Remifentanil-Induced Symmetric Drug-Related Intertriginous and Flexural Exanthema: A Diagnostic Challenge in an Intensive Care Patient

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Palabras clave: Reacción tardía de hipersensibilidad. Test de transformación linfocitaria. Pruebas epicutáneas. Remifentanilo. Exantema simétrico intertriginoso y de flexión relacionado con el fármaco (SDRIFE).

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is a rare, sharply demarcated symmetric erythema of the gluteal and/or inguinal areas and at least 1 other flexural localization resulting from exposure to a systemic drug. The interval between exposure to the drug and onset is usually short (days) and independent of previous sensitization [1-3]. The pathophysiology of SDRIFE is complex and not fully understood, although T cell–mediated delayed hypersensitivity reaction and excretion of specific drug metabolites from the eccrine glands on the affected areas appear to play a role [2,3]. Most cases are associated with antibiotics, particularly ß-lactams (aminopenicillins and cephalosporins), although other drugs have also been reported to be involved (eg, carbapenems, antifungal agents, antihypertensive agents, radio-contrast media, chemotherapeutic agents, and monoclonal antibodies) [2,4].

The diagnosis is based on 5 criteria: exposure to a systemically administered drug either at the first or subsequent doses (excluding contact allergens), sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/genital area, involvement of at least 1 other intertriginous/flexural localization, symmetry of affected areas, and absence of systemic symptoms and signs [5,6]. The diagnosis is supported by positive skin test and in vitro test results, although these are usually inconclusive [5].

Treatment involves discontinuation of the suspected drug, symptomatic control of pruritus, and administration of topical corticosteroids [5].

A 29-year-old, previously healthy, nonatopic man was admitted to the emergency department (ED) with trauma due to a motorcycle collision. On admission, he was hemodynamically unstable with a shock index of 1.89, corresponding to a high risk of mortality. Focused assessment with sonography in trauma (FAST) showed hemoperitoneum, and emergency exploratory laparotomy confirmed traumatic splenic rupture, resulting in splenectomy. He was admitted to the intensive care unit (ICU) and analgosedated with remifentanil and propofol. On day 3 of admission to the ICU, he was diagnosed with early-onset ventilator-associated pneumonia and started ceftriaxone. Midazolam was started to optimize analgosedation and improve patient-ventilator interaction. After 48 hours, the patient developed extensive demarcated erythema with a symmetrical presentation limited to the gluteal, perianal, inguinal, and flexural areas. Over the next 24 hours, the erythema progressed to vesicles and blisters at the flexures, some with loss of epidermal integrity. Since the patient was sedated, it was not possible to assess the pruritus. A laboratory work-up with complete blood count and liver and kidney function was unremarkable. Consultation with the Allergy and Clinical Immunology Department led us to consider a diagnosis of SDRIFE, which was corroborated by punch skin biopsy findings, namely, superficial perivascular eosinophils and rare neutrophilic infiltrates associated with intraepidermal blisters containing lymphocytes and isolated neutrophils. Ceftriaxone was discontinued on day 6 of the ICU stay, as it was considered the main culprit agent, given the prevalence reported in the literature. Antibiotic therapy was switched to ciprofloxacin based on antibiotic sensitivity testing and culture of the bronchoalveolar aspirate, which revealed *Neisseria meningitides*. A topical corticosteroid (0.5 mg/g clobetasol propionate ointment) was applied on the accessible areas. Considering the patient's state of immobilization owing to polytrauma, the extension and severity of his skin lesions (some of which involved loss of skin integrity), his septic status, and the need to monitor new possible sources of infection, we decided to add systemic corticosteroid therapy (intravenous prednisolone 0.5 mg/kg/d for 3 days). The patient's symptoms resolved. Improved hemodynamic and respiratory status enabled weaning from analgosedation, with suspension of midazolam on day 6 and remifentanil and propofol on day 7 of the ICU stay.

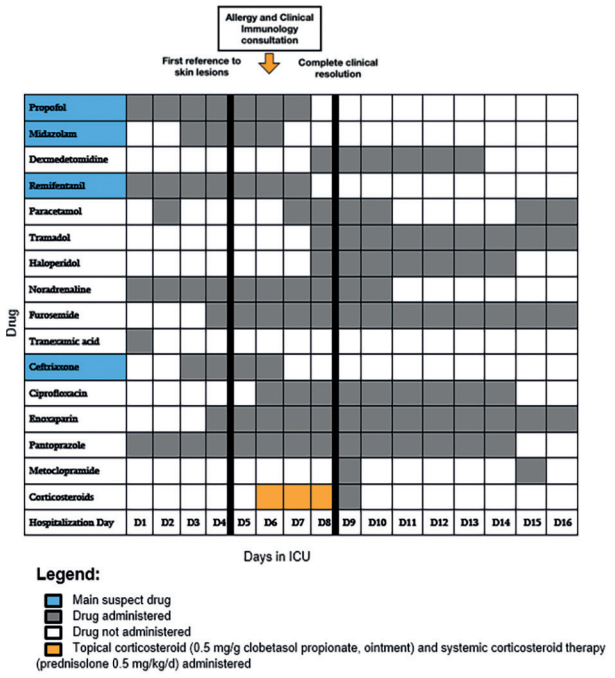

Figure. Timeline for drugs administered during the stay in the ICU. ICU indicates intensive care unit.

Eight weeks later, a diagnostic workup based on the drug timeline (Figure) ruled out latex allergy. Skin prick tests (SPTs) and intradermal tests (IDTs) with immediate and delayed readings were performed for the main suspected drugs at concentrations based on EAACI/ENDA recommendations: ceftriaxone (SPT, 2 mg/mL; IDT, 2 mg/mL), midazolam (SPT, 5 mg/mL, IDT, 0.5 mg/mL), remifentanil (SPT, 0.05 mg/mL; IDT, 0.005 mg/mL), and propofol (SPT, 10 mg/mL; IDT, 1 mg/mL), all with negative results. Patch tests were performed in accordance with the recommendations of the European Society of Cutaneous Allergy and Contact Dermatitis (ceftriaxone, midazolam, remifentanil, and propofol at 10% and 30% pet) and routinely included evaluation using the European baseline series, with readings on days 3, 4, and 7. Patch test results were positive for remifentanil at 10% and 30% on day 3. Lymphocyte transformation testing (LTT) was performed 12 weeks after symptoms had completely resolved. The recommended concentrations for LTT were used (3 × 5-fold dilutions of each drug), and the result was considered positive if the stimulation index (SI) was higher than 2 for 2 different concentrations [7]. The result was positive for remifentanil, with an SI of 2.1 and 2.3 for 100 µg/mL and 200 µg/mL, respectively, and negative for the remaining drugs tested. Drug provocation testing (DPT) was negative for ceftriaxone (cumulative dose, 1000 mg). DPT was not performed for the remaining suspected drugs owing to the potent pharmacological effects of these drug groups, namely, respiratory depression and sedation.

SDRIFE is a rare condition that has received little attention in the literature. In the case we report, the allergology work-up was carried out based on a detailed analysis of the complex drug chronology. Based on data from the literature, such as those reported by Häusermann et al [6], who found that antibiotics—mainly ß-lactams—were the main etiological agents in SDRIFE, ceftriaxone was initially considered the culprit agent in the present case. The results of skin testing and in vitro tests and the negative DPT result enabled us to exclude this hypothesis. Although the LTT is a safe in vitro test, few authors have performed the LTT to diagnose SDRIFE [8-9]. In the case of the remaining suspect drugs, patch and LTT tests were crucial for identification of the culprit drug, revealing positive results with remifentanil.

In the present case, the fact that all the diagnostic criteria for SDRIFE were met, the histopathological findings, and the positive patch and in vitro test results for remifentanil supported a diagnosis of remifentanil-induced SDRIFE, thus enabling us to avoid DPT and re-exposure risks. Additionally, these positive results support the involvement of a type IV hypersensitivity mechanism in SDRIFE.

Depending on the clinical context, the diagnosis of a delayed drug reaction can be more or less challenging, especially in ICU, polymedicated, and sedated patients. A detailed review of all exposures is essential to guide the search for the etiological agent.

The complex drug chronology, the presence of the drugs most frequently implicated in this type of hypersensitivity reaction (eg, ß-lactams), and the patient's sedation status made diagnosis of the allergy challenging in this case.

To the best of our knowledge, we report the first case of remifentanil-induced SDRIFE.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. De Risi-Pugliese T, Barailler H, Hamelin A, Amsler E, Gaouar H, Kurihara F, et al. Symmetrical drug-related intertriginous and flexural exanthema: A little-known drug allergy. J Allergy Clin Immunol Pract. 2020;8(9):3185-39.e4.
2. Nespoulous L, Matei I, Charissoux A, Bédane C, Assikar S. Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) associated with pristinamycin, secnidazole, and nefopam, with a review of the literature. Contact Dermatitis. 2018;79(6):378-80.
3. Can C, Yazicioglu M, Ozdemir PG, Kilavuz S, Tastekin E. Symmetrical drug-related intertriginous and flexural exanthema induced by two different antibiotics. Allergol Immunopathol (Madr). 2014;42(2):173-5.
4. Blanco Garcia-Granero D, Barranco R, García-Moguel I, Velasco V, Diéguez Pastor MC. First Case of Symmetric Drug-Related Intertriginous and Flexural Exanthema Induced by Meropenem. J Investig Allergol Clin Immunol. 2021;31(6):516-7.

5. Tan SC, Tan JW. Symmetrical drug-related intertriginous and flexural exanthema. Curr Opin Allergy Clin Immunol. 2011;11(4):313-8.
6. Häusermann P, Harr T, Bircher AJ. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? Contact Dermatitis. 2004;51(5-6):297-310.
7. Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. Allergy. 2007;62(12):1439-44.
8. Obara K, Maejima H, Katayama C, Takasu H, Amoh Y. A case of symmetrical drug-related intertriginous and flexural exanthema induced by acetaminophen. J Dermatol. 2014;41(12):1132-3.
9. Daito J, Hanada K, Katoh N, Katoh S, Sakamoto K, Asai J, et al. Symmetrical Drug-Related Intertriginous and Flexural Exanthema Caused by Valacyclovir. Dermatology. 2009;218(1):60-2.

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