

# Erythema Multiforme Induced by Topical Application of Viru-Merz® Ointment

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Viru-Merz® ointment, 1% tromantadine hydrochloride, is a topical antiviral agent used for recurrent herpes simplex. There are many reported cases of contact dermatitis by tromantadine. But erythema multiforme-like eruptions in association with Viru-Merz® ointment has not been reported. A 31-year-old woman, who applied Viru-Merz® ointment for a recurrent herpes simplex labialis, developed an allergic contact dermatitis. Erythema multiforme like eruptions with typical target feature followed around the eczematous lesions on the face, and spread progressively on the neck and trunk. A patch test revealed positive reaction to Viru-Merz® ointment. (*Ann Dermatol* 13(1) 66-69, 2001).

*Key Words* : Tromantadine, Contact dermatitis, Erythema multiforme

Viru-Merz® ointment, 1% tromantadine hydrochloride, is a topical antiviral agent used for recurrent herpes simplex. Since Fanta et al reported a case of contact dermatitis by this ointment in 1976, several cases have been reported. But erythema multiforme-like eruptions in association with Viru-Merz® ointment-induced contact dermatitis has not been reported. We report a case of erythema multiforme induced by this ointment. She developed contact dermatitis after using Viru-Merz® ointment, and then Erythema multiforme-like eruptions. To the best of our knowledge, this is the first report on the erythema multiforme in relation with allergic contact dermatitis by Viru-Merz® ointment.

## CASE REPORT

A 31-year-old woman presented with acute pruritic eczematous lesions with edema and grouped vesicles on the perioral area, and multiple erythematous targetoid lesions on her face and trunk. She had suffered from recurrent herpes labialis for ten years and treated with acyclovir ointment. Three weeks before a visit to our hospital, pruritic grouped vesicles developed on her lower lip, and healed with topical acyclovir ointment, but one week later vesicular lesion recurred again on right upper lip. Viru-Merz® ointment prescribed at a private clinic was applied for 2 days. After this, the lesions were aggravated with sudden swelling and severe oozing vesicles on the lips. Multiple erythematous targetoid lesions also developed on the face and trunk two days before visit.

Cold urticaria and allergy to beer and sulfa drugs were on her past medical history. But family history was unremarkable. Physical examination revealed grouped oozing vesicles within a well-demarcated edematous plaque on the right perioral area and multiple variable sized wheals and targetoid lesions on the face, neck and upper trunk (Fig. 1). Laboratory tests showed normal or negative blood cell count, liver function test, urinalysis and erythro-

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cyte sedimentation rate. And anti-herpes virus IgG was positive. A biopsy specimen from the targetoid lesion on her back showed spongiosis and a few necrotic keratinocytes in the epidermis, vacuolar changes in the basal layer and mononuclear inflammatory cells infiltrate in dermoepidermal junction and perivascular areas in the upper dermis(Fig. 2A, 2B). Patch tests with Korean standard series, acyclovir ointment and Viru-Merz®

ointment showed a positive reaction to Viru-Merz® ointment only(Fig. 3). She was diagnosed as erythema multiforme induced by contact dermatitis due to Viru-Merz® ointment and treated with oral steroids and antihistamines. The lesions disappeared in 10 days during the treatment. After the therapy, she had several attacks of herpes labialis, however, erythema multiforme like eruptions did not develop again.

**Fig. 1.** Grouped oozing vesicles within a well-demarcated edematous plaque on the right perioral area and multiple variable sized wheals and targetoid lesions on the face.

**Fig. 3.** Patch test with Viru-Merz® ointment showed a positive reaction.

**Fig. 2.** A biopsy specimen from the targetoid lesion on her back(Fig 2A, arrow) showed spongiosis and a few necrotic keratinocytes in the epidermis, vacuolar changes in the basal layer and mononuclear inflammatory cells infiltrate in dermoepidermal junction and perivascular areas in the upper dermis(Fig. 2B).

## DISCUSSION

Viru-Merz® ointment (Merz & Co. Frankfurt/Main, Germany) is a commercial

name of 1 % tromantadine hydrochloride (N-2-dimethyl-aminoethoxyacetyl-amino-amantadine), inhibitor of early and late events in herpes simplex virus replication<sup>1</sup>. It is used in the treatment of all skin disorders caused by the herpes simplex virus, as well as herpetic keratitis.

Fanta et al<sup>2</sup> reported a study of 240 patients with herpes simplex treated with tromantadine, in which 12 cases developed an allergic contact dermatitis. Since then, many cases of contact dermatitis caused by the agent have been reported<sup>3,6</sup>. Santucci et al<sup>4</sup> reported that the sensitization to tromantadine in molecular basis is due to the ring structure, adamantane, and not to the amine group present. Acute contact dermatitis by topical tromantadine is frequently reported, but systemic type contact dermatitis was extremely rare<sup>7</sup>.

The patch test by Viru-Merz® ointment in this patient showed a typical allergic contact dermatitis. The target shaped lesions in this patient was compatible to EM on the base of clinical feature and histopathological findings. Several contact allergens including plants, exotic woods, various chemical compounds have been reported to produce erythema multiforme-like eruptions in the literature<sup>8</sup>. In Korea, erythema multiforme-like eruptions related to application of Rhus, Gramoxone and diphenylcyclopropanone (DPCP) have been reported<sup>9,10</sup>. The clinical severities of the erythema multiforme by contact allergen have been reported to be from a mild localized exanthem to life-threatening toxic epidermal necrolysis. They were usually superimposed on acute allergic contact dermatitis. In this patient, erythema multiforme eruptions also started from the contact site of perioral area, and spread into the other sites of face, neck and trunk. The pathogenesis of erythema multiforme in relation to allergic contact dermatitis remains unclear. Irvine et al<sup>11</sup> suggested that a circulating antibody to the absorbed allergen could result in immune complex formation and its subsequent deposition in the microvasculature, resulting in type 3 hypersensitivity reaction.

The erythema multiforme caused by contact dermatitis might be differentiated from herpes associated erythema multiforme (HAEM). It is strongly sug-

gested that erythema multiforme which occurred in this patient should be related to the contact dermatitis by Viru-Merz® ointment, rather than that of HAEM. The following is the reasons. First, she had a single episode of erythema multiforme eruptions on the face and trunk, which were not predilection sites for HAEM<sup>12</sup>. Second, the initial eruption of erythema multiforme developed on the applied area of Viru-Merz® ointment, and similar eruptions spread over the trunk later. Third, in our follow-up observation, recurrent attacks of herpes labialis did not accompany with erythema multiforme-like eruptions after contact dermatitis episode.

As far as we know, this is the first case of erythema multiforme in association with Viru-Merz® ointment-induced contact dermatitis.

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