

Desquamating-nonpigmenting with onycholysis fixed drug eruption in a child due to amoxicillin. Cross-reactivity study

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Fixed drug eruption (FDE) is a delayed drug hypersensitivity reaction that rarely occurs in children. It typically appears as macules that are individual or in small number, erythematous, well-circumscribed, and oval causing intense pruritus, burning or pain. They are most frequently located on the lips, palms, soles, glans penis, and groin areas and usually resolve spontaneously after discontinuation of the culprit drug, leaving hyperpigmentation [1]. It is characteristic that they reappear in the same skin site if re-exposure to the drug occurs. The most frequent drugs that cause FDE are analgesics, antimalarials, barbiturates and antibiotics including amoxicillin [2,3]. A diagnosis of FDE includes skin tests and drug challenge tests (DCT) (4). There are rare clinical variants of FDE that include: nonpigmenting FDE (NPFDE), generalized FDE and other atypical presentations. NPFDE is a very rare FDE variant, characterized by not leaving any residual hyperpigmentation. There have been few cases of NPFDE described in adults [2] and only two cases in children [5,6]. We report a case of skin desquamation and onycholysis NPFDE selective to amoxicillin confirmed with a DCT. Since studies assessing cross-reactivity in delayed type reactions in beta-lactams are limited, we also evaluated cross-reactivity to other beta-lactams by performing a DCT.

The patient, a 17-year-old male with Down Syndrome and mild atopic dermatitis, presented 4 episodes of skin desquamation on the posterior part of his thumb and index finger of his right hand 24-48 hours after finishing 7 days of oral amoxicillin treatment prescribed for infections such as tonsillitis. The first episode happened at the age of 13 and reactions occurred once annually during the following 3 years after the intake of amoxicillin. In one of the 4 episodes, the extension of the reaction also produced onycholysis in his right index finger that recovered spontaneously after a few weeks. In all the episodes skin lesions disappeared in 6-7 days without leaving any residual lesion. The patient previously tolerated penicillin, amoxicillin and amoxicillin/clavulanic acid on several occasions.

The allergological work-up was initiated by performing patch tests on the upper part of the patient's back with amoxicillin, amoxicillin/clavulanic acid, penicillin and cefuroxime according to the European Society of Contact Dermatitis guidelines [7]. The patch test concentrations in petrolatum were: amoxicillin 50%, amoxicillin/clavulanic acid 50% (amoxicillin/clavulanic 875/125 mg), penicillin 10% and cefuroxime 10%. All tests were negative at 48 and 96 hours readings. We also performed the tests with amoxicillin on the lesion site, but they detached shortly after due to the lack of adhesion on the fingers.

We performed a DCT with amoxicillin 750mg every 8 hours for 7 days. The first dose was administered in our department at 60 minutes intervals (1/100, 1/10, followed by full dose) [4] and the patient remained under medical surveillance for 2 hours. The remaining doses were received at home. The patient presented desquamation from the distal posterior part of his thumb and index finger (Figure 1) 2 days after finishing the final dose of amoxicillin. The lesions resolved spontaneously within 7 days, leaving no residual pigmentation.

Four months after the positive DCT with amoxicillin, we evaluated cross-reactivity to other beta-lactams with and without identical side chains using a DCT with penicillin G and cefadroxil. The patient tolerated 750mg of penicillin G in our department (reached with a gradual increase) followed by a dose of 750mg at home every 8 hours for 7 days. Two months later, a DCT was performed with cefadroxil up to a total dose of 500mg under medical surveillance, which was negative. The next doses were administered at home every 12 hours, with the patient presenting stomach discomfort after the first two doses, resulting in discontinuation of the treatment, and inconclusive results for the evaluation of cefadroxil tolerance. Outside of the allergological study, the patient was also prescribed cefuroxime, a beta-lactam with different side chain, which was also tolerated. Therefore, the patient was diagnosed with desquamative NPFDE selective to amoxicillin. We forbade the administration of aminopenicillins and cephalosporins with the same side chain.

FDE has been suggested to be a form of classic delayed-type hypersensitivity mediated by CD8+ cells and it has been demonstrated that intraepidermal T cells expressing the receptor (TCR)- $\alpha\beta$ are abundantly detected between keratinocytes in the lesions of FDE(1). NPFDE is a rare delayed drug reaction. Only two cases have been reported in children: a 13-year-old teenager with palms and soles bullous desquamation NPFDE caused by amoxicillin and rifamycin [5] and a 10-year-old boy with penis swelling NPFDE caused by amoxicillin [6]. To our knowledge, there have been no reported cases of a selective desquamative type of NPFDE exclusively to amoxicillin, demonstrated by DCT, in a boy.

While better methods for diagnosing FDE are still being debated, a DCT is the most reliable for establishing the causative drug [1]. In this case, a positive amoxicillin DCT diagnosed a patient with negative patch tests. The use of patch tests has been controversial due to an elevated number of false negative results due to different causes [1].

While cross-reactivity between beta-lactams in immediate type-I reactions has been evaluated more extensively [8], it has been investigated less in delayed non type-I reactions [9]. A reason for cross-reactivity may be that amoxicillin and some early generation cephalosporins share identical side chains such as cefadroxil, cefatrizine and cefprozil, or similar side chains such as cefamandole and cefonicid [10]. Further research is still needed to evaluate cross-reactivity in fixed drug reactions caused by beta-lactams.

By studying cross-reactivity, we proved the amino-selectivity of the reaction and provided the patient with safe alternatives of other beta-lactams.

In conclusion, we present the first case, of skin desquamation and onycholysis nonpigmenting fixed drug eruption caused exclusively by amoxicillin in a teenage patient with tolerance to other beta-lactams with a different side chain. Currently, a drug challenge test is the most reliable method for the identification of the implicated drug in fixed drug eruption. An allergological work-up is important to provide safe beta-lactam alternatives to patients, but more research is needed to assess cross-reactivity in delayed reactions caused by beta-lactams.

Conflict of interest

All authors declare no conflict on interests related to this manuscript.

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Impact Statement

We report a rare case of skin desquamation and onycholysis nonpigmenting fixed drug eruption caused exclusively by amoxicillin in a teenage patient. Our findings support the idea that the most reliable method to identify the culprit drug is a drug challenge test. Since cross-reactivity in delayed reactions caused by beta-lactams has not been thoroughly studied, its assessment is important in order to provide safe beta-lactam alternatives to patients.

References

1. Shiohara T. Fixed drug eruption: pathogenesis and diagnostic tests. *Curr Opin Allergy Clin Immunol*. 2009;9:316-21.
2. Mahboob A, Haroon TS. Drugs causing fixed eruptions: a study of 450 cases. *Int J Dermatol*. 1998;37:833-8.
3. Galindo P A, Borja J, Feo F, Gómez E, Encinas C, García R. Nonpigmented fixed drug eruption caused by paracetamol. *Journal of Investigational Allergology and Clinical Immunology*. 1999;9(6):399-400.
4. Labrosse, R., Graham, F., Bégin, P., Samaan, K., Paradis, L., Des Roches, A., et al. A pediatric case of selective fixed drug eruption to amoxicillin. *Pediatric Allergy and Immunology*. 2017 Dec;28(8):848-50
5. Ponvert C, Rufin P, de Blic J. An unusual case of non-pigmenting fixed drug eruptions in a child. *Pediatr Allergy Immunol*. 2013;24:715–6.
6. Keli-Bhija Z; De Blic J. Ponvert C. An unusual case of penile non-pigmenting fixed drug eruption in a child. *Pediatr Allergy Immunol* 2015;26:294-296
7. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, et al. European society of contact dermatitis guideline for diagnostic patch testing – recommendations on best practice. *Contact dermatitis* 2015;73:195-221.
8. Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quarantino D, Gaeta F, et al. Cross-Reactivity and Tolerability of Cephalosporins in Patients with IgE-

- Mediated Hypersensitivity to Penicillins. *J Allergy Clin Immunol Pract* 2018;6:1662-72
9. Buonomo, A., Nucera, E., Pecora, Rizzi A, Aruanno A, Pascolini L et al. Cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins. *J Investig Allergol Clin Immunol*. 2014;24(5):331-7.
 10. Zagursky RJ, Pichichero ME. Cross-reactivity in β -Lactam Allergy. *J Allergy Clin Immunol Pract* 2018; 6:72-81

Figure 1. Skin non-pigmented desquamation fixed drug eruption induced by the challenge test with amoxicillin

