

Report

Dimethyl fumarate contact dermatitis of the foot: an increasingly widespread disease

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Abstract

Background Dimethyl fumarate (DMF) has been recognized as an extremely potent irritant and sensitizer found in sachets inside furniture. The first skin manifestations were correlated to contact with sofas, chairs, and other furniture. In these last years, some papers have reported a development of allergic contact dermatitis on the foot caused by DMF present in high concentration in shoes made in China.

Methods We report the case of a 37-year-old woman who presented with severe eczema on the foot shortly after having bought a new pair of shoes. The diagnosis was performed by patch tests with DMF in several dilutions, with pieces of internal and external parts of the shoes, and by chemical analysis of the shoes.

Results In the last three years, goods containing DMF increased diffusely despite the augmentation on global preventive measures by Europe.

Conclusions Therefore, new cases of contact dermatitis could be dependent on DMF, and it is of note that this allergen is not included in most series for patch testing.

Introduction

The methyl ester form of fumaric acid named dimethyl fumarate (DMF) is an effective mold-growth inhibitor, and it has a wide-spectrum biocide activity. It is used as a fungicide in order to prevent deterioration of products during transport and storage and, in particular, to preserve leather. It is contained in paper bags and can progressively evaporate contaminating leather, textiles, cosmetics, etc.

DMF is more lipophilic than monomethyl fumarate, and it shows better penetration into cells. Recently, studies have identified DMF as a potent contact sensitizer allergen responsible for epidemic contact dermatitis at concentrations as low as 1 ppm.¹⁻⁵

The aim of this paper is to report an acute case of shoe contact dermatitis by DMF, to present a concise review of the literature on DMF as a sensitizer present in several

objects, and to signal an emerging problem in order to increase the European security measures.

Report

We report the case of a 37-year-old woman who presented with severe eczema on the dorsum and the soles of both feet caused by contact with a pair of shoes made in China that she had bought a few days before (Fig. 1a,b). Some blisters were also present on the sole of the foot and on the toes. Erythematous and edematous plaques were observed on the lateral surface of the foot and the back of the fingers. On the back of the foot, lesions were present at the cross-sections of the sandal where there is contact with the skin (Fig. 1c,d).

The skin manifestations were accompanied by general symptoms, such as headache, fever, and chills. The



Figure 1 (a, b) Vesicular lesions on the sole of the foot, and the toes. (c, d) Eczematous lesions on the back of both feet

patient did not have an atopic history. The patient was treated by her family physician with general and topical cortico-steroids, a topical antimicrobial drug, and wet dressings. Despite the therapy, the lesions persisted for more than three months.

Patch testing and shoe analysis

After clearing of the dermatitis, the patient was patch tested with the standard SIDAPA series (Italian Society of Allergological, Occupational and Environmental Dermatology; F.I.R.M.A.[®], Florence, Italy) and with an extensive SIDAPA Shoes Series (F.I.R.M.A.[®]).

The presence of DMF in the shoes was suggested by the presence of DMF in the paper bag in the shoe box and by the place of origin of the shoes. The shoes' material was analyzed by chemical laboratory Buzzi spa, Prato, through headspace solid-phase micro-extraction coupled with gas chromatography mass spectrometry (HS-SPME-GC-MS).³

In order to assess whether the patient was DMF allergic, patch testing was performed according to the International Contact Dermatitis Research Group Guidelines. Briefly, DMF crystals (supplied by F.I.R.M.A.[®]) were dissolved in petrolatum, and a titration series of dilutions from 0.1% to 0.001% was used for patch tests. The same patch tests were applied on 10 normal individuals, indicated as controls. At the same time, the patient

was also patch tested with two pieces of shoes, one from the internal part and one from the external part. The series was applied to the upper back of the patient for two days using Finn-chambers (Epitest, Tuusula, Finland) on Scanpor tape[®].



Figure 2 DMF 0.1% in petrolatum after 96 h (Italian language)

Results

After 96 hours, the patient showed positive patch test reactions to the fragrance mix and nickel sulfate of standard SIDAPA patch test series. No reaction with the shoes series, whereas a strong positive reaction to DMF at the concentration of 0.1% (Fig. 2) and mild to 0.01% was observed. Patch tests with both shoes pieces were positive. Patch tests with DMF 0.1% and 0.01% pet in 10 healthy volunteers gave negative results. A diagnosis of acute allergic contact dermatitis by DMF was given.

Chemical analysis of the shoes demonstrated a concentration of DMF about 740 mg/kg, which is higher than the maximum admitted by European Union.

No relapse of the dermatitis was observed during the four-month observation period.

Discussion

The irritating and sensitizing properties of DMF were reported by De Haan *et al.*⁶ in a pilot toxicity study. DMF was shown as the most toxic fumaric derivative.

DMF may be responsible for inducing clinical manifestations, such as non-immunological urticaria, irritant, or allergic contact dermatitis at concentrations as low as 1 ppm. Recent reports have highlighted an increase of allergic contact dermatitis due to this potent sensitizer compound.^{1-5,7-11}

DMF is used as a fungicide for storage and transport of furniture made in China and imported in the European Union. Starting from 2006, cases of "epidemic" acute contact dermatitis affecting the arms, back, buttocks, legs, and feet acquired a lot of attention in Finland and the UK.¹⁻⁵ These were related to the exposition of new sofas, chairs, and other furniture manufactured in China.

Susitaival *et al.*² reported cases of patients in contact with chairs or sofas who complained of worsening of pre-existing asthma, wheezing, and sneezing.

Furthermore, a study by Foti *et al.*⁷ described the presence of DMF in working clothing, causing an occupational allergic contact dermatitis. In this report, a 40-year-old man developed dermatitis on the thighs, buttocks, scrotum, and inguinal folds a few weeks after having worn affected clothes.

In order to underline how this dermatitis has increased and become widespread in Europe, we reported an Italian case in which the cause of dermatitis resided in the shoes.

In our case, a woman presented with acute eczema with vesicles and bubbles on the foot, mainly around the shoe contact areas. Even after several months, the skin remained very sensitive.

Similar features were reported in a 62-year-old Portuguese woman by Fraga *et al.*⁸ and in another two Portu-

guese cases by Santiago *et al.*,⁹ and in a 34-year-old French woman by Vigan *et al.*¹⁰

Giménez-Arnau *et al.*¹¹ showed the prevalence of contact dermatitis by DMF on a cohort of 17 Spanish patients. In our case, the Italian woman had similar symptoms in accordance with the research of Giménez-Arnau,¹¹ in which 10 patients developed allergic contact dermatitis, eight irritant contact dermatitis, and two non-immunological contact urticaria.

Interestingly, in our case the patient was not only affected by severe vesicular lesions on the foot, but these manifestations also compromised her posture. The dermatitis was accompanied by general symptoms, such as headache, fever, and illness, rarely described in other reports.¹⁻¹¹ In agreement with other research,^{1-5,7-11} the symptoms appeared a few days after contact with DMF.

According to the literature studies, several different investigations were performed to make a diagnosis of allergic contact dermatitis by DMF. Patch tests and analyses of the materials contained in the shoes were also performed.

DMF was present in high concentration in the shoes, in particular in both internal and external parts. Patients showed a strong positive patch test reaction to DMF at the dilution of 0.1% and mild reaction at the dilution of 0.01%, while negative results were obtained in 10 healthy volunteers. These results were not in agreement at all with the study of Giménez-Arnau *et al.*¹¹, in which 13 of 17 patients were positive to DMF 0.1%, 13 of 17 to DMF 0.01%, and only five of 17 were positive to DMF 0.001%, and with the study of Lammintausta *et al.*¹², in which DMF 0.01% elicited positive reactions in all patients.

All the data suggest that there is no optimal DMF concentration for patch test and perhaps to use DMF 0.05% and not 0.001% in order to reveal the disease.

Although, since March 17, 2009, the European Commission has prohibited any trade with products containing a DMF concentration higher than 0.1 mg/kg, an emerging problem is arising with clothes, shoes, and furniture imported from China that contains a high level of DMF. For this reason, it is important to pay attention to the consequences of using the products described above and also bags and other leather objects from China.

We have reported this case in order to avoid an increase in the number of contact dermatitis cases and to stimulate an augmentation on global preventive measures against DMF exposure, and it is of note that this allergen is not included actually in most series for patch testing.

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