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An unusual case of penile non-pigmenting fixed drug eruption in a child.

Running title. A penile non-pigmenting fixed drug eruption in a child.

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To the Editor.

Fixed drug eruptions (FDE) are characterized by well-demarcated pigmented lesions on the skin and/or mucosal surfaces that typically begin 30 minutes to 8 hours after exposure to the drugs and reappear at the exact location when the patients are reexposed to the offending drugs. The principal areas involved are trunk and limbs, followed by lips and genitalia. FDE are rare in children, although they are probably under-recognized and under-diagnosed (1). The drugs most commonly associated with FDE are anti-infective sulfonamides, non-opioid analgesics, antipyretics, non-steroidal anti-inflammatory drugs, and non-sulfonamide antibiotics such as aminopenicillins, metronidazole and tetracyclines. Non-pigmenting FDE (NPFDE) resemble to FDE, but leave no residual pigmentation. A few cases of NPFDE have been reported to various drugs in adult patients, but, to our knowledge, only one case of pediatric NPFDE has been explored and reported (2).

From September 2005 to October 2014, a well-being boy born in September 2004 reported 4 or 5 episodes of non-pigmenting burning major swelling of the penis, with painful micturation, 3-6 hours after the start of treatments with amoxicillin. Each reaction was treated with oral antihistamines and corticosteroids, and resolved within 3-4 days without sequellae. His mother had not been treated with

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antibiotics, amoxicillin especially, during pregnancy, delivery and breastfeeding. From birthdate to the initial reaction, the child had tolerated treatments with cefpodoxime and NSAIDs, but had not been treated with amoxicillin. Between the reactions, the child had tolerated cefpodoxime, macrolides and NSAIDs.

Allergological work-up was performed 1 month after the most recent reaction. Clinical examination was normal and revealed no pigmented lesions of the penis skin, prepuce and glands mucosa. As previously reported (2), intradermal (ID) and patch-tests (on the back) were performed with the soluble form of the suspected betalactam (amoxicillin) and other betalactams from the same class and other classes (penicillin G, cefazoline), diluted with 0.9% sterile NaCl. The concentration used were 250-25 000 IU/ml for penicillin G and 0.25-25 mg/ml for the other betalactams for ID, and 250 000 IU/ml for penicillin G and 250 mg/ml for the other betalactams for patch-tests. A patch-test with amoxicillin was also performed on the external surface of the penile skin. Responses in skin tests, including the penile patch-test, were negative at 15-20 minutes (immediate reading, ID), 6-8 hours (semi-late, ID), 2-3 days (late, ID and patch-tests), and 6-7 days (hyper-late, ID and patch-tests), according to the EAACI/ENDA guidelines (3).

A challenge test (in the hospital) was performed orally with amoxicillin, as previously reported (2). Pruriginous penile erythema developed 3 hours after the appropriate cumulative dose for weight and age has been administered (Fig.1), and penile swelling developed one hour later (Fig. 2), although the child had been treated immediately with intravenous (IV) antihistamines and corticosteroids. The child was treated with oral (day 1, at home, in the evening) and IV (day 2, in the morning, in the hospital) antihistamines and corticosteroids, and the symptoms completely resolved at day 4 (Fig. 3). Challenge tests (CT), subsequently performed with penicillin V (1 day, in the hospital) and cefuroxime (3 days, at home) were tolerated.

Thus, we diagnosed isolated penile NPFDE to amoxicillin, with contra-indication of aminopenicillins, and of aminocephalosporins as a precaution.

To our knowledge, we report the first case of isolated penile NPFDE in a child. A few cases of pediatric penile pigmented FDE, diagnosed by means of clinical history, CT, and responses in the macrophage inhibiting factor assay, have been reported (4). As reported in adult patients with FDE, patch-tests with the offending drugs, especially when applied on the residual pigmented sites, including penile skin and glands penis mucosa, may help diagnosis, although their sensitivity is debated (5-7).

To our knowledge, the diagnostic value of patch-tests in NPFDE is unknown. We did not perform patch-tests on the glands mucosa of the child for practical and ethical reasons, and the suspected diagnosis was confirmed by means of CT, that are considered safe in FDE and NPFDE (1).

NPFDE are delayed-type hypersensitivity (DTH) reactions and, thus, may result from activation of T-cells by pharmacological-immunological (non-covalent and reversible) interactions of the drug with histocompatibility antigens expressed on antigen-presenting cells and the T-cell antigen receptors (p-i concept), as shown for several low molecular weight drugs (8). However, given the very short time interval between the first exposure to amoxicillin and the onset of the first reaction, the reaction may also be a consequence of a previous sensitization of the child to amoxicillin, leading to expansion of amoxicillin-specific T-lymphocytes. Given that the mother had not been treated with antibiotics during pregnancy, delivery and breastfeeding, and that the first reaction occurred at the start of a first treatment with amoxicillin, the child may have been sensitized by transplacental and/or breast milk transfer of penicillin contaminating foods ingested by his mother, and/or by direct ingestion of contaminated foods during his first year of life. It is well known that foods may be contaminated by drugs, that these drugs are excreted in the urine of exposed individuals (9), and can cause sensitization and allergic reactions (10,11). Moreover, it has been shown that drugs ingested by the mother can be transmitted to the children transplacentally and by breast milk (12,13).

In conclusion, the case of this young boy is probably exceedingly rare because : (i) the reactions strongly suggest an unusual type of FDE, without residual pigmentation (NPFDE), which is very rare in children (1,2), especially when located at the penis ; (ii) although the reactions may result from p-i interactions of amoxicillin with immune receptors, prior occult sensitization can also be suspected, resulting from transplacental and/or breast milk transfer of penicillin contaminating foods ingested by the mother, and/or from direct ingestion of drug-contaminated foods by the child during the first year of life. Finally, this case raises the problem of the methodology and diagnostic value of skin tests in NPFDE.

Conflict of interest. The authors declare that they have no conflict of interest in relation with this article.

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Legend Fig. 1 : pruriginous penile erythema (3^d hour after challenge).



Legend Fig. 2 : penile swelling (4th hour after challenge).



Legend Fig. 3 : complete recovery (day-4).

