

## Cold-induced Systemic Reactions Caused by Infusion of Intravenous Fluid

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Cold urticaria develops in response to exposure to cold stimuli, such as cold air, water or objects. Symptoms may vary from localized wheals to systemic reactions, sometimes leading to life-threatening conditions. Physicians need to be cautious when they administer cold fluid intravenously to patients who develop urticaria as a result of exposure to cold.

We report here a patient in whom cold urticaria and systemic symptoms occurred repeatedly after infusion of cold intravenous fluid. She developed both immediate and delayed reactions.

### CASE REPORT

A 23-year-old woman presented for evaluation of skin rash, nausea and vomiting that occurred reproducibly after infusion of intravenous fluid. The first event had occurred when she had visited hospital for fever and cough approximately one year previously. Thirty minutes after being intravenously dripped with normal saline, vomiting and generalized urticaria had developed. Fluid infusion was immediately stopped and these symptoms disappeared gradually.

The second event had occurred when she had visited hospital for abdominal pain 8 months previously. She was intravenously dripped with normal saline for a few hours during evaluation of the abdominal pain. No abnormalities were found and the abdominal pain disappeared, so she was discharged. Several hours later she developed generalized urticaria that persisted for several days and gradually disappeared.

The third event occurred when she went skiing for a month. Dyspnoea and wheezing developed suddenly, and she visited hospital again. After inhaling a fast-acting beta-2 agonist nebulizer in the emergency room the dyspnoea and wheezing disappeared. However, when she was intravenously dripped with dextrose and Hartmann solution (131 mmol/l sodium, 111 mmol/l chloride, 29 mmol/l lactate, 5 mmol/l potassium, 2 mmol/l calcium) generalized urticaria developed around the neck, trunk and both arms. Fluid infusion was not stopped but antihistamine was administered for symptom improvement. Nevertheless, the skin rashes persisted for a few days and then gradually subsided. She subsequently visited our outpatient clinic for evaluation of the recurrent skin rashes.

Physical examination yielded no remarkable findings and vital signs were stable. There were no urticarial skin lesions or associated clinical symptoms suggestive of an allergic reaction. Blood chemistry and serological tests revealed no evidence of infection or inflammatory disease. After confirming that there were no clinical abnormalities, we conducted a provocation test by intravenous infusion of normal saline while monitoring vital signs, since her symptoms had developed during the intravenous infusion of fluids. After 15 min of normal saline infusion, the patient complained of dyspnoea, but there was no wheezing, decreased oxygen saturation, or changes in vital signs. However, 6 h after discharge, she revisited the emergency room with perioral angioedema, generalized urticaria and dyspnoea with

wheezing. After administration of intravenous glucocorticoids, the symptoms were relieved.

Since we suspected that this patient's symptoms might be induced by cold exposure, we planned a second provocation test after admission by infusing normal saline and 5% dextrose after heating or cooling. On hospital day 1, a normal saline provocation test was conducted after the saline was cooled to 14°C or heated to 36°C. Heated normal saline was infused first for 1 h, followed by cooled normal saline, also for 1 h. However, no symptoms developed during or after the normal saline infusion.

On hospital day 2, we conducted a provocation test using 5% dextrose in the same manner as the previous day. There were no acute reactions during infusion of either the heated or the cooled 5% dextrose solution, but 4 h later generalized urticaria developed on both shoulders (Fig. 1) accompanied by mild itching. Since the latter was tolerable, rescue medication was not required. Next morning the generalized urticaria had extended to the dorsa of the hands and wrists. To confirm cold urticaria, we conducted an ice cube test. We placed an ice cube on the volar aspect of the patient's forearm for 5 min. On removal of the ice cube, erythema and pruritus was noted and a hive appeared within 10 min (Fig. 2). However, neither the generalized urticaria nor delayed reactions developed after the ice cube test.

The patient was educated to avoid cold exposure, especially infusion of cold intravenous fluid. In addition, she was prescribed antihistamine, glucocorticoids, and self-injectable adrenaline with appropriate education for prevention of further anaphylaxis.

### DISCUSSION

Cold urticaria is an unusual type of urticaria that develops in response to exposure to cold stimuli. It occurs in 1–3% of all patients with urticaria (1). Symptoms may be localized wheals that develop in areas that come into contact with cold stimuli. In systemic manifestations,



Fig. 1. Generalized skin rashes, which developed 4 h after a provocation test.



Fig. 2. A hive, on the forearm developed after 10 min of an ice cube test.

cold stimuli may lead to systemic reactions, such as wheezing, hypotension, laryngeal oedema and life-threatening cardiovascular collapse.

Wanderer et al. (2) classified cold urticaria based on the severity of reactions. Type 1 refers to reactions confined to the area of skin that came into contact with the cold. Type 2 refers to generalized urticaria not associated with cardiovascular or respiratory symptoms. Type 3 refers to patients having one or more episodes associated with symptoms and signs indicative of respiratory or cardiovascular compromise.

In the literature, there is a case report of cold-induced urticaria resulting from fluid infusion in the operating room (3). Another case developed after exposure to cold air in the operating room (4). In addition, there are several reports about delayed symptoms of cold urticaria (5–7).

The pathogenesis of cold urticaria is known to involve mast cell activation followed by degranulation. Mast cell-derived factors, including histamine, leukotrienes, platelet-activating factor, and prostaglandin D<sub>2</sub>, have been detected in the circulation after cold exposures (8, 9). Our case was unusual in that immediate and delayed-type reactions coexisted. Eady et al. (10) examined skin biopsies of 5 patients after cold challenge and demonstrated delayed inflammatory cell involvement in primary cold urticaria. Amplified inflammatory cell involvement due to sustained cold stimulation may contribute to delayed-type reactions (9).

Avoidance of cold stimuli is the most important element of the management of cold urticaria (11). Therefore, in patients who develop cold urticaria from cold intravenous fluids, heating of fluids can be a preventive measure, but it requires attention and alertness on the part of physicians. In recent guidelines, the recommended first-line treatments for urticaria are new-generation, non-sedating H<sub>1</sub>-antihistamines (12). However, the clinical efficacy of H<sub>1</sub>-antihistamines may be unsatisfactory in cold urticaria. Several groups have suggested that leukotriene receptor antagonists could

be used to relieve symptoms in patients with inadequate responses to antihistamines (13–15). In patients refractory to these conventional treatments, an anti-immunoglobulin E monoclonal antibody (omalizumab), etanercept (anti-tumour necrosis factor) and anakinra (anti-interleukin 1) could be considered (16, 17).

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