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Cold Urticaria Associated With Epstein-Barr Virus Mononucleosis

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To the Editor:

Physical urticarias are characterized by the appearance of wheals or angioedema after exposure to different physical stimuli. In cold urticaria, symptoms develop with cold. In the majority of these patients, no triggering agent is found, though in some cases it has been associated with viral or bacterial infections, autoimmune, hematologic, or thyroid diseases, or drug ingestion.¹

We present the case of a 14-year-old girl with no past history of interest, who was seen in June 2007 for episodes of facial wheals and pruritus after bathing in the sea wearing a neoprene suit. Cold drinks, ice creams, and cold air did not trigger the condition, nor did water at other temperatures. The urticaria appeared a few minutes after contact with cold water and disappeared spontaneously within 20 to 30 minutes. There was no angioedema, syncope, hypotension, Raynaud phenomenon, or purpura, and no other cardiovascular, respiratory, or gastrointestinal symptoms. At the time of consultation, the patient was asymptomatic. To confirm the diagnosis of cold urticaria, a provocation test was performed with an ice cube; a wheal of 3 by 2 cm appeared on the forearm after 5 minutes.

Two weeks before the first episode, the patient had suffered an episode of exudative pharyngitis with fever and submandibular lymphadenopathies. Suspecting cold urticaria secondary to infectious mononucleosis, serological tests were performed for Epstein-Barr virus (EBV), cytomegalovirus (CMV), and other viruses related with cold urticaria, such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). A complete blood count and basic biochemistry were performed, together with the levels of total immunoglobulin (Ig) E, complement, cryoglobulins, cryoagglutinins, and cryofibrinogen. This study revealed the presence of IgM to EBV, with negative or normal results of the other parameters. Subsequent follow-up showed a clinical improvement of the cold urticaria,

coinciding with seroconversion to anti-EBV IgG; the patient was asymptomatic 2 months after the onset of the condition (negative ice cube test). Until resolution of the disorder, she was advised to avoid contact with cold water, the principal trigger, and was given treatment with cetirizine at a dose of 10 mg/24 h.

Cold urticaria accounts for 2% to 3% of physical urticarias² and was first described in 1866 by Bourdon.³ It can be associated with other forms of physical urticaria such as dermographism (21%), heat urticaria (10%), and cholinergic urticaria (8%).⁴ Wanderer⁵ classified these conditions into 3 groups according to the severity of the clinical manifestations: type I (localized lesions), type II (systemic phenomenon without symptoms of hypotension), and type III (with hypotension or shock), which can be life-threatening.

No etiological agent is detected in more than 95% of patients with cold urticaria, and the condition is classified as primary or idiopathic.² A small percentage of cases are secondary to various viral or bacterial infections, such as *Mycoplasma*, *Treponema pallidum*, *Helicobacter pylori*, *Toxoplasma gondii*, rubella virus, EBV, CMV, HBV, HCV, and HIV.¹

The most common skin manifestation in patients with infectious mononucleosis is the generalized rash associated with treatment with β -lactam antibiotics⁶; in addition, 5% of patients present urticaria during the course of the disease.⁷ However, Doeglas et al,⁸ in a series of 39 patients with cold urticaria, found no significant differences with the control group with respect to EBV infection. In contrast, they found that other infections, such as those due to *Mycoplasma*, CMV, or herpes simplex virus, were more common in patients with cold urticaria.

In our patient, we observed a clear relationship between EBV infection and the cold urticaria: the clinical signs of urticaria and the positive IgM serology of the infectious episode coincided in time, and the cold urticaria resolved as seroconversion developed. In addition, attention is drawn to the short duration of the condition—8 to 9

weeks—compared to the mean duration of 6 to 9 years for the disease.⁴ It has been shown that the course of cold urticaria is considerably shorter when associated with a viral infection,⁴ as was the case in our patient.

The mechanism underlying the lesions of urticaria in patients with infectious mononucleosis is unknown. A cross-reaction of IgM or IgG with the IgE on the surface of mast cells, favoring degranulation, has been suggested.⁹ In other cases, it has been related to the presence of cryoproteins in the blood.⁶ In our patient, the urticaria coincided with high levels of IgM to EBV, and cryoglobulins and cryoagglutinins were not detected.

The diagnosis is confirmed by a provocation test: a wheal forms after applying an ice cube to normal skin. Some authors suggest that an early response to this test (less than 3 minutes) could be related to a possibly severe systemic reaction (type III).⁵

Treatment is based mainly on H1 antihistamines; cyproheptadine has traditionally been prescribed, but it is now more common to use cetirizine, which is more effective and has fewer adverse effects. There have been reports of cases treated with doxepin, terbutaline, H2 antihistamines, and leukotriene antagonists (montelukast).¹⁰ In matters of prevention, patients should wear warm clothes during the winter months, should not eat very cold foods, and should bathe in warm water.

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Conflicts of interest

The authors declare no conflicts of interest

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