

Coincident Cold Urticaria in a Married Couple: Case Report and a Literature Review

K P Leong,**MBBS, MRCP (UK)*, H H Chng,***FAMS, MBBS, M Med (Int Med)*

Abstract

We describe an interesting coincidence in which a woman developed acquired idiopathic cold urticaria and her husband systemic cold urticaria eight months later. The occurrence of cold urticaria in a tropical country like Singapore is rare. Each case illustrates the typical features of that particular type of cold urticaria, including the appropriate response to the challenge test and its self-limited nature.

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Introduction

Cold urticaria is an uncommon disorder in which pruritus, wheals and erythema form in response to contact with cold surfaces, air or water. We present a report of a couple who coincidentally manifested two types of cold urticaria eight months apart, followed by a literature review of this condition.

Case Reports

Case 1 (wife)

Mdm R T is a 40-year-old housewife who presented in December 1992 with a one-month history of painful and swollen fingertips on exposure to cold. Occasionally, urticaria developed on exposed regions of her legs when she woke up in the early hours of the morning for prayers. She also had urticaria when taking cold baths and reported discomfort in the throat and dyspepsia when drinking cold water or eating ice-cream. The patient had no previous medical history. She was not on any medication. She had delivered three healthy children. Clinical examination was unremarkable.

Her haemoglobin was 13.1 g/dl, total white blood cell count 8500/mm³, platelets 300 000/mm³, erythrocyte sedimentation rate 35 mm per hour, antinuclear antibody titre negative, cryoglobulin negative, C3 complement was 1.17 g/l (normal range 0.47 to 1.23), C4 complement 0.28 g/l (range 0.15 to 0.55), immunoglobulin G (IgG) 17.2 g/l (range 7.6 to 16.0), IgA 2.01 g/l (range 0.7 to 3.8) and IgM 1.59 g/l (range 0.3 to 1.6). Stools were negative for ova and cysts. Ice cube test was positive (Fig. 1). This test was carried out by placing an

ice cube on the patient's forearm for 4 minutes and the area observed for 10 minutes afterwards.' In a positive test, the area becomes pruritic about 2 minutes after removing the ice cube, and by 10 minutes, a large hive forms as shown (Fig. 1).

A diagnosis of idiopathic cold urticaria was made. She was prescribed terfenadine when cyproheptadine produced drowsiness in her. Over the next few months, her symptoms improved and by October 1993, she did not need any medication. When last reviewed in January 1994, she was asymptomatic and could tolerate cold baths and ice-cream.

Case 2 (Husband)

Mr I Z, the husband of Mdm R T, is a 45-year-old taxi-driver who presented in August 1993 with a two-month history of generalised urticaria on exposure to cold,

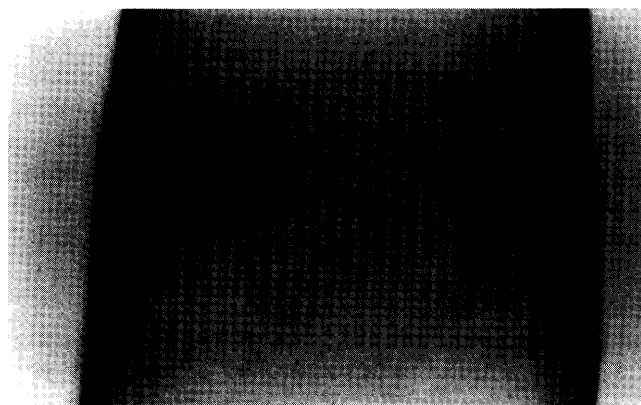


Fig. 1. Positive ice cube test.

* Registrar

** Consultant

Department of Rheumatology and Immunology
Tan Tock Seng Hospital

Address for Reprints: Dr Chng Hiok Hee, Department of Rheumatology and Immunology, Tan Tock Seng Hospital, Moulmein Road, Singapore 308433.

which was aggravated by sweating.

He noticed this while he was driving at night with the air-conditioner turned on. Within 20 minutes, he would develop pruritus and swelling starting with his fingers, and soon the urticaria would become generalised. It resolved when he warmed himself by switching off the air-conditioner. He did not have any associated giddiness, dyspnoea or abdominal colic. He soon learnt that he would not develop the lesions as long as he kept his environment above 18°C. He had no problems with cold food or drinks. Significant past history includes childhood asthma and hypertension, currently treated with methyl dopa. Clinical examination was unremarkable.

His haemoglobin was 15.3 g/dl, total white blood cell count 7500/mm³, with a differential count of neutrophils 57%, lymphocytes 31%, monocytes 9%, eosinophils 3%, platelets 275 000/mm³, erythrocyte sedimentation rate 31 mm per hour, VDRL negative, antinuclear antibody titre >1/640 (homogeneous pattern), cryoglobulin negative, C3 complement 1.3 g/l, C4 complement 0.25 g/l. Ice tube test was negative but systemic cold challenge (consisting of sitting in front of a fan in an air-conditioned room at 18°C for 20 minutes in light clothing) was positive.

He was diagnosed as having systemic cold urticaria. He was prescribed cyproheptadine but he preferred to practice avoidance measures. His symptoms resolved spontaneously in January 1994.

Discussion and Literature Review

It is interesting that both partners in a non-consanguineous marriage could manifest two types of cold urticaria consecutively. Firstly, we shall present the current views of cold urticaria in the medical literature and then we shall discuss our cases in the light of this knowledge.

Urticaria was first described by the School of Hippocrates in the fourth century B.C. Since then it has been known under various names such as nettles, knidosis and morbus porcellaneus until it acquired its current name in the 18th century.² Cold urticaria was first described in the 18th century. Systemic cold urticaria was only reported as recently as in 1984.

It is estimated that urticaria and angio-oedema affect 20% of the population at some point in their lifetime.³ There were 14 cases (2.5%) of cold urticaria in the classic review of 554 patients with urticaria and angio-oedema by Champion et al.⁴ The largest series of patients with cold urticaria, numbering 220, was reported by Neittaanmäki.⁵ Idiopathic acquired cold urticaria was found in 96% of the patients, secondary cold urticaria in 1%, cold-induced cholinergic urticaria in 0.9% and delayed cold urticaria in 1.8%.

Familial forms of cold urticaria usually present in the young. Acquired cold urticaria may start abruptly at any age, although the mean age of onset in Neittaanmäki's series was 25.1 years. Some authors note a slight female preponderance,⁵ while others feel that there is no sex predisposition.⁶ It is considered a self-limiting disorder because in the majority of cases it resolved spontaneously in 1½ to 2 years.⁶

Cold urticaria itself may be sub-classified and one scheme is presented in Table I (modified from reference 6). We are aware that alternative classification methods have also been published.^{2,3} Firstly, cold urticaria may be acquired or familial. As mentioned, the majority of cases are acquired. A certain familial cold-induced syndrome, called familial cold urticaria is not regarded by most authors as a true urticaria because patients with this condition have fever, maculopapular rash, burning pain (instead of itch), myalgia, arthralgia and leukocytosis on exposure to cold, but they never urticate.^{3,6} Similarly, cold-induced urticarial leukocytoclastic vasculitis has also been reported and this should not be regarded as a true urticaria. A form of true urticaria transmitted in an autosomal dominant manner has been described in one family.⁷

TABLE I: CLASSIFICATION OF COLD URTICARIA

Acquired
Cold urticaria with typical positive ice cube test
Idiopathic cold urticaria
Secondary cold urticaria
Cryoglobulin
Infections
Drugs
Other factors
Cold urticaria with atypical ice cube test
Systemic cold urticaria
Cold-dependent dermatographism
Cold-induced cholinergic urticaria
Delayed cold urticaria
Localised cold-reflex urticaria
Familial
Delayed cold urticaria

Secondly, acquired cold urticaria may be primary (idiopathic) or secondary. The majority are idiopathic.^{5,6} Patients with acquired idiopathic cold urticaria classically produce a positive result with the ice cube test. Those rare cases that give negative or atypical results are called the atypical cold urticarias. These atypical syndromes consist of systemic cold urticaria, cold-dependent dermatographism (in which wheals are produced by stroking the skin during or just before cooling,⁸ cold-induced cholinergic urticaria (in which urticaria is produced by exercising in a cold room), delayed cold urticaria (where urticaria develops only 12 to 48 hours after an ice

cube test) and localised cold-reflex urticaria (in which wheals form not directly at the cold-challenged site but 5 to 8 cm away).⁶

Some cases of cold urticaria are related to an underlying condition. Cold urticaria can be associated with the presence of cryoglobulin, cryofibrinogen, cold agglutinin and cold haemolysins,⁹ malignancies,^{10,11} infections,^{9,12} and drugs.^{13,14} The association between human immunodeficiency virus (HIV) infection and cold urticaria was first reported in 1993.¹⁵

Interest has concentrated mainly on the pathogenesis of acquired idiopathic cold urticaria. Early work established that cold urticaria could be induced by intradermal injection of a patient's serum into a normal person. In about 10% of cases, this transferred component was found to be IgE⁹ or, less commonly, IgM.¹⁶ In 1988, Gruber et al¹⁷ found antibodies directed against myeloma IgE in seven out of nine patients with cold urticaria. They hypothesised that these antibodies bind to mast cells and basophils at 4°C, and on re-warming, other cellular events take place which lead to degranulation. Hitherto, as observed by Wanderer,⁶ no IgE anti-IgE antibody has been reported in cold urticaria. IgG anti-IgE receptor antibodies were found to cause basophil degranulation and histamine release in 17 out of 26 patients with chronic urticaria.¹⁸ This interesting finding has yet to be reported in cold urticaria. In an interesting study of 11 patients with idiopathic cold urticaria, Kaplan et al¹⁹ showed that biopsied skin release histamine when it is cooled to 4°C and then re-warmed. Basophils from patients did not show this behaviour.

The diagnosis of cold urticaria requires three steps:⁶

- a) Ascertaining that urticaria occurs in response to cold to exclude other forms of chronic urticaria;
- b) Exclusion of possible underlying diseases, especially cryoglobulinaemias and malignancies; and
- c) Reproduction of the urticaria or angio-oedema with the appropriate challenge tests: ice cube test for localised urticaria and exposure to cold for systemic cold urticaria. One useful set of diagnostic standards is found in reference 2.

Advice to avoid exposure to cold is a very important part of the management. In particular, patients must not swim in cold water because hypotension, syncope and death have been reported. In a paper by Wanderer et al,²⁰ 70% of 50 patients experienced systemic reactions often during aquatic activities. The authors suggested that, in addition to education, those in the high-risk group (identified by a rapid positive result in the cold challenge test) should be given prophylactic antihistamine.

Cyprohetadine hydrochloride, a potent antagonist of the type I histamine receptor (H1) and the serotonin receptor, was first used in therapeutic trials of cold

urticaria in 1971.²¹ Recently, the second-generation non-sedating antihistamines cetirizine and loratadine have been reported to be effective and safe in cold urticaria. Ketotifen may be used in patients who do not respond satisfactorily to antihistamines as it may also reduce mast cell degranulation.

Cold de-sensitisation may be achieved by repeated exposures, which may have to be as frequent as once in four hours to once daily or else tolerance is breached.²² Diminished serum histamine release was documented in patients who became cold-tolerant. In view of this, de-sensitisation was thought to be due to histamine depletion in the mast cells, but more recent work using electron microscopy has shown that the granules are intact and instead the mast cells are thought to have somehow acquired a higher threshold for degranulation.²³

In our case report, Mdm R T illustrated all the typical features of acquired idiopathic cold urticaria. The urticaria started in adult life without an obvious precipitant, it developed on exposure to cold water, air and possibly even food, responded well to antihistamines and ran a self-limited course and resolved spontaneously. This patient illustrates that a second-generation anti-histamine like terfenadine could also be used to treat idiopathic cold urticaria.

On the other hand, her husband's condition was not typical of the usual cold urticaria in that the ice cube test was negative and the entire body had to be exposed to cold before urticaria developed. The diagnosis of systemic cold urticaria was clinched when the systemic cold challenge gave a positive result. He had a positive ANA test which was of no clinical significance.

We are not aware of any report in the literature of a married couple who has cold urticaria. Rare instances of cold urticaria occurring in mother-son and mother-daughter pairs have been reported.² Because of the different manifestations of cold-induced disease and the widely-separated dates of onset of a duration of eight months, we do not think a common aetiology, like a viral infection, is likely and we can only attribute this to a chance occurrence. When cold urticaria is related to a viral infection, the urticaria and symptoms of the infection occur at the same time.¹²

Since the decisive factor for the development of cold urticaria is a drop in temperature rather than the absolute temperature, it may occur in the tropics, though uncommonly. In addition to our two patients, two from Panama,²⁴ two from Pondicherry in India,²⁵ and a handful of paediatric cases from Thailand^{26,27} are the only reported tropical cases of cold urticaria.

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