Nonhistaminergic Idiopathic Angioedema: Clinical Response to Icatibant

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Chronic idiopathic angioedema is a disease with highly varied clinical manifestations. The 2 main types are histaminergic angioedema and bradykinergic angioedema [1].

In the histaminergic type, the edema is erythematous and pruriginous and responds to treatment with suitable doses of antihistamines and corticosteroids, although it sometimes requires treatment with adrenalin [1].

Bradykinin-mediated angioedema is characterized by the presence of areas of painless, nonpruriginous edema with no change in skin coloration, although it is sometimes preceded by clearly marginated erythema. The absence of urticaria is highly characteristic. This type of angioedema does not respond to treatment with optimum doses of antihistamines, corticosteroids, or adrenalin [1,2]. In recurrent, nonhistaminergic idiopathic angioedema, a hereditary or acquired C1-esterase inhibitor (C1-INH) deficiency must be ruled out. C1-INH is a complement system inhibitor involved in bradykinin synthesis [3,4], and an increase in bradykinin level induces most cases of nonallergic angioedema [5].

A 26-year-old Caucasian woman came to the Allergy Department of Hospital Clínico Lozano Blesa, Zaragoza, Spain with a history of recurrent angioedema. Ten years previously, she had presented symptoms of bilateral edema affecting her feet, which was subsequently accompanied by petechiae on her lower extremities, meningism, and uncontrollable vomiting. The results of lumbar puncture, computed axial tomography scan, and brain magnetic resonance imaging were unremarkable. The symptoms resolved in about 24 hours, and the patient remained under observation in hospital for a further 48 hours.

Since her discharge, the patient has had almost daily episodes of subcutaneous edema, erythema, and pain, but no pruritus or other accompanying inflammatory symptoms. These episodes last 48 hours and leave no residual effects. During her life, she has experienced more than 15 episodes of edema of the glottis requiring treatment with subcutaneous adrenalin, corticosteroids, and parenteral antihistamines. However, no immediate improvement was achieved and the symptoms resolved spontaneously within 48-72 hours. The episodes most frequently affected the glottis, the face, and the distal portion of the upper and lower extremities, with no abdominal involvement. The patient reported prodromal symptoms consisting of palpitations and pharyngeal discomfort before the episodes.

No link was established between the episodes of angioedema and the administration of food or medication (angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and oral contraceptives), trauma, or the menstrual cycle. Symptoms worsened when under stress at work. Blood tests disclosed the following values: C3, 84.5 mg/dL (normal); C4, 13.7 mg/dL (slightly low); antigenic C1 inhibitor, 21.2 mg/dL (normal); functional C1-inhibitor, 83% (normal); C1q, 126 μg/mL (normal); and tryptase 1.6 μg/L (normal). The results for thyroid hormones and antithyroid antibodies were normal, and testing for HBV and HCV was negative. The results of skin prick tests for common allergens were negative. A chest x-ray revealed no abnormalities. Pressure and vibration tests on the patient's skin were also negative. The medical history revealed no disorders affecting organs or systems, and the genetic study showed no mutation within exon 9 of coagulation factor XII.

The patient was prescribed daily treatment with antihistamines (rupatadine [10 mg/d], dexchlorpheniramine [6 mg/d], and ranitidine [150 mg/d]), which did not lead to a significant improvement, and 25 mg of hydroxyzine before work-related stress episodes.

This regimen was continued, and dapsone was added for 2.5 weeks at a dose of 50 mg/d, but had to be suspended because of headache. After 2 months, the patient was still experiencing 2 episodes of angioedema a week. She was later prescribed daily treatment with tranexamic acid, with a slight improvement, but the episodes of angioedema could not be controlled. She continues to take this medication (at a dose of 1 g/8 h) together with ranitidine (150 mg/d), although treatment has not significantly affected the frequency or intensity of episodes.

The patient's angioedema episodes were treated with the newest available medications in Spain. Treatment with 500 IU of C1-INH (CSL-Behring) produced no response. Treatment with icatibant acetate, on the other hand, stopped progression of the angioedema, although it did not notably accelerate resolution or reduce the frequency of episodes. Only a small number of episodes (2 a year) progressed to angioedema of the glottis, although without reaching the intensity observed before treatment with icatibant. This treatment was initiated 2 years ago at the standard dose (1 syringe of 30 mg). The patient currently treats herself at home with 1 syringe during episodes affecting the face, tongue, or upper airways. Exceptionally, she administers a second syringe if no response is obtained within 25 minutes of administration. The other treatments were discontinued, except tranexamic acid, which is only used for mild episodes that do not affect the face or upper airway.

Our patient was diagnosed with recurrent idiopathic angioedema, which can be triggered by stress [6], as in the case we report.

The drugs administered to treat the edema (antihistamines, corticosteroids, tranexamic acid, dapsone, and C1-INH) were not effective. The absence of response to high-dose systemic corticosteroids (prednisone, 60 mg/d) rules out the possibility suggested by some authors of a relationship between the presence of anti-IgE antibodies [7] and specific IgG antibodies against the high-affinity IgE receptor [8] in autoimmune angioedema.

New therapeutic options in hereditary angioedema have paved the way for potentially effective treatments in cases of idiopathic angioedema, in which bradykinin may play a role, although this has not yet been proven. However, icatibant, a selective bradykinin B2 receptor antagonist recently approved by the European Medicines Agency [9] for the symptomatic treatment of acute attacks of hereditary angioedema [10], proved effective in our patient. Administration of this treatment was requested off-label and approved by Hospital Clínico Lozano Blesa. In the case we report, subcutaneous administration of 1-2 injections of 30 mg of icatibant each per episode managed to stop progression of angioedema on numerous occasions, although it did not accelerate its resolution or prevent new episodes of angioedema of the glottis from occurring.

The efficacy of icatibant in our patient could indicate the involvement of bradykinin as a pathogenic mechanism and indicates that this agent could prove to be an effective treatment for recurrent idiopathic angioedema.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review.

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Occupational Allergy to Spanish Omelet

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Onion (*Allium cepa*) belongs to the Amaryllidaceae (Liliaceae) family, which also includes garlic, chives, and leek. Hypersensitivity to onion has been reported to cause contact dermatitis, rhinoconjunctivitis, and asthma in onion handlers [1]. Onions are widely used in Mediterranean and other cuisines owing to their edibility and price. We present a unique case of immunoglobulin (Ig)–mediated occupational urticaria and angioedema induced by exposure to onion.

A 29-year-old cook had previously been diagnosed with extrinsic asthma and rhinoconjunctivitis, atopic dermatitis, and fruit allergy. He experienced immediate oral pruritus and labial angioedema after eating raw onion and localized hives after touching raw onion. He reported recurrent generalized urticaria a few minutes after entering his restaurant, where Spanish omelet (which contains eggs, potatoes, and onion) was prepared, although he had no direct contact with the omelet. He tolerates fried and cooked eggs, as well as fried onion.

Skin prick test results were positive (wheal ≥3 mm) for the following allergens: pollens (grass mixture, *Olea europaea*, *Platanus acerifolia*, *Cupressus arizonica*, *Artemisia vulgaris*, *Chenopodium album*, *Plantago ovata*, *Parietaria judaica*, *Salsola kali*), mites, animal dander (dog and cat), *Aspergillus*, profilin (Pho d 2), peach (as a lipid transfer protein marker) and polcalcin-enriched date palm (ALK-Abelló SA). The results of prick-by-prick testing were positive to onion flesh (6 mm) and negative to the skin. Total IgE was 5722.9 IU/mL; specific IgE was positive (≥0.35 kU_A/L) to *Lolium perenne*, *O europaea*, *P acerifolia*, *C arizonica*, peach (42.90 kU_A/L), tomato, onion (92.10 kU_A/L), melon, pineapple, grape, and watermelon. We prepared a raw onion extract and tested it against the patient's serum using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting. Reactive bands were detected using enhanced chemiluminescence (ECL-Amersham Biosciences) [2,3]. Immunoblotting revealed bands at 10, 15, 20, 25, 37, 50, 75, 100, 150, and 250 kDa; SDS-PAGE showed 2 clear bands of 37 and 50 kDa in the raw onion extract (Figure).

Hypersensitivity to onion has been reported to cause contact dermatitis, rhinoconjunctivitis, and asthma in onion handlers. A case of urticaria and angioedema minutes after eating raw onion was reported in a patient who tolerated cooked onion [4]. Immunoblotting with the serum of that patient against onion extract showed a 15-kDa band and a 43-kDa double band. Pérez-Calderón et al [5] reported a case of exercise-induced anaphylaxis after ingestion of onion in a patient who was highly sensitized to this vegetable, although no cross-reactivity was found with the other members of the Liliaceae group [5]. *Artemisia*-derived lipid transfer protein was the primary culprit allergen causing hypersensitivity to onion in another case [6]. Garlic and onion powder demonstrated enhanced allergenicity in the processed dry form, and were more likely to become airborne. A 50-kDa cross-reactive allergen was found by immunoblotting in garlic and onion, although it was more prominent in garlic.

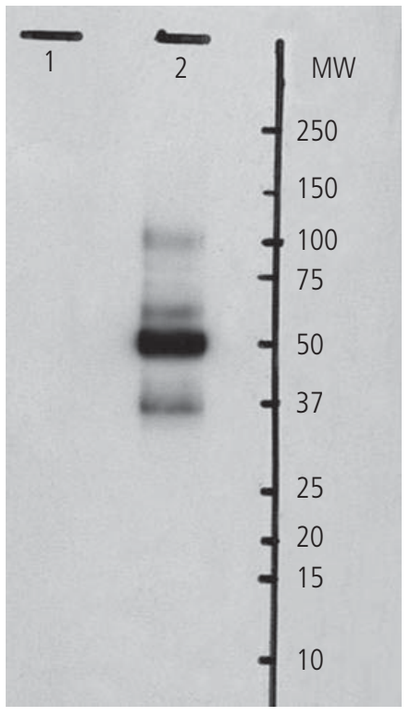

Figure. Sodium dodecyl sulfate polyacrylamide gel electrophoresis reveals 2 bands of 37 kDa and 50 kDa. Lane 1, negative control; lane 2, patient's serum with raw onion extract. MW indicates molecular weight.

To our knowledge, we present the first case of IgE-mediated occupational urticaria and angioedema due to onion in which the onion allergen was airborne. The patient's serum recognized 2 bands of 37 kDa and 50 kDa that have not been reported elsewhere, suggesting an IgE-dependent mechanism. The molecular weight of these bands indicates that they might not correspond to lipid transfer protein or profilin. Repeated exposure to allergen in our patient could have led to subsequent symptoms after inhalation.

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The Unique Clinical and Laboratory Characteristics of Nonepisodic Angioedema With Eosinophilia: A Case Series of 18 Patients

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Key words: Nonepisodic angioedema with eosinophilia. Eosinophilia. Interleukin 5. Angioedema.

Palabras clave: Angioedema no episódica con eosinofilia. Eosinofilia. Interleukin 5. Angioedema.

Angioedema, which presents as nonpruritic and nonpitting edema of vascular origin, is classified into several forms: hereditary, acquired, associated with allergic reactions (ie, latex allergy, adverse drug reactions, food allergy), and idiopathic. When associated with eosinophilia, the syndrome is called angioedema associated with eosinophilia (AAE) and is classified into 2 categories: episodic angioedema with eosinophilia (EAE) and nonepisodic angioedema with eosinophilia (NEAE) [1,2].

EAE was first described by Gleich et al [3], whose patients had recurrent attacks of angioedema, urticaria, and fever. Laboratory findings included a markedly high peripheral blood eosinophil count and a high level of serum immunoglobulin (Ig) M. Since then, a nonrecurrent, milder type (NEAE) has been reported from Asian regions [4-6]. In addition to the absence of recurrence, the characteristics of NEAE were reported to be predominance in young women, milder symptoms (such as localization of angioedema in the extremities), and normal serum IgM level.

However, precise clinical and laboratory characteristics have yet to be elucidated, since only case reports and small-scale case series have been published to date. Here, we present the largest case series on NEAE; our data will increase our understanding of this rare disease.

We retrospectively analyzed the clinical records of AAE patients who visited the Department of Allergy and Immunological Diseases of Tokyo Metropolitan Komagome Hospital, Tokyo, Japan from June 1981 to December 2007. The local ethics committee approved the study.

Ruling out other causes of edema is a major difficulty when diagnosing AAE. The differential diagnosis was initially made by ruling out pitting edema, such as that seen in hypoalbuminemia, cardiorenal failure, phlebitis, contact dermatitis, and venous occlusion. The differential diagnosis then included lymphedema and hypothyroidism, which cause nonpitting edema. Consequently, the edema experienced by our patients could be classified as angioedema. Types other than AAE, for example, hereditary angioedema, allergic reaction to specific antigens, and drug-related angioedema [1], were ruled out. Finally, if eosinophilia ($>0.5 \times 10^9$/L) coincided with the appearance and persistence of angioedema, patients were diagnosed with AAE.

The diseases ruled out in the differential diagnosis of eosinophilia were myeloproliferative disorders, adrenal hypofunction, allergic reactions to specific antigens, parasitic and

Table. Clinical Features and Laboratory Findings of Patients With Nonepisodic Angioedema With Eosinophilia

Patient	Sex	Age, y	Eosinophils, × 10^9/L	ECP, μg/L	IL-5, pg/mL	IgE, U/mL	IgG, g/L	IgA, g/L	IgM, g/L	LDH, IU/L	CRP, mg/L	ESR, mm/h
1	F	33	4.97	197	17.0	9.2	13.8	2.56	1.37	361	4.0	32
2	F	26	18.29	>150	19.4	839.0	13.97	2.25	2.32	639	5.0	19
3	F	30	2.82	63.4	13.4	26.3	10.57	2.39	1.08	233	1.0	4
4	M	27	15.41	237	27.0	75.0	0.851	1.53	0.74	464	2.0	0
5	F	25	12.22	149	NA	149.4	16.87	3.73	1.65	327	30.0	9
6	F	31	6.81	125	<8	40.0	8.23	1.66	2.31	219	6.0	11
7	F	33	13.32	>150	17.0	67.1	15.8	2.17	3.62	390	1.0	26
8	F	21	7.72	257	86.1	143.7	16.2	2.33	2.38	310	1.0	10
9	F	27	4.20	NA	NA	468.1	16.82	4.65	0.9	141	1.0	3
10	F	25	8.43	78.7	138.0	112.0	16.3	3.96	0.73	281	5.0	15
11	F	32	8.91	>150	NA	138.0	15.6	2.9	1.42	218	1.0	11
12	M	34	7.44	>150	23.3	272.8	10.4	3.39	0.57	273	2.0	10
13	F	31	8.13	130	<8	23.5	14.2	1.9	4.21	265	2.0	7
14	F	25	9.01	102	9.0	19.9	10.7	1.48	2.52	329	6.0	11
15	F	23	14.34	143	22	39	7.13	2.74	0.49	229	0	0
Reference range			<0.5	<14.7	<8	<170a	8.71-20.07	1.12-5.80	0.52-2.98	120-220	0-3	0-15

Abbreviations: CRP, C-reactive protein; ECP, eosinophilic cationic protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; IL, interleukin; LDH, lactate dehydrogenase.
[a]Reference range for adults

nonparasitic infection, connective tissue disease, and dermatologic autoimmune diseases. Atopic status was not recorded.

Since clinical data were irregularly and widely distributed, they are expressed as median and interquartile range (IQR), except for length of time, which is shown with a full range.

The Mann-Whitney test was used to compare laboratory parameters. A value of $P<.05$ was considered significant.

The 15 AAE patients consisted of 13 women and 2 men, with a median age of 27 (25-31.5) years at the time of diagnosis (Table). Nine patients (60.0%) had a history of atopic diseases: 4 had atopic dermatitis in childhood but all had outgrown it completely, and 6 had allergic rhinitis to Japanese cedar pollen (exclusively in spring). Twelve patients (80.0%) developed the disease from September to December, 1 developed it in March, and 2 developed it in June.

All 15 patients had edema in both lower limbs, 8 (57.3%) had edema of both the upper and lower limbs, 8 (57.3%) had arthralgia, and 8 (57.3%) had reddening of the skin. Only 1 patient had fever (37.4°C). The median maximum weight gain of the 7 patients with available data was 7.2% (4.6%-11.1%). No internal organ involvement was recorded.

The eosinophil counts at diagnosis of AAE and at their peak during the course of the disease were 8.432 (7.125-12.770) $\times 10^9$/L and 8.910 (7.581-13.374) $\times 10^9$/L, respectively. The serum eosinophil cationic protein level was markedly increased (149.5 [126.3-150] μg/L; reference range, <14.7 μg/L), whereas interleukin (IL) 5 levels (20.7 [17-26.1] pg/mL) were slightly higher than the upper limit of the reference range (8 pg/mL) except for 1 case (patient 10). Serum levels of IgE (75 [32.7-146] U/mL) and IgM (1.42 [0.82-2.35] g/L) were within the reference range (<170 U/mL) in 12 of the 15 patients, and below the upper limit of the reference range (2.98 g/L) for all but 2 patients. C-reactive protein levels were within or slightly higher than the normal range (0-3 g/L) at <6 g/L, except for 1 case. In contrast, lactate dehydrogenase level was above the normal range (277 [230-319] IU/L; normal range, 120-220) in 13 patients.

All patients with AAE achieved complete remission 6 to 9 weeks after onset. The mean duration of peripheral blood eosinophilia higher than the normal range was 55 days (range, 11-133 days). Antihistamine agents were administered to 10 patients, but no significant difference in disease duration was observed between those taking and not taking medication. None of the 15 patients required corticosteroids. Once the angioedema had subsided, it did not recur in any of the patients during the median follow-up period of 1496 (542-3323) days; thus, all of our AAE patients were finally diagnosed with NEAE.

Ours is the largest series of patients with NEAE to date; therefore, it is significant that the characteristic features of NEAE reported elsewhere [4-6] were confirmed. Furthermore, we show for the first time that NEAE is a self-limiting, transient disease that does not require specific treatment.

As for laboratory data, NEAE was generally not accompanied by an increase in inflammatory markers or immunoglobulins, except lactate dehydrogenase. This contrasts with EAE, in which levels of inflammatory markers increase [1,3]. IL-5 was only slightly above the upper limit of the reference range, except in 1 patient with NEAE, thus confirming the previous finding that IL-5 level was much lower in NEAE than in EAE [7], in which an abnormal T-cell clone

produces a large amount of IL-5, as occurs in lymphocytic hypereosinophilic syndrome [8,9]. This observation also suggests that NEAE cannot simply be attributed to endogenous causes such as EAE, and that external factors may contribute to its pathogenesis.

Six patients had atopic rhinitis when diagnosed with NEAE, but none were allergic to autumn pollens such as ragweed; therefore, no clear association could be established between atopic status and NEAE, which occurred mainly in autumn and winter. However, the clear seasonal variation seen in NEAE suggests that an unidentified antigen and a specific diathesis are involved. Further studies are expected to elucidate the underlying mechanism of the disease.

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Cross-Reactivity Between Cypress Pollen and Latex Assessed Using Skin Tests

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Palabras clave: Asma alérgica. Conjuntivitis. Polen de ciprés. Rinitis.

Cypress pollen is a common allergen in the Mediterranean area [1]. Testing for cypress pollen (*Cupressus sempervirens* and *Cupressus arizonica*) is performed in all patients attending the allergy clinic of our institution, and 20-30% of allergic patients present positive skin test results to cypress pollen [2,3]. However, only around 50% of patients have symptoms during the pollen season [3], suggesting that sensitized asymptomatic patients may have a different immune response. Several allergens have been identified in cypress pollen, and structural homology was recently found between a basic polygalacturonase, a major *C sempervirens* pollen allergen, and the major latex allergen Hev b 1 [4].

The most important allergens of occupational latex allergy are Hev b 5 and Hev b 6.02, whereas Hev b 1 and Hev b 3 are more important for spina bifida patients [5]. Skin tests to latex are carried out in our clinic using a 100 IR standardized latex extract (Stallergènes SA) containing Hev b 1 (0.24 μg/mL), Hev b 3 (0.13 μg/mL), Hev b 5 (0.18 μg/mL), and Hev b 6.02 (8.1 μg/mL) (Stallergènes SA).

In the present study, we investigated whether patients with a positive skin prick result to cypress pollen (asymptomatic or symptomatic during the pollen season) [6] present a positive skin test result to latex. Levels of specific IgE to cypress pollen, latex, or individual components of these allergens were not recorded. Patients were included retrospectively from our departmental database.

A first study was carried out in 300 consecutive patients (mean age, 34.1 years) with a positive skin prick test result to cypress pollen. Patients were tested from May 1, 2010 to April 30, 2011. A total of 137 (45.7%) were symptomatic during the cypress pollen season and 163 were not. Patients were compared to 50 consecutive patients (mean age, 31.4 years) with a positive skin prick test result to any of the inhalant allergens of the common battery used in the clinic and a negative result to cypress during the same period. All patients underwent skin testing with the same panel [7], which included latex.

Six of the 137 patients (4%) had symptoms during the cypress pollen season, a positive skin prick test result to cypress pollen, and a positive skin test result to latex. All 6 were sensitized to several allergens (mostly with cosensitization to house dust mite). Ten of the 163 asymptomatic patients (6%)

with a positive skin test result to cypress pollen had a positive skin prick test result to latex. Three of 50 patients (6%) with no sensitization to cypress pollens had a positive skin test result to latex. None of the 19 patients with a positive skin test result to latex had reported symptoms during latex exposure, as highlighted from their clinical history.

A second study was carried out in 15 patients with demonstrated occupational latex allergy (mean age, 40.8 years). All patients were tested with the common battery for inhalant allergens (7). A positive skin prick test result to cypress pollen was recorded in 9 patients (56.2%), and 2 of these presented symptoms during the cypress pollen season.

This screening study suggests that even when a standardized latex extract containing a sufficient amount of Hev b 1 is used, patients with positive skin test results to cypress pollen do not show a higher incidence of sensitization to latex. We did not perform a more detailed analysis using specific IgE determination or component-resolved diagnosis. Furthermore, our results suggest that it may not be useful to assess cross-reactivity between latex and cypress pollen in this group of patients. However, we cannot rule out the existence of different cypress species in other areas or the possibility of cross-reactivity. On the other hand, a large number of patients with occupational latex allergy have positive skin test results to cypress pollen in our region. Therefore, it could be important to assess immunologic cross-reactivity between Hev b 1 and basic polygalacturonase in these patients. No spina bifida patient was tested with the battery of inhalant allergens; consequently, checking cross-reactivity in this population may also be of interest.

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Chronic Granulomatous Disease With Gastrointestinal Presentation: Diagnostic Pitfalls and Novel Ultrastructural Findings

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Key words: Chronic granulomatous disease. Inflammatory bowel disease. Enterocyte ultrastructure. Chronic diarrhea. Crohn disease.

Palabras clave: Enfermedad granulomatosa crónica. Enfermedad inflamatoria intestinal. Ultraestructura de enterocitos. Diarrea crónica. Enfermedad de Crohn.

Chronic granulomatous disease (CGD) is a rare congenital disorder, characterized by defects in the nicotinamide adenine dinucleotide phosphate, reduced form, (NADPH) oxidase biochemical pathway, which is the most important cellular producer of superoxide anions in both phagocytic and nonphagocytic cells [1,2]. The main clinical problem in this disease is the occurrence of life-threatening infections caused by a large spectrum of bacteria and fungi [1]. Diagnosis is usually easily made in the first years of life and appropriate anti-infectious prophylactic treatment significantly increases overall survival. Furthermore, increasing knowledge of the disease has led to an increasing recognition of patients with a delayed and more insidious onset.

We report on a case of CGD in a child with an exclusive gastrointestinal presentation, which led to delayed diagnosis. We also document for the first time ultrastructural changes in the microvillous architecture in this syndrome.

A 14-month-old boy presented with acute diarrhea and severe dehydration, hypoalbuminemia, anemia, and hypergammaglobulinemia associated with leukocytosis, and increased markers of inflammation. His growth rate had slowed down since the age of 9 months. A diagnosis of celiac disease was made on the basis of positive serology (anti-gliadin immunoglobulin [Ig] A, 23 U/mL; IgG, >100 U/mL; anti-transglutaminase [TGAA] IgA, 42 U/mL) and mucosal alterations (shortened villi, reduction of brush border, and presence of inflammatory lymphoid cells, stage III). He did not recover after 6 weeks of gluten-free diet or 30 days of corticosteroid treatment (methylprednisolone 1 mg/kg/d). At the age of 16 months, his general condition was very poor and there were evident signs of dystrophy (weight, 8.270 kg [< -2 SD]; height, 73 cm [< -2 SD]; weight to height ratio, < -2 SD) associated with osmotic diarrhea (stool osmotic gap, 498 mOsm/kg) and steatorrhea. Laboratory tests revealed hypoalbuminemia, anemia, and raised markers of inflammation. IgG, IgM, and IgA levels were 22.3, 2.42 and 1.27 g/L, respectively. Repeated stool tests for ova and parasites, bacteria, rotavirus, and adenovirus

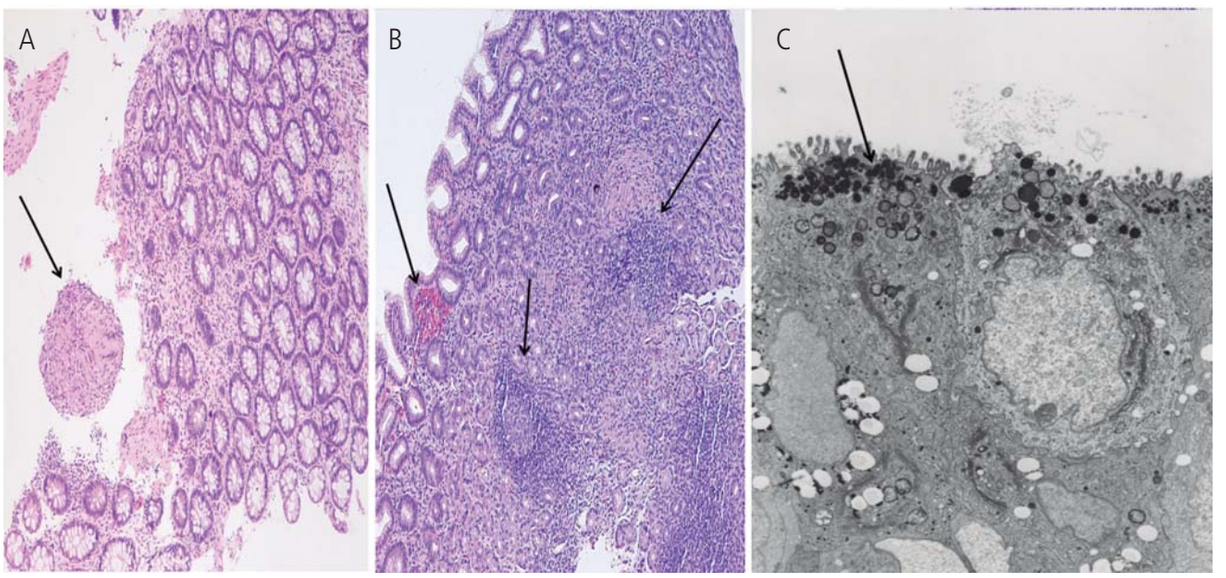

Figure. A, Sigmoid biopsy specimen. The arrow indicates the presence of a non-necrotizing epithelioid granuloma within an otherwise normal mucosa. There are no signs of inflammation. B, Enterocyte ultrastructure in our patient. Rare, shortened and poorly oriented microvilli are seen. The arrow indicates the typical cytoplasmic inclusions (dense granules and lipid vacuoles). C, Antral biopsy specimen showing multiple non-necrotizing epithelioid granulomas and an inflammatory infiltrate within the lamina propria. Some lymphoid aggregates are seen.

yielded negative results. *Clostridium difficile* enterotoxin A and B were negative on immunoassay. An abdominal ultrasound revealed a thickened distal ileum wall with signs of irregular peristalsis and enlargement of mesenteric lymph nodes. The child was started on parenteral nutrition on the day of admission. His course was complicated by a lobar pneumonia successfully treated with cephalosporin. Gastric biopsy specimens showed *Helicobacter pylori*–negative chronic active gastritis. Moderate-to-severe villous atrophy persisted at histology after 80 days of gluten- and cow milk protein–free diet (shortened villi with hyperplastic cryptae [villus height to crypt depth ratio, 0.7], pseudostratified and vacuolated superficial epithelium with increased lymphocytic infiltrate, and increased plasma cells in the lamina propria). A single noncaseating epithelioid granuloma within the lamina propria of the sigmoid biopsy specimen without inflammation was noted (Figure A). Multiple non-necrotizing epithelioid granulomas and inflammatory infiltrates within the lamina propria and the epithelium were detected along with some lymphoid aggregates (Figure B). Ultrastructural examination of enterocytes revealed rare, shortened, and poorly oriented microvilli with characteristic cytoplasmic inclusions (Figure C). Serum antienterocyte antibodies were negative. Fecal calprotectin and anti-*Saccharomyces cerevisiae* (ASCA) were positive (485 mcg/g and 30 U/mL, respectively). Based on these features, a diagnosis of Crohn disease was made according to the international Lennard-Jones criteria [3]. The presence of epithelioid granulomas associated with the occurrence of severe infectious episodes (sepsis, pneumonia) then led us to suspect a congenital phagocyte disorder. The nitroblue tetrazolium test revealed the absence of cells which properly reduced the dye to formazan. Neutrophil oxidative burst evaluated through dihydrorhodamine (DHR) staining and flow cytometry before and after stimulation of neutrophils with phorbol myristate acetate, peptide N-formyl-Met-Leu-Phe and *Escherichia coli* revealed no evidence of DHR fluorescence. Polymerase chain reaction failed to amplify exons 9 to 13 of the *CYBB* gene. Array-based comparative genomic hybridization was performed according to the manufacturer's protocols on a whole-genome CytoChip Oligo ISCA 180K array (BlueGenome) and revealed a microdeletion at Xp11.4, extending approximately 45.25 Kb from 37 549 100 base pairs to 37 594 353 base pairs, including the *CYBB* gene.

The child was started on antimicrobial and antifungal prophylaxis. After a year of a gluten-free diet, moderate-to-severe villous atrophy persisted and a liberalized diet resulted in adequate growth (weight to height ratio at the 50th percentile). The TGAA celiac marker remained negative (TGAA IgA, 0.5 U/mL). Chronic inflammatory and/or granulomatous lesions of the bowel have been described in up to 50% of patients with CGD [1,4]. CGD-related enteropathy lacks specific features and may thus mimic other common causes of chronic diarrhea. In our case, a diagnosis of celiac disease was initially made according to the ESPGHAN criteria; this was followed by a diagnosis of Crohn disease on the basis of the Lennard-Jones criteria [3]. A pathogenic link between these 2 entities was recently suggested based on evidence in patients with Crohn disease of abnormally low neutrophil recruitment and lower levels of the proinflammatory cytokines interleukin (IL) 8 and IL-1ß, suggesting that chronic inflammation might be the consequence of inadequate innate immunity [4-6]. In our patient, submicroscopical anomalies of microvilli were reminiscent of a microvillous inclusion disease. However, such alterations are not specific to any particular disease and may suggest the presence of poorly differentiated enterocytes involved in antigen transport to late endosomes, which perpetuate enterocyte antigen uptake due to chronic stimulation, similarly to what has been reported in Crohn disease [4,7,8].

Another issue for speculation in our case is the presence of the serologic markers of autoimmunity, TGAA and ASCA, which are generally considered biomarkers of celiac disease and Crohn disease, respectively. As for the latter, a recent study showed that the majority of CGD patients have high levels of antimicrobial antibodies, regardless of the presence or absence of colitis [9], suggesting that in CGD the ineffective clearance of specific microbial flora in the gut may result in antigen sensitization. As for the TGAA positivity, a possible explanation is that a loss of mucosal integrity may allow larger peptides to enter the circulation [10], leading to a specific humoral immune response.

In conclusion, the aim of this report is to alert physicians and pediatricians to the fact that CGD may present with exclusive gastrointestinal manifestations mimicking other causes of enteropathy. Diagnostic algorithms of granulomatous intestinal lesions thus should also include CGD.

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Commercial Dehydrated Egg White for Specific Oral Tolerance Induction (SOTI): An Easier Treatment for Egg Allergy

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Key words: Egg allergy. Food desensitization. Food allergy. Anaphylaxis. Allergy in children.

Palabras clave: Alergia alimentaria. Desensibilización a alimentos. Alergia a huevo. Anafilaxia. Alergia pediátrica.

Hen egg (HE) is one of the main causes of food allergy in children. Specific oral tolerance induction (SOTI) seems to be a promising approach for improving the quality of life of patients with food allergy and for minimizing risk in the event of accidental ingestion of an offending food [1].

SOTI to HE has generally been performed using lyophilized HE protein [1], powdered or pasteurized egg white [2,3], beaten egg, or boiled egg [4], but there are allergenic differences between these preparations, as egg is one of the foods whose allergenicity is most altered by cooking or processing. Since 2011, a commercial preparation of fixed-dose dehydrated egg white has been available in Spain that can be used for oral food challenge (OFC) testing and for SOTI. It is sold under the commercial name of OVODES NM (Nutrición Médica) and costs 50 Euro per kit. OVODES NM consists of 9 doses for the build-up period during SOTI and 8 doses for OFC. The doses are measured in mg of protein of egg white and are as follows: dose 1, 4 mg; dose 2, 20 mg; dose 3, 50 mg; dose 4, 110 mg; dose 5, 225 mg; dose 6, 450 mg; dose 7, 900 mg; dose 8, 1800 mg, and dose 9, 3600 mg. Doses 1 to 6 come in capsule form and doses 7 to 9 in packet form. The protocol may vary in patients who exhibit side effects, with an increase in the number of doses administered or the time between doses.

We performed an open prospective study using OVODES NM for SOTI in 16 children with a mean (SD) age of (7.88 [2.3] years) and 3 adults with a mean age of 28.3 [14.26] years, all of whom were recruited from the allergy department at Fundación Jiménez Díaz Hospital in Madrid, Spain. Two of the adults dropped out of the study for personal reasons, leaving 17 evaluable patients (16 children and 1 adult).

All of the patients had a history suggestive of immediate-type allergic reaction after ingestion of HE (urticaria, angioedema, vomiting, diarrhea, rhinitis or asthma); a positive skin prick test (wheal diameter 3 mm larger than that of the saline control diameter) to HE or its proteins (ovalbumin, ovomucoid [OVM]), as determined using commercial extracts supplied by LETI Laboratories; serum specific immunoglobulin (Ig) E (CAP Phadia) to HE (median, 3.6 kU/L; interquartile range [IQR], 0.73- 29.2 kU/L) and/or OVM (median, 2.4 kU/L; IQR, 0.3-24.5 kU/L), and total IgE (median, 439 kU/L; IQR, 147-833 kU/L); and a positive oral challenge test to HE in the 3 months prior to SOTI using OVODES NM or pasteurized

Table. Epidemiologic Characteristics of Study Population, Symptoms during Oral Food Challenge (OFC) and Specific Oral Tolerance Induction (SOTI), Premedication, and Time to Complete SOTI

Patient	Age, y/ Sex	SPT to HE/OVM, Wheal Size mm	Total IgE/IGE OVM Prior to SOTI, kU/L	OFC Prior to SOTI symptoms/ dose	Symptoms During SOTI	Premedication	Starting Dose/Time to Complete SOTI, wk	Total IgE/IgE OVM Acte SOTI, kU/L
1	6/M	4/3	708/2.40	AP, U/<4 mg	OP	–	1/9	191/2.34
2	7/M	5/3	226/<0.35	OP, V/<4 mg	–	–	1/9	272/<0.35
3	10/M	7/4	439/3.67	U/<4 mg	AP	–	1/9	NA/1.29
4	7/F	8/5	996/83.6	U, V/<4 mg	AP	–	1/9	1004/41.3
5	6/F	9/4	187/24.5	U/<4 mg	–	–	1/9	208/13.6
6	16/F	4/3	447/NA	U/<4 mg	–	–	1/9	262/<0.35
7	38/F	5/3	94/<0.35	OP, AE/<4 mg	OP, AD	Dexchlorpheniramine 5 mg	1/9	NA/<0.35
8	8/M	6/4	88.80/<0.35	AP, U/<4 mg	–	–	1/9	NA/<0.35
9	6/M	7/4	147/NA	V/<4 mg	–	–	1/9	957/1.47
10	6/F	8/5	2053/4.58	AE, C, U/225 mg	OP, E, C, AE	Budesonide 200 mcg, Salmeterol/fluticasone 25/250	4/6	1902/3.31
11	9/F	6/3	135/0.64	U/<4 mg	OP, AP, D	–	1/9	NA/1.03
12	10/M	5/<3	1128/1.88	U/3600 mg	AP	–	8/1	NA/NA
13	7/M	6/5	107/10.2	C, U /50 mg	AD, C, AP, D	Budesonide 200 mcg Salmeterol/fluticasone 25/250	2/9	231/16
14	7/F	9/7	2033/45.3	U, AP /225 mg	OP, AP	–	4/5	1296/30.2
15	7/M	7/4	833/NA	C, U/<4 mg	AP, V, U, C, A	Dexchlorpheniramine 5 mg	1/not completed	–
16	8/M	8/5	487/>100	AP, U/<4 mg	AP,V, C, OP, A	Cromoglycate 200 mg Budesonide 200 mcg Montelukast 5 mg	1/not completed	–
17	6/M	9/5	168/35.2	AE, U/<4 mg	OP, AP, D, V, U, AE, C, A	Budesonide 200 mcg Dexchlorpheniramine 5 mg	1/not completed	–

Abbreviations: A, anaphylaxis; AD, atopic dermatitis; AE, angioedema; AP, abdominal pain; C, cough; D, diarrhea; HE, hen egg; OP, oral pruritus; OVM, ovomucoid; U, urticaria; V, vomiting, NA: not available.

egg. Signed informed consent was provided by patients or by their parents or legal guardians in all cases.

The desensitization protocol was performed at the hospital's allergy day unit under the direct supervision of medical and nursing staff, and with full cardiopulmonary resuscitation measures and a pediatric intensive care unit available at the hospital.

In 4 (35%) of the 17 patients, OVODES NM was used for the OFC, eliciting a positive reaction in all cases. In these cases, SOTI was started with the previous highest dose tolerated. In the remaining 13 patient (65%), it was started with dose 1 of OVODES NM as the OFC had been performed with pasteurized HE. Two patients had a history of allergic asthma and were thus administered budesonide 200 mc/12 h during the entire SOTI procedure.

All the participants (or their parents/legal guardians) were provided with instructions regarding the medication needed in case of an allergic reaction and were given a symptoms chart to fill out in case of a reaction, as well as a direct telephone line for consultation.

Updosing was performed weekly at the allergy day unit if the previous dose was well tolerated at home. At each visit, baseline spirometry was performed and fraction of exhaled nitric oxide was measured prior to updosing. The mean duration of the build-up period was 7 weeks.

Twelve patients (70.5%) developed symptoms during SOTI, although in most cases these were mild or moderate. The symptoms observed were oral pruritus (41%), abdominal pain (36%), cough (18%), diarrhea (12%), angioedema (12%), and atopic dermatitis (5.8%) (Table). Most patients required premedication prior to SOTI during the build-up period. The most common medication administered was oral dexchlorpheniramine, which was suspended in all patients during the maintenance period (Table).

Five patients required additional steps because of uncontrolled asthma, urticaria and/or persistent vomiting; 3 of these developed anaphylaxis either during the final doses (8, 9) or during the maintenance period at home, and required intramuscular adrenaline. Two of these patients currently tolerate foods containing HE and the third also tolerates 1/8 of boiled HE white.

Fourteen patients reached the maintenance dose (3600 mg of egg white) and now (mean of 9 months after SOTI) tolerate at least 3 HEs per week, including raw HE and all foods containing HE.

Three patients were unable to reach the maintenance dose due to side effects; 2 have achieved tolerance of foods containing HE, and 1 remains under a strict avoidance diet.

In summary, OVODES NM is a useful preparation for SOTI to HE. The product is cheap, sterilized, easily handled by patients, and can also be useful for oral food challenge testing.

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ERRATUM

Lack of Association of Programmed Cell Death 1 Gene (PDCD1) Polymorphisms With Susceptibility to Chronic Urticaria in Patients With Positive Autologous Serum Skin Test
Z Brzoza, W Grzeszczak, W Trautsolt, D Moczulski
Issue 6, Volume 22, 2012
Page 434, Table 3
The line showing mean age of disease onset was inadvertently deleted from Table 3.
The correct table should read as follows:

Table 3. UAS7 and Age of Disease Onset in Patients With Chronic Urticaria With Different PD1.3 Genotypes

	Genotype Distribution		
	AG	GG	*P*
Mean (SD) UAS7 score	19.8 (8.79)	21.2 (7.58)	NS
Mean (SD) age of disease onset, y	36.7 (7.13)	32.3 (8.26)	NS

Abbreviations: NS, not statistically significant; UAS7, Urticaria Activity Score (1-Week Assessment).