Anaphylaxislike cholinergic urticaria

Darío Antolín-Amérigo MD Petruta Cristina Vlaicu MD Belén De La Hoz Caballer MD PhD Moisés Sánchez Cano MD PhD

Cholinergic urticaria (CU) can be defined as itching and whealing associated with exercise, hot showers, sweating, anxiety, or any other condition that increases the body's core temperature. Cholinergic urticaria might present in a local or generalized form. The latter is characterized by the abrupt appearance of small wheals surrounded by a pronounced erythematous flare reaction beginning over the upper thorax and neck and subsequently spanning practically the entire body. Exercise-induced anaphylaxis should be ruled out.

Case

A 21-year-old man was referred to our outpatient allergy division owing to a generalized itchy micropapular eruption accompanied by lip, facial, and eyelid angioedema; rhinorrhea; and conjunctival erythema after playing basketball. He was previously diagnosed with hypersensitivity to egg, nuts, fish, and shellfish; fruit-related oral allergy syndrome; latex hypersensitivity; rhinoconjunctivitis related to extrinsic asthma; and mild atopic dermatitis.

For 3 years before his visit to our clinic, he reported having a pruritic micropapular eruption on his thorax and limbs whenever he practised any kind of sport. He experienced the same cutaneous eruption after exposure to elevated ambient temperature while at rest. He also reported recurrent episodes of this eruption of increasing frequency and severity up to a point at which he required emergency treatment with intramuscular methylprednisolone, dexchlorpheniramine, and adrenaline to manage these symptoms. He reported no food or drug co-ingestion at the time of these episodes.

We performed an extensive allergologic examination, after receiving his informed consent, to elucidate the potential contribution of foods or aeroallergens. Biochemistry and blood cell count were both normal. His total immunoglobulin E (IgE) level was 4.76 mg/L; basal tryptase level was 2.12 µg/L; specific IgE level tested against Bet v 2 (birch) was 1.28 kU/L; and specific IgE level tested against latex was 3.07×10^{-3} mg/L. His serum CH50, C3, and C4 levels were normal. Test results for cryoglobulinemia, thyroid-stimulating hormone antibodies, thyroid antimicrosomal antibodies, and antithyroglobulin antibodies were all negative.

A skin-prick test against a common battery of aeroallergens had positive results for the following: *Dermatophagoides pteronyssinus*, *Alternaria* spp, grass mix, *Lolium perenne*, *Olea europaea*, *Cupressus arizonica*, *Platanus acerifolia*, egg white, egg yolk, ovalbumin, ovomucoid, blue fish mix, white fish mix, whiff (type of fish; also known as *megrim*), squid, shrimp, lobster, spider crab, nut mix, melon, profilin, lentil, and latex.

Results of an epicutaneous test against a common battery of foods (readings taken at 48 and 96 hours) were negative. A commercial epicutaneous test (TRUE Test) had positive results for thiuram mix allergy.

The patient underwent supervised exercise testing after a 6-hour fast. After 15 minutes, a generalized itchy micropapular eruption appeared, accompanied by lip, facial, and eyelid angioedema; rhinorrhea; conjunctival erythema; and nonsibilant dyspnea. Intramuscular methylprednisolone, dexchlorpheniramine, and adrenaline were administered. Complete remission of symptoms was achieved after 1 hour. There was no change in pulmonary function during this challenge compared with previous visits.

A component-resolved diagnosis was performed using the ImmunoCAP ISAC microarray (Phadia AB, Sweden). The results showed very high levels of IgE antibodies for the following allergen proteins: Ara h 2 (peanut), Hev b 6 (latex), Gal d 1 (egg white), tropomyosin (crustaceans, mites, and cockroaches), Phl p 1 (Timothy grass), and Alt

This article has been peer reviewed.
Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2013;59:745-6

EDITOR'S KEY POINTS

- Anaphylaxislike cholinergic urticaria is characterized by the appearance of a micropapular eruption while exposed to passive heating at rest, which differentiates it from exercise-induced anaphylaxis.
- This is the first reported case in which the antileukotriene montelukast has been successful in treating anaphylaxislike cholinergic urticaria. Mechanisms related to its suitability to treat this unique entity remain elusive and should be clarified in further investigations.

POINTS DE REPÈRE DU RÉDACTEUR

- L'urticaire cholinergique de type anaphylactique se caractérise par l'apparition d'une éruption micropapulaire pendant l'exposition à la chaleur passive au repos, ce qui la différencie de l'anaphylaxie induite par l'effort.
- C'est le premier cas signalé dans lequel l'antileukotriène montelukast a réussi à traiter l'urticaire cholinergique de type anaphylactique. Les mécanismes reliés à sa pertinence pour traiter cette entité unique demeurent vagues et devraient être précisés dans des investigations plus approfondies.

a 1 (*Alternaria* spp). Low levels of ω-5-gliadin (wheat) antibodies were found.

Discussion

We present an uncommon and complex case of CU with anaphylaxislike symptoms in a highly atopic patient. This condition might be considered a unique entity with its characteristic clinical properties. Appearance of a micropapular eruption while at rest differentiates this disease from exercise-induced anaphylaxis. The drug of choice for its management is either hydroxyzine (100 to 200 mg daily) or cetirizine (20 mg daily). Treatment with cetirizine and 10 mg daily of the antileukotriene montelukast has prevented additional anaphylaxislike CU episodes in this patient to date.

We performed a review of the literature using *urticaria*, *anaphylaxis*, *diagnosis*, and *leukotriene antagonists* as MeSH key words in PubMed, searching between the years 1990 and 2011. Consensus panel recommendations published in 2009 by Magerl et al[1] defined CU as a form of urticaria caused by an increase in the body's core temperature and not by an exogenous physical trigger on the skin; it is characterized by itching and wheaing after either active or passive heating of the body. The authors remarked that this urticaria must be differentiated from exercise-induced anaphylaxis because in the latter, no passive warming is involved. The review article also stated that food- or drug-related exercise-induced anaphylaxis should be considered in the differential diagnosis.

Current definitions of urticaria, which are mainly symptom-based, do not accurately describe the condition of our patient. Our patient has an overlap syndrome, which could be named *anaphylaxislike CU syndrome*. Horikawa et al[2] attempted to improve diagnostic criteria by means of a new pathophysiologic subclassification of CU. Our case might be considered a unique entity with its characteristic clinical properties. Appearance of a micropapular eruption at rest, related to passive heating, differentiates anaphylaxislike CU from exercise-induced anaphylaxis. Our patient performed a strict 6-hour fast (ingesting no food or medication) before exercise testing and experienced symptoms that did not match diagnostic criteria for exercise-induced anaphylaxis or CU. Supervision during exercise testing is important owing to the risk of anaphylaxislike symptoms, airway hyperresponsiveness, acute myocardial infarction, and other unexpected collateral effects or complications.

The ImmunoCAP ISAC microarray detects allergen sensitization at the component level and provides important information by defining both cross- and cosensitization to various allergen molecules using only a few microlitres of serum or plasma.[3,4] It has been demonstrated to be equivalent to standard specific IgE immunodetection. Besides, to date, ISAC constitutes the only means potentially able to provide a global picture of sensitization in a single patient. It is used especially in complex cases, such as the one we reported here.

Urticaria has been successfully treated with antihistamines[5] (not in severe CU), scopolamine,[6] danazol, β_2-adrenergic stimulants, β_2-adrenergic antagonists, anti-IgE antibodies, and desensitization with autologous sweat, but not previously with antileukotrienes.[7] Montelukast might be effective in chronic urticaria associated with hypersensitivity to acetylsalicylic acid or food additives or with autoreactivity to intradermal serum injection when taken with an antihistamine, but to date it has been unhelpful in both exercise-induced anaphylaxis and CU.

Conclusion

To our knowledge, this is the first reported case in which montelukast has been successful in treating anaphylaxislike CU. Mechanisms related to its suitability in this unique entity remain elusive and should be clarified in further investigations. Appearance of a micropapular eruption while at rest differentiates this disease from exercise-induced anaphylaxis.

Drs Antolín-Amérigo, **Vlaicu**, **De La Hoz Caballer**, and **Sánchez Cano** are physicians in the Allergy Division at the Hospital Universitario Ramón y Cajal in Madrid, Spain.

Acknowledgment
We thank **Dr Jorge Martínez-Quesada** for his contribution in performing the component-resolved diagnosis. This case report was partially presented as a poster communication at the 27th Congress of the Spanish Society of Allergology and Clinical Immunology, Logroño, Spain, November 10 to 13, 2010.

Competing interests
None declared

Correspondence
Dr Darío Antolín-Amérigo, Hospital Universitario Ramón y Cajal, Servicio de Alergia, Carretera de Colmenar Km 9,100 s/n, 28049, Madrid, Spain; telephone +34 91-3368000; fax +34 91-3580614; e-mail **dario.antolin@gmail.com**

References

1. Magerl M, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F, Mathelier-Fusade P, et al. The definition and diagnostic testing of physical and cholinergic urticarias—EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. *Allergy* 2009;64(12):1715-21. Epub 2009 Sep 30.
2. Horikawa T, Fukunaga A, Nishigori C. New concepts of hive formation in cholinergic urticaria. *Curr Allergy Asthma Rep* 2009;9(4):273-9.
3. Cabrera-Freitag P, Goikoetxea MJ, Beorlegui C, Gamboa P, Gastaminza G, Fernández-Benítez M, et al. Can component-based microarray replace fluorescent enzimoimmunoassay in the diagnosis of grass and cypress pollen allergy? *Clin Exp Allergy* 2011;41(10):1440-6. Epub 2011 Jul 13.
4. Melioli G, Bonifazi F, Bonini S, Maggi E, Mussap M, Passalacqua G, et al. The ImmunoCAP ISAC molecular allergology approach in adult multi-sensitized Italian patients with respiratory symptoms. *Clin Biochem* 2011;44(12):1005-11. Epub 2011 May 19.
5. Zuberbier T, Althaus C, Chantraine-Hess S, Czarnetzki BM. Prevalence of cholinergic urticaria in young adults. *J Am Acad Dermatol* 1994;31(6):978-81.
6. Tsunemi Y, Ihn H, Saeki H, Tamaki K. Cholinergic urticaria successfully treated with scopolamine butylbromide. *Int J Dermatol* 2003;42(10):850.
7. Di Lorenzo G, Pacor ML, Mansueto P, Esposito-Pellitteri M, Ditta V, Lo Bianco C, et al. Is there a role for antileukotrienes in urticaria? *Clin Exp Dermatol* 2006;31(3):327-34.