Remifentanil-Induced Symmetric Drug-Related Intertriginous and Flexural Exanthema: A Diagnosis 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 raresharply demarcated symmetric erythema of the gluteal and/or inguinal areas,and at least one other flexural localization, resulting from exposure to a systemic drug. The delay after exposure to the drug is usually short, occurring in days, and is independent of previous sensitization [1,2,3]. The pathophysiology of SDRIFE is complex and not fully understood; however, a T cell-mediated delayed hypersensitivity reaction and the excretion of certain drug metabolites from the eccrine glands on the affected areas appear to play a role [2,3]. Most cases are associated with antibiotics, particularlybeta-lactams,especially aminopenicillins and cephalosporins, but other drugs arereported,such ascarbapenems, antifungal, antihypertensives, radio-contrast media, chemotherapeutic agents, and monoclonal antibodies [2,4].

The diagnosis is based on five criteria: exposure to a systemically administered drug either at the first or repeated dose (excluding contact allergens), sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area, involvement of at least one other intertriginous/flexural localization, symmetry of affected areas, and absence of systemic symptoms and signs[5,6]. Positive skin tests or in vitro tests support the diagnosis,although they are usually inconclusive [5].

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

A 29-year-old, previously healthy,non-atopic male patient was admitted to the emergency department (ED) after trauma due to a motorcyclecollision.On the admission to the ED, the patient was hemodynamically unstable with a shock index of 1.89, corresponding to a high risk of mortality. Focused assessment with sonography of the trauma (FAST sonography)showedhemoperitoneum, and emergency exploratory laparotomy confirmedtraumatic splenic rupture, resulting in splenectomy.He was admitted to the Intensive Care Unit (ICU) and analgosedated with remifentanil and propofol. On D3 of ICU admission, the patient was diagnosed with early-onset ventilator-associated pneumonia, and started ceftriaxone. In order to optimize analgosedation and improve patient-ventilator interaction, midazolam was started.After 48 hours, he developed extensive demarcated erythema with a symmetrical presentation limited tothe gluteal, perianal, inguinal and flexural areas. Over the next 24 hours, the erythema evolved into vesicles and blisters presented at the flexures, some with loss of epidermal integrity. It was not possible to assess the pruritus due to the patient's sedation status.Laboratory evaluation with complete blood count, liver, and renal function were unremarkable. Allergy and Clinical Immunologywas consulted and considered the diagnostic hypothesis ofSDRIFE, which was corroborated by punch skin biopsy findings:superficial perivascular eosinophils and rare neutrophils infiltrates,associated with intra-epidermal blisters containing lymphocytes and rare neutrophils. Ceftriaxone was discontinued on D6 of the ICU stay, as it was consider the main suspected agent, given the prevalence reported in the literature.Antibiotic therapy was switched to ciprofloxacin, based on bronchoalveolar aspirate and antibiotic sensitivity test that identified *Neisseria meningitidis*.Topical corticosteroid (0.5 mg/g clobetasol propionate, ointment) was applied in the accessible areas. Consideringthe patient's state of immobilizationin the polytrauma clinical context, the degree of extension and severity of skin lesions, some with loss of skin integrity, the patient's septic status, and the need to control new possible sources of infection, it was decided to associate systemic corticosteroid therapy (prednisolone 0.5 mg/kg/day,endovenous) for three days, resulting in clinical resolution.Improved hemodynamic and respiratory status allowed weaning from analgosedation with suspension of midazolam on D6, remifentanil and propofol on D7 of the ICU stay.

Eight weeks later, the Allergy diagnostic workup was carried out based on the drug chronology (Figure 1). Latex allergy was excluded. Skin prick test (SPT)and

intradermal tests (IDT) with immediate and delayed readings were performed for main suspected drugswith concentrations according to EAACI/ENDA recommendations: ceftriaxone(SPT 2mg/mL; IDT 2mg/mL), midazolam (SPT 5mg/mL, IDT 0.5mg/mL), remifentanil (SPT 0.05mg/mL; IDT 0.005mg/mL), and propofol, (SPT 10mg/mL; IDT 1mg/mL), allwith negative results. Patch tests were performed in accordance with the European Society of Cutaneous Allergy and Contact Dermatitis (ESCD) recommendations (ceftriaxone, midazolam, remifentanil, and propofol at 10% and 30% petrolatum concentrations), androutinelyincluded European baseline series evaluation, with readings on D3, D4 and D7.Patch test results were positive for remifentanil at 10% and 30% on D3. Lymphocyte transformation tests (LTT) were performed 12 weeks after clinical resolution. Recommended concentrations for LTTwith 3 fivefold dilutions of each drug were used, and LTT result was considered positive if the stimulation index (SI) was higher than 2 for two different concentrations [7]. The result was positive for remifentanil, with a SI of 2.1 and 2.3 for 100mcg/mL and 200mcg/mL concentrations, respectively, and were negative for the remaining drugs tested.Drug provocation test (DPT) was negative for ceftriaxone (cumulative dose of 1000mg). Drug provocation tests were not performed for theremaining suspected drugs, due to potent pharmacological effects of these drugsgroups, namely respiratory depression and sedation.

SDRIFE is a rare condition, with few data in the literature. In our case report, the allergological diagnostic investigation was carried out based on a detailed analysis of the complexdrug chronology. Considering literature data, such as Häusermann et al [6], in which antibiotics, mainly the beta-lactam group, were the main aetiological agents in cases of SDRIFE, ceftriaxone was initially considered the main suspected agent in our case report. Based on skin and *in vitro* tests results, and negative drug provocation test, this hypothesis was excluded.Although the LTT is a safe *in vitro* test, only a few authors have performed the LTT for the diagnosis of SDRIFE cases [8,9,10]. For the remaining suspected drugs, patch and LTT tests were crucial to guide the identification of the culprit drug, revealing positive results to indicate remifentanil.

Given that our patient had all the diagnostic criteria for SDRIFE, the histopathological findings,and the positivity of patch and*in vitro*tests for remifentanil, the diagnosis of remifentanil-induced SDRIFE was established, avoiding the DPT and re-exposure

risks.Additionally, these positive resultssupport 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 drugs most frequently implicated in this type of hypersensitivity reaction, such as the beta-lactam group, and the patient's sedation state, made allergic investigation a diagnostic challenge in this case.

To the best of our knowledge this is the first case described of remifentanil- induced SDRIFE.

Conflict of interest
The authors have no conflicts of interest.

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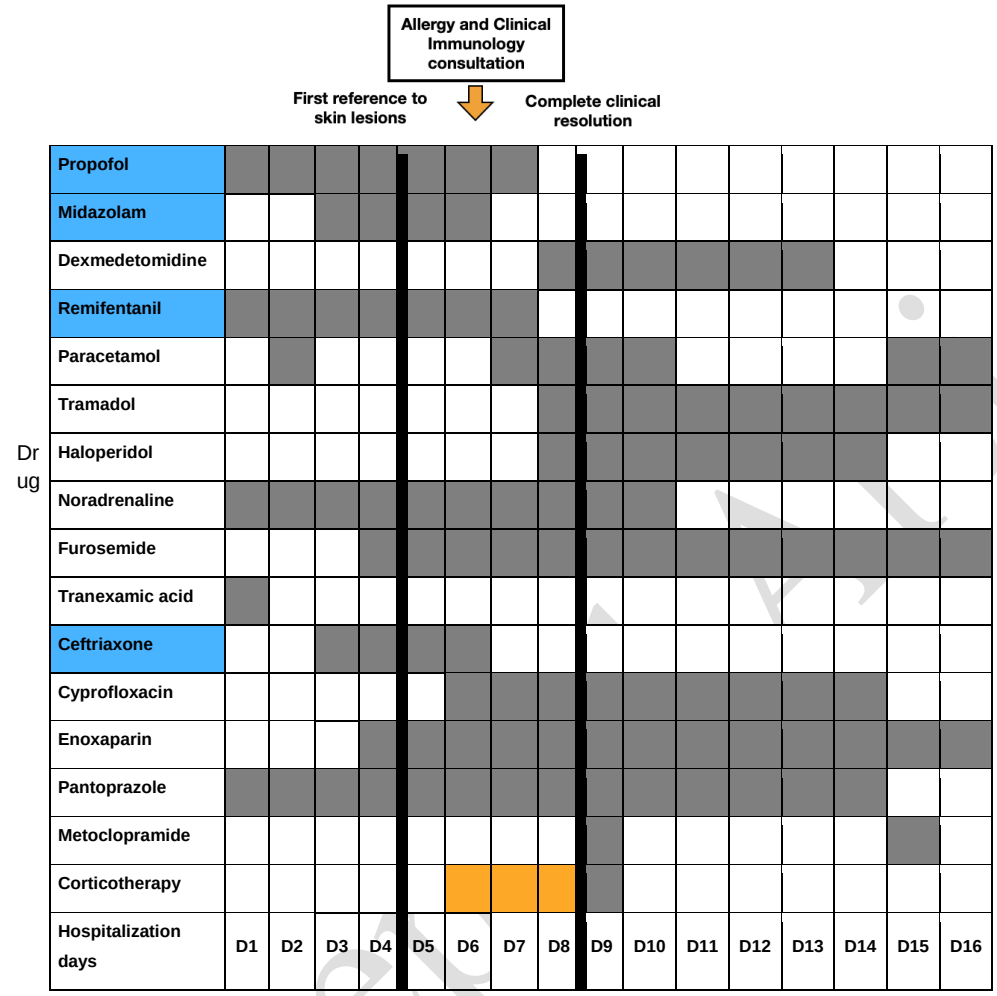
Figure 1.Drug chronology administered during ICU stay.



Legend:

- Main suspected drug
- Drug administered
- Drug not administered
- Topical corticosteroid (0.5 mg/g clobetasol propionate, ointment) and systemic corticosteroid therapy (prednisolone 0.5 mg/kg/day) administered

ICU – Intensive Care Unit