Allergic contact dermatitis to braces containing 4,4′-diaminodiphenylmethane, a previously unreported causative agent

Ambra Di Altobrando[1] | Colombina Vincenzi[1] | Michelangelo La Placa[1] | Claudia Tomasini[2] | Paolo Ravarino[2] | Iria Neri[1]

[1]Department of Experimental, Diagnostic and Specialty Medicine - Division of Dermatology, University of Bologna, Bologna, Italy

[2]Department of Chemistry "Giacomo Ciamician", University of Bologna, Bologna, Italy

Correspondence
Dr Ambra Di Altobrando, Department of Experimental, Diagnostic and Specialty Medicine - Division of Dermatology, University of Bologna, Via Massarenti, 1, 40138 Bologna, Italy.
Email: ambra.dialtobrando@studio.unibo.it

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4,4′-Diaminodiphenylmethane (4,4′-MDA, CAS no. 101-77-9), an aromatic amine, is the degradation product of 4,4′-methylenebis(phenyl isocyanate) (4,4′-MDI). 4,4′-MDA is used as a starting material in the production of polyurethanes and as a hardener for epoxy resins; therefore, exposure mainly occurs in workplaces.[1,2] However, exposure in domestic settings has been also reported.[2] Although the presence of 4,4′-MDI in orthopedic casts is very common and 4,4′-MDA allergy is thought to be in most cases secondary to MDI sensitization,[3] we describe here a case of allergic contact dermatitis (ACD) to 4,4′-MDA but not to 4,4′-MDI in a 56-year-old woman caused by an orthopedic support.

CASE REPORT

A 56-year-old woman was referred with a 1-week history of erysipelas of the right leg, which was resistant to the antibiotic therapy prescribed by the general practitioner. The patient had had a fracture of the fifth right metatarsal bone 20 days prior and had been wearing a leg brace made of polyurethane ever since (Figure 1A). The patient was otherwise healthy and denied any personal history of atopic or contact dermatitis. She had used the same orthopedic support 5 years before owing to a fracture also of the right foot. Physical examination revealed swollen, warm, shiny red plaques. Superficial fine vesiculation at the back of the foot, well-marginated borders, and itch were also present. The lesion was exactly in the sites of contact of the urethane foam parts of the brace with the right leg and foot, sparing noncontact areas (Figure 1B). Some scattered erythematous, swollen plaques with an erythema multiforme-like aspect were also observed on her abdomen and thighs (Figure 1C). A clinical diagnosis of ACD was made. Patch testing with the AL test (Euromedical, Calolziocorte, Italy) on Scanpor tape (Norgesplaster, Vennesla, Norway) fixed on the upper back with Hypafix (BSN Medical, Hamburg, Germany) and occluded for 48 hours was performed. The patient was tested with the Italian SIDAPA (Italian Society of Allergological, Occupational and Environmental Dermatology) baseline series, plastic series, rubber series, rubber pieces and urethane foam pieces of the brace, and bits of the cloth sock that had been interposed for a few days between the brace and the leg. Readings revealed a ++ reaction on day (D) 2 and D4 to 4,4′-MDA 0.5% pet. (Figure S1). The patient did not show any reaction to 4,4′-MDI and other *para*-amino substances. After switching the brace and treatment with systemic, tapered prednisone, a systemic antihistamine, and topical corticosteroids the lesions gradually cleared over 12 days.

The leg brace and its degradation products were analyzed in a chemical laboratory. Because the part where there was most dermatitis

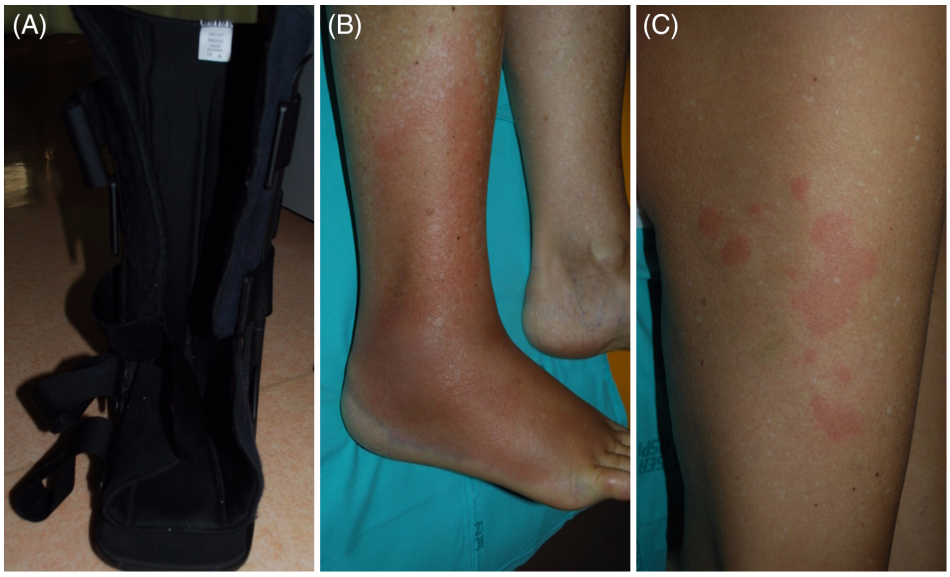

FIGURE 1 (**A**) Leg brace used by the patient. (**B**) Well-defined erythematous plaques in the sites of contact of the brace with the right leg and foot, saving noncontact areas, and (**C**) some scattered erythema multiforme-like lesions on her thighs

was made of urethane foam, small pieces of the urethane foam were cut from different parts of the brace, faraway one from the other: the upper part in contact with the shin, the back part in contact with the calf, and two pieces of the bottom part, one in contact with the sole and one with the toes, the latter having a white patina. Each piece of the foam was cut into two parts and soaked, one in methanol and the other in toluene, for 48 hours to extract the degradation products. This mild approach assures that no degradation occurs, as the pieces of urethane foam were unmodified after the 48-hour extraction; as a result, the extraction collected only free ingredients not bound within the polymer.

Then, an analysis with proton-nuclear magnetic resonance (^{1}H-NMR) and high-performance liquid chromatography-mass spectrometry (HPLC-MS) was carried out. Both the HPLC-MS and NMR spectra of the first three parts of the brace were similar, suggesting that only the common molecules, such as dyes, were dissolved, whereas remarkable differences were found in the extracts from the piece of the bottom part, that is, the one in contact with the toes. This piece had a white patina.

We analyzed both the methanol and the toluene extracts and found that in both cases we extracted some aromatic degradation products. The ^{1}H NMR spectra revealed signals placed between 7.00 and 7.30 ppm typical of aromatic groups.

The molecular weight of 4,4′-MDA and 4,4′-MDI is 198.27 and 250.26 respectively. The HPLC-MS analysis showed the presence of one peak with the retention time at 7.21 minutes, which showed a base peak of 250 *m/z* and two other interesting peaks at 372 and 721 *m/z*. The first peak could be attributed to 4,4′-MDI, although we expected the $[m + H]^+$ peak at 251. The latter two peaks reasonably corresponded to the $[m + Na]^+$ and $[m + 2Na]^{2+}$ signals of one compound with molecular weight 698 u, which is a degradation product of urethane foam. This derivative could release 4,4′-MDA by hydrolysis. The results, together with the analysis of the ^{1}H-NMR spectrum, confirmed that degradation products of urethane foam could be found in degraded pieces of the leg brace as a source of 4,4′-MDA.

DISCUSSION

Cutaneous complications in patients wearing orthopedic supports are frequent and include ACD, which may be caused by materials in the brace itself or in the straps or attachments.[4] The cases of brace-induced ACD reported in the literature have shown different allergens, such as *p-tert*-butylphenol formaldehyde, *p*-phenylenediamine, epoxy resins, *p-tert*-butyl catechol, fragrances present in moisturizers, talc and creams used by the patients, thioureas, and MDI.[3-5]

A case of ACD with erythema multiforme-like lesions caused by a knee brace has already been reported in the literature.[4] However, in that patient, patch testing was not performed and the exact causative agent was not identified.[6]

Regarding our patient, given the absence of the original box of the orthopedic device, it was impossible to obtain precise information about the ingredients of the brace or the manufacturer's name. Therefore, to prove directly that 4,4′-MDA was contained within the orthopedic support and confirm the diagnosis of ACD, analysis with ^{1}H-NMR and HPLC-MS was carried out. It is worth noting that the methylenedianiline derivatives were found only in the part of the brace that was most consumed and that they were probably released not only by the friction but also by the heat and humidity due to occlusion. Moreover, our patient was not primarily sensitized to 4,4′-MDI and therefore ACD to 4,4′-MDA should not be interpreted as a cross-reaction. To the best of our knowledge, this is the first case of ACD to 4,4′-MDA contained in a brace reported in the literature.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Ambra Di Altobrando: Conceptualization; data curation; supervision; validation; visualization; writing-original draft; writing-review and editing. **Colombina Vincenzi:** Conceptualization; data curation; supervision; writing-review and editing. **Michelangelo La Placa:** Data

curation; investigation; visualization. **Claudia Tomasini:** Investigation; writing-review and editing. **Paolo Ravarino:** Investigation; writing-review and editing. **iria neri:** Conceptualization; data curation; supervision; writing-review and editing.

ORCID

Ambra Di Altobrando https://orcid.org/0000-0003-3236-8822

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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