MAEDICA – a Journal of Clinical Medicine
2021; 16(2): 297-301
https://doi.org/10.26574/maedica.2021.16.2.297

MÆDICA - a Journal of Clinical Medicine

CASE REPORT

Drug Provocation Testing in the Diagnosis of Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE) Induced by Clarithromycin

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ABSTRACT

Introduction: *Hypersensitivity reactions to macrolides are rarely described in the literature wherefore they are considered one of the safest choices for antibiotic treatment. Out of the reported reactions, cutaneous manifestations have the highest frequency, particularly non-immediate ones.*

Materials and methods: *We report a case of a 71-year-old female who was referred to us for the drug allergy work-up of a rash unaccompanied by systemic signs, compatible with symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) induced by clarithromycin.*

Results: *The diagnosis was confirmed by a drug provocation test, which reproduced the index reaction.*

Discussion: *As SDRIFE is quite infrequent, it can easily be misdiagnosed if the patient cannot present a clear history of the index reaction or the causal connection with the incriminated drug is not clear. Despite the fact that macrolides rarely induce hypersensitivity reactions, they must not be overlooked in the assessment of a drug induced reaction, as they are a potential etiological factor.*

Keywords: clarithromycin, drug hypersensitivity, drug provocation test, rash, SDRIFE.

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Article received on the 9th of April 2021 and accepted for publication on the 7th of June 2021

INTRODUCTION

Hypersensitivity reactions to macrolides are rarely described in the literature (0.4-3% of all patients treated with the aforementioned), making them one of the safest choices of treatment for patients with hypersensitivity to other classes of antibiotics, especially betalactams (1, 2). Out of the reported reactions, cutaneous manifestations have the highest frequency, particularly non-immediate ones.

Although macrolides are known to have bacteriostatic activity, the most commonly used macrolides, including erythromycin, azithromycin and clarithromycin, have been proven to have bactericidal activity *in vitro* against *Streptococcus pyogenes* and *Streptococcus pneumoniae* (3).

The chemical structure of macrolides consists of a lactone ring varying in size, with 12 to 16 atoms, a criterion that leads to their classification (Figure 1). However, despite the structural similarity, there are few studies that support cross-reactivity between the representatives of this antibiotic class (4).

Erythromycin was the first macrolide antibiotic used for the first time in 1952. Its disadvantages led to the need to discover new macrolides – clarithromycin, introduced in 1992 and azithromycin, in 1994 – with a wider spectrum of action, including Gram negative bacilli like *Haemophilus influenzae* and *Neisseria* spp., a simpler dosage (once or twice daily) and a better safety profile, namely a significant decrease in gastrointestinal side effects such as nausea, abdominal cramps, diarrhea (1).

Macrolides are the recommended first-line therapy for atypical pneumonia in children and community-acquired pneumonia in adults, as well as an option for treating acute otitis media and streptococcal pharyngitis, according to current guidelines (5). Clarithromycin is frequently used in the clinical practice and is included in the treatment regimen for *Helicobacter pylori* infection. Macrolide antibiotics are also considered an alternative for the treatment of many infections in patients with a history of hypersensitivity reactions to beta-lactam antibiotics (6).

Despite the fact that macrolides are considered to be among the safest classes of antibiotics, they do not lack side effects such as gastrointestinal symptoms after oral or intravenous administration, transient ototoxicity or thrombophlebitis following intravenous infusion of erythromycin. However, side effects have been shown to be mild in most cases and subside with discontinuation of therapy (1).

The most frequently described hypersensitivity reactions to macrolides are cutaneous and may have variable degrees of severity. Most of those are late reactions (with onset more than 24 hours after drug administration). Their pathophysiological mechanism is still to be elucidated; allergy skin tests are negative in the majority of cases, which leads to drug provocation tests conducted in specialized centers (1, 4). ❑

MATERIALS AND METHODS

A 71-years-old female patient with no history of drug hypersensitivity was referred to our department for drug allergy work-up of a rash associated with oral use of clarithromycin.

Six months before admission, the patient was diagnosed with a febrile atypical pneumonia. It was decided to start an antibiotic therapy with clarithromycin, in a total daily dose of 1 000 mg, divided in two doses. On the day of the second

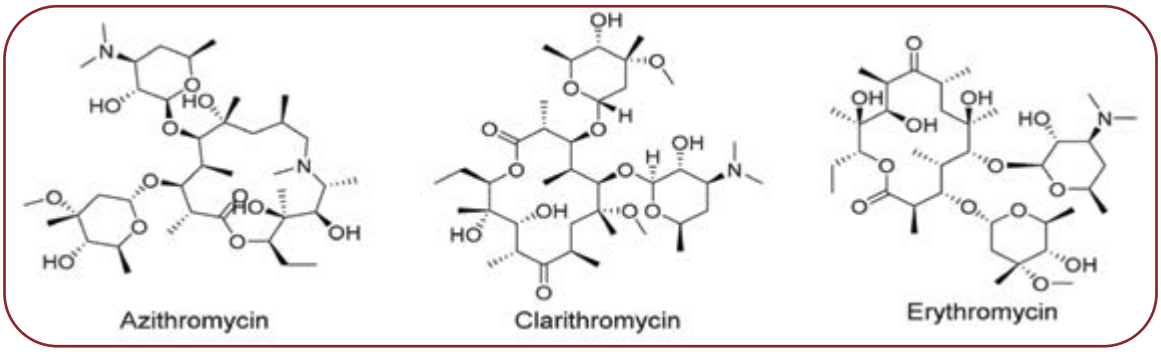

FIGURE 1. Chemical structures of the macrolides most frequently used. Adapted from (4)

dose of clarithromycin administration, an itchy progressive facial rash was developed, with gradual involvement (3-4 days) of submammary folds, the lower back, intergluteal cleft and thighs.

A drug hypersensitivity reaction was considered by a general practitioner, who recommended clarithromycin interruption, H1-antihistamine ingestion, topical and systemic corticosteroids use. Subsequently, the patients' rash has subsided, followed by desquamation of the afflicted areas. However, because of the unclear clinical history and uncertain causal connection with clarithromycin, a rather innocent drug, the patient was referred to our clinic six months later for drug allergy work-up.

At admission, we raised a suspicion of SDRIFE based on clinical history, although the described episode was not mentioned in any medical documents and no pictures were taken at the moment of the rash.

On physical examination, no modifications were noted. Complete blood count, liver and kidney function test, total serum IgE were normal; standard aeroallergenes skin prick testing revealed a (subclinical) sensitization to house dust mites: *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.

For the allergy work-up of the index reaction we performed clarithromycin skin prick testing, followed by intradermal and patch testing. An informed consent was signed by the patient before the procedures.

The concentrations used for skin prick tests were 25 mg/mL and for intradermal tests 1 mg/mL. Readings were performed at 15 minutes after prick tests and 20 minutes and 48 hours after intradermal tests. Furthermore, a patch test was carried out with 10% clarithromycin in petrolatum (7). The reading was performed at 48, 72 and 96 hours. All skin tests were negative. Considering the low incidence of hypersensitivity reactions to macrolides and the negative skin test results to clarithromycin, a drug provocation test with the same drug was conducted (Table 1).

TABLE 1. Oral provocation test with clarithromycin (TDD - Total Daily Dose)

Step	Dose	Time
Step I – 5% TDD	25 mg	0 min
Step II – 15% TDD	75 mg	30 min
Step III – 30% TDD	150 mg	60 min
Step IV – 50% TDD	250 mg	90 min

RESULTS

Clarithromycin allergy skin tests (prick, intradermal and patch) were negative. However, during the oral drug provocation test, the patient experienced diarrhea 50 minutes after the last dose, a common adverse reaction (8). Subsequently, after 8-9 hours, the patient developed an erythematous symmetrical rash of the face and upper torso that afterwards extended to the axilla, breasts, submammary folds and inguinal area (Figure 2).

No other clinical or paraclinical findings were evidenced, suggesting a late-onset skin-limited reaction, description compatible with the diagnosis of SDRIFE. The erythematous eruption resolved

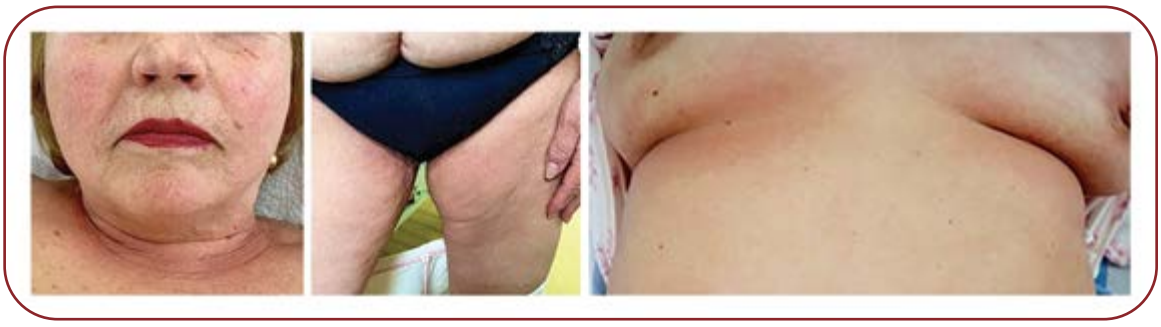

FIGURE 2. SDRIFE: erythematous plaques with fairly well-defined borders of the face and the intertriginous areas

within 1 to 2 days after a short course of systemic corticosteroids and H1-antihistamines. ❑

DISCUSSION

We conducted a literature search of MEDLINE/PubMed and Medscape databases to identify similar cases. To the best of our knowledge, there is only one reported case of clarithromycin induced SDRIFE up to the present (9). SDRIFE is a particular form of maculo-papular exanthema characterized by a typical distribution, involving the flexural and intertriginous areas. Initially, it was known as the baboon syndrome, due to the distribution and morphology of the lesions resembling the red callouses of baboons. In 2004, Hauserman suggested symmetrical drug-related intertriginous and flexural exanthema as a new name for the phenomenon, which is more adequate for this drug induced disorder (10).

The rash is well-delimited, erythematous, and it affects the genital, axillary and anal areas as well as other intertriginous areas. Palmoplantar, facial or mucosal involvement is rare (11, 12). Men may be affected more frequently than women. SDRIFE is easily differentiated from other drug-related cutaneous hypersensitivity reactions by the typical distribution of the lesions and the absence of systemic symptoms. Patient's general health status is not affected and there are no systemic findings. The skin lesions usually heal with residual desquamation (13).

The onset of the symptoms ranges from 24 hours to 14 days (usually 2-7 days) after the last administration of the drug, which would imply the involvement of a delayed type IV hypersensitivity mechanism (14, 15).

Considering how rare the disease is, it can easily be misdiagnosed if there is no clear correlation between the administration of the drug and symptom onset. The differential diagnosis of SDRIFE includes a series of dermatological conditions (Darier disease, intertriginous psoriasis and seborrheic dermatitis, which that must be excluded before establishing the diagnosis of a hypersensitivity reaction to drugs) and skin hypersensitivity reactions: contact dermatitis and drug reactions: fixed erythema, acute generalized exanthematous pustulosis, DRESS syndrome, contact urticaria, serum sickness like disease, contact dermatitis (16-20).

For etiologic diagnosis allergy skin test with late reading (intradermal reaction, patch tests), lymphocyte transformation tests (*in vitro*) and drug provocation tests can be performed. In accordance with previous reports, the oral drug provocation test remains the gold standard even for the diagnosis of SDRIFE. The other diagnostic tests have a high variability in results and are not reliable, less than half of the patients diagnosed with SDRIFE having a positive reaction to patch testing to the incriminated drug (12, 21).

SDRIFE is a self-limiting disease, the treatment involves supportive treatment in the acute phase, with systemic corticotherapy, H1-antihistamines for pruritus control and topical steroid treatment for expediting the healing. The trigger drug is contraindicated for further use (10).

The European Network for Drug Allergy published the new standardized protocols for the concentrations used for skin testing of both immediate and non-immediate reactions to beta-lactams and other antibiotics, but at the moment there are no specific recommendations regarding the diagnosis of hypersensitivity reactions induced by macrolides (22). A small number of studies investigated the sensitivity and specificity of skin tests in the diagnosis of hypersensitivity reactions to clarithromycin (23). Currently there is need of standardization for the concentrations used for clarithromycin skin testing in order to reduce the use of oral provocation test as means of diagnosis. However, because SDRIFE is not a severe, life-threatening reaction, most authors consider the oral challenge the gold standard for diagnosis in cases with unclear history (24). ❑

CONCLUSIONS

We presented a case of clarithromycin induced SDRIFE, in a patient with negative cutaneous tests (prick, intradermal and patch) to the culprit drug and a positive drug provocation test. Drug provocation testing remains the gold-standard in diagnosing drug hypersensitivity reactions to macrolides, especially when the patient cannot present a clear history of the index reaction or the causal connection with the drug incriminated is not clear. To conclude, even though SDRIFE occurs infrequently it should not be overlooked in the differential diagnosis of patients with history of drug-induced delayed cutaneous reactions. Furthermore, we should keep in mind that although

hypersensitivity reactions to macrolides are very rare, clarithromycin is not a harmless drug. ❑

Conflicts of interest: none declared.
Financial support: none declared.

Informed consent statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient to publish this paper.

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