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A case of contact dermatitis to dimethylfumarate in shoes identified in Italy

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Summary. The present paper describes a case of shoe contact dermatitis from DMF identified by the Poison Control Centre of Milan (PCCM), Italy, in 2009. A 35 year old woman was affected by irritant reactions while wearing shoes contaminated with DMF. Exposure to these shoes was limited to a 8 hour period and was not repeated. In the following days the patient suffered feet blistering and swelling limited to the area in contact with shoe vamp. Topical application of cortisone did not prevent development of bullous eczema. After 20 days from exposure, the lesions were healed but the skin remained red, dry and very sensitive. Chemical analyses of shoes quantified an average concentration of DMF of 383 mg/kg. The patient refused to be patch tested. The observation here reported confirm that DMF should be considered a possible causal agent in shoe contact dermatitis. Documentation of cases exposed to this chemical provide a relevant support to characterize clinical manifestations and to identifying contaminated articles.

Key words: dimethylfumarate, contact dermatitis, shoes.

Riassunto *(Un caso di dermatite da contatto da dimetilfumarato presente come contaminante nelle scarpe)*. In questo lavoro viene descritto un caso di dermatite da contatto esposto a scarpe contaminate con dimetilfumarato (DMF) identificato dal Centro Antiveleni di Milano nel 2009. Una donna di 35 anni mentre indossava per la prima volta un paio di scarpe ha iniziato a riportare effetti locali di tipo irritativo. Le scarpe furono indossate una sola volta per un periodo di otto ore. Nei giorni immediatamente successivi la paziente ha sviluppato reazioni di tipo eczematoso, quali vescicole e rigonfiamento, nei punti che erano stati in contatto con la tomaia delle scarpe. Nonostante queste lesioni siano state trattate con applicazioni locali di cortisone, sui piedi della paziente si sono manifestate lesioni bollose. Dopo 20 giorni dall'esposizione le lesioni sono guarite, tuttavia la pelle del piede risultava ancora arrossata, secca e molto sensibile. Le analisi chimiche effettuate sulle scarpe hanno quantificato una concentrazione media di questo composto pari a 383 mg/kg. La paziente ha rifiutato di sottoporsi a patch test. Le osservazioni riportate in questo rapporto confermano l'opportunità di considerare il DMF come un possibile agente causale nei casi di dermatite da contatto con scarpe. La sistematica rilevazione della casistica esposta a questo agente permette di caratterizzarne gli effetti clinici e l'identificazione e rimozione dal mercato dei prodotti contaminati.

Parole chiave: dimetilfumarato, dermatite da contatto, scarpe.

INTRODUCTION

Dimethylfumarate (DMF) is the methyl ester of fumaric acid. It is a potent immune modulator, able to induce apoptosis in human T cells [1], suppress lymphokine and monokine secretion as well as alloreactive and mitogenic lymphoproliferative responses [2, 3]. DMF is considered to be the active compound within the commercial mixture used for oral therapy of severe psoriasis which was registered in 1994 in Germany under the brand name Fumaderm® and whose registration is now pending in many European countries [3]. DMF is not considered suitable for topical treatment due to its contact-urticarial and sensitizing properties [4]. More recently, oral treatments with DMF have been

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suggested for patients affected by relapsing-remitting multiple sclerosis as effective in reducing new inflammatory lesions [5]. Side effects related to oral therapy are usually transient and consist of flushing, nausea, stomach pains, diarrhoea, tiredness, transient eosinophilia and lymphocytopenia [4, 5].

DMF is also a biocide, able to inhibit mould growth [6]. However, its use for consumer products has been forbidden in the European Union since 1998 under the Biocide Directive 98/8/EC since able to cause irritating and sensitizing reactions in humans. Despite that protective measure, DMF has been recently identified as the causal factor of an epidemic of severe contact dermatitis occurred in Finland and in the UK in 2006-2007, related to sofas and armchairs manufactured in China [7, 8]. Some cases of shoe dermatitis from DMF had been also documented [9, 10]. The source of exposure was found to be DMF in little bags inserted on interior of furniture or in footwear boxes. It thus evaporated and impregnated the product material. Taking into account these observations, in 2009 the European Union decided to require Member States to ensure adequate measure to avoid that products containing DMF are imported into the Community and made available on the market [11]. In accordance with that Decision, the Italian Ministry of Health (IMH) requires that the importers of goods from outside European Countries certify the biocide used to avoid their spoilage and performs systematic controls in order to verify their composition. Furthermore, IMH requires that health services notify cases with a diagnosis of allergic dermatitis due to contact with materials contaminated with DMF (*e.g.*, shoes, furniture, clothes, soft toys).

In the present report is a case of shoe dermatitis with documented exposure to DMF notified to IMH by the Poison Control Centre of Milan (PCCM) in 2009 is described.

CASE REPORT

On March 2009, a 35 year old woman, while wearing a new pair of shoes (brand name "Magie di fata", imported from China) for a 8 hour period started to experience feet itching. On the following day, she suffered an increase in feet itching, pain and redness. She consulted a pharmacist who considered these reactions possibly related to fungal infection and prescribed a topical treatment with antifungal cream and an anti-inflammatory agent (ketoprofen). In the subsequent two days the woman did not wear the shoes. Nevertheless, she experienced feet blistering and swelling limited to the area which was in contact with the shoes vamp. She consulted a general practitioner who considered the observed lesions suggestive of contact dermatitis and prescribed topical application of cortisone. Two days after the beginning of the treatment, the patient developed bullous eczema and referred to a first aid service for medication *(Figure 1)*. At hospital, the lesions were treated for a 15 day period with topical application of sulfadiazine and gentamicin. A course of oral antibiotic (amoxicillin) was also prescribed. Twenty days after the onset of symptoms, the patient was still suffering for the consequences of dermatitis, reporting skin redness, dryness, and pain. She refused to be patch tested and consulted the Poison Control Centre (PCC) of Milan in order to get information on possible shoe allergens. Considering recent reports [9, 10], a test for the presence of DMF in shoes materials was suggested. Following that indication, the shoes were sent to the National Institute of Health in order to be analysed. The analytical procedure was as follow: sample (1-5 g) from the shoes sole and vamp were extracted with 10 ml of acetonitrile in an ultrasonic warmed bath at 60 °C for 20 min. The extracted samples were filtered through 0.45 μm pore size Anotop (Millipore Corporation, Bedford USA) and preliminarily ana-

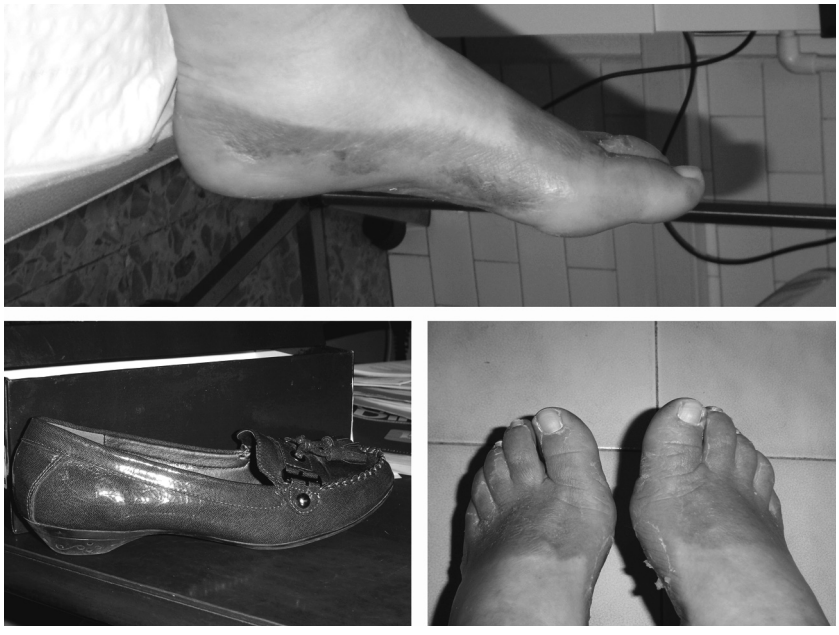

Fig. 1 | *A case of contact dermatitis characterized by feet blistering, swelling, and bullous eczema limited to the area in contact with the shoes vamp.*

lyzed by using high performance liquid chromatography (HPLC) Varian 9012 Q equipped with a diode array detector (DAD) Varian 9065 Polychrom. Chromatographic separation was performed on 250 mm x 4 mm Nucleosil 100-5 C18 column with 5 µm particle size. Acetonitrile (Carlo Erba, Rodano-Milano) and acidified (0.5%) water were used as mobile phase in gradient mode at the flow rate of 1.5 ml/min. The analytical confirmation of HPLC analyses was performed by using an Agilent System 6890 series Plus gas chromatograph (Agilent technologies, Palo Alto, CA, USA), equipped with an Agilent 5973 mass selective detector, an Agilent 7683 Autosampler and a split/splitless injector. Chromatographic separation was achieved on a 30 m x 0.25 mm i.d. HP-5ms capillary column (J & W Scientific, USA) with 0.25 µm film thickness. The following oven temperature program was adopted: 60 °C for 2 min, then up to 160 °C at 10 °C per-min and, subsequently, to a final temperature of 260 °C at 3 °C per-min, and isothermal at this temperature for 20 min. Helium was used as the carrier gas at a constant flow rate of 1.0 ml/min. Sample injection was carried out splitless at 240 °C. The injection volume was 1 µl. The mass spectrometer was used in electron ionization mode (EI) and in Single Ion Monitoring (SIM) with ionization energy of 70 eV. The transfer line temperature was kept at 280 °C. DMF 99.0% (Dr Ehrenstofen, Ausburg Germany) was used as standard material reference. The analyses quantified an average concentration of DMF of 171 mg/kg in the sole and of 595 mg/kg in the vamp.

The information on the patients and the results of the chemical analyses on the shoes were transmitted to IMH and notified to the European Rapid Alert System for All Dangerous Consumer Products (RAPEX) (No. of reference: 15 0627/09) [12]. The article was voluntary withdrawn from the market by the importer.

DISCUSSION

The case of foot dermatitis identified by the PCCM was characterized by a rapid onset of irritant reactions. Exposure to contaminated shoes was limited to a 8 hour period and was not repeated. Nevertheless, in the subsequent days the patient suffered feet blistering and swelling limited to the areas which were in contact with the upper and side parts of the shoes. Topical application of cortisone did not prevent development of bullous eczema. After 20 days from exposure, the lesions were healed but the skin remained red, dry and very sensitive. Chemical analyses quantified a higher concentration of DMF in the shoes vamp (595 mg/kg) in comparison to the sole (171 mg/kg), providing a possible explanation for delimitation of sites affected by contact dermatitis.

Cases with similar manifestations after the first exposure to shoes were observed in Spain and characterized by positive reaction with DMF at 0.001% [10]. The case here reported refused to be patch tested but can reasonably be considered a sensitized patients.

In 2009, other three cases of contact dermatitis from DMF were notified to the IMH by consumer organizations (A. Fonda, personal communication). All cases were females exposed in different part of Italy to shoes manufactured in China. The information available for each of these cases included a diagnosis of foot contact dermatitis and a quantification of DMF in shoes performed by private laboratories. The concentrations of DMF indicated in the reports were: 740 mg/kg (brand name "Mio Tempo"); 4.8 mg/kg (brand name "Bata"); 159 mg/kg (brand name "N&D Nedline Shoes Italy Style"). The articles associated with contact dermatitis were promptly withdrawn from the national market.

Surveillance activities, carried out in Europe according to Commission Decision 2009/251/EC [11], allowed identification of several footwear containing DMF, while reports on contaminated furniture or other articles were very limited [12]. The vast majority of the articles notified to RAPEX were available on the market at the moment they were identified. Occurrence of incidents related to DMF exposure was mentioned in some reports, indicating that surveillance of cases, especially those due to shoe contact, could provide a relevant support to market surveillance. Within this frame, a particular contribution to case identification is expected to be provided by dermatologists and consumer organisations. Nevertheless, the Italian case of shoe dermatitis here reported indicates that PCCs can also contribute to case identification, since they may be consulted to get information on possible allergens. Furthermore, PCCs could handle suspected cases of oral or dermal acute exposure to DMF found in anti-mould sachets, allowing rapid identification of goods escaping regular customs controls. With reference to this aspect, it is worth mentioning that in 2006-2009 the PCCM handled 8 symptomatic cases exposed to the content of sachets marked "mould-proof agent" (Davanzo, personal communication). One of them occurred in 2006 and 2008, respectively, two in 2007, and four in 2009. All case were children aged less than 4 years who found the sachets in footwear boxes. Clinical effects reported shortly after contact and/or suspected oral ingestion were considered suggestive of exposure to DMF. They included: hives (n. 4), rush (n. 3), oral cavity hyperemia (n. 1), lip oedema (n. 1), vomiting (n. 1), and diarrhea (n. 1). Unfortunately, no samples of the sachets contents were available for chemical analyses.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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