Zoledronic Acid-Induced Symmetrical Drug-related Intertriginous and Flexural Exanthema: A Case Report

Shatha Al Qassabi*, Asma Al Shidhani and Talal Al Lawati

Oman Medical Specialty Board, Muscat, Oman

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*Corresponding author: shathaalqassabi@gmail.com

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Abstract

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is an uncommon dermatological reaction in response to certain systemic medications. In this article, we describe a 57-year-old female patient who presented with a diffuse, non-tender, erythematous rash distributed symmetrically in the axilla and inguinal regions three days after receiving an infusion of zoledronic acid. Following a physical examination, and in light of the absence of systemic symptoms, the patient was clinically diagnosed with SDRIFE. She was treated with local steroids and antihistamines, with the rash subsequently disappearing a few days later. To the best of the authors' knowledge, only two cases of zoledronic acid-induced SDRIF have been previously reported in the literature.

Keywords: Drug-Related Side Effects and Adverse Reactions; Drug Eruptions; Zoledronic Acid, adverse effects; Exanthema, chemically induced; Case Report; Oman.

Introduction

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), previously known as baboon syndrome, is an uncommon cutaneous adverse drug reaction following exposure to specific systemic medications.[1,2] The reaction is characterized by a maculopapular rash that typically appears in the skin folds and flexural areas of the body, such as the armpits, groin, and under the breasts; as the name suggests, it is often symmetrical, meaning it appears on both sides of the body in corresponding locations. While the exact mechanisms behind SDRIFE are not fully understood, it is thought to occur due to a type IV hypersensitivity reaction.[2-4] SDRIFE is mostly reported about beta-lactam antibiotics.[1] We report a case of SDRIFE occurring in a middle-aged woman following an infusion of zoledronic acid.

Case Report

A 57-year-old woman presented to the rheumatology department in June 2023 with a recent diagnosis of osteoporosis, for which she was prescribed zoledronic acid. Three days after her first zoledronic acid infusion, she presented again with a two-day history of the sudden eruption of an itchy, erythematous rash involving the axilla and inguinal region bilaterally. This had been preceded by influenza-like symptoms of one day's duration.

A physical examination revealed a diffuse, non-tender, erythematous rash that was distributed symmetrically in the axilla [Figure 1A] and inguinal [Figure 1B] regions. There was no evidence of satellite lesions, scaliness, or discharge. Moreover, the rash did not have raised edges and did not worsen with time. The patient reported no rashes on any other sites of the body and no shortness of breath, swelling of the lips or tongue, or other features suggestive of anaphylaxis. She took over-the-counter antihistamine medications, which helped to resolve the itchiness, and was treated with local steroids, resulting in the complete resolution of the rash within a few days.

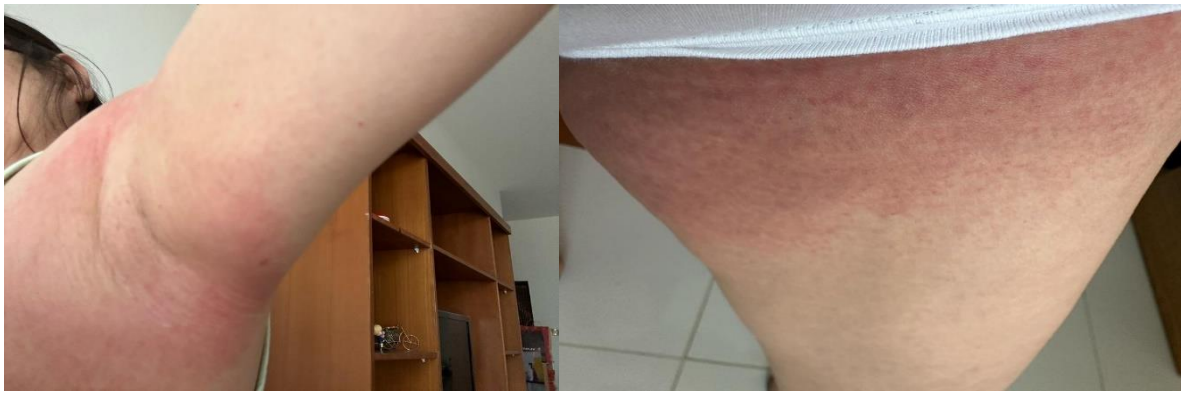

Figure 1: Clinical photographs of a 57-year-old woman with a diffuse, symmetrical, erythematous rash in the **(a)** axillary and **(b)** inguinal regions.

Discussion

Hypersensitivity reactions are characterized by an exaggerated immune response to an antigen or allergen. Unlike other types of hypersensitivity reactions, such as anaphylaxis, type IV hypersensitivity reactions are delayed rather than immediate, usually occurring ≥12 hours after exposure, and are mediated by a T-cellular response rather than by immunoglobulin E, G, or M antibodies.[4,5] Type IV hypersensitivity reactions are responsible for various immune-related conditions, including SDRIFE, contact dermatitis, tuberculosis skin tests, and certain autoimmune diseases.[4] Symptoms of SDRIFE include redness, itching, as well as the characteristic symmetrical rash, resulting in the condition formerly being known as baboon syndrome due to the visual similarity of the rash to the bright red buttocks of baboons.[6] Subcorneal pustules can also occur.[2]

The diagnosis of SDRIFE is made clinically, given the patient history, rash characteristic and exclusion of other possible causes. Most of the reports describes SDRIF rash as a plaques or maculopapular erythema.[6] The diagnostic criteria for SDRIFE include the following: (1) a one-off or repeated exposure to a systemic medication; (2) the presence of a sharp, well-demarcated, erythematous rash involving the gluteal or perianal area, and/or a 'V'-shaped, erythematous rash in the inguinal or perigenital region; (3) at least one other flexural ('bending') or intertriginous area affected; (4) symmetry of the affected area; and (5) the absence of systemic symptoms.[3,7] A skin biopsy of the affected area is usually not specific, with microscopic examination showing superficial perivascular lymphocytic infiltrates in the dermis.[1,7] Infective dermatological conditions like tinea cruris and erythema intertrigo should be excluded as part of the differential diagnosis; similarly, parvovirus B19 infection can result in flexural erythema of a similar appearance to SDRIFE. Other differential possibilities include inflammatory dermatological conditions, such as irritant or allergic contact dermatitis and inverse psoriasis.[7]

SDRIFE can also resembles other drug reactions, fixed drug eruption (FDE), generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). AGEP and DRESS are associated with wide spreading rash along with systemic Symptoms. FDE usually present as oval or round patches or plaques with residual hyperpigmentation, involving mucosa, genitalia and acral areas.[6] In our patient, tinea cruris was the top differential diagnosis apart from SDRIFE. However, given the sudden simultaneous bilateral eruption in the axilla and groin, along with absence of satellite lesions and scaliness, this possibility was discarded. Although inverse psoriasis should be kept in mind in this patient, the patient's less dramatic appearing rash compared to inverse psoriasis made it less likely. There was no history of exposure to local agents in the axilla and groin area, thus contact dermatitis was excluded. As there were no systemic signs and symptoms exist, the other mentioned differential are less likely.

In cases of SDRIFE, a drug provocation test is considered the gold-standard test for determining the specific medication responsible for the reaction; however, some authors have discouraged this, as repeat exposure can provoke a relapse, with the subsequent reaction being exacerbated or more severe compared to the initial eruption.[3,8] Common culprits include beta-lactam antibiotics, namely penicillin and amoxicillin; other medications reported in the literature to cause SDRIFE include clarithromycin, mefenamic acid, valaciclovir, proton pump inhibitors, and chemotherapeutic agents.[1,3,7-9] Interestingly, several recent reports have emerged describing cases of SDRIFE occurring post-coronavirus disease 2019 vaccination.[10,11] In addition, reactions may occur in response to exposure to fragrances and nickel.[2] Zoledronic acid is an intravenous aminobisphosphonate used to treat

conditions involving excessive bone resorption, such as osteoporosis, Paget's disease, and certain types of bone cancer.[12-14] While it is generally well-tolerated, this medication has been linked with SDRIFE in two prior case reports.[15,16]

It is important for individuals who suspect they may have SDRIFE to seek medical evaluation and consultation, as identifying the specific drug causing the reaction is crucial to management and treatment. Treatment is usually conservative, consisting of discontinuing the offending medication along with antihistamines to alleviate the symptoms and resolve the condition. Some authors have reported the use of local and systemic corticosteroids.[1,2] Generally, full recovery is expected within a few days to 3 weeks once the drug responsible has been discontinued.[3,15]

Conclusion

A female patient developed an erythematous, symmetrical rash involving the axilla and inguinal region after her first dose of zoledronic acid. In the absence of systemic involvement, the patient was clinically diagnosed with SDRIFE and successfully treated with local steroids and antihistamines. Although no provocation test was performed, zoledronic acid was identified as the drug responsible for the reaction as no other medications were being taken by the patient at that time. To the best of the authors' knowledge, this is only the third case of zoledronic acid-induced SDRIFE to be reported in medical literature.

References

1. Li DG, Thomas C, Weintraub GS, Mostaghimi A. Symmetrical drug-related intertriginous and flexural exanthema induced by doxycycline. Cureus 2017 Nov;9(11):e1836.

2. Lima Miranda O, Martins J, Almeida A, Formigo M, Pereira O, Rocha M, et al. Symmetrical drug-related intertriginous and flexural exanthema (baboon syndrome). Eur J Case Rep Intern Med 2021 Dec;8(12):003029.

3. Seok J, Kim JM, Park KY, Seo SJ. Symmetrical drug-related intertriginous and flexural exanthema: two cases and brief literature review. Ann Dermatol 2018 Oct;30(5):606-609.

4. Marwa K, Kondamudi NP. Type IV hypersensitivity reaction. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing, 2023.

5. Justiz Vaillant AA, Vashisht R, Zito PM. Immediate hypersensitivity reactions. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing, 2023.

6. Harbaoui S, Litaiem N. Symmetrical drug-related intertriginous and flexural exanthema. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing, 2023.

7. Cancela-Díez B, López-Delgado D, Aneiros-Fernandez J, Ruiz-Villaverde R. A case of intertriginous and flexural exanthema caused by amoxicillin. Sultan Qaboos Univ Med J 2019 Nov;19(4):e369-e371.

8. Bumbacea RS, Ali S, Ogneva DO, Motei C, Rusu C, Spiru L. Drug provocation testing in the diagnosis of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) induced by clarithromycin. Maedica (Bucur) 2021 Jun;16(2):297-301.

9. Spigariolo CB, Barei F, Maronese CA, Barberi F, Cattaneo A, Violetti SA. Three cases of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) induced by proton-pump inhibitors. Australas J Dermatol 2022 Nov;63(4):509-512.

10. Lim PN, Wylie G. Symmetrical drug-related intertriginous and flexural exanthema like eruption associated with COVID-19 vaccination. Clin Exp Dermatol 2022 Jan;47(1):175-176.

11. Hai J, Shawa H, Kim-Lim P, Wang JZ, Vy M, Fung MA, et al. Systemic drug-related intertriginous and flexural exanthema induced by the Pfizer-BioNTech COVID-19 vaccine: a report of 2 cases. JAAD Case Rep 2021 Dec;18:57-60.

12. Dhillon S. Zoledronic acid (Reclast®, Aclasta®): a review in osteoporosis. Drugs 2016 Nov;76(17):1683-1697.

13. Keating GM, Scott LJ. Zoledronic acid: a review of its use in the treatment of Paget's disease of bone. Drugs 2007;67(5):793-804.

14. Wang L, Fang D, Xu J, Luo R. Various pathways of zoledronic acid against osteoclasts and bone cancer metastasis: a brief review. BMC Cancer 2020 Nov;20(1):1059.

15. Kandala H, Gonzalez-Mosquera LF, Barua P, Podrumar A. Zoledronic acid-induced symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). BMJ Case Rep 2021 Sep;14(9):e245326.

16. Cohen PR. Zoledronic acid-associated symmetrical drug-related intertriginous and flexural exanthema (SDRIFE): report of baboon syndrome in a woman with recurrent metastatic breast cancer after receiving zoledronic acid. Dermatol Online J 2015 Aug 15;21(8):13030/qt5kk0g864.