

Reply to Comments on the Article “Cold Urticaria Triggered After Treatment With Amoxicillin-Clavulanic Acid”

García-Paz V^{1*}, Otero-Alonso A^{2*}

¹Allergy Department, Complejo Hospitalario Universitario de Ferrol, A Coruña, Spain

²Allergy Department, Complejo Asistencial de Zamora, Zamora, Spain

*Both authors contributed equally.

J Investig Allergol Clin Immunol 2024; Vol. 34(5): 356-357
doi: 10.18176/jiaci.1015

Key words: Cold urticaria. Amoxicillin. Urticaria.

Palabras clave: Urticaria a frigore. Amoxicilina. Urticaria.

To the Editor:

We are writing in reply to the article “Cold Urticaria Due to Amoxicillin-Clavulanic Acid” by Özdemir [1].

First of all, thank you for your interest in our case [1,2]. We take this opportunity to clarify the points raised.

The patient's urticaria was not chronic. Chronic urticaria lasts more than 6 weeks, with daily or almost daily outbreaks, and must be differentiated from other medical conditions, for example, anaphylaxis [3]. The patient we reported experienced a cold urticaria (ColdU) outbreak in 2016 after finishing treatment with amoxicillin-clavulanate for a urinary tract infection. This outbreak lasted 2-3 weeks before resolving completely. She did not experience any further outbreaks for 4 years until the one referred to in our article, and the patient herself did not seem to be overly concerned by the episode.

In the introduction of the article, we referred to the fact that ColdU is a subtype of inducible chronic urticaria [3-5]. But not in the case we report, since the patient experienced ColdU that was triggered by treatment with amoxicillin-clavulanic acid and resolved in 2-3 weeks, indicating secondary ColdU [5].

In March 2020, she was treated again for urinary tract infection with amoxicillin-clavulanic acid. After completing treatment, she developed new outbreaks of hive-like lesions that lasted 2-3 weeks. The lesions appeared only in exposed areas (not in areas covered with clothing) and in cold outdoor environments or when washing hands in running water and lasted for approximately 30 minutes after warming up [3,5].

In your letter [1], you suggested that the buttock lesions that developed when the patient was sitting on cold granite benches in Galicia may have been pressure urticaria. We would like to clarify that the patient did not present these lesions when sitting on the chairs in her kitchen or on the sofa at home. Similarly, she did not develop lesions on her shoulder with her handbag or on her arms from carrying shopping bags.

Granite is a hygroscopic material and, owing to the very humid climate of Galicia, it is very cold. In this region, patients who experience ColdU usually report outbreaks after contact with stone [4,5].

Furthermore, it is worth noting that the patient is a healthy young woman, with no relevant medical-surgical or family history, and she was not taking medications or oral contraceptives.

The fact that she was nonatopic at baseline means that she was nonatopic until the allergy study was performed. This did, in fact, reveal subclinical sensitization to house dust mites.

Sensitization to mites with no clinical relevance is very common in Galicia [6,7], a region in the northwest of the Iberian Peninsula with a temperate, rainy, oceanic climate and high humidity.

Analytical studies performed on the patient ruled out thyroid, rheumatic, and celiac disease, in addition to the fact that she did not present compatible symptoms with any of the aforementioned conditions. This is stated in the text.

Furthermore, we saw the patient for the first time in May, not when she experienced urticaria, ie, in March 2020; at this time, the ice cube test may have yielded a positive result. However, in May 2020 and during the following months, when the allergy study was complete, the patient was asymptomatic, and the result of the allergy work-up was negative. Word count restrictions made it impossible to provide this information.

On the day of the controlled oral exposure test with amoxicillin-clavulanate, the patient was asymptomatic and afebrile and had not experienced any further outbreaks of urticaria. At that time, she was also regularly bathing in the sea (Atlantic Ocean in Galicia), without developing urticaria. Similarly, she did not experience urticaria in contact with the cold or in any other context; consequently, we ruled out spontaneous chronic urticaria.

During the first consultation (May 2020), the patient underwent an ice cube test, which was negative. On the day of the test, the patient had not taken amoxicillin-clavulanate or any other drugs and did not have an infection. The blood tests performed to complete the allergy study were also negative.

At a subsequent appointment, the ice cube test was carried out prior to the tolerance test with amoxicillin-clavulanate approximately 1 hour before taking the first dose. The result was negative. Two hours after a cumulative dose of 1000 mg, the ice cube test was positive, thus confirming that this antibiotic is what triggered ColdU. No infections were reported on that day.

The pathophysiology of drug-induced ColdU remains unclear, as reported elsewhere [5].

Finally, we did not claim to have reported the first case of ColdU secondary to penicillin but merely reported a singular case, with no similar cases in the literature according to our search for ColdU induced by amoxicillin-clavulanic acid. Penicillins have been reported in previous articles as a pharmacological cause of ColdU, albeit without reference to a specific penicillin or description of the clinical picture [8,9].

Today, that is, 4 years later, the patient remains asymptomatic, has not experienced subsequent urticaria outbreaks but has used other penicillins without complications. She now only avoids aminopenicillins.

I agree with you that more knowledge is needed about ColdU and the mechanisms that trigger outbreaks.

We hope to have clarified your doubts and thank you again for your interest in this clinical case.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Özdemir Ö. Cold Urticaria Due To Amoxicillin-Clavulanic Acid. *J Investig Allergol Clin Immunol.* 2024;34(5). doi: 10.18176/jiaci.0999.
2. García-Paz V, Romero-Sánchez L, Otero-Alonso A, González-Rivas M, Fernández-Franco I, Vila Sexto L. Cold Urticaria Triggered After Treatment With Amoxicillin-Clavulanic Acid. *J Investig Allergol Clin Immunol.* 2023;33(6):495-7.
3. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy.* 2022;77(3):734-66.
4. Bizjak M, Košnik M, Dinevski D, Thomsen SF, Fomina D, Borzova E, et al. Risk factors for systemic reactions in typical cold urticaria: Results from the COLD-CE study. *Allergy.* 2022;77:2185-99.
5. Maltseva N, Borzova E, Fomina D, Bizjak M, Terhorst-Molawi D, Košnik M, et al; COLD-CE Steering Committee. Cold urticaria - What we know and what we do not know. *Allergy.* 2021;76(4):1077-94.
6. Romero-Sánchez L, Otero A, González-Rivas M, Lojo S, González-Quintela A, Vidal C. Der p 23 sensitization in patients with house dust mite respiratory allergy. *Eur Ann Allergy Clin Immunol.* 2024;56(2):79-85.
7. Vidal C, Chomón B, Pérez-Carral C, González-Quintela A. Sensitization to *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, and *Acarus siro* in patients allergic to house dust mites (*Dermatophagoides* spp.). *J Allergy Clin Immunol.* 1997;100(5):716-8.
8. Wandered A. Cold urticaria syndromes: Historical background, diagnosis classification, clinical and laboratory characteristics, pathogenesis and management. *J Allergy Clin Immunol.* 1990;85(6):965-81.
9. Fitzpatrick TB. Essential Cold urticaria. *Arch Dermatol.* 1963;87:495-7.

■ *Manuscript received April 23, 2024; accepted for publication May 8, 2024.*

■ Vanesa García Paz

Department of Allergy
Complejo Hospitalario Universitario de Ferrol
A Coruña, Spain
E-mail: vanesa.garcia.paz@sergas.es