

CASE REPORT

Localized heat urticaria in a patient is associated with a wealing response to heated autologous serum

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Summary

We report a case of localized heat urticaria in a 71-year-old woman who developed weals and loss of consciousness after taking a bath. Exposing her skin to heat at 40 °C or immersing her hands in water at 40 °C produced urticarial lesions and increased her plasma histamine level. Desensitization with hot water improved her symptoms and normalized her plasma histamine level after heat challenge. An intracutaneous injection of her serum produced no reaction, while an injection of her serum that had been heated at 40 °C for 15 min induced a weal flare response. Further examination revealed that the weal-inducing activity of her heated serum remained for at least for 6 h and that treatment of her serum at 60 °C for 2 h did not abrogate its weal-inducing activity. These findings indicate that certain materials in her serum that are activated by heat are responsible for the development of her anaphylactic and urticarial reactions and that these reactions may be mediated by histamine.

Key words: autologous serum, desensitization, heat urticaria, histamine, intracutaneous test

Localized heat urticaria is a rare skin disorder first described by Duke in 1924.¹ Since then, 48 cases of localized heat urticaria have been reported in the world.² Localized heat urticaria is characterized by flare and weal responses that are limited to skin areas exposed to heated materials.² The pathogenesis of this unique skin condition has not been clarified so far, although a few reports concerning its pathogenesis have been described, some showing increased plasma levels of histamine^{3–5} and prostaglandin D2^{6–9} after heat exposure.

Here we report a case of localized heat urticaria, in which we found that an intracutaneous test with the heated autologous serum induced a weal and flare reaction. We also have further characterized this activity of the serum in heat urticaria.

Case report

A 71-year-old woman presented with a history of having developed pruritic weals and flares over the past

3 months in limited areas of her skin exposed to heat. The urticarial response appeared within 10 min after heat challenge and lasted at least 1 h. She once experienced systemic symptoms such as dizziness and syncope after taking a warm bath. Hot foods and drinks did not induce swelling of her lips or throat, nor did physical exercise or sweating induce any symptoms. Her past medical history indicated an allergy to mackerel and there was no family history of this condition. Neither an ice cube test nor a test for dermographism showed an urticarial response. The following laboratory tests were within normal levels or were negative: blood counts, biochemical profiles, complement levels (C3, C4, CH50), hepatitis B surface antigen, antibodies to hepatitis C, antibodies to human immunodeficiency virus-1 and -2, standard serological tests for syphilis, rheumatoid factor, total IgE, and specific IgE for house dust, *Candida albicans*, mite, aspergillus, *Alternaria*, wheat, rice, soy beans, anisakis, and ascarid.

We first tested whether heat itself could induce the urticaria. Touching her left forearm for 10 min with a beaker filled with water at 40 °C clearly induced

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localized weals (Fig. 1). Immersing her hands in water at 40 °C or at 42 °C for 15 min also provoked weals. Exposure to materials at 39 °C or lower did not induce localized erythema and weals. To study whether the plasma histamine level increased after exposure to heat, her right hand and forearm were immersed in water at 40 °C for 15 min. Blood samples were collected from her left cephalic vein before and 10 min after the heat exposure and plasma histamine levels were measured by radio-immunoassay. The plasma histamine level after heat challenge increased about 10 times compared with the level prior to challenge.

We hypothesized that some serum factor(s) may play an important role in the induction of urticaria by heat. To address this hypothesis, the patient's serum was collected and an intracutaneous test using the autologous

serum was performed with the patient's consent, resulting in a negative response. Next, we heated the autologous serum at 40 °C for 15 min, cooled it down to room temperature for 10 min, and then injected it intracutaneously. Surprisingly, the heated serum provoked a weal-flare response at the injection site, showing an erythematous patch 20 mm in diameter (Fig. 2). We then further characterized the ability of her serum to induce weal and flare after heating. When the serum was heated at 42 °C for 15 min and thereafter left at room temperature for 6 h, it still induced a weak erythematous reaction (10 mm in diameter). When her serum was heated at 60 °C for 2 h or the IgG was removed by Protein A Sepharose



Figure 1. A well-demarcated localized weal was induced by exposure to a beaker filled with water at 40 °C for 10 min.



Figure 2. Intracutaneous injection using heated autologous serum induced a weal-flare response. The patient's serum was heated at 40 °C for 10 min, then cooled down to room temperature, and then 0.1 mL of the serum was injected into the skin. A weal-flare response was observed after 15 min at the site of injection of the heated serum (bottom), but not non-heated serum (top).

beads, it still induced a weal and flare response after intracutaneous challenge. Small molecules under 50 kDa in her serum were collected by filtration through a Microcon® membrane (Millipore, Bedford, MA, U.S.A.), and an intracutaneous test with the eluted fraction after heating was performed as mentioned above. The fraction of her serum under 50 kDa failed to show a positive intracutaneous test. Sera from three normal healthy volunteers were heated and autologously injected into the skin, showing no wealing response. Sera from three of four cold urticaria patients showed a positive skin response with no requirement of heating. Heating of these sera resulted in a slight increase of the wealing response.

Oral azelastine hydrochloride (2 mg/day) reduced her symptoms but did not completely clear them. To improve her quality of life, the patient was admitted to hospital and started on a course of heat desensitization. Both of her feet and the distal third of her lower legs were first exposed to warm water at 40 °C for 30 min. The exposed areas were gradually expanded (10–20 cm upward each time). The heat treatments were done two or three times a day. The weal response at sites heated previously became much weaker upon heat rechallenge (Fig. 3). After heat desensitization at 40 °C for 27 times, her entire body did not show a weal and flare response even when exposed to 40 °C for 30 min. A 9-time series of baths at 42 °C for 30 min (three times a day) were thereafter added to maintain her tolerance. After the desensitization treatment, her plasma histamine levels no longer increased after heat challenge. Her heated autologous serum did not provoke a positive response at the site of the heat-desensitized skin. Now she is able to take baths at 42 °C for 20 min without oral medication.

Discussion

The pathogenesis of localized heat urticaria has not been clarified. In our patient, the plasma level of histamine increased significantly upon heat challenge, and the rise of the plasma histamine level elicited by heat was completely reduced after the heat desensitization treatment. Histamine thus plays a significant role in this condition in our patient. This is in accordance with findings in previously reported cases, which suggested that histamine is a major mediator of localized heat urticaria.^{3–11} Prostaglandin D₂ has also been shown to be another chemical mediator involved in the pathogenesis of heat urticaria.^{5,6} Such evidence is compatible with the idea that mast cell degranulation



Figure 3. A representative picture showing a lack of responsiveness in an area of a previous heat challenge. The second challenge with heat induced a significant weal response on her thighs.

plays a significant role in the pathogenesis of localized heat urticaria.⁷ We demonstrated in this study that autologous serum from a patient with heat urticaria can induce a flare reaction when the heated serum was cooled down and then injected into the patient's skin. This evidence indicates that the serum contains some urticaria inducing factors which can be modified by heat. A similar, but probably not exactly the same, aetiology was proposed in the pathogenesis of cold urticaria. Several reports have demonstrated that cold urticaria can be transferred to normal healthy individuals by injecting the serum from patients with cold urticaria.^{12,13} Anti-IgE autoantibodies which bind to IgE following cold stimulation have been shown to play important roles in the cold-induced degranulation of mast cells.¹³ However, it has been unclear until now whether heat urticaria can also be induced by serum.

Wuthrich tried to show a passive transfer of the serum from a patient with heat urticaria into the skin of a rhesus monkey without any success.¹⁴ Our finding that heated serum can induce a weal response sheds light on the mechanism of heat urticaria.

We found that the activity of heated serum to induce a flare response was not detected in the eluted fraction under 50 kDa following membrane separation. The weal-inducing activity in the heated serum was rather stable and was still active 6 h after heating, although that activity was reduced slightly. Exposure to higher temperatures, such as 60 °C for 2 h, did not abrogate the activity. These findings suggest that a large molecule (over 50 kDa) in the serum is modified by heat into an active form which is relatively stable. IgE is unlikely to be that factor because IgE is usually inactivated by heating at 60 °C for 2 h. Various serum proteins can be unfolded by heat.^{15,16} We speculate that heat induces the unfolding of certain serum proteins, which are able to directly or indirectly activate mast cells, causing the mast cells to release chemical mediators including histamine. It is conceivable that unfolding the structure of serum proteins may allow them to bind to IgE and to stimulate mast cell degranulation.

Desensitization using repeated heat exposure seems to be the most effective in improving the symptoms of heat urticaria as it was for our patient.^{3,4,6,10,17,18} We found that histamine was no longer increased by heat challenge after the heat desensitization therapy. Since the lack of response to heat was localized to the area previously treated with heat, it is conceivable that a local rather than a systemic condition was altered. In the present case, the response to an intracutaneous injection with the heated serum became weaker and no increase of plasma histamine was observed in response to heat exposure after desensitization, suggesting that local responsiveness to the heated substances in the serum was impaired. This might be due to the increased stability of mast cells or to the depletion of chemical mediators.

In conclusion, we present a case with localized heat urticaria, whose serum contains certain histamine releasing substances that induce wealing following heat treatment.

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