Cold Urticaria due to Amoxicillin–Clavulanic Acid

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To the Editor:

We read with great interest the case report in Practitioner's Corner entitled "Cold Urticaria Triggered After Treatment With Amoxicillin–Clavulanic Acid", recently published in the Journal of Investigational Allergology and Clinical Immunology [1]. I think it would be very useful for the reader to clarify some issues about the case of cold urticaria in this exciting article.

Firstly, the main question in this case is whether the urticaria is chronic, as it lasted for several weeks, and whether it is typical cold urticaria, as it was not only triggered by cold. By definition, chronic urticaria lasts for more than 6 weeks [2]. The urticaria described here lasted for a few weeks, even if it recurred twice in 4 years. In total, it hardly exceeded 6 weeks over the 4 years.

The ice cube test is used to classify acquired cold urticaria as typical or atypical [3]. Since the ice cube test performed when the clinical findings were recorded was negative, despite being monitored for 30 minutes, it is difficult to say that the type of urticaria is typical cold urticaria. Furthermore, the example given in the alprazolam case shows a positive result at the onset of urticaria [3]. The case description leads me to think that the urticaria reported is somehow spontaneous/idiopathic and also triggered by cold. The fact that it occurred a few times outdoors and manifested on different parts of the body (generalized urticaria), such as the neckline, along with more intense episodes (greater area and number of annoying, long-lasting lesions), again confirmed that it is not typical cold urticaria. I wonder if the urticaria affecting the patient's buttocks after sitting on cold stone benches when the ambient temperature was about 10ºC was cold or pressure urticaria.

Chronic spontaneous/idiopathic urticaria can recur with some drugs or be triggered by different physical inducers [4,5]. In the case described, the fact that the ice cube test performed 2 hours after the drug tolerance test became positive despite the negativity of the ice cube test in the presence of the initial clinical findings raises suspicion about whether this is a typical cold-induced urticarial reaction in an atopic patient who I think may have chronic spontaneous urticaria. Could it be that the patient had experienced a flare-up of chronic spontaneous urticaria that day and the cold urticaria was induced by the ice cube test coincidentally? Could this not have happened after the drug provocation test? In this case, it is important to know exactly when the ice cube test was performed prior to oral provocation (how many hours before or if on the same day) and found to be negative. Moreover, how do the authors explain the pathophysiology of physical urticaria (cold urticaria) induced by a drug? With what degree of certainty can they claim that the ice cube test would have been negative or would not have become positive if there had been no drug provocation that day? Again, the idea that this patient does not have typical/simple cold urticaria is supported by the presence of urinary tract infection every time she developed urticaria. This infection itself may have caused or triggered chronic urticaria in her past medical history [5,6].

Secondly, the acquired form of cold urticaria can be typical or atypical, depending on the positivity or negativity of the ice cube test. Typical cold urticaria is categorized into 2 groups: primary (idiopathic) cold urticaria (72%) and secondary cold urticaria (28%) [7]. The known causes of the secondary type are cryoglobulinemia, hypothyroidism, celiac disease, infectious diseases, and drugs (eg, penicillin, oral contraceptives). Atypical forms of cold urticaria involve systemic forms, eg, cold-dependent dermographism, cold reflex urticaria, and delayed cold urticaria [3,7]. If the case described in the article is typical cold urticaria, is it secondary or primary (idiopathic) cold urticaria? It would be interesting to mention and discuss this in the article.

Cold urticaria is known to be familial or acquired [3,7]. I wonder whether the patient's family history had been thoroughly examined.

Thirdly, after mentioning that the patient was not atopic [1], the article later reports positive skin test results for mites such as *Dermatophagoides pteronyssinus* and *Lepidoglyphus destructor*, meaning that the person is atopic, even without known allergic disease.

Fourthly, since the patient is a woman, I wonder if it was questioned whether she was taking drugs such as oral contraceptives. Cold urticaria with oral contraceptive use has been reported [3,7]. Have autoimmune diseases such as celiac disease and other rheumatologic diseases been investigated in this patient?

Fifthly, it is also erroneous to claim that this is the first case of cold urticaria caused by a penicillin-type drug in the literature. Chronic urticaria, including physical/inducible urticaria, due to penicillin-type antibiotics has been reported [8,9]. A study performed in 2016 found that chronic urticaria was at least 3

times more common in self-reported cases of pencillin allergy in the community [10]. The findings of the study should be taken into consideration in the present case.

In conclusion, I consider that awareness of cold urticaria should be increased to enable its accurate differentiation from other, similar diseases.

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Conflicts of Interest

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