

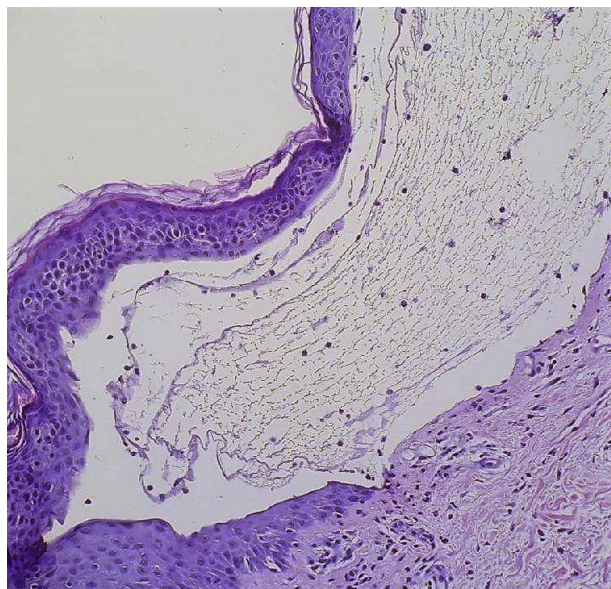


Figure 1. Low-power view of biopsy specimen with hematoxylin and eosin staining showing subepidermal vesicle formation containing neutrophils and abundant eosinophils.

or any anti-inflammatory medications. Examination 10 days after his initial reaction demonstrated resolution of any bullous lesions. Despite this reaction, the patient wished to continue allergen immunotherapy, and SCIT was resumed 4 weeks after his previous injection at a decreased dose of 0.25 mL of a 1:1 v/v concentration. He subsequently built back up to maintenance dosing and remains on immunotherapy with a self-reported 95% improvement of his allergic rhinitis symptoms. He has had no further local or systemic reactions.

Local reactions are typically defined as reactions occurring in the immediate vicinity of the injection site, and they are usually less than or equal to the size of the patient's palm. Most frequently these are associated with erythema, pain, tenderness, and induration. To our knowledge there has only been 1 other case report of a local reaction resulting in bulla formation from SCIT; this also occurred in a delayed fashion 1 hour after the injection.⁴ Regarding that case, the patient was treated with cephalexin and prednisone; however, cultures demonstrated no growth, and no skin biopsy was obtained. Our case suggests that such reactions are self-limited and

may not warrant treatment with antibiotics or steroids, similar to more typical local reactions. We also provide biopsy results to suggest that these rare, local bullous reactions after administration of SCIT are not typical of other better understood antibody-dependent autoimmune bullous processes. However, biopsies of more classic large local cutaneous reactions to venom immunotherapy have demonstrated findings with similar inflammatory infiltrates, which involved many eosinophils.⁵ The perivascular lymphohistiocytic inflammatory infiltration seen in this case, although a nonspecific histologic finding, can also be found in drug reactions.⁶

Consistent with both documented instances of cutaneous bullous reactions to SCIT, consideration can be given to continue immunotherapy in patients in whom such reactions occur, because no evidence has been found of correlation with future adverse reactions. However, more data on these reactions need to be collected when possible to suggest more definitive treatment recommendations when confronted with these rare occurrences.

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Beer allergy

When malt is the culprit

Beer is the most widely consumed alcoholic beverage in the world, and beer allergy is rare.^{1–3} The fundamental ingredients of beer, according to the Bavarian Purity Law, include barley malt, hops, yeast, and water, but each individual beer may differ in malt content and brewing procedures.⁴ Malt is obtained by roasting germinated cereal and is essential to beer flavoring.³ In

beer-allergic subjects, the most frequent allergenic sources involved are cereals, particularly barley malt² and wheat.³ Pan-allergens, namely lipid transfer proteins, also have been involved.⁵

The diagnostic workup for allergen identification in a patient suspected to have recurrent anaphylaxis to beer is presented.

A 71-year-old man was referred to our department after 3 episodes of anaphylaxis. His medical history included chronic obstructive pulmonary disease, hypertension, dyslipidemia, and osteoarticular disease. He was medicated daily with carvedilol,



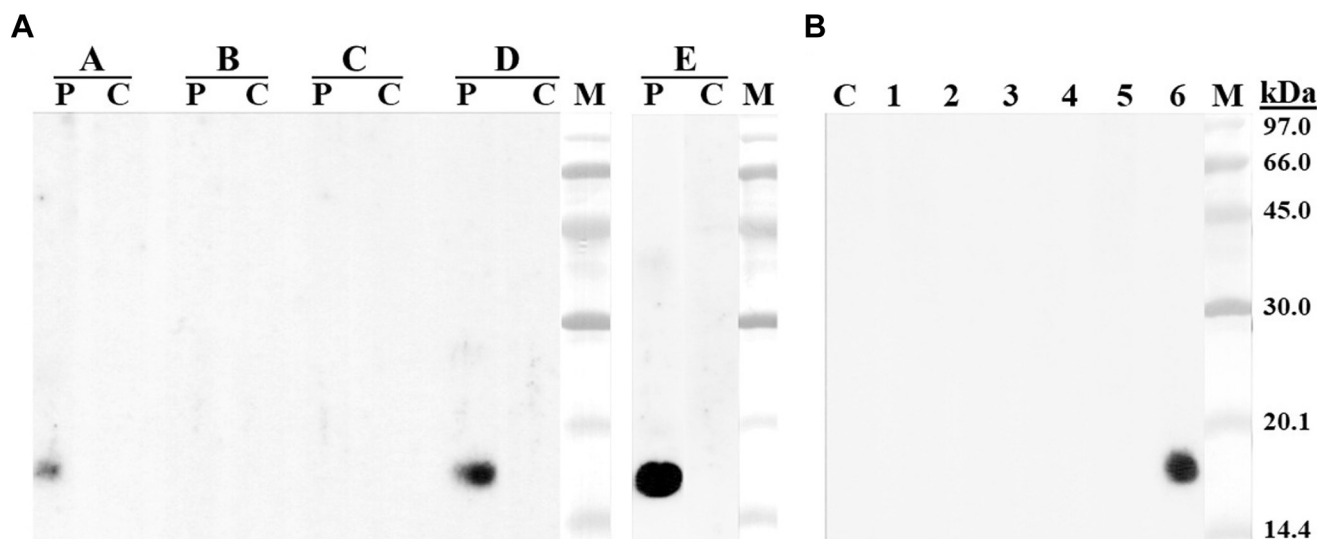


Figure 1. (A) Sodium dodecyl sulfate polyacrylamide gel electrophoresis immunoblotting. A) Barley malt syrup extract; B) Voll Damm double malt beer extract; C) Chimay beer extract (high fermentation beer); D) Carlsberg beer extract; E) Franziskener beer extract. Lane P: patient serum; Lane C: control serum (pool of sera from nonatopic subjects); Lane M: molecular mass standard. A positive control was performed in an adjacent lane to the studied samples: an extract of *Dermatophagoides farinae* was incubated with a pool of patient sera with a high IgE level against *D farinae* extract. (B) Sodium dodecyl sulfate polyacrylamide gel electrophoresis immunoblotting inhibition. Solid phase: Carlsberg beer extract. Lane C: control serum (pool of sera from nonatopic subjects); Lanes 1–6: Patient's serum pre-incubated with Carlsberg beer extract (1), with Franziskener beer extract (2), with Voll Damm beer extract (3), with Chimay beer extract (4), with barley malt extract (5), with lamb extract (6); Lane M: molecular mass standard. IgE, immunoglobulin E.

lisinopril, furosemide, inhaled indacaterol/glycopyrronium, and atorvastatin. He denied previous history of food allergy, anaphylactic reactions, urticaria/angioedema, or other atopic diseases.

Chart review of the emergency department records pertinent to anaphylaxis episodes were performed. In the first episode, immediately after the ingestion of beer and 2 meat patties, the patient experienced onset of abdominal pain, genital pruritus, and urticaria, followed by dyspnea, cough, wheeze, and epigastric pain. At the emergency department, hypotension (blood pressure 99/64 mmHg), bronchospasm, and desaturation (O_2 Sat 91%) were observed. He was treated with systemic steroids, with improvement within hours. Two weeks later, he had a similar reaction that resolved with the same treatment.

The last and most severe episode occurred 5 months later. Fifteen minutes after the ingestion of beer and smoked pork meat, he developed cervical and oral pruritus, tongue angioedema, and dyspnea that progressed to cardiac arrest. Advanced life support with orotracheal intubation was required. He was admitted and treated with epinephrine, steroids, and antihistamines, with complete recovery after 48 hours of surveillance. On comprehensive review, the beer SuperBock had been ingested in the immediate period before each episode. Notably, the patient denied any nonsteroidal anti-inflammatory drug use close to any reaction. Interestingly, SuperBock had been tolerated in the past. Subsequently, the ingestion of pork, beef, egg, spices, cereals (wheat, barley, maize), and wine were tolerated.

No recurrence of symptoms was reported after stopping beer intake for a follow-up period of 24 months.

Complete blood cell count, baseline tryptase levels, and lung function were normal. Skin prick tests with standard aeroallergens and foods, namely cereals, wheat, peach peel (Pru p 3 30 μ g/mL, ALK-Abelló), and profilin (Pho d 2, 75 μ g/mL, Roxall) were negative. Specific immunoglobulin E (sIgE) to yeast

(*Sacharomyces cerevisiae*), hops (*Humulus lupulus*), barley, wheat, rye, almond, peanut, walnut, lupine, paprika, and pork meat and ImmunoCap immuno-solid-phase allergen chip were negative. Skin prick-to-prick tests were negative to rye and barley and were positive for barley malt syrup and 7 brands of beer made with barley malt, including the culprit (SuperBock), which had the largest mean wheal size and higher allergenic potency (eTable 1).

Sodium dodecyl sulfate polyacrylamide gel electrophoresis immunoblotting was performed to assess the presence of sIgE antibodies in the patient's serum that recognized proteins present in different beer extracts and in barley malt syrup extract. Immunoglobulin E-binding bands were detected at 17.5 kDa in the beers made from barley malt, Carlsberg, and Franziskener and in barley malt extract (Fig 1A). Immunoblotting inhibition assay (Fig 1B) showed that the barley malt syrup was able to inhibit all the IgE binding to the Carlsberg beer extract.

Based on these results, we concluded that a barley malt protein was probably the culprit allergen.

We report a case of anaphylaxis to beer presenting later in life that may be explained by sensitization to a 17.5 kDa–IgE-binding protein from beer that is shared with barley malt in a patient that regularly ingests barley cereal. Specific cofactors (angiotensin converting enzyme inhibitor, nonsteroidal anti-inflammatory drugs, and the alcohol itself) may have enhanced the reactions.

One of the first cases of beer allergy was reported by van Ketel⁶ in 1980. Since then, only a few cases have been published, mainly in young adults.³ An 18-kDa IgE-binding protein has been described in beer allergy.⁷ The molecular mass of this protein is similar to our case and coincides with the molecular mass of some barley proteins identified in beer by proteomic technology such as α -amylase trypsin inhibitors, oleosin, and heat shock proteins.⁸

Other specific proteins have been seen in reactions to beer and were considered. The α -amylase trypsin inhibitors have been

recognized in barley and malt, but they may disappear, depending on the brewing process.⁹ Oleosins and heat-shock proteins are present in the developing barley seed,⁸ but they were also identified in wheat beers.⁸ The absence of reactivity in some of the beers may be explained by the mismatch of immunoreactivity between barley malt and barley plus wheat beers, the different production process used in each beer brand,¹⁰ and the potency of the beers. Another factor is the origin of the barleys used in the beer samples, which are frequently unknown because it is a manufacturing secret because of its importance for the beer flavor.

An 18-kDa IgE binding band was previously detected by similar immunoblotting analysis⁷ in beer, thought to be originated from barley. This case differs because our patient lacked sensitization to barley and tolerated daily consumption of barley cereal. The band detected in our study in beer and malt may have originated during the transformation process from barley to malt.

One limitation is the absence of an oral challenge with beer or barley malt, but given the severity of initial reactions and comorbidities, a confirmatory oral food challenge was deferred. Afterward, the patient denied interest in further testing. The absence of duplicate tests to document the skin prick-to-prick tests' precision and the different relative allergenic potency between beers (eTable 1) are a limitation, because this could explain the variability of allergenicity between beer brands. The culprit beer was not tested in the immunoblotting because it was performed in a different country, where SuperBock was not available. Nevertheless, the composition and beer brewing of Carlsberg procedures are similar.

Further studies are needed to identify the protein modification during malting and brewing. Both procedures may change the allergenicity and the availability of the major heat-stable protein from barley to malt and beer. These findings may have an impact on the understanding of future sensitizations and immunoreactivity as well as better anticipatory dietary guidance in beer-allergic patients.

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Supplementary Data

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Standardization of nasal cytologic testing in the workup of allergic rhinitis



Allergic rhinitis (AR) is a common disorder characterized by typical nasal symptoms and IgE-mediated inflammation.¹ Nasal type 2 inflammation is initiated by allergen exposure.² Mediators and cytokines are deeply involved in the cascade of inflammatory phenomena. A typical pattern of inflammatory cells infiltrates the nasal mucosa, including eosinophils, neutrophils, and mast cells. However, the paradigmatic characteristic of allergic inflammation is its reversibility because it depends on the allergen exposure. Actually, the pathophysiology of allergic inflammation may be investigated by 2 main lines of research: the natural allergen exposure (typical model is pollen allergy) and the experimental allergen exposure (typical model is allergen challenge).

Consistently, a clear-cut association between allergen exposure and nasal inflammation has been documented exhaustively using these criteria in the past.^{3–6}

In clinical practice, AR diagnosis is based on the consistency between clinical history and the assessment of allergen specific IgE.⁷ Nasal allergic inflammation may be documented by nasal cytologic testing as previously proposed,⁸ even though the main criticism is the lack of standardized criteria. In this regard, a series of statistical criteria should be required to standardize a test.⁹

On the basis of this background, we aimed to standardize nasal cytologic testing in a group of 52 symptomatic and untreated allergic patients (26 males; mean age, 32 years) evaluated in wall pellitory pollen season and in 52 healthy individuals (23 males; mean age, 27 years).

eTable 1

Meal Wheal Diameter of Skin-Prick-To-Prick Tests with Barley Malt Syrup and with 8 Undiluted Samples of 8 Different Brand Beers and Skin Test with Histamine Di-hydrochloride, 10 mg/mL, and Calculation of Allergen Potency^a

Beer tested	Mean wheal diameter (mm)	Conc = hist 10 mg/mL	BU/mL	HEP
Diluent, chlorine saline				
Histamine (10 mg/mL)	5.5	10	10,000.0	10.0
Barley malt syrup	6	0.65	15,450.5	15.5
Super Bock	11	0.03	320,000.0	320.0
<i>Barley malt</i>				
Super Bock Stout	6.5	0.43	23,054.4	23.1
<i>Barley malt</i>				
Erdinger Dunker	5.5	1.00	10,000.0	10.0
<i>Barley + wheat malt</i>				
Bohemia	5.5	1.00	10,000.0	10.0
<i>Wheat malt</i>				
Cristal	5	1.61	6,209.2	6.2
<i>Barley malt</i>				
Sagres	4.5	2.73	3,666.5	3.7
<i>Barley malt</i>				
Liefmans on the rocks	3	20.71	482.8	0.5
<i>Barley + wheat malt</i>				
Corona Extra	2	157.28	63.6	0.1
<i>Barley + rice malt</i>				

^aThe concentration of allergen causing a wheal of the same size as that of histamine di- hydrochloride and potency of the beers expressed as biological units (BU) and histamine equivalent in prick testing (HEP).