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CASE REPORT

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Drug-induced fixed urticaria because of hypersensitivity to non steroidal anti-inflammatory drugs

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Abstract

Drug-induced fixed urticaria (DIFU) is a rare skin reaction, characterized by pruritic hives that reappear in the same location after exposure to the triggering drug. In the few cases reported in the literature, it is considered as an atypical variant of fixed drug eruption (FDE). We present the case of a 10-year-old girl with allergic rhinoconjunctivitis, who had experienced three episodes of localized urticaria on the dorsal surface of both arms, 1 hour after taking ibuprofen. These manifestations did not appear when taking paracetamol, which she tolerated. Her father suffers from generalized urticaria to NSAIDs. An oral provocation test (OPT) was performed with ibuprofen, acetylsalicylic acid, and metamizole, which also caused the same fixed-location wheals and subsequent spontaneous resolution. She, however, tolerated an OPT with meloxicam. This case is notable because of the rarity of the DIFU and the familial aggregation of hypersensitivity to NSAIDs. In this case, as in those of DIFU described in the literature, the hives appeared shortly after the drug was administered and resolved rapidly. This feature distinguishes it from FDE, and it resembles acute drug urticaria, as in the patient's father, which raises questions concerning the pathophysiology of DIFU.

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Introduction

Drug-induced fixed urticaria (DIFU) is an immediate-type reaction, characterized by isolated pruritic wheals that

always appear in the same site after exposure to the responsible drug. DIFU was first described by Barbarroja-Escudero and colleagues in 2015 in two adult patients with atypical fixed drug eruption (FDE), caused by local anesthetics,

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and by paracetamol and metamizole, respectively. A suspected IgE-mediated mechanism was considered by the results of skin biopsies in both of them.¹ Another two adult patients with DIFU because of cross-reactive NSAID intolerance were described in 2019, being considered as a type of FDE that resembled a local form of NSAID-induced urticaria/angioedema (NIUA).² A fifth case in an adult caused by nivolumab has just been newly reported.³ We are aware of only two recently published pediatric cases, caused by NSAID and by plasma-derived activated prothrombin complex concentrate, respectively.^{4,5} We are reporting a third pediatric case (eight in adults and children) that presented at our center.

Clinical Case

This case concerns a 10-year-old girl who reported three episodes of localized urticaria on the dorsal side of both upper arms (Figure 1) and on the eyelid in the last 2-3 months, which occurred approximately 1 hour after taking ibuprofen. The wheals faded without treatment after 1 hour, although they did reappear with less intensity in the subsequent hours. She had previously taken ibuprofen, paracetamol, and metamizole with no adverse reaction. Her medical history included allergic rhinitis with sensitization to house dust mites. Her father also suffers hypersensitivity to NSAIDs, presenting with urticaria on his arms and other sites, as well as eyelid edema after taking ibuprofen, acetylsalicylic acid, and metamizole, but with good tolerance to paracetamol.

An oral provocation test (OPT) was performed with ibuprofen (1/10, 1/4, and 1/1 of the therapeutic dose in intervals of 1 hour; total cumulative dose 540 mg), which gave a positive result with the immediate appearance of a wheal on the left eyelid which disappeared and, 2 hours after administration, the appearance of itchy erythematous wheals on the dorsal surface of both upper arms that resolved spontaneously without treatment. Subsequently, OPT was conducted with acetylsalicylic acid (total cumulative dose 785 mg) and with metamizole (total cumulative dose 810 mg), which caused the appearance of the same wheals on the dorsal surface of her arms between 1 and 3 hours after administration, which resolved spontaneously. The wheals were completely similar to those occurring in previous episodes (Figure 1). No other skin manifestations or systemic symptoms were noted. The girl continues tolerating paracetamol, and also tolerated an OPT with meloxicam. Other laboratory tests or the performance of a biopsy were not considered useful nor convenient for this patient.

Discussion

Our case adds to the rare reports of patients with DIFU. The eight published cases to date, including the one presented in this report, are summarized in Table 1. Common characteristics of these patients are the mild course with the absence of systemic symptoms, the short interval between drug administration and urticarial lesions, usually 1 hour or less, and fast resolution even without treatment, in normally less than 1 to a few hours. DIFU may be more



Figure 1 Three different episodes of urticaria from the patient. Wheals appear in the same location in both upper arms 1-3 hours after the intake of different NSAIDs. The wheals faded away without treatment in about an hour and flared up again mildly some hours later. Pictures captured and supplied by her mother.

frequent than supposed, if patients and doctors are not worried about such a mild disorder.

Cross-intolerance to NSAID was the main cause of DIFU in four of the eight patients. In our patient, the father suffers from generalized urticaria because of hypersensitivity to NSAIDs. Although this familial aggregation is not reported in other cases of DIFU, a genetic component has been reported in both FDE⁶ and NSAID hypersensitivity.⁷

Allergy skin tests are mostly useless. Provocation tests should be performed for confirmation because they are safe and produce mild urticarial lesions in the same location as the index reaction. Provocation tests are also useful to find alternative drugs for the patient.

The biopsy performed in three of the patients shows findings of typical urticaria. Some authors consider DIFU as an atypical variant of FDE, with which it shares the recurring location of the wheals in the same site after exposure to the drug involved. However, FDE is a late hypersensitivity reaction that usually presents as erythematous-violaceous wheals with well-defined edges that appear between hours to days after administration of the causative drug. The wheals subsequently heal leaving a residual post-inflammatory hyperpigmentation.^{6,8} In contrast, in all cases reported in the literature with DIFU, the typical wheals developed and faded rapidly, without leaving residual lesions nor skin pigmentation. Patients with DIFU seem to share characteristics that are halfway between FDE and acute drug urticaria, and are also similar to some rare cases of food-induced fixed eruption.^{9,10} Therefore, DIFU may be considered either as an atypical variant of FDE or as a peculiar form of acute drug-induced urticaria.

Although the treatment consists in avoiding the drug or drugs involved, repeated administration or desensitization have been performed when the drug was essential.^{3,5}

Conclusions

DIFU is a mild disorder characterized by repeated episodes of wheals in the same location after the administration of the same drug(s). DIFU is frequently associated with NSAID hypersensitivity, although its underlying physiopathology

Table 1 Characteristics of published patients with drug-induced fixed urticaria.

Case	1	2	3	4	5	6	7	8
Age	30 years	50 years	48 years	50 years	16 years	10 years	51 years	10 years
Sex	Female	Female	Female	Female	Male	Male	Female	Female
Reference	1	1	2	2	5	4	3	Actual
Atopic or other diseases	Allergic rhinoconjunctivitis			Psoriatic arthritis	Hemophilia A with inhibitor FVIII	Allergic rhinitis	Metastatic melanoma	Allergic rhinitis
Culprit drug(s)	Local anesthetics: mepivacaine, lidocaine	Paracetamol, metamizole	Ibuprofen	Ibuprofen, dexketoprofen, ASA, metamizole, diclofenac	Plasma-derived activated prothrombin complex concentrate	Ibuprofen and ASA	Nivolumab	Ibuprofen
Time to reaction	20 minutes	15-20 minutes	5-50 minutes	30 minutes	Sudden onset	20-60 minutes	30 minutes	1-3 hours
Time to spontaneous resolution	15-30 minutes	30 minutes	Less than 6 hours			2 hours	3 hours	1 hour, but may flare up again mildly some hours later
Lesion location	Outer face of her right arm	Upper abdomen (epigastrium)	Right superciliary region	Right superciliary region	Both antecubital regions	Both armpits	Décolleté	Dorsal side of both upper arms. Occasionally eyelid wheal
Allergy tests	Skin prick and intradermal tests negative to mepivacaine. Patch test negative to mepivacaine and lidocaine	Patch test negative to paracetamol and metamizole			Family rejected patch test	Patch test positive to ibuprofen and negative to acetylsalicylic acid (ASA)	Prick, intradermal, and subcutaneous tests negative to nivolumab	
Reproduced index lesion after provocation tests	Subcutaneous challenge test positive to mepivacaine	Open challenge test positive to paracetamol and to metamizole	Single-blind oral challenge test positive to ASA	Single-blind challenge test positive to diclofenac	Reappearance after open administration of the culprit drug in spite of antihistamine premedication	Oral provocation test (OPT) positive to ibuprofen	Reappearance after repeated administration of nivolumab	Oral provocation test positive to ibuprofen, ASA, and metamizole

(continues)

Table 1 Continued.

Case	1	2	3	4	5	6	7	8
Other tests	Subcutaneous challenge test negative to bupivacaine		Single-blind oral challenge tests negative to paracetamol, meloxicam, and celecoxib. Negative test to diverse physical stimulations (scratching, heat, and cold)	Single-blind oral challenge tests negative to paracetamol, meloxicam, and celecoxib. Negative test to diverse physical stimulations (scratching, heat, and cold)		OPT negative to paracetamol		Oral provocation test negative to meloxicam
Biopsy	Urticarial lesion	Neutrophilic-type urticarial pattern	Patient rejected	Patient rejected	No	No	Superficial perivascular dermatitis with dermal edema and eosinophils	No
Treatment	No	No	Cetirizine with resolution in 15 minutes	Antihistamines with resolution in less than 1 hour	Antihistamine premedication ineffective	No	No	No
Outcome		Tolerates other NSAIDs			Rapid desensitization protocol successful in spite of urticarial plaques in both antecubital regions resolved with hydroxyzine after 45 minutes		Completes 4 cycles of nivolumab	Tolerates paracetamol
Proposed mechanism	Type I hypersensitivity reaction	Type I hypersensitivity reaction	Type of fixed drug eruption (FDE) resembling a local form of NSAID-induced urticaria/angioedema (NIUA)	Type of FDE resembling a local form of NIUA	Atypical presentation of FDE	Atypical presentation of FDE	Localized memory T-cell-induced mast cell activation via non-IgE pathways	Atypical variant of FDE or peculiar form of acute drug-induced urticaria

and long-term outcomes remain unknown because of the scarce number of patients who have reported to date. Provocation tests are safe and necessary for diagnosis.

Disclosure

The authors declare no potential conflicts of interest with respect to research, authorship, and publication of this article.

Author's Contribution

All authors contributed equally to this article.

Conflicts of Interest

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