

Anaphylaxis associated with antiphospholipid syndrome

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Background: To our knowledge, no previously published reports have described food-induced anaphylaxis associated with the antiphospholipid syndrome.

Objective: We undertook a study of four patients with thrombosis associated with the antiphospholipid syndrome after each patient experienced anaphylaxis attributable to ingestion of vegetal foods.

Methods: IgE antibody levels to various foods were determined in serum specimens from the study patients, and skin prick tests with the same allergens were conducted to determine their in vivo responses. Hematologic, cardiopulmonary, vascular, and rheumatologic studies were also performed. IgG anticardiolipin antibody levels were determined by ELISA.

Results: All four patients fulfilled the criteria for antiphospholipid syndrome and had high levels of specific IgE antibodies for certain food allergens. By immunoblot analysis, the presence of serum IgE specific for a 45-kD protein band in an almond extract was detected in these four patients who experienced food-related anaphylaxis. No specific IgE was detected in sera from normal subjects. No IgE antibodies specific for the food panallergen lipid transfer proteins were detected.

Conclusions: This is the first report of severe food-precipitated anaphylaxis associated with the antiphospholipid syndrome and the first description of a patient with allergy to blackberry. The possible involvement of food panallergens distinct from lipid transfer proteins is also discussed.

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INTRODUCTION

IgE-mediated reactions after consumption of fruits and vegetables are not uncommon in patients with allergic symptoms caused by pollen.¹ Recently, several different families of plant defense proteins, such as class I chitinases, lipid transfer proteins (LTPs), cereal inhibitors of α -amylases, and thaumatin, have been identified as

major allergens in grains, fruits, vegetables, and pollens.^{2–4}

Severe allergic reactions to food have been reported to involve the gastrointestinal, cutaneous, ocular, respiratory, and cardiovascular systems. Anaphylactic reactions to foods nearly always occur immediately after the implicated food has been eaten. The food responsible for the allergy can be diagnosed by skin tests and food challenges, but the delayed clinical complications of this syndrome have not been completely characterized yet.

We describe four patients who had anaphylactic reactions to food, followed by severe thrombosis. In one of these patients, the anaphylaxis was precipitated by eating blackberries and other fruits that belong to the Rosaceae family. Although blackberries are widely consumed, to our knowledge

this is the first report of allergy to blackberry.

REPORT OF CASES

Case 1

A 45-year-old male wine merchant, who resided in a rural area, had experienced urticaria and throat swelling for 25 years after eating blackberries, strawberries, and raspberries, as well as after drinking certain fruity white wines. He had experienced similar symptoms after eating peanuts and certain margarines. Two months before an allergy study, he ate two blackberries and, in a few minutes, had hives, itchy eyes, throat swelling, a wheezing cough, chest tightness, vomiting, cramps, diarrhea, and loss of consciousness. He required emergency treatment with epinephrine, corticosteroids, and oxygenation to maintain his cardiorespiratory function. His symptoms subsequently resolved. Two days after the anaphylactic episode, he experienced thrombosis of both iliac veins, which was confirmed with phlebograms. Analyses of blood samples obtained at that time showed leukocytosis with neutrophilia, an erythrocyte sedimentation rate of 50 mm in 1 hour, thrombocytopenia (37×10^9 platelets/L), and lengthening of the activated partial thromboplastin time (APTT) consistent with lupus anticoagulant. Additional studies revealed high levels of anticardiolipin (aCL) IgG antibodies: 76.6 units IgG phospholipid (UGPL)/mL (normal levels: <10). Results of other hematologic, cardiopulmonary, and rheumatologic studies were normal, and vasculitis, infections, metabolic disorders, and other known causes of thrombosis were excluded. The patient was diag-

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nosed with primary antiphospholipid syndrome (APS).

Subsequently, skin tests to various implicated foods were performed. A skin prick test with blackberry fruit and with 1/10 (wt/vol) extract of blackberry produced a wheal that was 20 by 15 mm in diameter. Sensitization to *Chenopodium*, peanut, wheat, barley, and rye was demonstrated by skin prick tests with commercial extracts and specific IgE level measurements (Table 1). Consent for double-blind oral-challenge tests was not obtained.

Case 2

A 20-year-old male student, who resided in an urban area, had been diagnosed with rhinoconjunctivitis caused by grass pollen when he was 12 years old. After 3 years of specific immunotherapy (ALK-Abelló Laboratories, Madrid, Spain) with a standardized extract of *Lolium perenne* (rye grass pollen) and *Cynodon dactylon* (Bermuda grass pollen), the patient's respiratory symptoms diminished and immunotherapy was discontinued. Four years later, immediately after eating a lentil soup, he had hives, itchy eyes, throat swelling, diarrhea, hypotension, and loss of consciousness. After treatment for acute anaphylaxis, the symptoms resolved.

An allergy study (skin prick tests and specific IgE level determinations) revealed sensitization to lentils, wheat, barley, green pea, almond, latex, chestnut, rye grass, and Bermuda grass. When these allergens were avoided, the patient showed definite improvement. Nevertheless, 1 year later, he suffered three more anaphylactic episodes immediately after eating mustard, a tomato salad, and strawberries, respectively. He required emergency treatment. Skin prick tests and high levels of IgE revealed sensitization to these foods (Table 1). Two months after the first of these most recent anaphylactic crises, he complained of pain and swelling in the lower extremities and was diagnosed with thromboses in both iliac veins and the inferior vena cava. Laboratory studies showed leu-

kocytosis with neutrophilia, lengthening of the APTT, and moderate levels of aCL IgG antibodies (28.7 UGPL/mL). Other preexisting conditions known to cause thrombosis were excluded, and the diagnosis was primary APS. Psychologically, the patient was extremely distressed, to the point of attempting suicide. Oral-challenge tests were not suitable.

Case 3

A 19-year-old male student, who resided in an urban area, had been diagnosed with rhinoconjunctivitis caused

by grass pollen when he was 8 years old. After 3 years of specific immunotherapy with a standardized extract of *L. perenne* (Aristegui, Bilbao, Spain), the patient's symptoms decreased and immunotherapy was discontinued.

At age 18 years, after drinking beer and eating six almonds, the patient experienced hives, itchy eyes, throat swelling, wheezing, vomiting, diarrhea, and loss of consciousness. These symptoms resolved after specific treatment for anaphylaxis. One month later, he showed positive results of skin

Table 1. In Vivo and In Vitro IgE Antibody Responses to Food, Pollen, and Latex Allergens and Serum Levels of Anticardiolipin Antibodies

Case	Allergen	Wheal diameter (mm)*	Specific IgE (kU/L)†	aCL IgG (UGPL/mL)	
				First Study	Second Study
1	Blackberry	20×15	...	77	84
	<i>Chenopodium</i>	6×10	10.0		
	Peanut	5×6	1.5		
	Wheat	5×5	1.4		
	Barley	3×2	1.6		
	Rye	2×3	1.2		
2	Lentils	20×30	517.0	29	39
	Wheat	12×10	14.0		
	Barley	10×10	10.8		
	Green pea	13×10	15.6		
	Almond	10×10	3.5		
	Latex	8×5	5.1		
	Chestnut	12×19	32.0		
	Rye grass	12×12	7.6		
	Bermuda grass	13×8	6.9		
	Mustard	5×8	8.9		
	Tomato	10×10	7.5		
	Strawberry	12×15	14.0		
3	Almond	5×5	24.2	23	28
	Green pea	2×2	1.6		
	Wheat	2×2	1.7		
	Barley	5×5	2.6		
4	Wheat	5×5	1.9	32	40
	Rye flour	5×5	7.8		
	Barley	6×8	8.8		
	Almond	3×3	0.4		
	Lentil	6×6	49.7		
	Tomato	8×8	7.9		
	Chestnut	4×5	37		
	Soybean	4×4	0.5		
	Hazelnut	6×6	1.6		
	Bermuda grass	6×6	6.9		
	Rye grass	10×10	6.9		

* Determined 15 minutes after skin prick tests with the allergens.

† Negative control for specific IgE assays was >0.35 kU/L.

prick tests and high levels of IgE antibodies to almond, green pea, wheat, and barley (Table 1).

A year later, the patient ate almonds and drank beer again, and a few minutes later, he experienced severe anaphylaxis that was followed by bloody diarrhea and abdominal pain. He did not consent to undergo colonoscopy. This episode was accompanied by severe urticaria, pain, and swelling of the lower extremities. A vascular study revealed thromboses of both iliac veins. Laboratory studies showed leukocytosis with lymphocytosis, thrombocytopenia (19×10^9 platelets/L), lengthening of the APTT, and moderate levels of aCL antibodies (23 UGPL/mL). The patient was diagnosed with APS. Informed consent for performance of oral-challenge tests was not obtained.

Case 4

A 27-year-old male student, who resided in an urban area, had been diagnosed with rhinoconjunctivitis caused by grass pollen when he was 17 years old. Treatment consisted of symptomatic measures and environmental control.

At age 24 years, the patient experienced an anaphylactoid syndrome (hives, throat swelling, diarrhea, and hypotension) immediately after eating lentils and drinking beer. Two years later, he returned to the emergency department with a similar reaction 5 minutes after eating a tomato, salami, and cheese pizza. He had high levels of IgE antibodies to wheat, rye flour, barley, almond, lentil, tomato, chestnut, soybean, hazelnut, Bermuda grass pollen, and rye grass pollen by skin prick tests (Table 1). These allergens were subsequently avoided, but after 25 days, he reported pain in his left lower extremity. After a vascular study, he was diagnosed with thrombosis of the left iliac vein. Laboratory studies showed leukocytosis, lengthening of the APTT, and moderate levels of aCL antibodies (32 UGPL/mL). After exclusion of other possible causes, the patient was diagnosed as having APS. Consent for performance of oral-challenge tests was not obtained.

METHODS

Skin Prick Tests

Skin prick tests were performed by a conventional procedure with a Morrow-Brown needle (Bayer, Madrid, Spain) and with use of standardized diagnostic extracts (from ALK-Abelló Laboratories). A response was considered positive when the mean wheal diameter was at least 3 mm greater than that produced by the saline control.

Serum Specimens

Serum specimens used in this study were from the four patients, a pool of nonallergic patients, and four control participants with APS and systemic lupus erythematosus in conjunction with thrombosis. No control participants reported allergic symptoms.

Anticardiolipin Antibodies

Anticardiolipin antibodies were measured by ELISA, following the commercial recommendations (INOVA Diagnostics, Inc, San Diego, CA). In this kit, the reference levels are as follows: 10 to 20 UGPL/mL low positive, 20 to 80 UGPL/mL medium positive, and >80 UGPL/mL high positive. Two months after the first test, serum specimens were obtained again from the four patients and tested again for aCL IgG antibodies (Table 1).

IgE Levels

Specific IgE levels were determined with use of the Pharmacia CAP System fluorescence enzyme immunoassay (Pharmacia Diagnostics, Uppsala, Sweden), in accordance with the manufacturer's instructions.

Allergens

The following materials were used for in vitro studies.

1. A 1/10 (wt/vol) blackberry extract was obtained after extraction with 1.8% NaCl for 1 hour at 4° C. After centrifugation (10,000 rpm for 25 minutes at 4° C), the supernatant was sterile filtered through a 0.22- μ m filter, 50% glycerinated, and stored at -20° C until used. The filters were supplied by ALK-Abelló Laboratories.

2. A 1/10 (wt/vol) almond extract was obtained and prepared in a manner similar to the foregoing blackberry extract.
3. LTPs from peach and chestnut were prepared as described elsewhere.³

Electrophoresis and Immunodetection

Samples of blackberry and almond extracts, LTPs from chestnut and peach, and controls (negative control of blackberry extract and negative control of almond extract) were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis on a 10% to 20% tricine precast polyacrylamide gel (Novex, San Diego, CA), with use of nonreducing conditions, and electrotransferred onto nitrocellulose membranes as described by Towbin et al.⁵ Approximately 200 μ g of protein extract was applied per lane. After a blocking process with 5% bovine serum albumin in phosphate-buffered saline (PBS) for 2 hours at room temperature, the blots were incubated overnight with each individual serum specimen (1:5 dilution in 0.5% bovine serum albumin; 0.05% Tween 20 in PBS). After washing with 0.1% Tween 20 in PBS, membranes were overlaid with mouse anti-human IgE monoclonal antibody HE-2 ascitic fluid (1:3,000 dilution; supplied by ALK-Abelló Laboratories)⁶ for 2 hours and then washed and incubated with a rabbit anti-mouse IgG peroxidase-conjugated antibody (DAKO A/S, Glostrup, Denmark) for 1 hour. Detection of IgE-binding components was achieved by enhanced chemiluminescence, following the manufacturer's instructions (Amersham, Little Chalfont, United Kingdom). Serum specimens from patients not sensitized to fruit and from four patients with systemic lupus erythematosus and thrombosis, as well as dilution buffer, were used as negative control samples.

RESULTS

The patients' levels of IgE antibodies to foods, pollen, and latex and their IgG antibody levels to aCL are shown in Table 1. All patients had persistently

medium to high levels of aCL antibodies. The four patients also showed sensitization to different plant sources, but seeds from cereals, legumes, and the Rosaceae family seemed to have an important clinical role.

Because immunoblotting experiments with all extracts were not possible, an almond extract was used (Fig 1). Almond was selected because the extract is very stable and has high protein performance. In addition, almond is the most common nut related to Rosaceae hypersensitivity in the Mediterranean area, where our patients resided. Although only one patient (case 3) ate almonds immediately before the anaphylactic episode that preceded the thrombotic event, all four patients had increased levels of IgE antibodies to almond.

Results of the immunoblotting analysis with the almond extract, the patients' serum specimens, and anti-IgE antibodies are depicted in Figure 1. Several IgE protein bands, ranging from approximately 25 to >50 kD, were detected in the almond extract in each patient's serum. As shown in lanes 3, 5, 6, and 9, these bands demonstrated a similar pattern not found in control specimens (such as lane 7). The relatively intense 45-kD almond protein band was recognized by IgE antibodies from all four patients. The molecular mass of this band indicates that it is not an LTP or other previously purified plant allergen.³ In agreement with this, a serum sample from a patient with a high IgE titer to chestnut (case 2, Table 1) did not recognize purified chestnut LTP (lane 4). Another patient (case 1) also showed the presence of antibodies for blackberry proteins (lane 2), including a 45-kD molecular mass. Lanes 1 and 8 depict negative control specimens of blackberry and almond extract, respectively, and do not show protein bands.

DISCUSSION

Because anaphylaxis is potentially a life-threatening state, the prevention of anaphylaxis and anaphylactoid reactions concerns all physicians. To maximize the prevention of recurrences,

causal factors should be determined.⁷ Nevertheless, identifying the cause and predicting unexpected complications can be difficult.

We describe four patients with food-related anaphylaxis associated with primary APS. Certain patients with antibodies to phospholipids experience episodes of venous arterial thrombosis, repeated miscarriage, and thrombocytopenia.⁸ Further, the lupus anticoagulant and aCL antibody tests likely detect antibodies with overlapping specificities.⁹ The term primary APS has been introduced to categorize and study these patients with APS who do not fulfill the criteria for systemic lupus erythematosus or any other well-defined conditions, such as infections or neoplasms.⁹ Some clinicians have proposed that livedo reticularis, migraine headaches, chorea, endocardial lesions, and transverse myelopathy

might be features of APS.¹⁰ Because of these common features, the true clinical and serologic boundaries of APS are vague and will probably remain so until affected patients are studied over time. For our patients, aCL antibodies persisted and could be related to previous episodes of anaphylaxis. On the basis of the international consensus preliminary classification statement,¹¹ we think that our four patients fulfill the clinical and laboratory criteria for APS.

The occurrence of food hypersensitivity in adults is infrequent. A recent national survey in the United States, however, suggested that peanut and tree nut allergies together affect 1.3% of adults.¹² The allergenic components of foods consist primarily of proteins, and closely related foods (legumes, cereal grains, and other seeds) frequently contain allergens that crossreact immu-

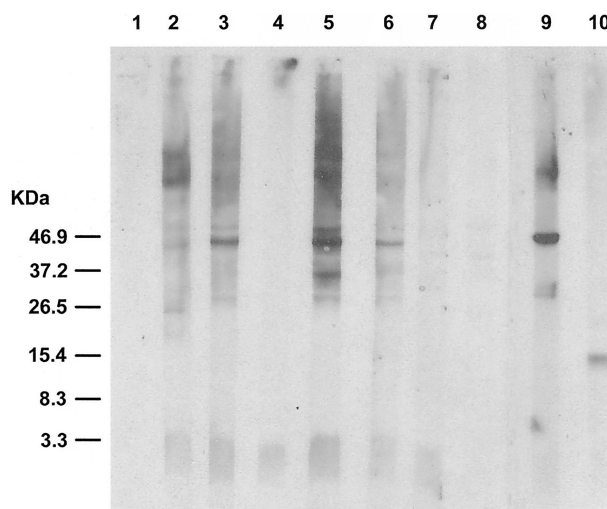


Figure 1. Detection of IgE antibodies to almond allergens by immunoblotting. The almond extract, blackberry extract, LTPs from peach and chestnut, and negative control samples were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to nitrocellulose membranes, and then different lanes were incubated with the patients' serum specimens. IgE antibodies were detected with mouse anti-human IgE and peroxidase-conjugated rabbit anti-mouse IgG. The photograph shows a composite of the following lanes: lane 1 = negative control of blackberry extract (serum of patient nonallergic to this fruit); lane 2 = blackberry extract overlaid with serum from patient 1; lane 3 = almond extract overlaid with serum from patient 1; lane 4 = chestnut LTP overlaid with serum from patient 2; lane 5 = almond extract overlaid with serum from patient 2; lane 6 = almond extract overlaid with serum from patient 3; lane 7 = almond extract overlaid with a serum pool from four patients with antiphospholipid syndrome, systemic lupus erythematosus, and no history of anaphylaxis; lane 8 = negative control of almond extract (serum of patient nonallergic to almond); lane 9 = almond extract overlaid with serum from patient 4; and lane 10 = peach LTP overlaid with serum positive for peach. The molecular masses, obtained from prestained molecular mass markers, electrophoreses in parallel, are indicated on the left.

nologically (on skin prick tests and radioallergosorbent tests) but only rarely crossreact clinically.¹²

Allergy to Rosaceae fruits is frequently associated with birch pollinosis in the United States, Canada, and central and northern Europe. This cross-sensitization has been mainly explained by the presence of homologous allergens in both the pollen from trees of the Fagales order and the fruits or vegetables mentioned. Proteins of 16 to 18 kD that share common IgE epitopes with Bet v 1, the major birch pollen allergen, have been characterized in alder, hazel, and hornbeam pollen as well as in edible parts of celery, cherry, and carrot.¹³ In patients without birch pollinosis, profilin and Bet v 1-related structures are not involved in Rosaceae fruit allergy. In these patients the symptoms are usually more severe.¹⁴

The patients allergic to Rosaceae fruits and seeds whose sera were tested in the current study lived in cereal-cultivating areas free of birch and other Fagales trees and, therefore, could not be directly sensitized to pollens from these trees. Instead, they had previous sensitization to grass pollen. A type of allergic population, frequently observed in the Mediterranean countries, consists of patients who have IgE antibodies for a major 9-kD allergen found in various Rosaceae fruits (LTPs).^{1,3,14} In our study, the four patients demonstrated sensitization to different vegetable foods, but Rosaceae fruits and seeds seem to have a clinically important role. Consequently, a role for LTPs as relevant panallergens was initially suspected in these patients. With limited quantities of reagents, performance of immunoblot studies with all extracts was not possible; therefore, an almond extract was used. Almonds do have an LTP with >80% sequence homology to peach and apple LTPs,³ and almonds are the most common nut related to Rosaceae hypersensitivity in our geographic area.¹⁵ The IgE immunoblot (Fig 1) showed, however, that the four patients had high levels of IgE for several almond proteins, ranging from 25

to >50 kD, and a 45-kD band was clearly recognized by the four sera tested. This 45-kD protein is not an LTP because these proteins have a molecular mass of approximately 13 kD in sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and it is not a protein from the Bet v 1 family (16 to 18 kD). Further, one patient (case 2) who had high levels of IgE to chestnut did not have IgE antibodies specific for purified chestnut LTP. Overall, our results suggest that, in addition to LTPs and the Bet v 1 family of allergens, other panallergens could be important in food allergy crossreactivity.

Is a relationship possible between the sensitization to seed and fruit proteins and the APS in these four patients? In this regard, IgE specific for a 45-kD protein was detected in the serum specimens from four patients, who were previously sensitized to grass pollen and had different causes of their anaphylactic syndrome. Perhaps certain food or seed proteins might behave similarly to β_2 -glycoprotein-I, the necessary cofactor for the interaction between aCL and the antigen.¹⁶ This hypothesis is speculative and demands additional supportive data because such patients are uncommon. Platelets have a role in anaphylaxis, and recent data^{16,17} suggest that platelet activation in patients with APS is related to anti- β_2 -glycoprotein-I.¹⁷ No episodes of thrombosis related to APS have previously been reported in patients with anaphylaxis. Perhaps in these patients, the food-induced anaphylaxis was profoundly severe and the IgE was specific for β_2 -glycoprotein-I cofactor. Analyses of larger numbers of patients with food-associated anaphylaxis could confirm such a relationship.

The prevalence of food allergies has increased during the past 15 years. A recent study¹⁸ found that 17% of young adults claimed that a particular food almost always caused illness or discomfort when eaten, presumably because of either food intolerance or food allergy. The reasons suggested are changes in dietary behavior and the evolution of food technologies. New food-processing techniques can in-

crease the allergenicity or create neoallergens, and storage conditions may induce the synthesis of allergenic, stress, or pathogenesis-related proteins. Genetically modified plants may cause allergenicity; thus, a methodologic investigation may be necessary to evaluate any possible risks.^{19,20} A recent consensus statement on APS encourages additional studies to document additional features of this syndrome.¹¹

To our knowledge, this is the first report of food-induced anaphylaxis associated with APS. In addition, we also document the first description of allergy to blackberry. This fruit, because of its frequent consumption and allergenic potential, should be considered in patients with a history of allergy to other fruits of the Rosaceae family.

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