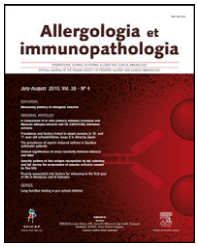
Allergol Immunopathol (Madr). 2012;40(4):253–263

Allergologia et immunopathologia

www.elsevier.es/ai



RESEARCH LETTERS

Urticaria caused by dimenhydrinate

To the Editor,

Dimenhydrinate is an H1 antihistamine of the ethanalamine group with important anticholinergic, antiserotoninergic and sedative properties.[1] It is used in various disorders such as vertigo, motion sickness (car and boat sickness), nausea, vomiting.

Allergic reactions after administration of dimenhydrate are rare, in view of the frequency of employment.[2]

We present the case of a 52-year-old woman who, 1 h after taking a dimenhydrinate pill, reported the appearance of urticaria on the abdomen, on lower and upper limbs, on face and neck and total body itch. These symptoms disappeared in few hours after treatment with betamethasone 4 mg i.m. and oxatomide 30 mg orally. One month later the patient had another allergic reaction taking a dimenhydrinate chewing gum, the symptoms were similar to those of the first reaction but after 1 h, yet on this occasion, there was complete remission of the reaction only taking oral antihistamines.

The patient was suffering from Behcet's disease (BD), a complex multisystem disease of unknown etiology, and Hashimoto's thyroiditis (HT) in treatment respectively with infliximab for six months and levothyroxine 100 mcg for nearly 23 years, moreover she reported hypertension and diabetes in treatment respectively with ramipril 5 mg/hydrochlorothiazide 25 mg for 4 years and metformin 500 mg for 2 years.

The patient's personal history was negative for allergic diseases other than episodes of erythema using a metal watch; moreover in the past she tolerated antihistamines from other groups (rupatidine, levocetirizine).

Therefore allergological evaluations were carried out including a skin prick test with commercial extracts (Stallergenes, Saronno, Varese, Italy) of the most common inhalants (house dust mites, moulds, *Parietaria judaica*, grass pollen, dog and cat dander) and food (milk proteins, egg yolk, egg white, cod, shrimp, *Anisakis simplex*, peanut, soybean, tomato, wheat flour, celery, carrot, potato, bean, eggplant, apple, orange). A patch test was conducted with commercial series: standard European series and preservatives (Lofarma, Milan, Italy); specific IgE antibodies (Phadia CAP System fluorimetric test, Uppsala, Sweden) for the above reported inhalants and food allergens. Skin prick tests and specific IgE for the most common inhalant and food allergens were negative as were patch tests.

The patient was advised not to take dymenidrinate and she did not report any allergic reaction.

The temporal correlation, few hours between intake and clinical manifestations in both cases, and the absence of urticaria without drug assumption establish a probable cause-effect relationship between drug and urticaria according to the Naranjo algorithm (Naranjo score: 5).[3]

There are few known cases of dimenhydrinate allergic reactions exclusively characterised by fixed drug eruption (FDE).[1,2,4,5]

We considered it important to report this case because the patient showed only urticaria and not erythema fixed as in the other cases cited; according to the new subclassification of delayed type IV immune reactions, FDE is a type IVc reaction in which cytotoxic T cells play the predominant role,[6] while the complex nature of the pathogenesis of urticaria has many features in addition to the release of histamine from dermal mast cells.[7]

Therefore we can find in the clinical history of the patient a motivation for the singularity of the adverse reactions to this molecule. In fact on the one hand Lichting et al.[8] showed that the number of mast cells is increased in reactive and spontaneous skin lesions of BD when compared with apparently normal skin of BD or those with other skin diseases. They also reported that mast cell degranulation might have a role in the pathogenesis of BD. On the other hand a cross-linking of IgE receptors of mast cells induced by anti-thyroid antibodies, in HT, may presumably be a cause of histamine release.[9]

Therefore we referred this case for its singularity, as it is the first case, to our knowledge, of urticaria after taking dimenhydrate, while FDE is the clinical manifestation in the other cases cited. Probably its singularity is justified by the presence of BD and HT, which may create a state of mast cell instability, in our opinion, able to cause urticaria as clinical manifestation of dimenhydrate adverse reaction.

References

1. Rodríguez-Jiménez B, Domínguez-Ortega J, González-García JM, Kindelan-Recarte C. Dimenhydrinate-induced fixed drug erup-

tion in a patient who tolerated other antihistamines. J Investig Allergol Clin Immunol. 2009;19:334–5.
2. Saenz de San Pedro B, Quiralte J, Florido JF. Fixed drug eruption caused by dimenhydrinate. Allergy. 2000;55:297.
3. Naranjo C, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–45.
4. Smola H, Kruppa A, Hunzelmann N, Krieg T, Scharffetter-Kochanek K. Identification of dimenhydrinate as the causative agent in fixed drug eruption using patch-testing in previously affected skin. Br J Dermatol. 1998;138:920–1.
5. Gonzalo-Garijo MA, Revenga-Arranz F. Fixed drug eruption due to dimenhydrinate. Br J Dermatol. 1996;135:661–2.
6. Ozkaya E. Fixed drug eruption: state of the art. J Dtsch Dermatol Ges. 2008;6:181–8.
7. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau A, et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy. 2009;64:1417–26.
8. Lichting C, Haim S, Hammel I, Friedman-Birnbaum R. The quantification and significance of mast cells in lesions of Behçet's disease. Br J Dermatol. 1980;102:255–9.
9. Rottem M. Chronic urticaria and autoimmune thyroid disease: is there a link? Autoimmun Rev. 2003;2:69–72.

Isidora Paffumi[a], Salvatore Saitta[a,*], Stefania Isola[a], Sebastiano Gangemi[a,b]

[a] *School and Unit of Allergy and Clinical Immunology, Department of Human Pathology, University of Messina, Italy*
[b] *Institute of Biomedicine and Molecular Immunology-National Research Council, Palermo, Italy*

* Corresponding author.
E-mail address: saittasalvatore@tiscalinet.it (S. Saitta).
doi:10.1016/j.aller.2011.05.009

Type I leucocyte adhesion deficiency (LAD I). Report of a case

Leucocyte adhesion deficiencies (LADs) are a group of primary immunodeficiencies in which the leucocytes are unable to migrate from the circulation towards the areas of inflammation. Three types of LAD have been described to date[1–3]:

1. Type I leucocyte adhesion deficiency (LAD I), characterised by mutations in the common chain (CD18) of the β2 integrins family. These patients suffer serious recurrent infections of the skin and mucosal membranes. In the more serious presentations the patients die early if haematopoietic precursor cell transplantation is not carried out.[1–3]
2. Type II leucocyte adhesion deficiency (LAD II), characterised by the absence of the fucosylated ligand in neutrophils needed for binding to selectins E and P in the activated endothelium. Clinically, these patients suffer less serious infections but present retarded psychomotor and weight and body height development.[1–3]
3. Type III leucocyte adhesion deficiency (LAD III), characterised by a defect in the activation of integrins β1, β2 and β3. These patients suffer serious infections and bleeding disorders.[1–3]

We present a case of type I leucocyte adhesion deficiency (LAD I).

The patient in this case was a 3-month-old boy, the first offspring of consanguineous parents (first cousins). There had been no previous miscarriages. The female first cousin of the parents had died 15 days after birth due to non-established causes. Pregnancy and delivery were without complications. The patient was born to term with a body weight concordant with the gestational age. Weight and height progression was normal. Seven days after birth the patient was admitted due to omphalitis, with culture positive for penicillin-sensitive *Streptococcus mitis* and multisensitive *Escherichia coli*. Blood culture proved negative, and the complete blood count showed 42,500 leucocytes/mm^3 with a normal formula. At 2 months of age the patient was again admitted due to urinary infection caused by multiresistant *E. coli* and staphylococcal impetigo. At 3 months of age he was admitted due to left-side acute otitis media. The complete blood count showed 33,600 leucocytes/mm^3 (56.9% neutrophils and 31.6% lymphocytes). Two weeks later the patient developed an ulceration in the lumbar and intergluteal zone that again required admission to hospital. The patient was found to be in good general condition, with a weight of 6 kg and no fever. A rounded, ulcerated non-suppurative lesion with an erythematous margin was confirmed in the lumbar and intergluteal zone (Table 1 and Fig. 1). Blood tests: leucocyte count 26,500 cells/mm^3 (31% neutrophils and 53.9% lymphocytes), C-reactive protein 6 mg/l, erythrocyte sedimentation rate 11 mm/h, with negative blood and lesion sample cultures. Empirical antibiotic treatment was started with meropenem. An immune study was carried out, revealing the following lymphoid population distribution: LB 18%, LT 62%, LT4 46%, LT8 15%, absolute LT4 6578/mm^3. IgM: 3038 mg/l, IgG: 4627 mg/l, IgA: 437 mg/l, IgE: 47 kU/l. Neutrophil oxidative capacity test 96%, as determined by flow cytometry with dihydrorhodamine. Leucocyte adhesion deficiency (LAD) was suspected, as a result of which flow cytometry with anti-CD11/CD18 monoclonal antibodies was carried out, revealing the absence of CD18 in leucocytes (Fig. 2). The blood group corresponded to A+ (discarding group hh Bombay present in type II leucocyte adhesion defect). An ITGB2 gene mutation analysis was performed, revealing the presence of genetic mutation p.Gly-169-Arg (also known as p.G169R) in exon 5 of the mentioned gene and in both alleles (homozygosis). Given the compatible clinical manifestations, the total absence of CD18 expression in peripheral blood leucocytes, and the presence of mutation p.G169R, we concluded that the patient suffered a severe type I leucocyte adhesion defect. Study of both parents was decided on in order to establish the segregation pattern of the detected mutation. Flow cytometric analysis of both parents revealed CD18 present in 98% of the leucocytes,