A Case of Anaphylactic Reaction Following Matsutake Mushroom Ingestion: Demonstration of Histamine Release Reaction of Basophils

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ABSTRACT
Background: Matsutake mushroom is not recognized as a common food allergen. However, several case reports have suggested that this mushroom can induce anaphylaxis on rare occasions.
Case Summary: We report a woman with bronchial asthma, who experienced two episodes of Matsutake-induced anaphylaxis. Both the prick-to-prick test and basophil histamine release test showed positive reactions to this mushroom in this patient, but not in control subjects.
Discussion: Matsutake mushroom can, on rare occasions, cause anaphylaxis in sensitized people, a reaction so far observed only in Japan. Not only the in vivo prick-to-prick test but also the in vitro basophil activation test utilizing the patient's blood represent useful methods for allergen identification and also for identification of sensitized subjects.

KEY WORDS
anaphylaxis, basophils, food allergy, histamine release, Matsutake mushroom

INTRODUCTION
Food allergy is a common disease, and its prevalence rate is reported to be as high as 2 to 4% in Japan and the United States.1,2 The symptoms related to food allergy often include eczema and digestive disorders; anaphylaxis requires special clinical attention because this reaction usually occurs unexpectedly and worsens very rapidly. Various foods are well known to be potential allergens capable of inducing anaphylaxis, but mushrooms are generally overlooked due to the rarity of allergic patients. Here, we report a patient with past anaphylactic episodes induced by Matsutake mushroom, confirmed by the skin test and basophil activation test.

CLINICAL SUMMARY
A 38-year-old woman with bronchial asthma told us, at a scheduled visit at the outpatient clinic of our hospital, that she had experienced immediate hypersensitivity reactions following Matsutake mushroom ingestion.
She developed atopic asthma at two years of age and has undergone specific immunotherapy with monthly subcutaneous injections of house dust extract since she was 23 years old. During childhood, she had no history of food allergy or eczema. At the age of 27, ingestion of a soup containing several kinds of vegetables and Matsutake mushroom was almost immediately—within ten minutes—followed by an anaphylactic reaction consisting of systemic urticaria, dyspnea and consciousness disturbance. She recov...
Histamine release by the patient’s basophils when exposed to Matsutake mushroom extract. Aqueous mushroom solutions were prepared by vigorous extraction of raw mushrooms in a 5-fold amount (weight/weight) of saline followed by clearing through 0.45-μm pore filters. Basophil preparations were assessed for degranulation immediately (A) or after 3-day culture with IL-3 at 300 pM (B). Cells were incubated with either polyclonal anti-IgE antibody, or Matsutake or Shiitake mushroom extract, and release of histamine was analyzed. Data shown indicate the percentages of induced release over spontaneous release (less than 3% of total histamine). Mean values of duplicate determinations are shown. Fresh basophils showed nearly no release in response to anti-IgE antibody (A), indicating that the patient’s basophils had a non-releasing phenotype.

PATHOLOGICAL FINDINGS

Since a standardized extract solution of Matsutake mushroom for skin tests is not commercially available, we decided to perform a prick-to-prick test, using raw mushrooms according to previous case reports. The patient showed a positive reaction in this test (wheal of 5 × 4 mm and flare of 26 × 15 mm at 15 minutes) for Matsutake mushroom, but was negative for Shiitake mushroom. On the other hand, ten healthy volunteers showed negative results to this test.

Next, a histamine release test was performed using the patient’s basophils, after she granted informed consent. However, we found that her basophils had a non-releasing phenotype, lacking the ability to liberate histamine even when stimulated with optimal doses of IgE-crosslinking anti-IgE antibody (Fig. 1A). In the next experiment, her basophils were cultured with IL-3 at 300 pM for 3 days, as reported previously, and then stimulated with various dilutions of extract solutions or with anti-IgE antibody. IL-3-cultured basophils demonstrated obvious release of histamine in response to anti-IgE antibody (Fig. 1B). In addition, the cultured basophils were sensitive to Matsutake mushroom extract: the cells released 7.2% of total histamine in response to 500-fold dilution of the extract. In parallel experiments, basophils were obtained from healthy volunteers, cultured and stimulated with Matsutake extract, but these cells never showed release of histamine.

Lastly, we assessed whether her serum contained Matsutake-specific IgE antibody capable of sensitizing basophils. Basophils from healthy volunteers were pretreated with IgE-stripping lactate buffer, pH 3.7, sensitized with the patient’s serum for 2 hours at
37°C and then stimulated with mushroom (Matsutake and Shiitake) extracts. However, there was no apparent release of histamine from the sensitized cells (data not shown). We thus can only assume that Matsutake-specific IgE antibody in her serum must be low in either concentration or potency, and therefore incapable of inducing obvious sensitization in vitro.

**DISCUSSION**

Matsutake mushroom belongs to the Kishimeji family, and its scientific name is *Tricholoma matsutake*. This mushroom is available solely in the autumn season in Asian countries, and it is eaten after baking or boiling. Matsutake is quite expensive and thus much less often cooked in homes compared to other common mushrooms such as Shiitake. Anaphylaxis caused by Matsutake mushroom is rare: a total of only 13 cases have been reported to date, all in Japan.

Our present patient told us that her two episodes of anaphylactic reaction might be clinically related to Matsutake mushroom, and that other mushrooms had never led to allergic symptoms. The prick-to-prick test was useful for allergen determination, consistent with other reports. We further assessed the *in vitro* histamine release reaction using the patient’s basophils and found that Matsutake mushroom extract induced degranulation of her basophils, but not of cells from nonallergic donors. These results clearly indicated that Matsutake was the causal food of her anaphylactic events. Thus, we strongly recommended that she should continue strict allergen (Matsutake) avoidance.

In the initial experiments using the patient’s basophils, we found that they possessed a nonreleasing phenotype, i.e., they did not release histamine (<5% of total histamine) in response to optimal doses of anti-IgE antibody. After *in vitro* treatment by 3-day culture with IL-3, however, those nonreleasing basophils successfully converted to releasing cells, as reported in previous studies: the cultured basophils demonstrated a histamine release reaction in response to a Matsutake extract. The precise antigenic molecules or epitopes in Matsutake mushroom extract have not been determined, but our *in vitro* findings and *in vivo* skin tests collectively suggest that her anaphylactic episodes were mediated by specific IgE and water-soluble antigen(s). We failed to induce passive sensitization of normal basophils with her serum, presumably due to low potency of the IgE. Other future cases showing a stronger basophil response would permit re-assessment of IgE involvement, allergen molecule determination and its precise heat-stability. Thus, *in vitro* analyses using basophil preparations are thought to be a safe and useful approach, capable of giving us insight into the pathogenesis of anaphylactic reactions.

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