

# Oral Mite Anaphylaxis Caused by Mite-Contaminated Okonomiyaki/Pancake-Mix in Japan: 8 Case Reports and a Review of 28 Reported Cases

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## ABSTRACT

**Background:** Anaphylaxis after the ingestion of foods contaminated with mites has recently been recognized. Case series and case reports thus far have shown that mite-contaminated wheat flour is the major cause of oral mite anaphylaxis. However, we have found 8 cases of oral mite anaphylaxis which were caused by mite-contaminated okonomiyaki-mix, a savory Japanese style pancake mix, in our hospital.

**Methods:** In addition to our 8 cases, the databases of MEDLINE and ICHUSHI were systematically searched for patients with oral mite anaphylaxis in Japan.

**Results:** Thirty-six patients including our 8 cases with oral mite anaphylaxis were identified. Thirty-four out of 36 cases (94%) ingested okonomiyaki or takoyaki, prepared at home using okonomiyaki-mix or takoyaki-mix which was previously opened and stored for months at ambient temperature. Microscopic examination of culprit mixes of 16 cases including our 1 case revealed contamination of mites such as *Dermatophagoides farina* (*Der f*) (5 cases), *Tyrophagus putrescentiae* (*Tyr p*) (4 cases), and *Dermatophagoides pteronyssinus* (*Der p*) (3 cases). The specific IgE to each mite is generally upregulated in these patients. Especially, the titers of specific IgE to *Der p* and *Der f* were more than class 2 in all cases.

**Conclusions:** Mite-contaminated flavored flour is the major cause of oral mite anaphylaxis in Japan.

## KEY WORDS

anaphylaxis, food allergy, Japan, mite, okonomiyaki

## INTRODUCTION

In 1993, the first case of systemic anaphylaxis by mite-contaminated food, oral mite anaphylaxis, was reported.<sup>1</sup> Oral mite anaphylaxis is an immediate and potentially life-threatening reaction caused by the ingestion of mite-contaminated food in patients with a medical history of allergic rhinitis and/or atopic asthma.<sup>1,2</sup> Thereafter, there have been many reports

of cases of oral mite anaphylaxis from various countries.<sup>3-8</sup> Case series and case reports thus far have shown that mite-contaminated wheat flour is the major cause of oral mite anaphylaxis.<sup>9-11</sup>

In Japan, Matsumoto *et al.* have reported two cases of oral mite anaphylaxis in 1996.<sup>3</sup> Since 2001, several cases of oral mite anaphylaxis with okonomiyaki-mix have been reported.<sup>12-22</sup> Okonomiyaki-mix is a savory Japanese style pancake mix that is composed of flour,

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dried scallop, bonito, mackerel, and so on. Although the association of aspirin intolerance with oral mite anaphylaxis has often been reported, it seems to be less common in Japan.<sup>9-11,16,18,22</sup> Therefore, there may be some differences in clinical manifestations of oral mite anaphylaxis in Japan and other countries.

Here, we summarize the clinical manifestations and laboratory testing of reported cases of oral mite anaphylaxis with our 8 new cases in Japan. We demonstrated that the most Japanese patients of oral mite anaphylaxis were caused by the ingestion of okonomiyaki-mix, and that the frequency of aspirin intolerance was lower in Japan than that in other countries.

## METHODS

Eight new cases of oral mite anaphylaxis were retrospectively identified by reviewing medical records in the Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami-hara National Hospital. Case reports for oral mite anaphylaxis in Japan were systematically searched from MEDLINE or ICHUSHI database until March 2012. Information on patient characteristics, interview contents, implicated foods, results on specific IgEs to various mites, wheat, pollen and other antigens, results of skin prick tests for mite allergen (Torii Pharmaceutical, Tokyo, Japan), culprit powder, and new powder, and microscopic examination on culprit powder was collected as possible.

## RESULTS

### OKONOMIYAKI IS THE MAJOR IMPLICATED FOOD OF ORAL MITE ANAPHYLAXIS IN JAPAN

Patient characteristics of oral mite anaphylaxis in Japan are shown in Table 1. As previously described,<sup>9</sup> the prevalence rate of allergic airway diseases was remarkably high, especially in bronchial asthma (66%). Seventy-eight percent of the patients had allergic rhinitis and/or bronchial asthma. Furthermore, many patients also had family history of bronchial asthma (43%). On the contrary to recent reports,<sup>10,11</sup> only 10% of patients was intolerant to aspirin in Japan.

The most implicated food of oral mite anaphylaxis in Japan is okonomiyaki (82%). Okonomiyaki is a savory Japanese style pancake made from wheat flour, eggs, yams, cabbages, and pork. After mixing together, the paste is roasted on a frying pan. Because of the convenience and time and money savings involved, okonomiyaki-mix which consists of wheat flour, dried scallop, bonito, mackerel, and so on is usually used instead of pure wheat flour. In fact, all cases developed anaphylaxis by eating the okonomiyaki made from a okonomiyaki-mix. Every package of okonomiyaki-mix was preserved at room temperature for at least one month after opening the packages (Fig. 1), in accordance with the previous reports showing the importance of the preservation methods

of opened wheat packages.<sup>9-11</sup> Takoyaki, which is a ball-shaped Japanese snack made from a wheat flour-based paste, is the second implicated food (11%). Okonomiyaki-mix or Takoyaki-mix, a powder like Okonomiyaki-mix, was used in all cases of anaphylaxis caused by eating takoyaki. Oral mite anaphylaxis by pancake is less frequent in Japan (11%), although pancake is the primary cause of oral mite anaphylaxis in European and American countries.<sup>7,10</sup>

### CLINICAL MANIFESTATIONS AND SEVERITY OF ORAL MITE ANAPHYLAXIS IN JAPAN

Clinical manifestations of the patients with oral mite anaphylaxis are shown in Figure 2. While the most frequent symptom was wheal/angioedema (64%), a considerable number of patients developed severe respiratory manifestations such as dyspnea (53%) and wheezing (44%). Remarkably, three fourths of patients with oral mite anaphylaxis exhibited severe anaphylactic symptoms (score of grade 4), according to the grading of food-induced anaphylaxis.<sup>23</sup> The majority of the patients exhibited symptoms within thirty minutes after the ingestion of the implicated foods (Fig. 3), consistent with previous reports.<sup>9-11</sup>

### SPECIFIC IgE ANTIBODIES AND SKIN PRICK TESTS AGAINST VARIOUS ALLERGENS

The available data of specific IgE antibody against mites are summarized in Table 1. The titers of IgE antibody against each mite were widely upregulated in most cases. Especially, the titers of specific IgE to house dust mites of two species, *Dermatophagoides pteronyssinus* (*Der p*) and *Dermatophagoides farina* (*Der f*), which are the major sources of allergens associated with allergic diseases, tended to be higher than those to storage mites, *Acarus siro* (*Aca s*) and *Tyrophagus putrescentiae* (*Tyr p*).

The results of skin prick tests for the culprit powder are shown in Table 1. All oral mite anaphylaxis patients tested for skin prick test for okonomiyaki-mix showed positive results for the culprit okonomiyaki-mix but negative results for new okonomiyaki-mix. One negative case for mite allergen became positive by an aspirin load. The results of skin prick tests for other allergens were rarely mentioned.

It has been reported that both house dust mites and storage mites cause oral mite anaphylaxis.<sup>5,6,8,12,13,16,20,22</sup> The microscopic examination of the culprit okonomiyaki-mix revealed that *Der f*, *Tyr p*, and *Der p* were frequently observed in the culprit powder (Table 1). Mite observed in the okonomiyaki-mix of our case (42 year-old female) is shown in Figure 4.

## DISCUSSION

We have summarized the characteristics of Japanese patients with oral mite anaphylaxis. We found that 34 patients (94%) including our 8 cases ingested ok-

**Table 1** Clinical data of patients with oral mite anaphylaxis

| Author                                                | Sex | Age | PH                        | FH                | AI | Culprit food | An Score | CAP-RAST (class) |       |       |       |    | Total IgE | SPT mite | SPT culprit | ME    |
|-------------------------------------------------------|-----|-----|---------------------------|-------------------|----|--------------|----------|------------------|-------|-------|-------|----|-----------|----------|-------------|-------|
|                                                       |     |     |                           |                   |    |              |          | Der p            | Der f | Tyr p | Aca s | HD |           |          |             |       |
| Shibata (2003)                                        | F   | 15  | BA                        | NM                | -  | O, P         | 4        | 5                | 5     | NM    | NM    | NM | NM        | NM       | NM          | Mite  |
|                                                       | F   | 17  | BA                        | NM                | -  | O, P         | 2        | 4                | 4     | NM    | NM    | NM | NM        | NM       | NM          | Mite  |
| Ikeda (2004) <sup>13</sup>                            | F   | 22  | BA                        | NM                | -  | O            | 4        | 5                | 5     | NM    | NM    | NM | NM        | NM       | NM          | NM    |
| Matsumoto (1996) <sup>3</sup><br>(2001) <sup>12</sup> | M   | 14  | -                         | NM                | -  | O            | 4        | 3                | 3     | 3     | 3     | NM | 160       | +        | +           | Tyr p |
|                                                       | F   | 9   | BA                        | NM                | -  | O            | 4        | NM               | NM    | 2     | NM    | NM | NM        | NM       | NM          | Tyr p |
|                                                       | M   | 16  | BA                        | NM                | -  | O            | 4        | 6                | NM    | NM    | NM    | NM | NM        | NM       | NM          | Der p |
|                                                       | F   | 8   | BA AR                     | NM                | -  | O            | 4        | 6                | NM    | NM    | NM    | NM | NM        | NM       | +           | Der p |
|                                                       | M   | 13  | -                         | NM                | -  | P            | 4        | 6                | NM    | NM    | NM    | NM | NM        | NM       | +           | NM    |
|                                                       | F   | 11  | AR                        | NM                | -  | P            | 4        | 6                | 6     | 2     | 1     | NM | 839       | +        | +           | Tyr p |
| Doi (2005)                                            | F   | 67  | -                         | -                 | -  | O            | 5        | 4                | 4     | NM    | NM    | NM | 535       | +        | +           | NM    |
| Hara (2006) <sup>14</sup>                             | M   | 21  | -                         | NM                | -  | O            | 4        | 4                | 4     | NM    | NM    | NM | NM        | NM       | NM          | NM    |
| Ohshiro (2006)                                        | F   | 44  | BA                        | NM                | -  | O            | 4        | 4                | 4     | NM    | NM    | NM | NM        | NM       | NM          | NM    |
| Ogura (2007) <sup>15</sup>                            | F   | 45  | AR                        | BA AD<br>FA (egg) | -  | O            | 4        | 4                | 4     | 2     | 2     | NM | 268       | +†       | NM          | NM    |
|                                                       | F   | 11  | BA FA (egg)               | AR AD             | -  | O            | 5        | 5                | 5     | 3     | 3     | NM | 716       | +        | NM          | NM    |
| Ueno (2008) <sup>16</sup>                             | F   | 32  | BA AR                     | NM                | -  | O            | 4        | 5                | 4     | 3     | 3     | NM | NM        | +        | +           | NM    |
|                                                       | F   | 37  | AR AD                     | NM                | -  | O            | 4        | 3                | 3     | NM    | 1     | NM | NM        | +        | +           | Der p |
| Kobayashi (2009)                                      | F   | 26  | AR AD                     | NM                | -  | O            | 4        | NM               | NM    | NM    | NM    | NM | NM        | NM       | +           | Der f |
| Sato (2009) <sup>17</sup>                             | F   | 12  | BA                        | -                 | -  | O            | 4        | 5                | 5     | NM    | 2     | 5  | 245       | NM       | NM          | NM    |
|                                                       | M   | 15  | -                         | BA                | -  | O            | 4        | 5                | 4     | NM    | 2     | 4  | 242       | NM       | NM          | NM    |
| Inaba (2010) <sup>18</sup>                            | F   | 50  | AR                        | NM                | -  | O            | 3        | 4                | 4     | NM    | 3     | NM | 190       | +        | NM          | NM    |
|                                                       | F   | 28  | BA AD                     | NM                | +  | O            | 5        | 5                | 5     | NM    | 3     | NM | 637       | +        | +           | Der f |
| Ito (2010) <sup>19</sup>                              | F   | 36  | BA                        | BA                | -  | O            | 3        | 2                | 2     | NM    | NM    | 2  | 168       | NM       | +           | Der f |
| Ogawa (2010)                                          | M   | 36  | -                         | NM                | -  | O            | 4        | NM               | 4     | 2     | 3     | NM | NM        | +        | +           | NM    |
| Nakamura (2011) <sup>20</sup>                         | M   | 13  | BA AD                     | NM                | NM | T            | 4        | 6                | NM    | NM    | NM    | NM | NM        | NM       | NM          | Tyr p |
|                                                       | M   | 10  | BA                        | NM                | NM | T            | 4        | 5                | 5     | 2     | 1     | NM | NM        | NM       | NM          | Mite  |
|                                                       | F   | 15  | BA                        | NM                | NM | O            | 2        | 6                | 6     | 3     | 3     | NM | NM        | NM       | NM          | Der f |
| Noguchi (2011) <sup>21</sup>                          | M   | 61  | Urticaria                 | NM                | NM | O            | 5        | 5                | 5     | 5     | 5     | NM | 4147      | +        | +           | Der f |
| Isozaki (2011) <sup>22</sup>                          | F   | 37  | BA AD                     | AD FA             | NM | O            | 4        | 6                | 6     | NM    | NM    | 6  | 1710      | +        | +           | NM    |
| Takahashi (2013)                                      | F   | 40  | BA AD S FA<br>(buckwheat) | -                 | -  | O            | 4        | NE               | NE    | NE    | NE    | 5  | 323       | NE       | NE          | NE    |
|                                                       | F   | 42  | BA                        | NE                | +  | O            | 4        | 6                | 6     | NE    | NE    | 6  | 923       | +        | +           | Mite  |
|                                                       | F   | 31  | BA AR S                   | BA AD             | -  | T            | 4        | 4                | NE    | NE    | NE    | NE | 186       | +        | +           | NE    |
|                                                       | M   | 24  | BA AR                     | Urticaria         | -  | O            | 4        | 4                | NE    | NE    | NE    | NE | 368       | +        | +           | NE    |
|                                                       | F   | 33  | BA AR                     | BA                | -  | O            | 4        | NE               | 2     | NE    | NE    | 1  | 86        | +        | +           | NE    |
|                                                       | F   | 36  | BA AR AD<br>FA (egg)      | BA AD             | -  | T            | 4        | NE               | NE    | NE    | NE    | NE | 333       | +        | NE          | NE    |
|                                                       | F   | 16  | -                         | -                 | +  | O            | 1        | 5                | 5     | NE    | NE    | 5  | 896       | +        | +           | NE    |
|                                                       | F   | 18  | BA AR                     | AR                | -  | O            | 4        | 6                | NE    | NE    | NE    | NE | 1280      | +        | +           | NE    |

AR, Allergic rhinitis; BA, Bronchial asthma; AD, Atopic dermatitis; FA, Food allergy; S, Sinusitis; PH, Past history; FH, Family history; AI, Aspirin intolerance; O, Okonomiyaki; T, Takoyaki; P, Pancake; An, Anaphylaxis; SPT, Skin prick test; ME, Microscopic examination; NM, Not mentioned; NE, Not examined. † Positive case after an aspirin load.

onomiyaki or takoyaki, which was cooked at home using okonomiyaki-mix or takoyaki-mix that was pre-

viously opened and stored for months at room temperature. Yi *et al.* have reported that mite contamina-

tion depends on the presence of wheat in the sample.<sup>24</sup> However, we cannot find any case of oral mite anaphylaxis caused by plain flour in Japan. In this regard, Inaba *et al.* have shown that house dust mites proliferate preferentially in okonomiyaki-mix rather than in plain flour, because okonomiyaki-mix is rich in amino acids suitable for mite growth.<sup>18</sup>

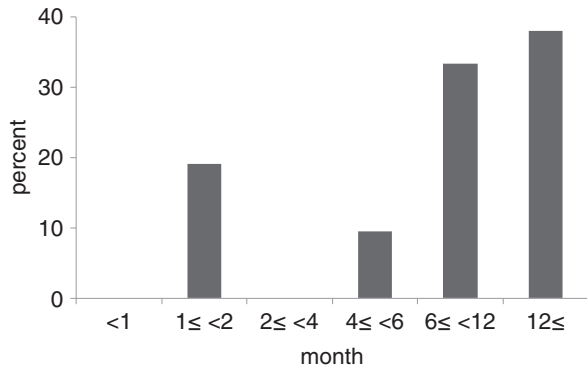


**Fig. 1** Storage time of the culprit okonomiyaki-mix after opening the sack ( $n = 21$ ).

Sánchez-Borges *et al.* have described the thermoresistance of mite allergens. They showed significantly reduced but remaining allergenicity by skin tests after heating mite-contaminated flour at 100°C for 1 hour.<sup>10</sup> Since Der 2 is known as a heat stable component, it is possible that Der 2 is the most important allergen for oral mite anaphylaxis. Alternatively, because the center of pancake/okonomiyaki/takoyaki tends to be insufficiently heated, Der 1, which is the most sensitized but heat unstable component, could be an important allergen for oral mite anaphylaxis. This may be the reason why oral mite anaphylaxis is frequently caused by the ingestion of pancake, okonomiyaki, or takoyaki.

We found that the association of aspirin intolerance was relatively rare in patients with oral mite anaphylaxis in Japan (10%). The previous study has reported that approximately 70% of Venezuelan patients with oral mite anaphylaxis are intolerant to aspirin.<sup>5,6</sup> Sánchez-Machín I *et al.* have also shown that 50% of patients with oral mite anaphylaxis are aspirin intolerant.<sup>11</sup> It is suggested that the secretion of salicylaldehyde analog, 2-formyl-3-hydroxybenzyl formate, from opisthonotal gland of *Der p* might be involved in the

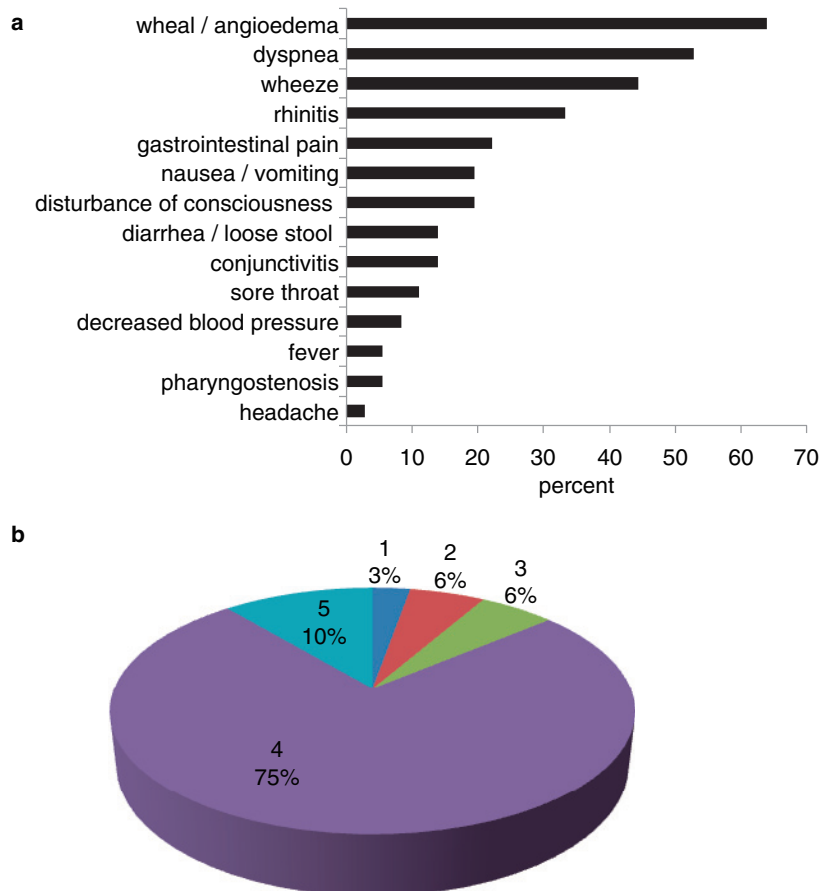


**Fig. 2** Symptoms and severity of oral mite anaphylaxis. **a.** Percentage of symptoms ( $n = 36$ ). **b.** Clinical severity score ( $n = 36$ ).

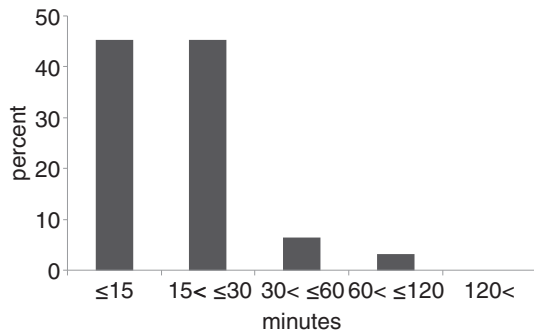


**Fig. 3** The onset of symptoms after the ingestion of implicated foods ( $n = 31$ ).

high prevalence of aspirin intolerance.<sup>25</sup> The reason for the difference in the frequency of aspirin intolerance in patients with oral mite anaphylaxis between Japan and other countries is currently unknown.

Regarding the comorbidity of oral mite anaphylaxis, Sánchez-Machín I *et al.* have shown that 57% of the patients had bronchial asthma.<sup>11</sup> Similarly, our search revealed the high prevalence of bronchial asthma and allergic rhinitis in Japanese patients with oral mite anaphylaxis (Table 1). The sensitization to dust mites such as *Dermatophagoides* spp. generally affects the development of bronchial asthma and allergic rhinitis in Japan and worldwide.<sup>26-28</sup> Our search also revealed that dust mites (*Der p* or *Der f*) were frequently detected in the culprit okonomiyaki-mix in Japan. This seems to be one of the reasons why oral mite anaphylaxis occurs in high frequency in patients with bronchial asthma and/or allergic rhinitis.

We found that the titers of specific IgEs to *Der p* and *Der f* were higher than those to storage mites even in the patients who developed oral mite anaphylaxis by storage mite-contaminated foods. A previous report has shown that increased serum IgE to storage mites including *Tyr p* is found in 46% of patients who are sensitized to *Der p* and that increased prevalence rates of IgE titers to storage mites are associated with higher IgE levels to *Der p*.<sup>29</sup> These findings suggest that the sensitization to *Der p* and/or *Der f* leads to the sensitization to storage mites and the development of oral mite anaphylaxis. It is also possible that specific IgE to *Der p* and/or *Der f* directly causes oral mite anaphylaxis by storage mite-contaminated foods because of the cross-reactivity. Further studies are needed to identify the mechanism underlying oral mite anaphylaxis caused by storage mite-contaminated foods.

Sensitization to mite allergens is suggested to be a prerequisite for the development of oral mite anaphylaxis. However, although a large number of patients with atopic asthma or allergic rhinitis are sensitized to mite allergens, only a small number of the patients suffer from oral mite anaphylaxis. Assuming that the mite contamination in the mixes occasionally hap-



**Fig. 4** Photograph of mite observed in okonomiyaki-mix.

pens, the disruption in the epithelial barrier of the digestive tract to mite allergens and/or the digestion of mite allergens might be involved in the pathogenesis of oral mite anaphylaxis.

In conclusion, oral mite anaphylaxis occurs immediately after the ingestion of mite-contaminated foods in mite-sensitized patients with atopic asthma and/or allergic rhinitis. We need to be aware of oral mite anaphylaxis especially in patients who develop anaphylaxis by the ingestion of okonomiyaki or takoyaki in Japan.

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