Cholinergic Urticaria With Anaphylaxis: Hazardous Duty of a Deployed US Marine

Kent S. Handfield, MD, MPH; Christopher K. Dolan, MD; Michael Kaplan, DO

Practice Points

- Cholinergic urticaria can be a life-threatening condition and should be diagnosed in a controlled clinical setting where airway can be maintained.
- Cholinergic urticaria can be a profession-limiting condition, affecting people whose work involves exposure to heat or physical activity such as members of the military.

Cholinergic urticaria (CU) is triggered by a rise in body temperature and can be complicated by bronchial hyperresponsiveness and anaphylaxis. It primarily affects young adults who actively engage in strenuous exercise, such as servicemen and servicewomen. If the patient reports a history of wheezing or difficulty breathing with urticaria, a water challenge test in a warm bath can be performed to confirm the presence of anaphylaxis. The test should be conducted in an environment in which the patient's airway can be secured and epinephrine can be administered if necessary. Nonsedating antihistamines commonly are used to treat CU, but few other treatments have been thoroughly evaluated for cases that are refractory to antihistamines. We present the case of a 27-year-old US Marine with CU and anaphylaxis confirmed by a water challenge test in a warm bath.

Cutis. 2015;95:241-243.

Cholinergic urticaria (CU) is a condition that primarily affects young adults. It can severely limit their activity levels and therefore job performance. Rarely, this condition can be associated with anaphylaxis, requiring a high index of suspicion by the clinician to ensure proper evaluation and treatment to prevent future respiratory compromise. We present the case of a 27-year-old US Marine with CU and anaphylaxis confirmed by a water challenge test in a warm bath.

Case Report

An otherwise healthy 27-year-old white man who was a US Marine presented with a concern of hives that appeared during strenuous exercise when he was deployed in Afghanistan approximately 1 year earlier. He initially began to experience urticarial lesions when taking warm showers with concomitant shortness of breath and wheezing. He reported no history of hives or asthma. Despite using diphenhydramine as needed to control symptoms for several months, he noted that the episodes of urticaria occurred with light-headedness, dizziness, or vomiting even with

Drs. Handfield and Dolan are from the Division of Dermatology and Dr. Kaplan is from the Allergy, Immunology, and Immunizations Clinic, all at Walter Reed National Military Medical Center, Bethesda, Maryland.
The authors report no conflict of interest.
The views in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.
Correspondence: Kent S. Handfield, MD, MPH, Division of Dermatology, Walter Reed National Military Medical Center, 8901 Wisconsin Ave, Bethesda, MD 20889 (Kent.handfield@med.navy.mil).

Copyright Cutis 2015. No part of this publication may be reproduced, stored, or transmitted without the prior written permission of the Publisher.

mild physical activity or common daily activities. Symptoms typically would resolve 30 to 90 minutes after he stopped exercising or cooled off. Over the course of approximately 1 year, the patient was prescribed a variety of sedating and nonsedating antihistamines (eg, diphenhydramine, hydroxyzine, doxepin, cetirizine, loratadine, fexofenadine, montelukast) by primary care while deployed, some of which mitigated his symptoms during warm showers and outdoor activities but not during exercise.

After returning from his deployment, the patient was initially referred to the dermatology department. No lesions were noted on physical examination. Based on his history, he was advised to avoid strenuous exercise and activity. During subsequent visits to dermatology an exercise challenge test was considered but not initiated due to lack of facilities to provide appropriate airway monitoring. The allergy department was consulted and the patient also was prescribed leukotriene receptor antagonists in addition to the antihistamines he was already taking. It was decided that a water challenge test in a warm bath would be performed in lieu of an exercise challenge to confirm a diagnosis of CU versus CU with anaphylaxis. If the patient did not have a reaction to the water challenge test, an exercise challenge would be offered.

After stopping treatment with antihistamines and leukotriene receptor antagonists for 1 week, a water challenge test was performed. A heparin lock was placed in the untested left arm for intravenous access. The right arm was immersed in a warm bath for 5 minutes without incident. After confirming no reaction, the arm was immersed for another 5 minutes, after which the patient reported flushing, warmth, and itching with visible 2- to 3-mm urticarial lesions on the back (Figure, A) and chest (Figure, B). The arm was subsequently removed from the water. No lesions were noted on either of the arms. The patient developed a cough after removing the arm from the water and his peak expiratory flow rate dropped from 520 to 440 L/min. After 5 minutes his peak expiratory flow rate recovered to 500 L/min and the coughing subsided. He also reported mild nausea and a headache. He was rapidly cooled with ice to abort any further reaction. An epinephrine autoinjector was on hand but was not used due to rapidly resolving symptoms. The diagnosis of CU with anaphylaxis was confirmed.

Comment

Urticaria is a heterogeneous group of disorders that includes both cholinergic and exercise-induced variants. Cholinergic urticaria affects as many as 11.2% of young adults aged 15 to 35 years, with a peak incidence of 20% between 26 and 28 years of age.[1] Clinical presentation consists of wheals (central swelling with peripheral erythema) that are 1 to 5 mm in diameter[2] with associated itching/burning that typically resolves within 1 to 24 hours. Cholinergic urticaria is the result of a rise in core body temperature independent of exercise status; it is distinguished from exercise-induced urticaria, which occurs in response to vigorous exercise and is not related to a rise in body temperature.[3] In particular, these forms of urticaria can severely impact the lives and careers of young servicemen and servicewomen who are routinely deployed to warm environments.

A provocation test is recommended by Magerl et al[4] in patients with a suspected diagnosis of CU. First, an exercise challenge test using a bicycle, treadmill, or similar equipment is recommended, with the patient exercising for 15 minutes beyond the start of sweating. Readings for urticaria are made immediately following the

Erythematous eruption with 2- to 3-mm urticarial lesions on the back (A) and chest (B).

Copyright Cutis 2015. No part of this publication may be reproduced, stored, or transmitted without the prior written permission of the Publisher.

test and 10 minutes later. If the test is positive, a water challenge test in a hot bath (42°C) is then recommended for 15 minutes beyond an increase of 1°C in baseline core body temperature.[4] One study demonstrated that 43% (13/30) of patients with CU experienced bronchial hyperresponsiveness on methacholine challenge testing.[5] These findings suggest a possible utility in testing CU patients for potential disease-related respiratory compromise. A practical limitation of this study was that it did not examine a link between bronchial hyperresponsiveness and anaphylaxis during cholinergic urticarial flares. An exercise challenge test was not performed in our patient due to a history of wheezing and shortness of breath with exercise; instead we went directly to the water challenge test. We felt that limited immersion in the water (ie, only 1 arm) further minimized the risk for anaphylaxis compared with full-body immersion.

Any activity that raises core body temperature in a patient with CU can induce onset of lesions. One case report described a patient who experienced symptoms while undergoing hemodialysis, which resolved when the dialysate temperature was decreased from the normal 36.5°C to 35°C.[6] However, most cases are triggered by daily activities or work. The mainstay of treatment of CU is nonsedating antihistamines. Cetirizine has demonstrated particular efficacy.[7] For unresponsive cases, treatments include scopolamine butylbromide[8,9]; ketotifen[10]; combinations of cetirizine, montelukast, and propanolol[11]; and danazol.[12]

Conclusion

Cholinergic urticaria is mostly prevalent among young adults, with highest incidence in the late 20s. Active duty servicemen and servicewomen are among those who are at the greatest risk for developing CU, especially those deployed to tropical environments. Frequently, CU is associated with bronchial hyperresponsiveness and also can be associated with anaphylaxis, as was seen in our patient. Care must be taken before provocative tests are conducted in these patients and should be done in a controlled environment in which airway compromise can be properly assessed and treated if anaphylaxis were to occur.

REFERENCES

1. Zuberbier T, Althaus C, Chantraine-Hess S, et al. Prevalence of cholinergic urticaria in young adults. *J Am Acad Dermatol*. 1994;31:978-981.
2. Kontou-Fili K, Borici-Mazi R, Kapp A, et al. Physical urticaria: classification and diagnostic guidelines. an EAACI position paper. *Allergy*. 1997;52:504-513.
3. Zuberbier T, Asero R, Bindslev-Jensen C, et al; Dermatology Section of the European Academy of Allergology and Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy*. 2009;64:1417-1426.
4. Magerl M, Borzova E, Giménez-Arnau A, et al; EAACI/GA2LEN/EDF/UNEV. The definition and diagnostic testing of physical and cholinergic urticarias—EAACI/GA2LEN/EDF/UNEV consensus panel recommendations [published online ahead of print September 30, 2009]. *Allergy*. 2009;64:1715-1721.
5. Petalas K, Kontou-Fili K, Gratziou C. Bronchial hyperresponsiveness in patients with cholinergic urticaria. *Ann Allergy Asthma Immunol*. 2009;102:416-421.
6. Morel V, Hauser C. Generalized cholinergic heat urticaria induced by hemodialysis. *Kidney Int*. 2006;70:230.
7. Zuberbier T, Aberer W, Burtin B, et al. Efficacy of cetirizine in cholinergic urticaria. *Acta Derm Venereol*. 1995;75:147-149.
8. Tsunemi Y, Ihn H, Saeki H, et al. Cholinergic urticaria successfully treated with scopolamine butylbromide. *Int J Dermatol*. 2003;42:850.
9. Ujiie H, Shimizu T, Natsuga K, et al. Severe cholinergic urticaria successfully treated with scopolamine butylbromide in addition to antihistamines. *Clin Exp Dermatol*. 2006;31:588-589.
10. McClean SP, Arreaza EE, Lett-Brown MA, et al. Refractory cholinergic urticaria successfully treated with ketotifen. *J Allergy Clin Immunol*. 1989;83:738-741.
11. Feinberg JH, Toner CB. Successful treatment of disabling cholinergic urticaria. *Mil Med*. 2008;173:217-220.
12. La Shell MS, England RW. Severe refractory cholinergic urticaria treated with danazol. *J Drugs Dermatol*. 2006;5:664-667.

Copyright Cutis 2015. No part of this publication may be reproduced, stored, or transmitted without the prior written permission of the Publisher.