

CONTACT POINTS

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Systemic contact dermatitis of the eyelids caused by formaldehyde derived from aspartame?

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Key words: allergic contact dermatitis; aspartame; eyelids; formaldehyde; systemic contact dermatitis.

Formaldehyde is a common and ubiquitous contact allergen. Sources of exposure include hair and skin care products, cosmetics, topical medications, permanent press clothing, cleaning agents, disinfectants, paper and even smoke. Sensitization is reported in between 2.2 and 9.6% of patients patch tested (1, 2).

Case Report

A 60-year-old Caucasian woman presented with a 6-month history of eyelid dermatitis. A corticosteroid-containing ophthalmologic ointment improved but did not clear the rash. She failed to improve when she discontinued the use of all eyelid cosmetics and nail polishes for 2 months. She had had a facial dermatitis in 1995, for which she had been patch tested and found to be allergic to formaldehyde, quaternium-15 and fragrances. She had also had incidental, non-relevant reactions to neomycin and ethylenediamine. Her dermatitis had resolved with a change to formaldehyde-, quaternium-15- and fragrance-free facial and nail cosmetics. There was no personal or family history of atopy or psoriasis. Her only oral medication was celecoxib that she had taken for years prior to the onset of her blepharitis. She had also taken multivitamins, calcium and flaxseed oil for many years. She worked as a home-maker and library volunteer.

Her eyelid dermatitis was kept clear with tacrolimus 0.03% ointment $\times 2$ daily. She underwent patch testing to the North American Contact Dermatitis Group standard tray, the University of Kansas' supplemental standard tray, and to her cosmetics, cleansers, skin and hair care products and topical medications. She had relevant positive reactions at days 2 and 4 to formaldehyde (++) , quaternium-15 (++) , diazolidinyl urea (+) , DMDM hydantoin (+) and imidazolidinyl urea (++) , her hair care products and cleansers containing multiple sources of these allergens. She was extensively instructed in avoidance of formaldehyde and formaldehyde releasers, as well as that of her multiple, currently non-relevant allergens, including fragrance, benzalkonium chloride, neomycin, bacitracin, *p*-phenylenediamine and black rubber mix.

By strictly avoiding formaldehyde and all formaldehyde releasers for the next 3 weeks, she improved only slightly. Her problem, however, was subsequently solved when a local pharmacist advised her to avoid aspartame. She had begun using an aspartame-based artificial sweetener 5 months prior to the onset of her dermatitis. Within 1 week of discontinuing the aspartame, her eyelid dermatitis resolved completely and has not recurred over 18 months without specific treatment. Unfortunately, she refused to undergo rechallenge with the sweetener.

Discussion

The artificial sweetener, aspartame, is consumed by 54% of adults in the USA (3). It has been reported to cause dry eyes and difficulty in wearing contact lenses (3) but never allergic contact dermatitis. Aspartame, an L-aspartyl-L-phenylalanine methyl ester, is hydrolysed in the intestine to phenylalanine (50%), aspartic acid (40%) and aspartic acid methyl ester (10%). The methyl ester is then converted to methyl alcohol (methanol)

and carried by the portal vein to the liver. Methanol is there oxidized to formaldehyde that is converted into formic acid (formate) by alcohol dehydrogenase, aldehyde dehydrogenase and the microsomal oxidase pathway. This occurs not only in the liver but also in other organs containing high levels of these enzymes, including the eye (4, 5).

Formaldehyde binds proteins and nucleic acids, forming adducts difficult to eliminate via metabolism. Trocho et al. (6) demonstrated the formation of formaldehyde adducts with DNA and proteins after administration of 20 mg/kg ^{14}C -labelled aspartame to rats, concluding that these adducts were responsible for functional alterations of proteins and for DNA mutations leading to autoimmunity, cell death or malignant transformation.

In contrast to Trocho et al. (6), McMartin et al. (7) studied formaldehyde levels after large doses (3 g/kg) of ^{14}C -labelled methanol and ^{14}C -labelled formaldehyde in monkeys, which unlike rats are sensitive to the toxicities of methanol. No increased formaldehyde derived from methanol was found. High levels of formic acid were found in all monkeys that were given methanol or formaldehyde. Based on the work of McMartin et al. (7), Tephly (8) concluded that the radioactive carbon from methanol, which was found in DNA and protein by Trocho et al., was due to the normal physiologic flow of single-carbon units through the folate pathway.

Stegink et al. (9) have shown that doses of 100 mg/kg or greater of aspartame are required to increase methanol blood levels (and, thus, presumable formaldehyde/formic acid levels) above control. This would be equivalent to consuming 35 cans of diet beverage at one sitting for a 70 kg person. Leon et al. (10) studied doses of 75 mg/kg of aspartame daily for 24 weeks and found no change in blood or urine methanol levels and no symptoms of methanol toxicity. The dose used in Leon's

study is 25 times the 90th percentile daily consumption of aspartame (11).

Our patient was consuming an average of 80 mg (1.3 mg/kg) of aspartame daily, well below the levels previously studied. However, it is possible that the eye, with its high level of metabolic activity, could be affected by methanol (and subsequently formaldehyde) released from these low levels of aspartame and respond as a localized target organ to minute amounts of her known allergen, formaldehyde, or its metabolite, formate. It is also possible that the amplifying effects of cell-mediated immunity might detect trace amounts of a chemical not identified by more standard assays, such as blood or urine levels. Such a hypothesis might explain why her dermatitis was limited to the eyelids and give clinical support to Trocho's theory of formaldehyde adducts. Unfortunately, without rechallenging her with aspartame, we cannot test this hypothesis. Nonetheless, her long-lasting remission following discontinuation of aspartame intake suggests that its breakdown to formaldehyde may have been a possible mechanism for her prior blepharitis.

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Metal sensitivity in a patient with a total knee replacement

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Key words: chromate; cobalt; copper; dermatitis; knee replacement; metal sensitivity.

Case Report

A 57-year-old male patient was referred from the orthopaedic services with complaints of an itchy, slightly exudative

dermatitic lesion over his left knee and leg for the last 10 months. This had developed 2 months after a total knee replacement with a condylar knee (Zimmer Warsam, Indianapolis, IN, USA) at the site of the incision scar. The components of the joint were (i) femoral component (Zimaloy) (Cu²⁺–Cr³⁺ alloy); (ii) Charnley-type acetabular cup with cement restrictor and a larger long posterior wall. There were no complaints pertaining to the replaced joint. There was no history of atopy or any history of metal sensitivity. The X-ray showed no sign of reaction around the implant. An assessment of the serum metal levels showed values of copper of 118 µg/100 ml (70–140 µg/100), nickel 7 µg/100 ml (<1 µg/l) and chromium 20 µg/100 ml (0.12–2.1 µg/100 ml) (by atomic absorption spectrophotometry). Cobalt and molybdenum levels could not be assessed. Patch test results performed postoperatively were as summarized in Table 1. No patch tests had been performed preoperatively.

Discussion

Several metal alloys are used in orthopaedic prostheses. The original metal-on-metal hip joints of the 1960s were associated with sensitivities to cobalt, nickel and chromate and with loosening of the prosthesis (1, 2). Metal ions such as nickel, cobalt and chromate are haptens with immunogenic potential, causing contact dermatitis in as many as 10–15% of the exposed population. Postoperative cutaneous complications after orthopaedic implants are rare (3, 4). Prior to the 1980s, there have been sporadic reports of patients suffering from urticarial or eczematous dermatitis attributed to the presence of an implanted metallic prosthesis (5, 6). Patch tests with metals have often given positive results; with removal of the implant leading to resolution of the dermatitis (7). The sensitization potential of newer orthopaedic implants, however, remains undetermined (4). An association between nickel allergy and prosthesis loosening in some subjects has been suggested, but the question has yet to be addressed in a prospective study.

Most allergic cutaneous reactions are caused by static implants, and dynamic implants have a low allergenic potential (3, 4). Our report draws attention to a dynamic implant, causing a cutaneous reaction without loosening of the joint.

Table 1. Patch test results postoperatively

Allergens	Results	
	D2	D3
Potassium dichromate (0.5% pet.)	+	+
Nickel sulfate (5% pet.)	–	–
Cobalt chloride (1% pet.)	+	+
Copper sulfate (5% aq.)	+	++

The serum values assessed in our study were within the normal range, suggesting that the release of particulate metal is in such small quantities that it does not bring about a significant rise in the serum levels. Although many investigations have been carried out (8), the exact immunologic mechanisms responsible for the recognition of metal ions by T cells and eliciting adverse immune reactions causing contact dermatitis still remain to be determined.

The follow-up studies on modern metal-on-metal joint prostheses conducted so far report, at the worst, a loosening rate of 10%, but their immunological potential has not yet been addressed and remains unclear.

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Occupational airborne contact allergy to tetrazepam

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Key words: airborne; allergic contact dermatitis; benzodiazepines; drug reaction; occupational; tetrazepam.

Case Report

A 36-year-old geriatric nurse, with known allergic rhinitis due to grass pollen and house dust mites, presented with intermittent skin reactions appearing periorbitally and later on involving the whole face. At weekends or on holidays, she was symptom free. On the geriatric ward, she was responsible for the old people's medication. She had to break-up some of the drugs with a mortar to make them amenable to nasogastric tubes.

Patch testing with the European standard and a disinfectant series showed no positive reactions. But, testing drugs that she had to deal with (drops and syrups undiluted, tablets crushed in NaCl 0.9%) (Finn Chambers on Scanpor[®], Epitest, Tuusula, Finland) showed an isolated

positive skin reaction to tetrazepam after 24 h lasting 10 days and, in addition, a flare-up reaction on the face lasting 7 days. Negative controls with tetrazepam tablets crushed in pet. have already been published (1). Furthermore, other benzodiazepines (bromazepam, clonazepam, diazepam, flunitrazepam, lorazepam, midazolam and oxazepam) were patch tested with no positive reactions.

On the basis of the clinical history and patch testing, contact allergy due to occupational airborne contact with crushed tetrazepam was diagnosed. Considering additional systemic contact allergy, we wondered whether the patient could tolerate benzodiazepines orally. We did not dare to challenge with tetrazepam, but midazolam was tolerated without any symptoms. 10 h after the administration of flunitrazepam, the patient suffered from itching of the eyes, and the day after, swelling (periorbitally), which in our opinion was probably mainly caused by the beginning of the grass pollen season.

Discussion

The usefulness of patch tests was shown in all previous reports, not only in the case of orally induced tetrazepam allergy but also when contact allergy was suspected (1–4). In our case, we again describe an occupational airborne contact allergy in a geriatric nurse who had to work with crushed tablets. 2 cases of contact allergy in a pharmaceutical factory working with tetrazepam powder (2) and 1 case of a woman crushing tablets with her fingers (3) have previously been reported. Thus, not only repeated handling of the drug but more particularly contact with powders and crushed tablets seems to be a risk factor for the development of a contact allergy to tetrazepam.

Patch test reactions to other benzodiazepines could not be shown in our patient. These have been demonstrated in other patients with positive patch tests to diazepam, though it is not clear whether these were due to group or concomitant sensitization (3, 4). In our opinion, the patient may still work as a nurse as long as she prevents further contact with tetrazepam. Additionally, we recommended that she should avoid the systemic intake of tetrazepam.

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Concomitant allergic reaction to cetyl alcohol and crotamiton

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Key words: allergic contact dermatitis; cetyl alcohol; crotamiton; medicaments.

Case Report

A 60-year-old Japanese woman presented with pruritic erythematous macules on the neck and in the left cubital fossa, where she had previously applied Mentholatum AD[®] ointment (Rohto Pharmaceutical Co. Ltd, Osaka, Japan). A 2-day (D) closed patch test using the

ointment as sold produced positive reactions at D2 (++), D3 (++) and D4 (++), with flare-up phenomena. 30 days later, a second patch test was performed using each of the ointment's ingredients provided by the company. This second test produced positive reactions to cetyl alcohol (30% pet.) at D3 (+) and D4 (+) and crotamiton (5% pet.) at D2 (+), D3 (+) and D4 (+), respectively.

Discussion

Cetyl alcohol, often combined with stearyl alcohol under the INCI name cetearyl alcohol, is an ingredient in many medicaments and cosmetics, in which it acts as an emulsifier and stabilizer (1). Only rarely do we see cases of allergic reaction to either of these agents, as cetearyl alcohol has limited ability to penetrate intact skin (1, 2). Occasionally, allergic contact dermatitis due to cetearyl alcohol can occur, usually accompanied by positive reactions to other constituents of the topical product (3). Rademaker and coworkers (4) reported 5 cases of positive reactions to both cetearyl alcohol and multiple associated allergens, including fragrances, preservatives, vehicles and proprietary medicaments, leading them to conclude that the risk of allergy increases with polypharmacy following sensitization by cetearyl alcohol. In the present case, absorption of cetyl alcohol may have been facilitated by exudative inflammation of the skin due to pre-existing allergic contact dermatitis from crotamiton. As cetyl alcohol is widely used in both medicaments and cosmetics, allergic reactions to it may be more common than is generally realized.

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Triple allergic contact sensitivities due to ferbinac, crotamiton and diisopropanolamine

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Key words: allergic contact dermatitis; crotamiton; diisopropanolamine; erythroderma; ferbinac; medicaments; non-steroidal anti-inflammatory drugs.

The use of compresses containing non-steroidal anti-inflammatory drugs (NSAIDs) to reduce muscle pain has been associated with both allergic contact and photocontact dermatitis from NSAIDs as well as to other ingredients of such compresses (1–6). In addition to NSAIDs, other ingredients in compresses that may induce allergic contact dermatitis include crotamiton (7), diisopropanolamine (8), parabens (9), and propylene glycol (10). Here, we report the observation of ferbinac as an additional sensitizing agent associated with NSAID compress use.

Case Report

A 65-year-old Japanese man presented with an extremely pruritic eruption

following the use of Seltouch[®] compresses (Wyeth-Lederle Japan, Tokyo, Japan) for 1 day. He had no personal or family history of atopic dermatitis. There was a rectangular-shaped, severely pruritic exudative erythematous macular area on the right shoulder and upper arm and diffuse erythema on the chest, abdomen, back and extremities (Fig. 1). Similar rectangular-shaped eruptions had also developed 2 years previously after application of Seltouch[®] compresses. Despite being advised to avoid the use of this compress, he had erroneously used Seltouch[®] the day before presentation.

Following the diagnosis of allergic contact dermatitis, we treated the patient with intravenous prednisolone 20 mg, diflorasone diacetate ointment, dexamethasone valerate ointment and oral antihistamine for 4 days. Oral antihistamine and diflu-

prednate ointment to the rectangular area was added for 7 days. After discontinuing the compress and following medical treatment, the patient had no recurrence of the rash.

Ferbinac and other ingredients in the Sertouch[®] compress were provided by the manufacturer. Pyrocut A[®] ointment (Toyama Chemical Co. Inc., Toyama, Japan), containing piroxicam, Vesicum[®] ointment (Hisamitsu Pharmaceutical Co. Inc., Tosu, Japan), containing ibuprofen, Idomethine Kowa[®] ointment (Kowa Co. Inc., Nagoya, Japan), containing indomethacin, and Topalgic[®] ointment (Azwel Co. Inc., Osaka, Japan), containing suprofen, were provided or purchased.

Patch testing of the patient demonstrated positive reactions to ferbinac 1% pet., crotamiton 1% pet., diisopropanolamine 1% pet. and Pyrocut A[®] ointment as formulated (containing

diisopropanolamine) (Table 1). We re-patch tested ferbinac 0.1, 1 and 5% pet. to confirm the positive reaction to ferbinac. Positive reactions to ferbinac 1 and 5% were observed (Table 1).

Because contact dermatitis due to ferbinac has not been described previously, we patch tested ferbinac 1 and 5% pet. in 20 healthy normal volunteers. All of these showed negative reactions.

Discussion

This case of allergic contact dermatitis from ferbinac demonstrates the potential of this agent to be a contact sensitizer like other NSAIDs. Both crotamiton and diisopropanolamine have relatively low sensitization potentials (7, 8). The present patient demonstrated contact sensitivity to 3 low-potency sensitizers: ferbinac, crotamiton and diisopropanolamine. This suggests the possibilities of either multiple sensitization or cross-sensitization. We speculate that sensitization to these 3 agents occurred sequentially, following induction of regional allergic contact dermatitis by an initial sensitization, most likely by ferbinac. The absorption of crotamiton and diisopropanolamine may have been enhanced via exudative inflammation of the skin, particularly under occlusive conditions, facilitating sensitization to these other agents.



Fig. 1. A 65-year-old Japanese man presented with a rectangular-shaped, severely pruritic exudative erythematous macular area on the right shoulder and diffuse erythema on the chest and abdomen.

Table 1. Results of patch testing

	Concentration	D2	D3
Ferbinac	5% pet.	+	+
Ferbinac	1% pet.	+	+
Ferbinac	0.1% pet.	–	–
Crotamiton	1% pet.	+	+
Diisopropanolamine	1% pet.	+	+
Propylene glycol	5% aq.	–	–
Tartaric acid	3% aq.	–	–
Methyl paraben	5% pet.	–	–
Propyl paraben	5% pet.	–	–
Castor oil	as is	–	–
Glycerin	10% aq.	–	–
Sorbitol	10% aq.	–	–
Pyrocut A [®] ointment	as is	+	+
Vesicum [®] ointment	as is	–	–
Idomethine Kowa [®] ointment	as is	–	–
Topalgic [®] ointment	as is	–	–
Petrolatum	as is	–	–

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Erythrodermic cutaneous adverse drug reaction to oral pseudoephedrine confirmed on patch testing

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Key words: cutaneous adverse drug reactions; erythroderma; positive patch test; pseudoephedrine.

Case Report

A 44-year-old Caucasian woman was admitted with an acute generalized, blistering, erythrodermic dermatitis. 6 h prior to admission, she had taken a combination of acrivastine and pseudoephedrine hydrochloride (Benadryl Plus[®]; Pfizer, Sandwich, UK) for her intermittent allergic rhinitis, which had become increasingly symptomatic over the previous month. In the past, she had taken acrivastine (Benadryl[®]; Pfizer) with no adverse effect.



Fig. 1. Erythrodermic dermatitis causing large blisters on the lower limbs.

Examination revealed a coalescing erythrodermic dermatitis, sparing the face, including large blisters on the lower limbs (Fig. 1) but sparing of mucous membranes. Although afebrile, investigations revealed a neutrophilia ($28.2 \times 10^9/l$) with a C-reactive protein of 189 mg/l; a septic screen including culture of skin swabs, urine and blood was negative, and a chest radiograph was unremarkable. Histology of a skin biopsy from a non-blistered site demonstrated a mild superficial dermal mononuclear infiltrate. The patient was managed with intravenous fluid, prednisolone (30 mg daily, reducing by 5 mg every third day), coamoxiclav and chlorpheniramine. The eruption cleared within 10 days, with normalization of the C-reactive protein level and neutrophil counts.

Following discharge, the patient was patch tested 6 weeks later to the departmental standard series and to 20% dilutions of Benadryl[®] and Benadryl Plus[®]. We observed a ++ allergic reaction (infiltrated erythema with vesicles) after 48 h with Benadryl Plus[®] (containing pseudoephedrine) but no reaction to Benadryl[®]. Testing to Benadryl Plus[®] elicited no reaction in 15 controls, and the blue and white components of the Benadryl Plus[®] capsule elicited no reaction in our patient.

Discussion

Despite pseudoephedrine's widespread use as an oral decongestant, we could find only 4 previous reports of a similar cutaneous adverse drug reaction (CADR) (1–4). The time course and morphology of the dermatitis in our patient is similar to those reported in the 4 previous cases, in which the time of onset ranges from

3 h to 2 days following ingestion of pseudoephedrine, with a duration of dermatitis of around 5 days.

Members of the phenylamine family other than pseudoephedrine include ephedrine and norephedrine, both structurally very similar to pseudoephedrine and both of which cross-reacted strongly with pseudoephedrine in the patient reported by Tomb et al. (2). In the case reported by Rochina et al. (1), patch testing to the phenylamine family was negative, but an oral challenge with pseudoephedrine reproduced the systemic contact dermatitis.

Pseudoephedrine has also been reported to cause fixed drug eruptions (5) and acute generalized exanthematous pustulosis (6). In addition, allergic contact dermatitis has also been reported to other members of the phenylamine family, including phenylephrine eye drops (7) and topical epinephrine (8), and systemic allergic contact dermatitis reported with oral ephedrine (9).

Recent guidelines on patch testing have been published to help clinicians in their investigation and reporting of suspected CADR (10). The sensitivity and specificity of skin tests for drugs are largely unknown, and controls must therefore be used to avoid false-positive reports (11).

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Oral lichenoid lesions and contact allergy to dental mercury and gold

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Key words: contact allergy; dental metals; gold; mercury; oral lichenoid lesions.

The role of dental amalgam restorations in the aetiology of oral lichenoid lesions (OLLs) remains controversial. Recent studies suggest that OLL occurring in the absence of cutaneous lesions of lichen planus may be due to cell-mediated (type IV) hypersensitivity to dental restorative metals, in particular, mercury in amalgam. Some authors report that 2/3 of subjects with OLL have contact sensitivity to mercury, although other studies show a much lower figure (1, 2). Martin et al. (3) suggest that corrosion of amalgams and the presence of a galvanic effect from dissimilar dental metals in continuous contact (bimetalism) are associated with an increased risk of OLL.

We share our experience of OLL and allergy to dental metals. Our aim was to assess the frequency of sensitization to dental mercury and to other metals used in dentistry, particularly gold, in patients with OLL referred to our unit.

Patients and Methods

We performed an observational audit of patients with OLL referred from an Oral Medicine Clinic for investigation of dental allergy over a 3-year period (2000–2002). 55 patients, 38 women and 17 men, mean age 56 years, were investigated by patch testing to the British Contact Dermatitis Society standard series (including nickel, cobalt and chromate) and to a specialized dental and metal series that included ammoniated and metallic mercury, together with commercially available salts of gold, platinum, palladium, zinc and copper. Readings were taken at day 2 and 4 and often at day 7 as well.

Results

Overall result: of the 55 patients, 25 (45%) showed allergic positive patch test(s) to 1 or more dental metals and 30 (55%) were negative to the same (Fig. 1).

Reactions: of the 25 positive to dental metals, 19 (76%) were positive to mercury, 5 (20%) to mercury and gold and 1 (4%) to gold with nickel and palladium.

Relevance: it was thought that all the reactions to mercury were potentially relevant, but this was not so for gold, as only 2 of the 6 gold-positive patients had had dental restorations with gold (the other 4 were also positive to mercury, which was relevant in each case).

Co-allergens: allergic-positive reactions not regarded as relevant included nickel 4, fragrance mix 3, benzoyl peroxide 3, *p*-tertiary-butylphenol-formaldehyde resin 3, lanolin alcohol 2 and *p*-phenylenediamine 2.

Negative findings: 30 (55%) had no allergic positive reactions to dental metals and 14 of these (46%) were negative to all tested substances. Reactions in others included nickel 6 (20%), Myroxylon Pereirae (balsam of Peru) 3 (10%) and fragrance mix 3 (10%).

Follow-up data: of the 25 who were patch test positive to dental metals, removal of the metal was suggested in 21. 2 declined removal and 2 refused, as they had become asymptomatic; the result in the other 4 is not known. 13 had dental metal removed: of 9 available for follow-up after 1 year, the OLL improved and was asymptomatic in 8.

Comment

In all, 25 of 55 (45%) subjects with OLL referred for investigation of allergy to dental metals had a relevant positive on patch testing. Sensitization to mercury and, to a lesser

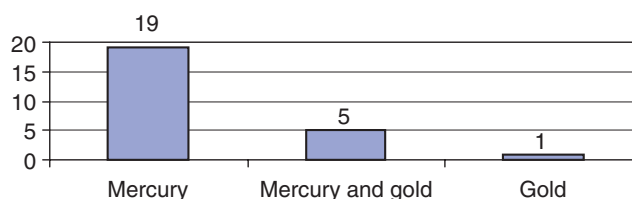


Fig. 1. Patch test results in 55 patients with oral lichenoid lesion.

extent, to gold was potentially relevant to the OLL. Compared with all other studies (1), the proportion of patients patch test positive to mercury is lower, but we found more subjects who reacted to gold. On follow-up, in 8 of 9 who had dental metals removed, OLL was improved after 1 year. There remains a possibility that replacement of the amalgam removed a physical agent that was causing OLL by an irritant mechanism.

In conclusion, cell-mediated hypersensitivity to mercury in dental amalgam, or to a lesser extent, to gold in dental restorations seems to be relevant to the causation of OLL in a proportion of subjects but would not seem to be the only mechanism for induction of the condition.

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Contact dermatitis from red tattoo pigment (quinacridone) with secondary spread

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Key words: allergic contact dermatitis; patch test; quinacridone; red ink; scarification test; secondary spread; tattoo.

Case Report

4 weeks after having her right calf tattooed, a 43-year-old woman presented with marked localized erythema and severe pruritus. The central area, which had been tattooed in red, had slowly thickened and hardened; no changes were evident in the black outline of the tattoo. 8 months after receiving the tattoo, the patient reported gradual worsening, with severely pruritic red papules on her chest, forearms, back of the hands and right calf. There was no history of allergies; she took no medication, and there was no evidence of atopic diathesis.

Patch tests with standard series of dyes, emulsifiers, solvents (HAL ALLERGIE GmbH, Duesseldorf, Germany) and the tattoo pigments (red, yellow, brown and black) were read at D1, D2 and D3. For patch testing, we used Haye's test chambers with integrated blotting-paper (Haye's Service B.V., Amsterdam, The Netherlands), held in place on the back with Fixomull[®] stretch tape (BSN medical GmbH & Co KG, Hamburg, Germany). Prick testing was conducted for standard allergens (pollen, animals, dust mites and mould) (HAL ALLERGIE GmbH). Scratch testing was also performed for tattoo dyes (red, yellow, brown and black) on the inner right forearm, using a lancet. Biopsies were taken from the tattoo and the site of the positive scratch test (see below). The tattoo artist sent us the dyes that he worked with; we used them in unaltered and undiluted form for all of the tests we conducted.

According to the tattoo artist, the code of the red pigment was DC 99060 (manufacturer unknown), containing an aqueous pigment preparation, ethanol, eucalyptol, thymol, menthol, methyl salicylate, poloxamer 407, benzoic acid, sodium benzoate, caramel, CI 73915 (quinacridone) and CI 77891 (natural titanium dioxide). The yellow, brown and black tattoo dyes contained the same ingredients, although with different CI numbers.

On patch testing, no Type IV sensitization could be demonstrated; the immediate reaction to prick testing was also negative. On scratch

testing, there was no reaction after 20 min or after 6 h; serous blisters and erythematous papules developed 5 days later, only at the scratch test site of the red pigment.

Histological findings from the calf: deposits of tattoo ink in the upper and central corium with a strong lymphohistiocytic inflammatory response that strongly resembled pseudolymphoma.

Histological findings from the test site (red): largely superficial cutaneous vascular mixed-cell inflammatory response with infiltration of some eosinophilic granulocytes. Seen in conjunction with the epidermal changes, this indicated changes secondary to a positive Type IV test reaction.

Discussion

We concluded that the patient had allergic contact dermatitis with secondary spread due to the red tattoo pigment quinacridone; to date, there have not been any descriptions of an allergic reaction to quinacridone and concomitant secondary spread in medical journals. Our diagnosis was derived from the clinical symptoms, the delayed reaction to the scarification test and the histological findings. Atopic genesis of the skin changes is unlikely, given a low total IgE value, negative Erlangen atopy score, negative prick testing and the patient's anamnesis.

Much has been published about lichenoid, granulomatous and pseudolymphomatous reactions to red tattoo pigment (1, 2). The changes described, however, were always limited to the tattoo and could be confirmed by patch testing only in individual cases. The reason offered as an explanation is that the mechanisms affected by transepidermal allergen penetration can be circumvented. The antigen that triggers a reaction to a tattoo is very probably located in the dermis and is probably presented there by the local dermal dendritic cells. Another theory is that the dyes are practically insoluble and thus do not penetrate the dermis (3).

A pruritic eruption, like the one we observed, was described only by Ashinoff et al. (4) in 2 cases in which tattoos were to be removed for cosmetic reasons; here both a local and a generalized reaction took place immediately after laser treatment with a Q-switched Nd:YAG laser. In

these case reports, dye particles were probably released, triggering secondary spread.

This case demonstrates that idiopathic generalized pruritic eruptions and concomitant inflammation of tattoos may indicate the present of allergic contact dermatitis with secondary spread. To confirm the diagnosis, we recommend a scarification test of the corresponding tattoo pigments with late reading after 3–5 days. Caution should be exercised in using quinacridone, because this organic pigment seems to have allergic properties that are not fully known and which need to be further investigated. Quinacridone is a light-fast pigment used in paints, printing inks and plastics as well as in tattoos.

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Allergic contact dermatitis from methenamine in an antiperspirant spray

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Key words: allergic contact dermatitis; antiperspirant; cosmetics; formaldehyde releasers; methenamine.

Case Report

A 65-year-old male office worker presented with acute eczema of the feet that had started a week after beginning again to use an antiperspirant spray (Pedi-Relax[®], Pierre Fabre Ibérica, Barcelona, Spain). The patient had already used the same product on previous occasions. Patch tests were carried out with the Spanish Contact Dermatitis Research Group standard series, the product itself (Pedi-Relax[®]) and the components of the antiperspirant. Positive reactions were seen at D2 and D4 to formaldehyde 1% pet., caine mix 7% pet. (dibucaine 1% pet., tetracaine 1% pet., benzocaine 5% pet., Marti Tor, Barcelona, Spain), *p*-phenylenediamine (PPD) 1% pet., quaternium-15 1% pet., Pedi-Relax[®] as is and methenamine 1% pet., which is an ingredient of Pedi-Relax[®].

Discussion

Methenamine (hexamethylenetetramine, hexamine and aminoform), a quaternary ammonium compound with formaldehyde-releasing capacity, has rarely been implicated in allergic contact dermatitis (1, 2). It is used as a preservative in cosmetics and other products applied topically as well as being used in processes such as the manufacture of rubber and the production of phenolic resins (1–3).

The presence of methenamine in commercialized antiperspirants may not be unusual, in view of its properties as an antiseptic and the formaldehyde that it liberates in an acid medium (4, 5). In spite of this, we have found no published case reports of allergic contact dermatitis caused by methenamine contained in antiperspirant products.

In this patient, as well as an allergy to formaldehyde, a simultaneous sensitivity to methenamine and quaternium-15 was demonstrated, which is more probably related to their close chemical structure than to their common formaldehyde-releasing capacity (3).

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Melkersson–Rosenthal syndrome associated with allergic contact dermatitis from octyl and dodecyl gallates

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Key words: allergic contact dermatitis; antioxidants; dodecyl gallate; Melkersson–Rosenthal syndrome; octyl gallate; orofacial granulomatosis.

Melkersson–Rosenthal syndrome comprises the triad of recurrent orofacial swelling, relapsing facial palsy, and fissured tongue (lingua plicata) (1). The aetiology of this condition is unknown, but the role of contact sensitivity to food additives in some patients has been described (2–6).

Case Report

A 54-year-old woman presented with a 5-year history of recurrent lip swelling which had recently become more persistent. A biopsy of her upper lip, in 2001, showed a mixed inflammatory infiltrate in the lamina propria, with no granulomata. In 1983, she had had an episode of right facial palsy, that resolved in weeks. She had no history of atopy or inflammatory bowel disease. On examination, she had diffuse swelling of her upper and lower lip and fissuring of the dorsal surface of her tongue.

She was patch tested with the European standard series and a lip series. At D3, there were positive reactions (++) to octyl gallate (0.3% pet.) and dodecyl gallate (0.3% pet.) and (+) reactions to thiuram mix (1%), potassium dichromate (0.5%) and cocamidopropylbetaine (1%).

The reactions to thiuram mix, potassium dichromate and cocamidopropylbetaine were not thought to be of present relevance, and she was given appropriate advice for avoidance. She was advised to avoid foods (Table 1) and lip preparations that contained gallates. This resulted in a marked reduction of episodes of lip swelling over the ensuing months, although some residual enlargement of the upper lip persisted.

Comment

This woman had the classical triad of signs of Melkersson–Rosenthal syndrome. Absence of granulomata on biopsy does not exclude the diagnosis (1). The concept of orofacial granulomatosis (OFG) was introduced in 1985 to encompass a number of conditions with orofacial swelling, including Melkersson–Rosenthal syndrome (7). A number

of reports describe an association between OFG and contact sensitivity to food additives with variable responses to dietary manipulation (2–6). The implicated substances include: cinnamyl alcohol, cinnamaldehyde, sodium metabisulfite, essence of chocolate, benzoic acid, glutamic acid, butylated hydroxyanisole, eugenol and isoeugenol (2); cinnamaldehyde and cinnamyl alcohol (3); carmoisine, sunset yellow and monosodium glutamate (4); cinnamon, cinnamaldehyde, piperitone and carvone (5); and peppermint oil, menthol and dodecyl gallate (6).

Gallates are used as antioxidants in cosmetics, medicaments and foodstuffs. Many foods, including oils, margarine, fat products, mayonnaise and butter, can develop a rancid taste and odour when oxidized. Propyl, octyl and dodecyl gallates are added to these foods to retard the oxidative process (8). These additives are labelled as E310, E311 and E312 (propyl, octyl and dodecyl, respectively) in Europe. Avoidance of gallate-containing foods in our patient led to definite improvement of her lip swelling.

It remains unclear whether contact sensitivity to foodstuffs has a primary role in the aetiology of Melkersson–Rosenthal syndrome. It is more likely that only a subset of these patients have contact sensitivity to food additives that exacerbate an underlying disease process. These patients may respond to appropriate elimination diets. Patch testing may help identify responsible dietary factors, which can then be avoided.

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Contact dermatitis due to para-tertiary-butylphenol-formaldehyde resin in a wetsuit

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Key words: allergic contact dermatitis; patch testing; polychloroprene-rubber adhesive; PTBP-FR; wetsuit.

Case Report

A 58-year-old woman had a history of dermatitis from urushiol, a wristwatch and earrings. She had started scuba diving 5 years ago. 1 year ago, after

Table 1. Foods that may contain gallates

Fats
Oils
Margarine
Peanut butter
Lard
Salad dressings
Shortening
Dried cereals
Snack foods
Processed meats/fish

only 12 h of wearing a new wetsuit, she began to experience itchy erythema on her neck and thighs. She showed no eruption where her swimsuit was worn, erythema developing only on areas directly in contact with the wetsuit.

On patch testing, the patient reacted positively at D2 to para-tertiary-butylphenol-formaldehyde resin (PTBP-FR), mercuric chloride, potassium dichromate, urushiol and a piece of her wetsuit (outside made of nylon lining and polychloroprene rubber, and inside made of nylon lining). She showed no reactivity to other materials from the wetsuit, a piece of another wetsuit, the Japanese standard series, a series of plastics and glues, rubber chemicals and a series of dyes (Japanese Society for Contact Dermatitis).

Discussion

p-tert-Butylphenol-formaldehyde resin is an alkylphenol resin made from PTBP and formaldehyde. It is included in many adhesive formulations, because of its adhesive power, durability, heat resistance and elasticity. Glues containing PTBP-FR are used in leather products such as shoes, watchstraps, handbags, building materials, motorcars and electrical products (1). Since the 1950s, PTBP-FR has become commercially available and popular as a resin ingredient in adhesives, especially leather and rubber products (2). *p*-tert-Butylphenol-formaldehyde is a common sensitizer, and several cases of contact dermatitis due to PTBP-FR have been reported in Japan (1, 3, 4). The patch test-positive ratios for PTBP-FR are not so high, reported as 2.3% (1984), 1.7% (1996) (5) and 2.2% (2000) (6) (Research Group of the Japanese Society for Contact Dermatitis).

We suspected that the causative allergen was present in the adhesive of the wetsuit. The adhesive was made of the same rubber material, namely polychloroprene rubber. Polychloroprene-rubber adhesives contain PTBP-FR as a tackifier. She had a history of contact dermatitis from a pair of shoes and a wrist-watch. The causative allergens in previous wetsuit dermatitis cases were found to be thiourea derivatives (7). To our knowledge, this is the first case of allergic contact dermatitis from PTBP-FR in the adhesive of a wetsuit.

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Occupational protein contact dermatitis from flour and cuttlefish

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Key words: cuttlefish; grain flours; occupational; pizza making; protein contact dermatitis; rye; wheat.

The term protein contact dermatitis was introduced by Hjorth & Roed-Petersen (1) to describe a form of chronic recurrent dermatitis caused by contact with proteinaceous material, observed in kitchen workers. Patch tests were usually negative, but prick or scratch tests with the responsible protein were positive. In some cases, specific immunoglobulin E (IgE) to the substance could be detected.

Case Report

A 47-year-old woman, with no personal history of atopy, had been employed in a restaurant as a pizza-maker for 3 years. After 2 years in this job, she developed oedematous erythema, papules and vesicles, with itching on the hands, forearms and face. Some few months later, she began to experience oedema of the eyelids and rhinoconjunctivitis within minutes of flour contact. She did not wear protective gloves. The patient reported that when she ate flour products, her eczema worsened and she suffered from acute diarrhoea.

Patch tests with the GEIDC standard series and additional series were negative. Patch testing with the patient's own wheat flour was negative.

Prick tests with a series of common inhalants and food allergens were positive to both wheat and rye (wheals 3 mm larger than negative control). A prick test with the patient's own wheat flour was even more positive. CAP assays for wheat and rye (Pharmacia Diagnostics, Uppsala, Sweden) were both positive, specific IgE against wheat being 18.5 KU/l and rye 22.3 KU/l. Total IgE was 962 KU/l. Oral antihistamines and topical corticosteroids were prescribed, with partial improvement of lesions.

Clinical signs and symptoms regressed after the patient was taken off work and given a diet without cereal protein, but 6 months later, at follow-up, she reported the same symptoms when handling cuttlefish (*Sepia madokai*). Prick-by-prick testing with cuttlefish was strongly positive.

Discussion

Food can act as both irritant and allergen, and food handlers like our

patient are at risk of developing dermatitis on the hands due to sensitization by foods or damage from their irritant effect, as well as from the wet work that so often accompanies the preparation of food (2).

Our patient's history and test results (prick and CAP) strongly indicate an occupational Type I allergic reaction to rye and wheat. Occupational protein contact dermatitis from flours is relatively frequent in food handlers and bakers (1–5). Patients present with chronic hand dermatitis, sometimes with spread to the forearms and face, as in our patient. They may also report itching or urticarial lesions while working with flour. Not infrequently, rhinoconjunctivitis and/or asthma occur (5). The oral ingestion of these foods may provoke in the patients a generalized eczematous rash or a dyshidrosiform reaction on the fingers, palms and soles (6).

Molluscs are recognized as a common cause of food hypersensitivity reactions (7, 8). Allergic reactions in seafood workers develop after occupational exposure and in consumers after preparation and/or ingestion of Crustacea (9). Dermatological manifestations include flushing, urticaria, angioedema and dermatitis. Other reactions include gastrointestinal (nausea and diarrhoea) and respiratory (rhinitis and asthma) (10, 11).

The mechanism of protein contact dermatitis is unknown; characteristically, its allergic nature is rarely detected by patch testing, and the responsible allergen is almost always detected by immediate-type allergy tests (prick and CAP) (1–5). However, the negativity of patch tests may be related not only to the possibility that the procedure may not reproduce the conditions of exposure, but also to the fact that they are performed on the back and not on the site of previous lesions (12).

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Erythema multiforme with occupational rubber contact sensitivity

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Case Report

A 41-year-old man was hospitalized for a widespread eruption that had developed within 1 week. He had been working for 3 weeks in an interim factory of a rubber-piping company. After 2 weeks, he observed an erythematous eruption localized to the abdomen and upper legs. His work consisted of extracting rubber piping from its cast, detachment being facilitated by the use of a gel. Protective equipment comprised leather gloves. He used to wipe excess gel onto his clothes.

Clinical examination showed an erythematous bullous and purpuric dermatitis. Histological examination demonstrated slight spongiosis and some vesicles, without keratinocyte necrosis, suggestive of eczema. Topical betamethasone dipropionate improved the eruption. After 5 days, we noted the lesions to worsen. Target and urticarial lesions appeared at the periphery of the initial lesions.

An erythema multiforme-like eruption was diagnosed, confirmed by histological examination, which then showed focal epidermal necrosis with lymphohistiocytic exocytosis and slight spongiosis. A blood count showed an eosinophilia of 3720 cells/mm. The patient's eruption improved significantly on treatment with systemic and topical corticosteroids.

Patch testing was carried out 8 weeks later with the European standard series, a rubber series (Chemotechnique, Malmö, Sweden), medicaments, clean detachment gel and rubber-contaminated detachment gel. Patch tests were positive to many rubber chemicals: tetramethylthiuram monosulfide, tetramethylthiuram disulfide, dipentamethylenethiuram disulfide, mercaptobenzothiazole and dimethyldithiocarbamate. The patch test with rubber-contaminated gel was positive, while that with clean gel was negative.

Discussion

Erythema multiforme-like eruptions associated with contact dermatitis begin as eczema at the contact site, secondarily spreading as an erythema multiforme (1, 2). Usually, they are

due to strong sensitizers (especially drugs but also occupational allergens) (3–5). To our knowledge, there has never been described an erythema multiforme with contact dermatitis from rubber vulcanization agents.

The lesions were the consequence of indirect occupational contact with rubber piping via the intermediary of a detachment gel able to absorb and concentrate rubber allergens. The clinical course of the disease was biphasic: initially, an acute eczema with poor response to topical corticosteroids and then erythema multiforme requiring systemic corticosteroids. The pathophysiological mechanism could be a systemic response due to the strength of the allergen or cytotoxicity as in erythema multiforme with herpetic infection (4, 5).

We were amazed by the rapidity of this sensitization to rubber vulcanization agents. An occupational survey found other workers presenting with a similar eruption at the same factory.

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A multilingual European patch test software concept: WinAlldat/ESSCA

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The ready availability of a computer database for standardized patch test data has great scientific and public health benefits (1). The patch test software 'WinAlldat/ESSCA' has been developed as a tool to (i) collect and analyse patch test data on a local level and (ii) export this (anonymized) data to a data centre for further pooled analyses. Commissioned by the EU project ESSCA-DC (QLK4-CT-2001-00343), WinAlldat/ESSCA has successfully been used since early 2002 to collect data in the context of the European Surveillance System on Contact Allergies (ESSCA) (www.essca-dc.org). In addition to its ability to cater for special local research interests and documentation requirements, multilingual capabilities make WinAlldat/ESSCA a candidate software for individual departments or national contact dermatitis groups in search of a suitable tool, with or without the intention to (yet) contribute to ESSCA. We invite colleagues to evaluate WinAlldat/ESSCA, clearly with the hope that they might wish to contribute to, and thus broaden the base of, ESSCA at some stage. Naturally, contributions to ESSCA are more easily incorporated when delivered in a standard format, such as that provided by the WinAlldat/ESSCA software.

The scope of anamnestic items is shown in the history sheet [case record form (CRF)] available online under <http://www.ivdk.gwdg.de/essca/doc/>. In addition to these core and optional items, local users can easily supplement the basic CRF with additional questions and corresponding pick lists. Additionally, if non-categorical data is to be recorded, respective database extensions and input and report modules can be programmed, e.g. using Visual Basic (Visual Studio™, Microsoft Corp., Redmond, WA, USA). This, however, may require the involvement of information technicians or programmers. Concerning occupations, the ISCO-88 COM classification is used for the sake of compatibility with European statistical requirements. The International Classification of Diseases, 10th revision (ICD-10) has not been included in the core version, because relevant diagnoses are not well represented in this catalogue. Moreover, the ICD-10 classifies dermatitis diagnoses according to selected causative substances, which is redundant to other parts of the WinAlldat/ESSCA database. However, it is possible to supplement the database with a set of ICD-10 diagnoses, if required. The objective of future software development will be to include the support of the XML standard for printing purposes (HTML), export and the integration into hospital information systems. Furthermore, the development of a Java-based WinAlldat/ESSCA client for information retrieval and standard reports tool is being considered.

Translations into languages other than English (core version) can be performed utilizing a translation tool kit, which requires MS Access™ (Microsoft Corp., Redmond, WA, USA). This process involves catalogue lists (e.g. diagnoses, anatomical sites, occupations, allergen names) of the database, screen field labels, online help texts and a written manual. Clearly, a translation needs to be done by just one centre, and translated versions can subsequently be delivered to other centres interested in a particular language version, once the translation has been integrated into the installation package. So far, translations and respective program versions for Italian, French and Polish are currently in the final testing phase. For German-speaking areas, the sister-version of the software, WinAlldat/

IVDK, is available (www.ivdk.org) which is fully compatible with ESSCA standards.

Concerning hardware, Intel-based personal computers with Pentium or AMD CPU (clock speed >800 MHz), 128 MB RAM minimum (recommended: 256/512 MB), hard disk drive with at least 2 GB available free space, floppy disk drive 3.5" (1.44 MB) and a CD-ROM drive (recommended: 24× speed) is required. A WindowsTM 98, Windows NT 4.0, Windows 2000 or Windows XP operating system is also required. Additionally, the database system MS Access 97/OfficeTM 97 or 2000 is required to execute custom reports and additional program features based on MS Access. While single computer installations are easily done

following the stepwise instructions contained in the installation package, any network installation do require more support at a local level, and need to be done in close co-operation with the local IT department.

For contact and further enquiries, please consult the project co-ordinators or the data centre north (covering central and northern Europe) or south (covering French speaking and Mediterranean countries) via the ESSCA website (www.essca-dc.org).

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