Acute Localized Exanthematous Pustulosis Due to Alendronate

Bautista-Villanueva S[1], Galleani C[1], Barranco R[1,2,3], Bellón T[3,4], Blanco M[5], García-Moguel I[1]
[1]*Allergy Department, Hospital Universitario 12 de Octubre, Madrid, Spain*
[2]*RETIC ARADyAL, Instituto de Salud Carlos III, Madrid, Spain*
[3]*PIELenRed Consortium*
[4]*Drug hypersensitivity group. Hospital La Paz Institute for Health Research (IdiPaz), Madrid, Spain*
[5]*Pathology Department, Hospital Universitario 12 de Octubre, Madrid, Spain*

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Acute localized exanthematous pustulosis (ALEP) is an acute skin reaction characterized by acute, localized, nonfollicular, sterile pustules on an erythematous base. While generally drug-related, cases associated with spider bites [1] and herbal medicines [2] have been described. ALEP usually affects the face, neck, and trunk, although cases affecting the upper and lower extremities have been reported [3]. The term ALEP was coined in 2005 by Prange et al [4] to describe a patient with diagnosis of localized acute generalized exanthematous pustulosis on the face.

The skin lesions usually occur within 72 hours of administration and resolve a few days after withdrawal of the culprit drug. The skin lesions may be accompanied by fever and elevated peripheral blood leukocytes [5].

Since ALEP is considered an unusual form of acute generalized exanthematous pustulosis, its diagnosis is similar. These pustular reactions are T cell–mediated, neutrophilic, inflammatory processes (type IVd reactions). Given that ALEP is a nonimmediate reaction, an appropriate diagnosis should include a meticulous history, patch tests, and delayed-reading intradermal tests [6].

We report a case of pustular reaction due to alendronate.

A 55-year-old man was referred to our department on suspicion of an adverse drug reaction. His medical history included ulcerative colitis, allergy to mesalazine (confirmed by a positive oral challenge result), and allergy to golimumab (confirmed by positive intradermal skin test results). Fifteen days after initiating treatment with alendronate 70-mg weekly for severe osteoporosis, he developed a skin reaction, which he reported vaguely as a maculopapular exanthema located on both calves. Therefore, he discontinued treatment of his own accord. The cutaneous lesions resolved within a week. The patient denied desquamation, hyperpigmentation, vesicles, and mucosal lesions and failed to remember the development of pustules or fever associated with the skin rash. No other medications had been started in the previous 8 weeks.

Five months after the initial reaction, we performed an allergological study in our outpatient clinic. This comprised patch testing with alendronate at 20% and 10% in petrolatum, with readings at 48 and 96 hours, as previously described by Kimura et al [7]. Twenty-four hours after the application of the patch test on the upper back, the patient developed a flare-up that manifested as erythematous papules with a central pustule on both calves (Figure). The patient reported that the lesions reminded him of the initial reaction. Biopsy of the skin on the left calf revealed a subcorneal pustule with neutrophils and eosinophils, dermal edema, and mild spongiosis around the pustule (Supplementary Material, Appendix A), thus confirming the diagnosis of ALEP. The patch tests were not positive at the application site, although since the patches had been removed when the reaction appeared, they were applied for only 24 hours (ie, not 48 hours).

A lymphocyte transformation test (LTT) yielded a positive result for alendronate with a stimulation index of 2.07 at 50 µg/mL and 2.12 at 10 µg/mL (normal value, <2) [8], thus confirming T cell–mediated sensitization to alendronate.

The LTT was based on a wide range of concentrations (4-fold each) (Supplementary material, Appendix B). Despite the absence of controls, we observed that from the 1-µg/mL concentration on, the response was dose-dependent until it reached its highest point, where the curve leveled off (Supplementary material, Appendix C).

ALEP was diagnosed based on clinical characteristics, in vivo tests (skin biopsy of the flare-up after application of alendronate patch skin tests), and in vitro tests (LTT).

The patient was advised to avoid all bisphosphonates. No other bisphosphonates were tested since he had an alternative treatment (denosumab) and did not wish to undergo a further allergological study. No cross-reactivity has been reported between golimumab, mesalazine, and alendronate. However, multiple drug hypersensitivity can develop in some patients [9].

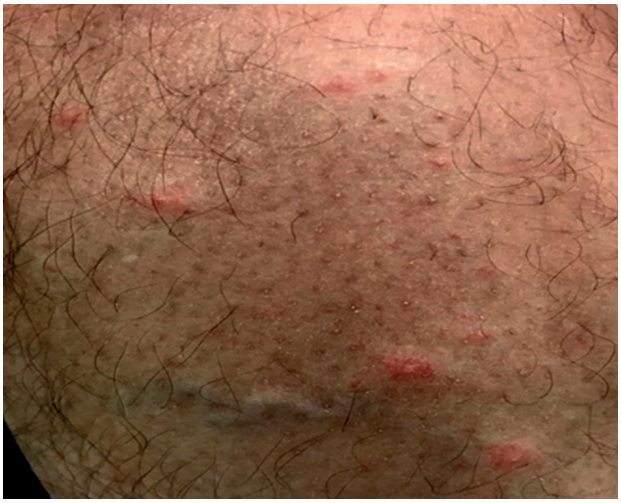

Figure. Erythematous papules with a central pustule during a flare-up on both calves.

The bisphosphonate alendronate acts as an osteoclast inhibitor and is commonly used throughout the world to treat osteoporosis. Despite its frequent use, associated allergic reactions are unusual.

Further cases of alendronate allergy have been reported, although only 5 involved nonimmediate reactions, of which 4 were assessed using an allergological study (Supplementary material, Table 1) [7,10,11].

Kimura et al [7] reported a patient who developed numerous red papules and petechiae on the lower extremities 10 days after receiving alendronate. Patch tests, scratch-patch tests, and LTT were performed. Scratch-patch tests at 20% and 10% in petrolatum and LTT yielded positive results, thus confirming the diagnosis of drug eruption due to alendronate.

Brinkmeier et al [10] reported the case of a 60-year-old woman with maculopapular skin lesions on the head and neck 4 months after taking alendronate. Patch testing (scratch chamber) with alendronate at 50% in petrolatum and water yielded a positive result; open testing (rub, prick, scratch) with alendronate was negative. Since patch tests at the same concentrations on 10 healthy patients revealed some weakly positive results, and given the probability of a false positive, an oral challenge test with alendronate was carried out, yielding a positive result.

Barrantes et al [11] presented 2 cases of nonimmediate allergic reactions to alendronate. Patient 1 was a 70-year-old man who developed an erythematous rash after taking alendronate. The diagnosis was confirmed by positive patch tests with alendronate 1% in petrolatum and 0.1% and 1% in water. Patient 2 was a 78-year-old woman who developed a desquamative rash on both eyelids. The patch tests were negative, but the delayed-reading intradermal skin test with alendronate at 0.1% in water was positive.

Even though no extensive studies on cross-reactivity between bisphosphonates have been performed, some authors suggest an absence of cross-reactions, thus enabling one drug to be replaced by another [12].

In conclusion, after observing a flare-up during patch testing with alendronate at 20% and 10% in petrolatum, with a skin biopsy result compatible with ALEP and a positive LTT result, we report, to the best of our knowledge, the first case of ALEP due to alendronate.

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Conflicts of Interest

García-Moguel I has received payment for advisory boards and for serving as a speaker/researcher for Novartis, AstraZeneca, Teva, GSK, Sanofi Genzyme, Chiesi, Allergy Therapeutics, Leti, Stallergenes, ALK-Abelló, Mundipharma, Pfizer, and Orion Pharma.

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The remaining authors declare that they have no conflicts of interest.

References

1. Lahouel M, Mokni S, Denguezli M. Acute Localized Exanthematous Pustulosis Induced by a Spider Bite. Am J Trop Med Hyg. 2020;103(3):937-8.
2. Tsutsumi R, Yoshida Y, Adachi K, Nanba E, Yamamoto O. Acute localized exanthematous pustulosis caused by a herbal medicine, dai-kenchu-to. Contact Dermatitis. 2018;79(4):257-9.
3. Villani A, Baldo A, De Fata Salvatores G, Desiato V, Ayala F, Donadio C. Acute Localized Exanthematous Pustulosis (ALEP): Review of Literature with Report of Case Caused by Amoxicillin-Clavulanic Acid. Dermatol Ther (Heidelb). 2017;7(4):563-70.
4. Prange B, Marini A, Kalke A, Hodzic-Avdagic N, Ruzicka T, Hengge UR. Akute lokalisierte exanthematische Pustulose (ALEP) [Acute localized exanthematous pustulosis (ALEP)]. J Dtsch Dermatol Ges. 2005;3(3):210-2. German.
5. Ryder ENC, Perkins W. Acute localized exanthematous pustulosis: Case report, review of the literature and proposed diagnostic criteria. Australas J Dermatol. 2018;59(3):226-7.
6. Romano A, Viola M, Gaeta F, Rumi G, Maggioletti M. Patch testing in non-immediate drug eruptions. Allergy Asthma Clin Immunol. 2008;4(2):66-74.
7. Kimura M, Kawada A, Murayama Y, Murayama M. Drug eruption due to alendronate sodium hydrate. Contact Dermatitis. 2003;48(2):116.
8. Cabañas R, Calderón O, Ramírez E, Fiandor A, Caballero T, Heredia R, et al. Sensitivity and specificity of the lymphocyte transformation test in drug reaction with eosinophilia and systemic symptoms causality assessment. Clin Exp Allergy. 2018;48(3):325-33.
9. Pichler WJ, Srinoulprasert Y, Yun J, Hausmann O. Multiple Drug Hypersensitivity. Int Arch Allergy Immunol. 2017;172(3):129-38.
10. Brinkmeier T, Kügler K, Lepoittevin JP, Frosch PJ. Adverse cutaneous drug reaction to alendronate. Contact Dermatitis. 2007;57(2):123-5.
11. Barrantes-González M, Espona-Quer M, Salas E, Giménez-Arnau AM. Bisphosphonate-induced cutaneous adverse events: the difficulty of assessing imputability through patch testing. Dermatology. 2014;229(3):163-8.
12. Weber I, Olaiwan A, Bonte I, Artigou C, Pras-Landre V, Moguelet P, et al. Adverse cutaneous drug reactions to ibandronate. Eur J Dermatol. 2011;21(4):591-4.

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Sara Bautista-Villanueva
E-mail: sara.bautista.villa@gmail.com

