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## SUPPORTING INFORMATION

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

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# Vulvar allergic contact dermatitis to metronidazole

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Genital areas are highly susceptible to irritants and allergens and development of contact dermatitis due to several factors such as occlusion, humidity and friction.<sup>1,2</sup>

We report a case of allergic contact dermatitis (ACD) of the vulva related to the use of topical metronidazole during self-treatment.

## CASE REPORT

A non-atopic 58-year-old woman was referred to us for intense vulvar erythema with scattered oozing erosions, vulvovaginal itching and burning sensation accompanied by a cottage cheese-like vaginal discharge, progressively worsening. She was applying an ointment containing clotrimazole 20% and metronidazole 4% (Meclon, Alfasigma, Bologna, Italy) and occasionally with an ointment containing lidocaine 2% (Vagisil, Combe Italia s.r.l., Milan, Italy). Patient's history revealed recurrent vulvovaginal candidiasis self-treated on demand during the last months. The two topical products were stopped and genital lesions and symptoms promptly disappeared after treatment with mometasone furoate ointment (once daily for 10 days) and oral fluconazole (200 mg daily for 2 days). Six weeks after clinical resolution, the patient was patch-tested with the SIDAPA (Società Italiana Dermatologia Allergologica Professionale Ambientale) baseline series (SmartPractice, Rome, Italy) and the

two topical products "as is". Patch tests were applied on the back and left in occlusion for 2 days, using the Haye's Test Chambers (Haye's Service, Alphen aan den Rijn, The Netherlands) on Soffix tape (Artsana, Grandate, Italy). Readings were performed on day (D) 2, D4 and D7,<sup>3,4</sup> and positive reactions at D4 and D7 to nickel sulfate (++), fragrance mix-I (++) and Meclon cream (++) were observed. Subsequently, patch tests with clotrimazole 5% pet. and metronidazole 1% pet. were performed, with positive reaction to metronidazole (++).

## DISCUSSION

Patients with genital dermatitis are often reluctant to seek medical consultation with the risk of improper management. Vulvar contact dermatitis is one of the commonest conditions diagnosed in vulvar clinics, although its exact prevalence is unknown.<sup>2</sup> Studies performed in secondary and tertiary referral centres have shown that ACD was diagnosed in a wide range of patients (13%–49%) with vulvar complaints.<sup>2</sup>

Diagnosis of vulvar ACD can be challenging as it is sometimes associated with other genital dermatoses and can also be caused by treatments used for these preexisting dermatoses.<sup>1</sup>

The allergens most frequently implicated in vulvar ACD are fragrances, preservatives, and topical drugs, including corticosteroids, antibiotics and anaesthetics.<sup>2</sup> Among the topical medications used to treat vulvovaginal diseases, clotrimazole and metronidazole have rarely been reported as causes of ACD.<sup>5,6</sup> Kumagai et al. described a patient with

ACD related to the use of metronidazole intravaginal ovules, which was characterized by a symmetrical drug-related intertriginous and flexural exanthema pattern.<sup>6</sup> Cases of ACD in patients using metronidazole gel or cream for rosacea have been described.<sup>7,8</sup>

Metronidazole is a nitroimidazole with structural similarities to other imidazole derivatives. A case of cross-reactivity between metronidazole and bifonazole and tioconazole has been described.<sup>9</sup> In other reports,<sup>7,8</sup> patch testing in patients with ACD to metronidazole did not disclose cross-reactions with other imidazoles. Corazza et al. described a patient with vulvovaginal ACD to clotrimazole who had negative patch test reactions to miconazole, metronidazole, and isothiazolinones.<sup>5</sup> A possible cross-reaction between imidazoles and isothiazolinones has also been hypothesized.<sup>10</sup>

The diagnosis of iatrogenic ACD should be considered in patients with genital dermatoses and/or symptoms that worsen during treatment with topical drugs. We emphasize the importance of performing patch tests with patient's own products in such circumstances.

#### AUTHOR CONTRIBUTIONS

**Caterina Foti:** Conceptualization; methodology; writing – review and editing; supervision. **Gianluca Calianno:** Data curation; methodology; writing – original draft. **Nicoletta Cassano:** Writing – original draft; methodology. **Gino Antonio Vena:** Writing – original draft; methodology; validation. **Katharina Hansel:** Writing – review and editing; supervision; validation. **Luca Stingeni:** Validation; writing – review and editing; supervision. **Paolo Romita:** Conceptualization; writing – original draft; writing – review and editing; methodology; supervision.

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#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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## Allergic contact dermatitis from hydroxyacetophenone in an anti-wrinkle facial serum with flare-up reactions triggered by the repeated open application test

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