

Contact dermatitis caused by pharmaceutical ointments containing 'ozonated' olive oil

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Olive oil is a mixture of several glycerides of (mainly) oleic acid, but also palmitic, linoleic, stearic and arachidic acids, and also contains squalene, phytosterol, tocopherol and phenolic compounds. It is considered to be a weak irritant and a low-risk sensitizer (1), with the actual allergen(s) being unknown. Apart from its culinary use and its presence in cosmetics, it may also be used in topical pharmaceutical products (including compounded formulations). It is also occasionally used as a vehicle for patch testing. We report 2 patients with contact dermatitis caused by topical pharmaceuticals containing so-called 'ozonated' olive oil, that is, olive oil enriched with ozone (O₃). Such oil may be partially or fully ozonated, with the former being more liquid and having a green-yellowish colour (more closely resembling plain olive oil), and the latter being white to colourless and having greater viscosity (2).

Case Reports

Patient 1

A 23-year-old atopic female was seen at the Antwerp department with a history of dry, cracked lips and angular cheilitis, which had been present for a few months, and had been attributed to her atopic constitution. She denied frequent lip-licking. However, she reported that, following treatment with Neomycolog[®] ointment (a yellowish and rather liquid ointment, containing partially ozonated olive oil as an ingredient; Sanofi Aventis, Diegem, Brussels, Belgium), she had experienced severe worsening of

her skin condition, for which she was referred to us. Clinical examination showed an itchy but mainly burning, very sharply demarcated perioral dermatitis, without secondary spreading (Fig. 1). Patch tests, as advised in cases of cheilitis extending beyond the vermilion border of the lips (3), were performed with the Belgian baseline series, a cosmetic series, a fragrance and a bakery series (all from Chemotechnique, Vellinge, Sweden), the patient's own cosmetics (including toothpastes and lip care products), and the (partially) ozonated olive oil, all of which were applied on her upper back with Allergeaze[®] patch test chambers (SmartPractice, Calgary, Canada) occluded for 2 days with Fixomull[®] stretch (BSN Medical, Hamburg, Germany). Readings were performed on day (D) 2 and D4, according to recently published guidelines from the European Society of Contact Dermatitis (4). No positive reactions were observed, and no reactions later than D4 were reported. A patch test with extra virgin olive oil also gave negative results. A repeated open application test (ROAT), in which the patient applied a small amount of the partially ozonated olive oil twice daily on the forearm for 1 week, a prick test with the suspected ointment and a radioallergosorbent test for olive (f342; *Olea europaea*) also gave negative results. The patient refused further work-up (including a re-challenge test), but, following treatment with a topical corticosteroid (methylprednisolone aceponate) and complete avoidance of the ointment, her dermatitis cleared and did not recur.

Patient 2

A second 23-year-old non-atopic female, known to have nickel contact allergy, was referred to the Leuven department for additional patch testing because of recalcitrant foot dermatitis that she had been suffering from for >2 years. She was patch tested with a baseline series (excluding nickel) and a shoe series, both from Trolab[®] (Hermal, Reinbeck, Germany), along with her personal

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Fig. 1. Contact dermatitis in patient 1 caused by a pharmaceutical ointment containing (partially) 'ozonated' olive oil; note the sharp demarcation of the perioral eczema without any spreading reaction, indicating irritant rather than allergic contact dermatitis.



Fig. 2. Strong positive patch test reaction (++) to a pharmaceutical preparation containing 'ozonated' olive oil, extending outside the patch test chamber, in patient 2.

skin care products, pieces of her own shoes, and the topical pharmaceuticals that she had used, including a fully ozonated olive oil preparation (Farmaline, Tongeren, Belgium) consisting of a colourless and waxy ointment. Olive oil was not tested separately. Van der Bend® test chambers (van der Bend, Brielle, The Netherlands) were applied on the upper back, and covered with Mefix® (Mölnlycke, Göteborg, Sweden). Readings were performed on D2 and D4, as in the first case, and showed a ++ reaction to the ozonated olive oil preparation, extending outside the patch test chamber (Fig. 2), on D2 and D4, along with a doubtful and non-relevant reaction to neomycin (+?). Despite treatment with a strong topical corticosteroid (betamethasone dipropionate 0.05%), and avoidance of the aforementioned preparation, her dermatitis did not heal. However, upon replacement of her own shoes, contaminated with the ozonated olive oil ointment, with new shoes, her dermatitis settled and did not recur.

To confirm the contact-allergic mechanism in this case, the patch test with the ozonated olive oil was repeated, and showed the same morphological reaction. Moreover, 20 control patients were patch tested with this



Fig. 3. Irritant patch test reaction to a fully ozonated olive oil (from patient 2) in a control patient.

fully ozonated olive oil, and a surprisingly high number of them (8/20) showed a clear irritant response, that is, a sharply demarcated, slightly burning (rather than itchy) and sometimes crusty skin reaction without focal spreading (Fig. 3).

Discussion

'Ozonated' olive oil is a relatively new application whereby the addition of ozone is believed to give the oil bactericidal, virucidal and fungicidal properties, making it a treatment for (infected) superficial skin wounds (5). In the first patient, it was prescribed as a treatment for a (suspected) *Candida albicans* infection as the cause of angular cheilitis, but, rapidly after the treatment had been started, its use led to a strong skin reaction. A tentative diagnosis of irritant, rather than allergic, contact dermatitis caused by ozonated olive oil was made, on the basis of: (i) the clinical aspect, that is, very sharp demarcated dermatitis, rather burning than itching; (ii) the absence of a spreading reaction [as also shown by Kränke et al. (1) for irritant contact dermatitis caused by plain olive oil]; and (iii) a negative patch test result and a negative ROAT result on the skin of the back and on the skin of the volar arm, respectively.

The case of this atopic patient is somewhat reminiscent of a previously published series, in which 19 of 20 atopic patients presented with perioral dermatitis resulting from contact irritation caused by a new tartar-control toothpaste (6).

Olive oil, because of its high level of oleic acid and low level of linoleic acid, has a negative impact on the skin barrier, causing reductions in the thickness and integrity of the stratum corneum, and therefore might, by itself, exacerbate atopic dermatitis (7), which actually might have happened in our patient. One could argue that the

irritant effect of olive oil might be even more pronounced when it is applied onto skin with an already thin to nearly absent stratum corneum (i.e. the lips and their vermillion border), as opposed to the skin of the back, where the patch test was performed.

The (erroneous) application of the ointment on the lips and the lip mucosa [which is actually discouraged by the medication leaflet, although mucosal application has been described (5)] might also be relevant in this regard.

Although some authors have suggested that oxidation (by O_2) of the unsaturated lipids of olive oil might transform it into a non-sensitizer (8), it may also enhance its irritant properties (9). According to the literature, ozone (O_3) may have both toxic and beneficial effects, depending on the dose, the length of exposure, and the antioxidant capacity of the tissue involved (5). Owing to its strong oxidative and pro-inflammatory capacity, it may thus also be capable of having harmful effects on the skin. Several mechanisms, among which is the formation of free radicals, with subsequent antioxidant depletion and oxidation of lipids and proteins, have been described (5). Elaborating on this, one might speculate that when ozone, primarily acting at the level of the stratum corneum (5), is added to olive oil, it might put skin with an already thin stratum corneum (such as the lips) under additional oxidative stress, creating an even greater risk of irritation. Differences between various anatomical skin sites, with different thicknesses of the stratum corneum, might have to be taken in account when the potential irritancy of such ozonated olive oil is evaluated. Moreover, as shown during the work-up of our second patient, the high number of control patients (8/20) showing clear irritant reactions to a fully ozonated olive oil seems to suggest that the irritant effect of such oil might be even more important than the irritant properties of plain olive oil, being often used as a vehicle for patch testing (8), although this would have to be shown in future comparative studies.

With regard to the negative ROAT result with the partially ozonated olive oil after 1 week in the first patient, it is interesting to note that it might take much longer (up to 4–5 weeks) before one can observe an erythematous irritant effect of olive oil when it is applied onto the skin of the forearm (7).

Although irritancy may be a possible explanation in the first patient, there is nothing to exclude contact allergy to a substance present in the ointment at a concentration too low to give a positive patch test reaction but high enough to elicit dermatitis on frequent exposure. In accordance with a previous report (8), the exact sensitizer among the components of olive oil remains to be shown, including in those cases published hitherto concerning plain olive oil. Chromatography might help in obtaining

different fractions of olive oil, containing potential sensitizer(s), for patch testing.

In the second case, in which a contact-allergic mechanism is very likely, contamination of previously used shoes, despite the wearing of socks, was sufficient to induce contact allergy, hence explaining the ongoing contact dermatitis. This is very plausible, as the strong patch test reaction (++) indicates that even a very low amount of the allergen may trigger a reaction. A similar observation has been reported for other (strong) allergens [e.g. ketoprofen (10) and methylisothiazolinone (11)], where contaminated personal objects elicited strong reactions in previously sensitized subjects.

Olive oil, because of its inherent irritant properties, which are potentially even more prominent when ozone is added, may cause irritant contact dermatitis and a risk of subsequent sensitization to one of its allergenic components, especially when it is used under occlusion, for example by the wearing of shoes, as in our second case.

Occupational allergic hand dermatitis caused by plain olive oil has been previously reported in pedicurists (12), masseurs (13, 14), and pizza makers (15). Also, occupational contact urticaria and protein contact dermatitis of the hands, together with perioral itching and swelling, caused by olives have been reported in a pizza chef (16). Interestingly, owing to its presence in pharmaceutically compounded ointments, olive oil was reported to be the cause of contact allergic cheilitis (8) and of contact irritant leg dermatitis (stasis or venous dermatitis) in 4 of 5 cases in which the oil was usually also applied under occlusion (1). In the latter report, only 1 case was considered to be truly contact-allergic, according to the morphology of the patch test with olive oil (being sometimes very difficult to differentiate from an irritant reaction) and the occurrence of a secondary spreading reaction. At the K.U. Leuven department, where olive oil has been patch tested as such in 722 patients since 1990, 14 additional contact-allergic cases (7 females and 7 males) were identified, in the majority of these patients (13/14) again because of its presence in pharmaceutical ointments (mainly compounded creams, e.g. hand or wound care creams). Although some reports have mentioned the occurrence of perioral complaints in individuals who became skin-sensitized to olive oil (8), others have highlighted the fact that these patients often tolerate the ingestion of olive oil as part of a normal diet (13–15).

Another point of interest is the type of olive oil that is used for patch testing. Indeed, Wong et al. reported a patient who showed a relevant, positive patch test reaction to 'extra virgin' olive oil, but not to 'regular' olive oil, which differs in composition (15). Williams et al. have

reported that olive oil (unspecified) only rarely produces false-positive or irritant patch test reactions (e.g. when used as a patch test vehicle) (14), whereas others have stressed that this might occur (1, 9). Taking this into account, it has been advocated to preferentially use 'extra virgin' and freshly prepared olive oil (1), or oil of a pharmaceutical grade (free from contaminants such as, for example, pesticide residues) (8). Ideally, it should also be protected from light and stored in N₂, to prevent autoxidation, which might boost the irritant properties of the oil

(9), possibly leading to irritant skin and patch test reactions (1). A ROAT (1) or a use test (13) may be a useful additional tool with which to gather more information on the type of reaction pattern involved, that is, contact allergy or contact irritation.

In conclusion, we here illustrate irritant and allergic contact dermatitis as potential side-effects of olive oil, and we hypothesize that these adverse reactions may even be enhanced by the addition of ozone.

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