



In Patient_2, bortezomib was discontinued in October 2017 since she had reached partial response with decrease of the monoclonal component. Nine months later, biochemical progression and new bone lesions, with 18% of plasma cells in the bone marrow aspirate, prompted her hematologists to consider starting another proteasome inhibitor. Although no previous reports on tolerance to alternative proteasome inhibitor in patients with a history of severe skin reactions to bortezomib had been published, we set out to try carfilzomib (KYPROLIS®, Amgen Inc., Thousand Oaks, CA, USA), since its molecular structure was different enough to predict a low level of cross-reactivity. SPT (2 mg/mL) and IDT (0.2 mg/mL) to carfilzomib were negative both at immediate and delayed reading. A controlled intravenous challenge with carfilzomib (20 mg/m²) was performed in a hospital setting in July 2018, with good tolerance. The patient received two more cycles without any side effects.

Here, we present two new cases of confirmed delayed hypersensitivity to bortezomib with positive late-reading intradermal tests that suggest an underlying T-cell mechanism. To our knowledge, this is the first report of a desensitization schedule to bortezomib and the first evidence that carfilzomib is well tolerated and can be considered as a safe alternative in patients with delayed hypersensitivity to bortezomib.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

Keywords

bortezomib, carfilzomib, desensitization, drug hypersensitivity, skin test

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Allergic contact dermatitis to (meth)acrylates involving nail technicians and users: Prognosis and differential diagnosis

To the Editor,

Acrylates and methacrylates are formed by polymerization of acrylic monomers. These monomers can cause allergic contact dermatitis,

and, in the last years, an increasing number of cases have been reported among nail esthetics professionals and users, manifesting as chronic hand eczema¹ with occupational consequences.² The aim of

this study was to analyze the clinical variables, allergens positivity and, specifically, the prognosis and differential diagnosis, in patients with suspected sensitization to (meth)acrylates from three Dermatology Services in Spain ("Complejo Hospitalario Universitario Insular Materno-Infantil," Las Palmas de Gran Canaria; "Hospital Universitari Son Espases," Palma de Mallorca; and "Hospital Arnau de Vilanova," Valencia).

We undertook a retrospective study of patients assessed for possible sensitization to acrylates used in manicures between January 2008 and December 2017. The study was approved by the local ethics committee. Informed consent was obtained from each participant.

The variables recorded were age, sex, history of atopic dermatitis, occupation, year of diagnosis, clinical characteristics, patch-test positivity and latency time to develop the clinical lesions. Patients

with suspicious of manicure-related sensitization to acrylates but with negative results were also recorded.

All the patients underwent patch testing according to the guidelines of the International Contact Dermatitis Research Group with the standard Spanish series (True Test SmartPractice® Phoenix, USA and AllergEAZE® Calgary, Canada) and the acrylate series "nails" (13 allergens) from Chemotechnique Diagnostics® (Vellinge, Sweden) in one Department and AllergEAZE® (Calgary, Canada) in another Department (eight allergens). The third Department used the acrylate series "adhesives, dental and others" (15 allergens) from Chemotechnique Diagnostics® (Vellinge, Sweden), adding the AllergEAZE® series (Calgary, Canada) in the second half of 2017 (12 allergens). Relevance was established according to the clinical history. An adequate follow-up was carried out by the clinical records or phone calls when necessary.

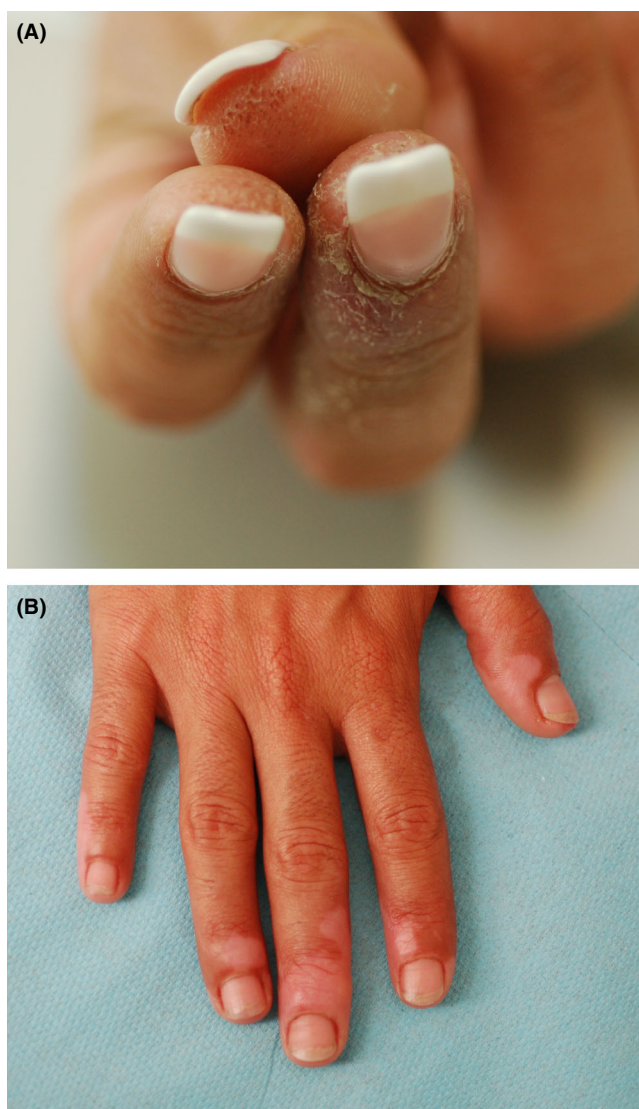


FIGURE 1 A, Chronic dermatitis on the fingertips of the first three fingers of the professional hand that hold the brush during the manicure. B, Acquired leukoderma in a patient sensitized to acrylates after repeated episodes of acute dermatitis on the fingertips

TABLE 1 Positive results of the (meth)acrylates patch tests

Acrylates	Concentration	Total positive	Total patch tested	% Positive
2-HE methacrylate	2.0% pet	64	66	97
HP methacrylate	2.0% pet	58	66	87.9
EG dimethacrylate	2.0% pet	53	66	80.3
2-HE acrylate	0.1% pet	35	44	79.5
Triethylene glycol dimethacrylate	2.0% pet	19	66	28.8
Ethyl acrylate	0.1% pet	16	44	36.4
1-6 hexanediol diacrylate	0.1% pet	12	43	27.9
Tetrahydrofurfuryl methacrylate	2.0% pet	11	43	25.6
Tetraethylene glycol dimethacrylate	2.0% pet	10	26	38.5
Methyl methacrylate	2.0% pet	8	49	16.3
Triethylene glycol diacrylate	0.1% pet	8	17	47.1
Urethane dimethacrylate	2.0% pet	6	26	23.1
1-4 butanediol dimethacrylate	2.0% pet	6	26	23.1
Bis-GMA	2.0% pet	6	26	23.1
Ethyl methacrylate	2.0% pet	5	21	23.8
Butyl acrylate	0.1% pet	4	21	19.1
Butyl methacrylate	2.0% pet	3	43	7
Ethyl cyanoacrylate	10.0% pet	2	49	4.1
Dimethylaminoethyl methacrylate	0.2% pet	3	26	11.5
Trimethylolpropane triacrylate	0.1% pet	0	17	0
Bis-MA	2.0% pet	0	26	0

Bis-GMA, bisphenol A glycerolate dimethacrylate; Bis-MA, bisphenol A dimethacrylate; EG, ethylene glycol; HE, hydroxyethyl; HP, hydroxypropyl.

TABLE 2 Positive results of the patch tests (other than acrylates)

Other allergens	Concentration	N (%)
Nickel sulfate	200 µg/cm ²	31 (47)
Cobalt chloride	20 µg/cm ²	9 (13.6)
Paraphenylenediamine	80 µg/cm ²	6 (9.1)
Sodium thiosulfate gold	75 µg/cm ²	4 (6.1)
Thiomersal	7 µg/cm ²	3 (4.5)
Balsam of Peru	800 µg/cm ²	3 (4.5)
Potassium dichromate	54 µg/cm ²	3 (4.5)
P-tert-butylphenol formaldehyde resin	45 µg/cm ²	2 (3)
Caine mix	630 µg/cm ²	2 (3)
Mercury	0.1% pet	2 (3)
Diazolidinyl urea	550 µg/cm ²	1 (1.5)
Chloroacetamide	0.2% pet	1 (1.5)
Disperse blue 106	50 µg/cm ²	1 (1.5)
Colophony	1200 µg/cm ²	1 (1.5)
Methylisothiazolinone	0.2% aq	1 (1.5)
Methylisothiazolinone+Cl-methylisothiazolinone	0.02% aq	1 (1.5)
Bisphenol A	1.0% pet	1 (1.5)
1 2-dibromo-2 4-dicyanobutane	0.3% pet	1 (1.5)
Dimethylaminopropylamine	1.0% aq	1 (1.5)
Isoeugenol	2.0% pet	1 (1.5)
Ethylenediamine dihydrochloride	50 µg/cm ²	1 (1.5)

TABLE 3 Comparison of the symptoms between the patients sensitized and not sensitized to (meth)acrylates

Lesion site	Acrylates sensitized patients (%) (N = 66)	Acrylates nonsensitized patients (%) (N = 23)
Fingertips	55 (83.3)	3 (13)
Hands other than fingertips	31 (47)	14 (60.9)
Face	10 (15.2)	9 (39.1)

Of a total of 2844 patients, an acrylate series was applied to 208 (7.3%), of which 89 (3.1%) were manicure-related. Sixty-six (74.1%) were positive for at least one of the acrylate allergens. The MOAHLFA index was analyzed for both the positive and negative tested cases (Table S1).

All the manicure-related sensitized patients were women, with a mean age of 34.5 years (20–62). Forty-six (69.7%) were professionals, 11 were users (16.7%) and 9 (13.6%) were both professionals and users. Fifty-five cases (83.3%) had lesions located on the fingertips of the first three fingers ("prehensile pattern") (Figure 1A). Of the non-professional users, six patients (9.1%) showed a "prehensile pattern," 6 (9.1%) had periungual lesions, two presented with both patterns and three with other locations affected. Eleven cases (16.7%) had dysesthesia, which resolved in all cases after a few months. One case had acquired leukoderma in the fingertips (Figure 1B). The latency period from the initial contact was recorded in 54 cases

(81.8%) and varied, from 7 days to 19 years, with a mean of 42 months.

Table 1 and 2 show the positive results of the patch tests. Two-hydroxyethyl methacrylate was positive in 97% (n = 64) of patients.

We managed a valuable follow-up in 42 technicians (76.4%). Of these, 24 (57.1%) left their jobs. Among the 18 patients who continued working, 11 were given a different work activity in areas of less or no contact with acrylic nail esthetic procedures. Eight patients who went on working continued to have lesions despite taking avoidance methods (change of work activity or use of gloves).

All 23 patients (25.8%) with negative patch testing were women, nine of them (39.1%) were occupationally exposed. Seventeen patients (73.9%) had hand involvement, with just three cases (13%) involving the fingertips (Table 3). Ten patients (43.5%) had other positivities in the patch testing, of which four were considered to be of present relevance. The final established diagnosis was as follows: 8 (34.8%) irritant contact dermatitis, 6 (26.1%) allergic dermatitis not related to acrylates, 4 (17.4%) atopic dermatitis, 3 (13%) dyshidrotic eczema and 2 (8.7%) seborrheic dermatitis (facial involvement).

Our results showed that almost three out of every four patients patch tested due to suspected manicure-related sensitization to acrylates proved to be sensitized to acrylate monomers. The symptoms were bouts of acute and chronic hand dermatitis, mainly affecting the fingertips of the first fingers. Interestingly, in the group of users, those who developed lesions on the fingertips were those who admitted to apply the products themselves. Kits for home use applied by inexperienced hands may be increasing the prevalence of sensitization to (meth)acrylates.^{3,4}

All the patients except two would have been diagnosed of acrylate allergic contact dermatitis using 2-hydroxyethyl methacrylate. This allergen is positive in over 90% of cases of published articles, and these results, therefore, would justify its isolated use at least as a screening method for selected patients.^{5,6} Wilkinson et al recently published the European baseline series and recommended additions for 2019, including 2-HEMA as screening allergen for acrylates. They take into account some considerations: in children or adult males, where no obvious exposure has occurred, it would be reasonable to exclude 2-HEMA from the European baseline series.⁷

At least 11.7% of patients left their jobs according to the literature.² In our study, two out of three of the technicians changed their jobs or were relocated due to their skin lesions. Among those who continued working, neither the use of gloves nor relocation in the same workplace were able to prevent the appearance of new lesions. Our patients did not currently use 4H gloves (North Safety Products by Honeywell, Smithfield, RI, USA), facial masks or protective glasses due to their inconvenience and specially the appearance of danger to the client. Ursberg et al⁸ studied an in vivo system simulating a nail technician's work exposure using several glove materials and different exposure times showing no positive reactions. Although not suitable in real life for our patients, strict physical protection with adequate clothes, masks and gloves should be the best preventive measures.⁹

In our experience, negative cases occurred mainly in users, without fingertip affectation and with more facial and leg involvement. The final predominant diagnosis was irritant hand dermatitis which should be always reached after ruling out sensitization to acrylates.

As conclusions, our study confirms a prehensile pattern in patients who apply the substance (professionals or "do it yourself" users) and a different clinical location of lesions in negative patch tested patients. We highlight the limitation in work ability created in our patients which in many cases required a definitive change of job, and the potential sensitization to acrylates in general population, specially when these substances are self-applied by the user.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

Keywords

allergic contact dermatitis, dermatology, occupational allergies, prevention

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SUPPORTING INFORMATION

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

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Idiopathic nonhistaminergic angioedema: A single-center real-life experience from Italy

To the Editor,

Angioedema (AE) is a reversible, localized swelling of the subcutaneous and/or submucosal tissue, caused by mediators that enhance vascular permeability.¹ Although it is frequently associated with other skin lesions, mainly wheals, recurrent angioedema may also

occur separately.^{1,2} A recent clinical classification describes five conditions that can manifest with recurrent AE only: idiopathic histaminergic acquired AE (IH-AAE), idiopathic nonhistaminergic acquired AE (InH-AAE), acquired angioedema related to angiotensin-converting enzyme inhibitor therapy (ACEI-AAE), hereditary

Table S1. MOALHFA index in the whole population, the positive cases and the negative cases.

MOAHLFA	Whole patch-tested population (N=2844) (%)	Total acrylates positive (N=66) (%)	Total acrylates negative (N=23) (%)	p-value**
Male	29.68	0	0	-
Occupational	10.46*	83.33	39.13	<0.001
Atopy	18.35	15.15	21.73	0.333
Hand	36.84	98.48	73.91	0.001
Leg	12.31	0	13.04	0.016
Face	23.38	15.15	39.13	0.020
Age (>40 years)	65.79	27.27	43.47	0.120

*Information collected from CHUIMI and Arnau de Vilanova.

** Pearson's chi-squared test (χ^2) between acrylate positive and acrylate negative cases.