Acute Localized Exanthematous Pustulosis Due to Alendronate

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**Key words:** Acute localized exanthematouspustulosis. Alendronate. Lymphocyte transformation test. Epicutaneous test. Flare-up phenomenon.

**Palabras clave:** Pustulosis exantemática localizada aguda. Alendronato. Test de transformación linfocitaria. Pruebas epicutáneas. Fenómeno flare-up.

**Clinical implications**

To our knowledge, we present the first case of acute localized exanthematouspustulosis due to alendronate. Diagnosis was confirmed with flare-up after epicutaneous tests with alendronate 20% and 10% in petrolatum, skin biopsy and lymphocyte transformation test.

Acute localized exanthematouspustulosis (ALEP) is an acute skin reaction characterized by the development of acute, localized, non-follicular, sterile pustules on an erythematous base. Despite generally drug related, cases associated with spider bites [1], and herbal medicines[2] have been described. It is usually localized on the face, neck and trunk, however cases of ALEP in the upper and lower extremities have been reported [3]. The term ALEP was first described in 2005 by Prange et al. to report a patient with diagnosis of localized acute generalized exanthematouspustulosis (AGEP) on the face [3].

The skin lesions usually occur within 72 hours after drug administration, and resolve a few days after the withdrawal of the culprit drug. In conjunction with the skin lesions, fever and elevated peripheral blood leukocytes can also appear[4].
Since ALEP is considered an unusual form of AGEP its diagnosis is similar. These pustular reactions are T cell mediated, neutrophilic, inflammatory processes (type IVd reactions). Being ALEP a non-immediate reaction, an appropriate diagnosis should comprehend a meticulous anamnesis, epicutaneous tests (patch tests) and delayed-reading intradermal tests[5].

We report a case of a pustular reaction due to alendronate.

A 55 year old male was referred to our department on suspicion of an adverse drug reaction. His medical record included ulcerative colitis, allergy to mesalazine (confirmed by positive oral challenge) and allergy to golimumab (confirmed by positive intradermal skin test). Fifteen days after initiating treatment with 70mg of alendronic acid weekly, due to severe osteoporosis, he developed a skin reaction. The patient vaguely described amaculopapular exanthema located in both calves, so he decided to discontinue treatment on his own with remission of the cutaneous lesions within a week. The patient denied any desquamation, hyperpigmentation, vesicles or 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 prior 8 weeks.

Five months after the initial reaction an allergological study was performed in our outpatient clinic. Epicutaneous test with alendronate at 20% and 10% in petrolatum with readings at 48 and 96 hours were carried out, as previously described by Kimura et al.[6]. Twenty-four hours after the application of the patch test on the upper back, flare-up with erythematous papules with a central pustule in both calves appeared (Figure 1). The patient referred that the lesions reminded him of the initial reaction. A skin biopsy of the left calf was performed, showing 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 on the application site, nevertheless patch tests were removed when the reaction appeared so they were not applied for 48h, but for 24h instead.

A lymphocyte transformation test (LTT) showed a positive result for alendronate with a stimulation index (SI) of 2.07 at 50ug/ml and SI of 2.12 at 10 ug/ml (normal SI<2) [7], thus confirming T-cell mediated sensitization to alendronate.

The LTT was performed as follows: a wide range of concentrations were tested (Supplementary material - Appendix B), and every concentration was fourfold tested. Even though there were no controls, we can observe that from the 1ug/ml concentration on, the response is dose-dependent until it reaches its highest point where the curve assumes a plateau shape (Supplementary material - Appendix C).

In our case the diagnosis of ALEP was established through clinical characteristics, in vivo (skin biopsy of the flare-up after application of alendronate epicutaneous skin tests) and in vitro tests (LTT).

Our patient was advised to avoid all biphosphonates. No other biphosphonates were tested since he had an alternative treatment (denosumab) and did not wish to continue an allergological study. No cross reactivity among golimumab, mesalazine and alendronate has been described. However, multiple drug hypersensitivity can develop in certain patients[8].

Alendronate is a biphosponate that acts as an osteoclast inhibitor; it is commonly used around the globe to treat osteoporosis. Despite its frequent use allergic reactions due to alendronate are unusual.

Even though more cases of alendronate allergy have been reported, only 5 consist of non-immediate reactions, of which 4 have an allergological study (Supplementary material - Table 1) [6, 9, 10].
Kimura et al. reported a patient who developed numerous red papules and petechiae on the lower extremities 10 days after alendronate administration. Patch tests, scratch-patch tests and LTT were performed. Scratch-patch tests at 20% and 10% in petrolatum and LTT turned out positive, establishing the diagnosis of drug eruption due to alendronate[6].

Brinkmeier et al. reported a 60-year-old woman with maculopapular skin lesions in the head and neck after 4 months of alendronate intake. Patch testing (scratch-chamber) with alendronate at 50% in petrolatum and water, were performed with a positive result; open testing (rub, prick, scratch) with alendronate was negative. Since epicutaneous skin tests at the same concentrations on 10 healthy patients revealed some weak positive results, and in case it was a false positive, an oral challenge test with alendronate was carried out with a positive result[9].

Barrantes et al. presented 2 cases of non-immediate allergic reactions due to alendronate. Case 1 was a 70-year-old male who developed an erythematous rush after alendronate intake. Positive patch tests with alendronate 1% in petrolatum and 0.1% and 1% in water confirmed the diagnosis. Case 2 was a 78-year-old woman who suffered a desquamative bilateral rash on the eyelids. The patch tests were negative but the delayed-reading intradermal skin test with alendronate at 0.1% in water turned out positive[10].

Even though no extensive studies about cross reactivity among BPs have been performed, some suggest there is an absence of cross-reactions, thus allowing the substitution of one BP by another[11].

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

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References


Figure legend

**Figure 1.** Erythematous papules with central pustule during flare-up in both calves.