Cold urticaria triggered after amoxicillin-clavulanic acid treatment

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Cold urticaria (ColdU), a chronic inducible urticaria subtype (CIndU) is characterized by appearance of wheals and/or angioedema with risk of anaphylaxis and life-threatening reactions, in response to cold exposure (air, solids or liquids) of the skin or mucosa [1–5]. Its prevalence in patients with chronic urticaria and CIndU is 7.62% and 26.1% respectively [2]. Diagnosis is based on clinical history (mainly in atypical forms) as well as cold provocation tests (ice cube and/or Temp Test) [1,4–6]. Treatment is based on cold avoidance, second-generation H1-antihistamines in increasing dose until reaching clinical control [7], and Omalizumab used off-label [4,5].

We report the case of a 32-year-old female patient without atopy who developed ColdU after treatment with amoxicillin-clavulanic acid. Due to a tract urinary infection in 2016, she was prescribed Amoxicillin-clavulanate for ten days. Seven days after ending treatment she presented outbreaks of wheals. Initially she did not associate it with any trigger, but later she noticed outbreaks of urticaria after being outdoors and washing her hands with running cold water. This episode lasted 2-3 weeks and she did not have any more outbreaks of urticaria until March 2020, when she was prescribed amoxicillin-clavulanate again for 10 days due to cystitis. A week after completing the antibiotic treatment, she reported once more an outbreak of generalized urticaria in the corporal areas exposed while being outdoors (hands, face and neckline), also after washing her hands with cold water or even after sitting on cold stone benches, she had wheals on her buttocks. The ambient temperature was approximately 10ºC typical in Galicia (northwest of Spain). Cutaneous lesions disappeared in about 30 minutes after warming her up. She felt that these episodes were more intense, (greater area and number of annoying, long lasting lesions). Outbreaks resolved after 2-3 weeks and she even was able to bath in sea water in summer of 2020, in Galicia´s beach (Atlantic Ocean average temperature 15ºC); and to eat an ice-cream and cold drinks without reaction, she had none outbreaks when doused with cold water. She is now asymptomatic.

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Allergy study was performed with prick and intradermal reaction tests with Penicillin and Beta-lactam derivatives: BP-OL (Benzylpeniciloil Octa L-lisine) and DM (Sodium Benzylpeniloate) from Diater Laboratories (Madrid, Spain), Penicillin G, Ampicillin, Amoxicillin, Amoxicillin-clavulanate, Cefuroxime and Ceftriaxone with negative results in immediate and late reading.

Skin prick tests with aeroallergens and staple foods in our area, latex, anisakis and panallergens as lipid transfer protein (LTP) and profillin (commercial extracts ALK-Abelló Laboratories) were performed with positive result for Dermatophagoides pteronyssinus and Lepidoglyphus destructor, without clinical repercussions.

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

General blood analysis was performed: complete blood count, basic biochemistry, thyroid hormones, antithyroid antibodies, proteinogram, cryoglobulins and cold agglutinins, all within normal parameters. Total IgE 69 IU/ml, Dematophagoides pteronyssinus 5.21 KU/L, rDerp1 1.38 KU/L, rDerp2 1.68 KU/L, rDerp23 1.6 KU/L, Lepidoglyphus destructor 3.79 KU/L. sIgEs for Penicillin G, Penicillin V, Ampicillin, Amoxicillin and Clavulanic acid were negative.

Given the negative allergy study, an oral challenge test with Amoxicillin-clavulanic acid with pre and post ice cube test was scheduled. Cube test prior to the oral provocation test was negative. The oral tolerance test with Amoxicillin-clavulanate up to 1000 mg was carried out with correct tolerance. An ice cube test was performed 2 hours after finishing the last dose of Amoxicillin-clavulanate, being positive within 5 minutes exposure.

ColdU secondary to amoxicillin-clavulanic acid was confirmed. After the oral provocation test, the patient presented outbreaks of ColdU again for a week, which later resolved. The patient was scheduled for an oral challenge test with Cefuroxime with previous and post ice cube test with a negative result, confirming Cefuroxime tolerance without triggering cold urticaria.

Many attempts were made to complete amoxicillin oral challenge (without clavulanic acid) to reach a more precise diagnosis, but it was impossible because the patient rejected it, so the ban on amoxicillin and clavulanic acid (which is linked to amoxicillin) was maintained.

The pathogenesis of ColdU is not well defined, but 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 divided into the typical symptoms that can be reproduced by cold stimulation, but also in atypical cold-

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induced wheals or atypical response to cold stimulation [4]. Moreover, ColdU can be also classify in primary (idiopathic) and secondary form. Several causes of secondary ColdU have been described such infections, autoimmune or lymphoproliferative diseases, hymenoptera sting or certain drugs or foods [4,8]. Regarding to drugs, penicillin, combined oral contraceptives, angiotensin-converting enzyme inhibitors, anti-tetanus serum, griseofulvin [4] and alprazolam [9] had been described as potential causes or had clinical associations to ColdU. In addition, tattoo-induced ColdU has also been reported [10].

Symptoms of ColdU may vary from mild localized wheals to anaphylaxis. Due to the risk of anaphylaxis (21.49%) [2,3], an adrenaline auto-injector should be prescribed in some range of patients (with a cold provocation test of less than 3 minutes or with negative results [4]). In our patient, clinical presentations were exclusively cutaneous without systemic repercussions, symptoms were not only fleeting but also controlled just with antihistamines. Moreover, symptoms were only triggered when two factors coexisted: previous antibiotic treatment with amoxicillin/clavulanic-acid and cold exposure. This same pattern was described by Gandolfo-Cano et al [9] with alprazolam.

ColdU continues to be a pending topic for more research and studies, more case descriptions and case series are needed in order to better understand this clinical entity and its etiopathogenesis. We present this singular case, we have not found similar reports in the literature, of ColdU induced by Amoxicillin-clavulanic acid. It must be said that a more precise diagnosis could not be made with the oral challenge test with Amoxicillin (without clavulanic-acid) because the patient refused the test and due to the general shortage of standalone Amoxicillin (she consents to this publication).

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Conflict of interest

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