Cold Urticaria Triggered After Treatment With Amoxicillin–Clavulanic Acid

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Cold urticaria (ColdU) is a subtype of chronic inducible urticaria (CIndU) characterized by the appearance of wheals and/or angioedema with a risk of anaphylaxis and life-threatening reactions in response to exposure of the skin or mucosa to cold (air, solids, or liquids) [1-5]. Its prevalence in patients with chronic urticaria and CIndU is 7.62% and 26.1%, respectively [2]. Diagnosis is based on the clinical history (mainly in atypical forms) and cold provocation tests (ice cube and/or Temp Test) [1,4-6]. Treatment is based on cold avoidance and second-generation H_1-antihistamines in increasing doses until clinical control is achieved [7]. Omalizumab can be used off-label [4,5].

We report the case of a 32-year-old nonatopic woman who developed ColdU after treatment with amoxicillin–clavulanic acid. She had been prescribed amoxicillin-clavulanate for 10 days owing to a urinary tract infection in 2016. Seven days after completing treatment she developed wheals. Initially, she did not associate these with a trigger, although she later noticed outbreaks of urticaria after being outdoors and washing her hands with cold water. This episode lasted 2-3 weeks, and she did not experience any further outbreaks of urticaria until March 2020, when she was prescribed amoxicillin-clavulanate again for 10 days owing to cystitis. A week after completing antibiotic treatment, she again reported an outbreak of generalized urticaria in the areas exposed while being outdoors (hands, face, and neckline) and after washing her hands with cold water. She even developed wheals on her buttocks after sitting on cold stone benches. The ambient temperature was approximately 10ºC, which is typical in Galicia (northwest Spain). The cutaneous lesions disappeared after about 30 minutes once she had warmed up. She felt that these episodes were more intense (greater area and number of annoying, long-lasting lesions). The outbreaks resolved after 2-3 weeks, and she even was able to bathe in sea water in the summer of 2020 at a beach in Galicia (Atlantic Ocean, average

temperature 15ºC) and to eat ice-cream and cold drinks without reaction. She did not experience outbreaks after showering with cold water. She is now asymptomatic.

An allergy study (prick and intradermal tests) was performed with penicillin and ß-lactam derivatives: benzylpenicilloyl octa-L-lysine and sodium benzylpenilloate (Diater Laboratories); and penicillin G, ampicillin, amoxicillin, amoxicillin-clavulanate, cefuroxime, and ceftriaxone. The results were all negative in the immediate and late readings.

Skin prick tests were performed with aeroallergens and staple foods in our area, latex, *Anisakis*, and panallergens such as lipid transfer protein and profilin (commercial extracts, ALK-Abelló Laboratories). The results were positive for *Dermatophagoides pteronyssinus* and *Lepidoglyphus destructor*, with no clinical repercussions.

ColdU was suspected, and an ice cube test performed with exposure for 5, 10, 15, and 30 minutes yielded negative results.

We then carried out a general blood work-up comprising complete blood count, basic biochemistry, thyroid hormones, antithyroid antibodies, proteinogram, cryoglobulins, and cold agglutinins. All results were within normal parameters. The IgE results were as follows: total IgE, 69 IU/mL; *Dematophagoides pteronyssinus*, 5.21 kU/L; rDer p 1, 1.38 kU/L; rDer p 2, 1.68 kU/L; rDer p 23, 1.6 kU/L; and *Lepidoglyphus destructor*, 3.79 kU/L. sIgEs for penicillin G, penicillin V, ampicillin, amoxicillin, and clavulanic acid were negative.

Given the negative allergy study result, we scheduled an oral challenge test with amoxicillin–clavulanic acid and a pre- and post- ice cube test. The ice cube test prior to the oral provocation test was negative. The oral tolerance test with amoxicillin-clavulanate up to 1000 mg revealed appropriate tolerance. An ice cube test performed 2 hours after the last dose of amoxicillin-clavulanate was positive within 5 minutes' exposure.

ColdU secondary to amoxicillin–clavulanic acid was confirmed. After the oral provocation test, the patient developed outbreaks of ColdU again for a week, although these subsequently resolved. We scheduled an oral challenge test with cefuroxime and a pre- and post -ice cube test. The results were negative, thus confirming tolerance to cefuroxime without triggering cold urticaria.

Many attempts were made to complete the oral challenge with amoxicillin (without clavulanic acid) to reach a more precise diagnosis, although this was impossible, because the patient refused to undergo further testing. Therefore, the ban on amoxicillin and clavulanic acid (which is combined with amoxicillin) was maintained.

The pathogenesis of ColdU is not well defined. However, the release of mast cell mediators seems to be an essential component. Histamine, prostaglandin D2, platelet-activating factor, and tumor necrosis factor α have been found in the skin and serum of patients with ColdU [1,4]. ColdU can be classified as having typical symptoms, which can be reproduced by cold stimulation, and atypical, cold-induced wheals or an atypical response to cold stimulation [4]. ColdU can be also classified as primary (idiopathic) and secondary. The various reported causes of secondary ColdU include infections, autoimmune or lymphoproliferative diseases, Hymenoptera venom, and certain drugs or foods [4,8]. In the case of drugs, penicillin, combined oral contraceptives, angiotensin-converting enzyme inhibitors, antitetanus serum, griseofulvin [4], and alprazolam [9] are potential causes or are clinically associated with ColdU. Tattoo-induced ColdU has also been reported [10].

Symptoms of ColdU may vary from mild localized wheals to anaphylaxis. Given the risk of anaphylaxis (21.49%) [2,3], an adrenaline autoinjector should be prescribed in specific cases (patients with a cold provocation test of less than 3 minutes or with negative results [4]). In the present case, the clinical presentations were exclusively cutaneous without systemic repercussions, and the symptoms were fleeting and controllable with antihistamines only. Moreover, symptoms were only triggered when 2 factors coexisted: previous antibiotic treatment with amoxicillin–clavulanic acid and exposure to cold. This same pattern was described by Gandolfo-Cano et al [9] with alprazolam.

Further research on ColdU is warranted. In addition, more case descriptions and case series are needed in order to better understand this clinical entity and its etiology and pathogenesis. We present a singular case. Our literature search yielded no similar reports on ColdU induced by amoxicillin–clavulanic acid. Of note, a more precise diagnosis could not be made with the oral challenge test with amoxicillin (without clavulanic acid) because the patient refused to undergo the test and owing to the general shortage of stand-alone amoxicillin. The patient gave her consent for her data to be used in this publication.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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