Erythema Multiforme Following Allergic Contact Dermatitis: Case Report and Literature Review

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Sir,

Erythema multiforme (EM) is characterized by symmetrically distributed target or "iris" lesions with specific histopathological features that may be accompanied by mucous membrane involvement (1). The most common and best-described cause of EM is a recent herpes simplex virus (HSV) type 1 or type 2 infection. Other common factors comprise mycoplasma infection, drug hypersensitivity, particularly to anticonvulsives and antibiotics, vaccination and drug-virus interaction (2). EM induced by contact dermatitis is rare (3).

CASE REPORT

A 14-year-old female patient was admitted to the outpatient clinic of our department with a severe erosive dermatitis on the head and neck (Fig. 1). A week earlier she had applied a black hair dye that had immediately caused itching sensations and erythema of the whole capillitium. The pre-auricular and jugular lymph nodes were enlarged and sensitive to palpation. Interestingly, the patient developed additional lesions 3 days later (13 days after application of the hair dye): these lesions were located mainly on her arms and hands and appeared as targetoid lesions characteristic for EM (Fig. 2). Oral and ocular mucosae were not affected. IgM and IgG values to HSV type 1 and type 2 were negative. She was not taking any medication and had not had any vaccination recently. The only cause of EM determined was extensive contact allergy to a strong allergen. Although the acute dermatitis resolved quickly after topical treatment with potent glucocorticosteroids, the targetoid lesions were followed by hyperpigmentation, which remained for several months. Ingredients of hair dyes were strongly suspected, and since the dye was black, the suspected causative agent was paraphenylene diamine (PPD), which later proved to be a constituent of the applied dye. Thorough examination of the whole skin revealed a depigmented area on her right upper arm in the shape of a dolphin. Five years previously she had had a semi-permanent henna tattoo painted on the right upper arm; a dolphin, during her holidays in Greece. The tattoo had been repainted shortly before the patient travelled home, as is the custom with this sort of souvenir (4). Dermatitis had subsequently developed in the area of the tattoo, which was treated topically with steroids and antibiotics. The dermatitis then induced a post-inflammatory pseudo-leucoderma. This history suggested sensitization to PPD caused by the paint-on henna tattoo.

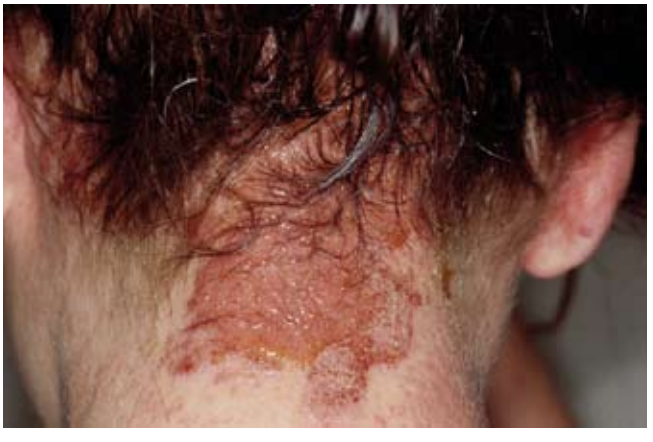

Fig. 1. Extensive contact dermatitis caused by dark hair dye: the capillitium and the neck of the patient show multiple vesicles, erosions on widespread erythema 10 days after application of the hair dye.

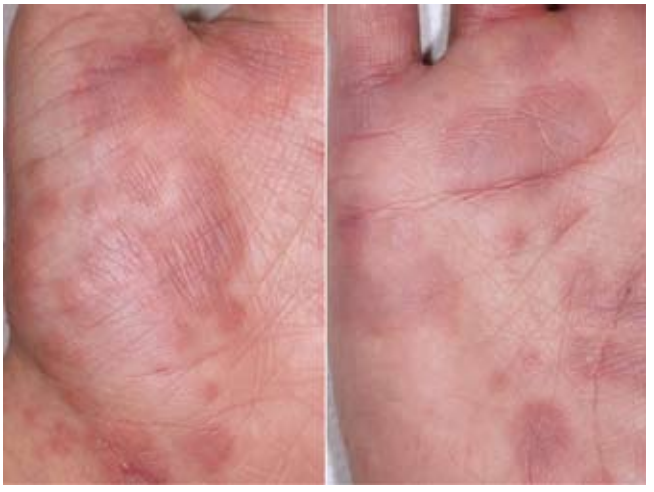

Fig. 2. Multiple targetoid lesions typical for erythema multiforme (EM) on the palms of the hands 13 days after application of the hair dye.

Once the skin lesions had resolved, the suspected PPD allergy was confirmed by patch-testing. Because of the extensive contact dermatitis experienced by the patient we diluted the usually recommended test concentration of 1% PPD in petrolatum, which had been eliminated from the standard series due to its sensitization potential (5) to 0.1, 0.25 and 0.5% PPD in petrolatum. This material was tested on the left upper arm; readings were performed 2 and 3 days later. The patient showed (+++)-positive patch-test reactions to all three concentrations of PPD. The patient and her mother refused any further patch-tests, as they were concerned about the strong test reactions to PPD, even though the importance of possible cross-reactivity between PPD, azo dyes and other para-amino compounds was explained.

DISCUSSION

Several allergens have been reported in the literature to cause contact dermatitis followed by EM (Table I). These are all potent sensitizers, and include metals such as nickel, exotic plants, chemicals, external antibiotics and anti-phlogistics (6). Less potent allergens may also lead to severe contact dermatitis and EM; however, in these cases repeated exposure and/or high allergen

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concentrations are essential (7). False henna-tattoos do not only contain the natural reddish henna dye 2-hydroxy-1,4-naphthochinone (Lawson) but usually also PPD, which is responsible for the black colour of the typical tattoo-paints acquired by tourists during their holidays in Mediterranean countries. It is likely that our patient developed a sensitization to PPD due to the semi-permanent henna tattoo on her arm 5 years previously and had experienced the first contact dermatitis to PPD when the tattoo was repainted, which had led to a strong inflammation. Unaware of her sensitization to PPD, she had black hair dye applied and subsequently developed a strong allergic immune response followed by the rare phenomenon of EM. After the lesions had resolved, the suspected PPD allergy was confirmed by patch-testing. Investigation of possible cross-reactivity between PPD and further para-amino compounds and hair dye ingredients would have been of great interest and value to the patient. Unfortunately, the patient and her mother refused any further patch-testing because the test reactions to PPD had been so strong and had led to temporary hyperpigmentation of the patch-test area. This is the second case of PPD-induced contact dermatitis with subsequent EM seen at our clinic (4).

EM arises during acute contact dermatitis or after the primary site of inflammation has nearly resolved. EM due to contact dermatitis shows the same features as common EM caused by infection. The underlying pathogenetic mechanism has not yet been clarified. A possible explanation is acute type IV hypersensitivity characterized by cytotoxic T cells. Another hypothesis discusses the allergen absorption through the skin and a subsequent type III allergic reaction involving circulating immune complexes that deposit in the cutaneous microvasculature (8). In fact, IgM, IgA, C3 and fibrin deposition can be detected in the superficial blood vessels of some iris lesions in EM.

The works of Aurelian et al. (9) and Brice et al. (10) have elucidated the understanding of the post-herpetic EM. HSV particles are present in peripheral blood mononuclear cells of patients with post-herpetic EM. It is thought that the fragmented form of HSV travels preferentially in CD34+ cells that differentiate into epidermal Langerhans' cells. The whole genome of HSV, however, could not be isolated from EM lesions. It is discussed that the Langerhans' cells will finally clear of the fragmented virus particles and stop maintaining an inflammatory process. At least *in vitro* it was shown that CD34+ cells became HSV-negative after 7 days in culture. In recurrent EM this feature of clearing may be altered (10, 11).

We assume that PPD might finally reach the skin at distant sites from the primary contact by travelling in peripheral mononuclear cells via the blood stream. The epidermal expression of adhesion molecule intercellular adhesion molecule-1 (ICAM-1) is increased in targetoid lesions, as is the number of CD4+ T cells (12, 13). ICAM-1 may facilitate the epidermal invasion of lymphocytes in targetoid lesions where the expression of retained allergen particles takes place. As not all patients with severe contact dermatitis or HSV infection develop an EM, there have to be predisposing factors as well. EM is particularly associated with increased expression of HLA-B15, HLA-B35 and HLA-DR53. Also, virus-drug interactions may play an important part in the pathogenesis of EM. The development of EM to amoxicillin with concurrent Epstein-Barr virus infection has been reported (14). Furthermore, photosensitivity or photoactivation and simultaneous drug intake are precipitating factors in EM. The exact pathogenetic mechanism of EM remains unclear. It is not known what initiates the inflammatory process in the skin that causes the morphology of an iris lesion and what the details of this immune reaction are. Histopathologically, increased expression of intercellular ICAM-1 and HLA-DR molecules by keratinocytes is found in the epidermis. The inflammatory infiltrate is composed of lymphocytes, mainly T-helper cells and cytotoxic T cells as well as histiocytes. There is also an increase in the number of Langerhans' cells. Further research is necessary to fully understand the underlying immune phenomenon of EM. In fact, there are case reports discussing EM as a rare variant of id-reaction in *Trichophyton mentagrophytes* infection (14). Interestingly, there are reports on EM following polymorphic light eruption (PLE), which is thought to be an abnormal immune response to an endogenous cutaneous antigen induced by UV. The development of EM undermines the theory that PLE is a T-cell mediated type IV hypersensitivity response to a photo-induced antigen within the skin (15).

Table I. *Allergens that have been reported to cause contact dermatitis followed by erythema multiforme (EM) in sensitized patients*

Chemicals	Drugs	Miscellaneous allergens	Plant allergens
Bromofluorene	Antiphlogistics (bufexamac)	Nickel	Poison ivy
Colophony	Antibiotics (lincosamine)	Rubber	Tea tree oil
Fragrances	Progesterone derivatives		Weeds
Epichlorhydrine	Acetaminophen		Primula obconica
Para-phenylene diamine	Triamcinolone acetonide		Thuja essential oil
1,2 ethanedithiole	Desoxymethasone		Alpinia galanga
Epoxy resin			

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