
Case report

Clustered sensitivity to fungi: anaphylactic reactions caused by ingestive allergy to yeasts

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Background: Respiratory allergy to environmental molds is relatively common, and fungal allergen-specific reactivity seems to cluster in certain persons. However, generalized reactions caused by ingested fungi have seldom been described.

Objective: To describe a mold-sensitized patient who developed multiple anaphylactic reactions after ingesting a yeast preparation widely used by the food industry as flavoring in, for example, powdered and ready-made sauces.

Methods: Skin prick tests and serum IgE tests were performed with inhalant and food allergens, including molds and yeasts, 2 pasta sauces consumed by the patient, individual sauce ingredients, and a food-quality yeast extract. Radioallergosorbent test inhibition was used for specificity studies.

Results: Skin prick and serum IgE test results were positive to several molds (*Cladosporium herbarum*, *Alternaria alternata*, *Aspergillus fumigatus*, and *Penicillium notatum*), baker's yeast (*Saccharomyces cerevisiae*), *Malassezia furfur*, and champignon and to the 2 pasta sauces, the yeast ingredient, and a food-quality yeast extract. Radioallergosorbent test inhibition studies confirmed that the sauces contain cross-reacting yeast and mold allergens.

Conclusions: This patient has a clustered sensitization to fungi characterized by allergy to environmental fungal allergens and to yeast extracts used in the food industry. Yeasts should be considered as possible ingestive allergens in mold-allergic patients.

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INTRODUCTION

Several fungal species are present in the outdoor and indoor environments and can induce allergic symptoms in the respiratory tract, mucous membranes, and skin.¹ Fungal allergen-specific reactivity seems to cluster in certain persons, and the term *multiple fungi sensitization* has been used to describe patients sensitized to 2 or more fungi species.^{2,3}

Fungal allergen exposure generally leads to respiratory and skin symptoms, whereas generalized reactions are rare. A few cases of anaphylaxis have been described with fermented rice, some molds, and edible mushroom as allergens.^{4–7} We report novel data of IgE-mediated sensitization to environmental fungal allergens associated with allergy to the ingestion of a yeast preparation commonly used by the food industry as a flavoring in, for example, pasta sauces.

CASE REPORT

A 29-year-old American woman was admitted to the Skin and Allergy Hospital, Helsinki University Central Hospital, for multiple severe anaphylactic reactions induced by ingested food. She has had pollen and animal dander allergy and asthma since childhood but was otherwise in good health. She previously experienced an anaphylactic reaction in the United States to contrast media and in 1999 to ingested beer, which

she has avoided ever since. Subsequent anaphylactic reactions occurred in August 2003, September 2003, and September 2004 in Finland.

The patient was initially investigated at the Skin and Allergy Hospital in October 2003. In August 2003, ingested red wine had induced a mild anaphylactic reaction that she treated with an epinephrine autoinjector and antihistamine. In September 2003, just minutes before the allergic reaction she had a meal of industrially made spaghetti Bolognese sauce, pasta, and bread. The reaction was treated in an emergency unit with 3 subsequent doses of epinephrine, intravenous corticosteroid and theophylline, and inhaled salbutamol. Skin prick test (SPT) results were positive for soya, various nuts and seeds, food additive E163 (anthocyanin), and beer malt containing barley, but no conclusive etiologic agent was confirmed.

The next anaphylactic reaction took place in September 2004. The asthma, previously in good balance, had been labile for the past year. A few minutes before the reaction, the patient had had a meal of industrial-made olive sauce, pasta, and feta cheese. Neither physical exercise nor the use of any drug preceded this or any other anaphylactic reaction. The patient could not use her epinephrine autoinjector because of the severe allergic symptoms, including angioedema of the throat, difficulties in breathing, and near loss of consciousness; as the emergency unit reached her she was cyanotic, with a blood oxygen level of 56%, and disoriented. She was treated with 5 doses of epinephrine, intravenous corticosteroid and theophylline, inhaled ipratropium bromide, and ox-

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ygen. Three weeks later, she was reinvestigated at the Skin and Allergy Hospital.

METHODS

Skin Prick Tests

The SPTs were performed using commercial test solutions (ALK-Abello, Horsholm, Denmark) and 7 separate ingredients of the Bolognese sauce, including a yeast preparation provided by the manufacturer. In addition, a commercial food-quality yeast extract preparation (Sensient, Strasbourg, France) and several brands of red and white wine containing wine yeast were tested.

Serum Allergen Specific IgE and Inhibition Tests

Serum mold and yeast specific IgE levels were measured using the commercial CAP-FEIA System (Pharmacia, Uppsala, Sweden). In addition, in-house ImmunoSpot and radioallergen sorbent test (RAST) methods were used to evaluate specific IgE to mold and yeast skin test extracts and to the 2 pasta sauces, individual sauce ingredients, the commercial yeast extract preparation, and the wines.⁸ Native and denatured yeast allergens were evaluated in an IgE immunoblot after sodium dodecyl sulfate–polyacrylamide gel electrophoresis.

The RAST inhibition was used to appraise specific and cross-reacting allergens.⁸ In brief, the patient's serum was first incubated with an extract made from the sauce mix, the 2 yeast extracts, and a yeast and mold skin test extract (*Saccharomyces cerevisiae* and *Cladosporium herbarum*). The remaining IgE-binding capacity to the respective commercial solid-phase mold and yeast antigens was subsequently measured using a specific IgE blood test (ImmunoCAP; Pharmacia).

RESULTS

The patient was atopic, as determined by positive SPT reactions to pollen and animal dander. In the same test series, a strong positive reaction to *C herbarum* was detected (wheal, 10 mm; positive histamine control, 5 mm). The patient also had a positive SPT reaction (>3 mm) to other molds tested (*Alternaria alternata*, *Aspergillus fumigatus*, and *Penicillium notatum*), baker's yeast (*S cerevisiae*), *Malassezia furfur*, and champignon. In addition, both pasta sauces were positive (4 mm). Of the 7 separate ingredients of the Bolognese sauce mix obtained from the manufacturer (bay leaf, garlic, oregano, paprika, pepper, rosemary, and yeast extract), only the yeast extract yielded a positive reaction (5 mm), and its strict composition was not given. Other ingredients of both sauce mixes (black olive, green olive, capers, monosodium glutamate, chili, tarragon, garden sage, basil, onion, potassium nitrate, and sodium nitrate) produced negative results. Results of SPTs with the yeast extract preparation in 20 healthy volunteers were negative.

The allergens of the yeast extract were stable, because baking, frying, microwaving, and freezing of the extract did not alter the SPT reaction (wheal, 5–7 mm). The commercial food-quality yeast extract preparation produced similar SPT

results (5 mm), whereas maltodextrin present in the mix as a carrier tested negative. Red and white wines gave variable SPT reactions (3–5 mm). No controls were tested, and the reactions were interpreted as negative (nonspecific) because no specific IgE for various wine brands could be detected in the immunospot assay (data not shown).

The serum total IgE concentration was slightly elevated (127 kU/L), consistent with the atopic diathesis. The specific IgE level for *C herbarum* was 4.79 kU/L (positive cutoff limit, 0.35 kU/L), for *A alternata* was 3.52 kU/L, for *A fumigatus* was 8.56 kU/L, for *P notatum* was 3.71 kU/L, and for *S cerevisiae* was 2.74 kU/L. Immunospot studies showed specific binding of the patient's serum IgE to fungal allergens, both sauce mixes, and the yeast extract preparations immobilized on a nitrocellulose membrane (Fig 1). Yeast extract showed specific IgE binding even after baking, frying, microwaving, and freezing (data not shown).

In-house RAST with the commercial yeast extract showed high IgE binding of the patient's serum (8% of the total activity) compared with binding of the nonatopic control serum and the atopic control serum of pooled timothy IgE-positive sera (0.3% binding each). In immunoblot, no distinct IgE binding was detected after sodium dodecyl sulfate–polyacrylamide gel electrophoresis with native or denatured yeast

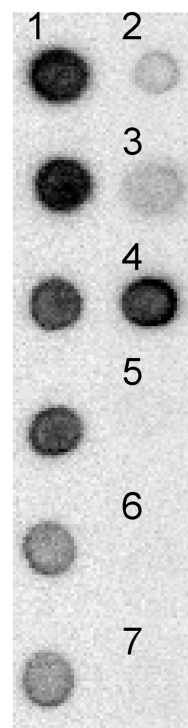


Figure 1. Autoradiogram of IgE binding of the patient's serum to yeasts and molds in immunospot. 1 indicates yeast extract (1:4 wt/vol) and two 2-fold dilutions in duplicate; 2, *Alternaria alternata*; 3, *Aspergillus fumigatus*; 4, *Cladosporium herbarum*; 5, *Penicillium notatum*; 6, *Saccharomyces cerevisiae*; and 7, *Malassezia furfur*. Bound IgE was detected by using iodine 125-labeled anti-human IgE antibody.

allergen extracts. At most, faint staining was seen at the start line and at the lower solvent front. This poor response is probably due to glycoproteins present in yeast extracts.⁹

In RAST inhibition, preincubation of the patient's serum with the Bolognese sauce mix and the 2 yeast extracts significantly reduced IgE binding to yeast (*S cerevisiae*) and mold (*C herbarum*) antigens (45%–49% inhibition with the sauce mix and 70%–84% inhibition with the yeast extracts) (Fig 2). This indicates that the patient has cross-reacting IgE for the fungal antigens present in the food mix and the yeast extracts.

DISCUSSION

The prevalence of allergy to environmental fungi, particularly *C herbarum* and *A alternata*, is estimated to be 3% to 20% in the general population.^{10,11} A recent survey¹² from the United States reported a prevalence of 12.9% for *Alternaria*. Fungal allergen-specific reactivity seems to cluster in certain persons, leading generally to respiratory and skin symptoms and only seldom to food-allergic reactions.^{4–7} Despite the high prevalence and clustering effect of fungal allergy, ingested yeast species have not previously been recognized as potential allergens.

The patient described herein is an American woman with labile asthma. She had experienced multiple severe anaphylactic reactions after ingesting food or drinks. The initial intense SPT reaction to *C herbarum* led us to suspect fungal allergy, and the subsequent investigations with the yeast-

containing pasta sauces and pure yeast samples confirmed this suspicion.

The only ingredient of the pasta sauce to which the patient showed a positive SPT response and specific IgE was the yeast extract. The in vitro IgE response was unambiguous in immunospot and RAST studies, but in immunoblotting, only faint binding at the start and at the lower front could be detected. The reason for this is not clear, but allergen proteins may appear in aggregates and remain on the start line. Alternatively, they may be split into small peptides that go off electrophoresis gel or penetrate the nitrocellulose sheet when transferred from the gel. The detailed content of the yeast preparations was not available, but at least the commercial extract contained maltodextrin, which may hamper electrophoresis.

All the severe reactions took place in autumn, when the concentration of molds in the air is generally high in Finland. The patient had experienced considerable mental stress during the previous year because of a chronic disease of her child, and this may have contributed to the worsening of the previously stable asthma. The inhalative exposure to mold aeroallergens in autumn may have increased the patient's sensitivity to the yeast species ingested. During the investigations, she had had 3 more minor anaphylactic reactions after the ingestion of yeast species (between November 2004 and January 2005) that she successfully treated herself with an epinephrine autoinjector and peroral corticosteroid. Because of the repeated severe anaphylactic reactions, a food

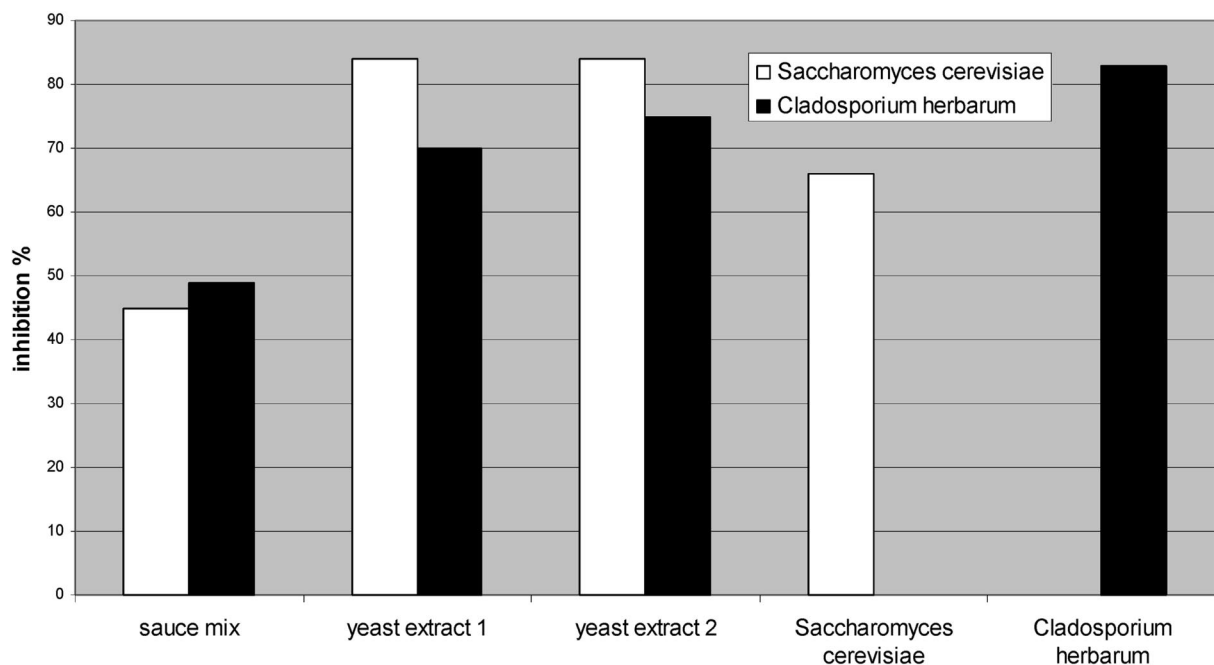


Figure 2. Inhibition of the binding of the patient's serum IgE to mold allergens. In radioallergosorbent test inhibition, the patient's serum was first incubated with the Bolognese sauce mix, the 2 yeast extracts, and control antigens (*Saccharomyces cerevisiae* or *Cladosporium herbarum* skin test extract) before probing with the solid-phase antigens (*Saccharomyces* or *Cladosporium* ImmunoCAP).

challenge test was not justifiable. However, an elimination diet has been effective: the patient is now doing fine (at 1 year) by carefully avoiding all foods containing industrial yeast extracts. In fact, the strict avoidance has resulted in a reduction in her yeast specific IgE binding from 8% to 4% in 10 months.

It is of interest that the patient can freely eat bakery products but experiences severe allergic reactions after eating sauces and other foods containing yeast as a flavoring. This can be explained by differences in yeast species used in the extracts and possibly also by chemical modification required in the extraction of the yeast. The extracts typically contain species such as *S cerevisiae* (baker's yeast or brewer's yeast) or *Saccharomyces pastorianus* (lager yeast). *Saccharomyces* species show high variability at the genotypic and phenotypic levels.¹³ Our patient has been avoiding beer since the first anaphylactic reaction in 1999, and our commercial yeast extract used for IgE assays is derived from *S pastorianus*, suggesting that this species is the main allergen for the patient. Based on the data presented herein, we suggest that yeasts should be considered as possible ingestive allergens in persons sensitized to fungi.

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