cytomegalovirus, Epstein–Barr virus, and human herpesviruses-6, -7, and -8 could not be detected.

Investigated cases were: typical HFMD (1 case; petechial adult maculopapules or vesicles on the extensor surfaces of hands, feet, and oral mucosa), atypical HFMD (5 cases; absence of involvement of 1 typical site or involvement of adjacent sites, such as the face, scalp, and ankles), and atypical exanthems (4 cases; maculopapular eruption over the whole body). As seen in Table I, 9 cases had oral papulovesicles or petechiae, 5 cases had cutaneous erythematovesicles (on the hands and feet), 4 cases had maculopapules with petechiae, and 3 cases had erythematous papules on the trunk. Other affected body sites included the face, scalp, elbows, legs, and buttocks. Lesions were reported as burning/itchy. Two patients presenting with maculopapules on the buttocks were coinfected with PVB19. Cases 3 and 6 developed early complications—orchiepididymitis and onychomadesis, respectively. On average, clinical resolution occurred in 12 days.

The 10 patients were followed-up for 2 years. Clinical examinations highlighted conditions that may be considered sequelae of the initial infection (Table I): case 3 developed degenerative mitral valve disease and maintained low-level CV-A6 viremia, indicating that the virus had established low-level persistence in the host; cases 2, 8, and 10 developed persistent myalgia/arthralgia. Notably, case 2 (negative at the onset for antinuclear antibodies, antineutrophil cytoplasmic antibodies, and rheumatoid factor antibodies) developed symmetric polyarthritis with rheumatoid factor positivity and antibodies to cyclic citrullinated peptides. PVB19 was not detected in any cases.

The variable clinical expression at onset[3] and the development of changeable longstanding sequelae in patients infected by the same virus type could be linked to the unpredictable expression pattern of the multiple EV receptor types in different subjects.[4,5]

In closing, severe atypical HFMD may be followed by long-term sequelae. It is therefore important to recognize different HFMD forms and to obtain detailed virology reports. It is also important to use long-term follow-up programs to uncover the possible longstanding sequelae of this condition that is emerging in adults.

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