Acute Pancreatitis in the Context of Abdominal Attack of Hereditary Angioedema

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Palabras clave: Angioedema hereditario. Dolor abdominal. Edema pancreático. Pancreatitis. C1 inhibidor.

Hereditary angioedema (HAE) is a rare autosomal dominant disease (1:50 000 individuals) [1]. The most common forms of HAE result from mutations in the C1 esterase inhibitor (C1-INH) gene (*SERPING1*) that lead to a quantitative or qualitative C1-INH deficiency. The 3 types of C1-INH that have been described to data are as follows: C1-INH-HAE type 1, which is characterized by C1-INH quantitative deficiency; C1-INH-HAE type 2, which is characterized by C1-INH qualitative deficiency; and nl-C1-INH-HAE, which is characterized by normal C1-INH levels and function and is due to a heterogeneous gene mutation that includes FXII-HAE (*F12* gene), ANGPT1-HAE (angiopoietin 1), PLG-HAE (plasminogen), KNG1-HAE (kininogen 1), and UNK-HAE (unknown) [1]. Clinically, HAE is characterized by recurrent, nonpruritic edema, which typically involves subcutaneous tissue (face, extremities) and mucosal tissue (oropharyngeal, laryngeal, and gastrointestinal) and may last up to 3-5 days without treatment [1]. Involvement of the upper airways and gastrointestinal system can lead to airway obstruction, asphyxia, and abdominal attack [1,2]. Early diagnosis is therefore fundamental.

Abdominal attack is characterized by abdominal pain with or without other symptoms such as nausea, vomiting, diarrhea, and abdominal distension. These symptoms are secondary to transient edema of the wall of the intestinal tract and fluid shifts into the intestinal lumen or the peritoneal cavity [2]. In rare cases, abdominal attack manifests with signs of pancreatitis. Our aim was to increase physicians' awareness of pancreatitis as a sign or complication of abdominal attack in HAE. We report a case of acute pancreatitis due to abdominal attack of HAE with exclusively pancreatic edema and elevation of pancreatic enzymes in which C1-INH therapy was essential for clinical resolution. A 39-year-old woman with type 2 C1-INH-HAE and a history of multiple episodes of angioedema of the extremities since age 16 years was seen in our Outpatient Department at age 25 years. Her laboratory values were as follows: C3, 140 mg/dL (90-180); C4, 3 mg/dL (10-40); C1-INH, 56 mg/dL (18-32); and functional C1-INH, 30% (>68). She was initially treated with aminocaproic acid, which partially controlled the angioedema. At age 35 years, she presented with several episodes of abdominal pain and vomiting and started treatment with stanozolol 2 mg/d, which improved her symptoms. At age 39 years, under irregular treatment with stanozolol, she went to the Emergency Department with a new episode of intense and colicky epigastric pain in association with nausea and vomiting. She has no history of alcohol consumption or trauma and was not taking other medications. Abdominal ultrasound revealed a globular and swollen pancreas, with a heterogeneous and hypoechoic structure. There were no other relevant findings, including no free intraperitoneal fluid. C-reactive protein (CRP) had increased by 17.3 mg/dL and pancreatic enzyme values were elevated (lipase, 512 U/L; amylase, 374 U/L). No other analytical changes were recorded (leukocytes, hematocrit, bilirubin, and transaminases). The patient was treated with several analgesics (acetaminophen, butylscopolamine, and tramadol), although her symptoms did not improve. HAE was accepted as being the cause of the acute pancreatitis and, 8 hours after the onset of abdominal attack, 1000 U of C1-INH concentrate (Berinert, CSL Behring) was administered; her symptoms resolved within about 30 minutes. She was hospitalized for observation without the need for analgesics. After 24 hours, a second abdominal ultrasound scan did not reveal pancreatic changes but did reveal the presence of a moderate amount of free fluid in the Morrison space and in the pouch of Douglas that were not evident in the first scan. CRP and pancreatic enzyme levels had decreased. The patient was discharged 96 hours later; she was asymptomatic and had been diagnosed with abdominal attack of HAE with exclusively pancreatic involvement.

Gastrointestinal tract involvement is one of the most common features of HAE, and attacks affecting the abdomen are almost as common as those affecting the skin (>90% of patients) [3]. The difficulty in associating gastrointestinal symptoms with an abdominal attack of HAE often leads to an incorrect diagnosis, such as irritable bowel syndrome or renal colic. Appendicitis, intestinal obstruction, and cholecystitis may be suspected and consequently lead to unnecessary surgical procedures. One study concluded that one third of HAE patients with abdominal symptoms underwent unnecessary abdominal surgeries [2]. In rare cases, abdominal

Table. Recently Published Cases of Pancreatitis Secondary to Abdominal Attack of Hereditary Angioedema (adapted from Lopes-Veronez et al, Front Med (Lausanne). 2019;6:80

Paper	Gender, Age	Lipase, U/L	Amylase, U/L	Treatment	Clinical Evaluation	Gastrointestinal Surgeries
Our case	F, 39	512	374	C1 inhibitor	Improvement in 30 min	No history
Lopez-Veronez et al [3]	M, 21	1.159	292	Icatibant	Improvement in 3 h	No history
	F, 47	ND	210	Icatibant	Improvement in 1 h	Appendectomy
Loudin et al [4]	F, 56	663	ND	C1 inhibitor	Improvement in 30 min	Cholecystectomy
Maamer et al [5]	F, 73	1235	869	Danazol	Improvement in 5 d	No history
Czaller et al [6]	F, 29	1452	2615	C1 inhibitor (2 times)	Improvement in 4 h	Appendectomy
Cancian et al [7]	F, 32	ND	470	C1 inhibitor	Improvement in 30 min	ND

Abbreviations: F, female; M, male; ND, not determined.

attacks of HAE are associated with acute pancreatitis. Although this association is not fully documented, it is thought that pancreatic edema may cause obstruction of the pancreatic duct or the ampulla of Vater, leading to episodes of pancreatitis [3]. The Table shows several published cases [3-8] of acute pancreatitis due to abdominal attack of HAE. All patients were treated with specific HAE therapy, and symptoms improved. This improvement was faster in patients undergoing treatment of an acute attack.

The unspecific symptoms of abdominal attack of HAE can hamper diagnosis and, in the absence of clinical suspicion, treatment may be postponed altogether. In addition, laboratory parameters remain largely unchanged, except for an increase in hematocrit, which is probably secondary to hemoconcentration, dehydration, and translocation of fluid into the intestinal wall, as well as leukocytosis [9]. A recent study [10] found a correlation between CRP levels and abdominal attack of HAE: increased CRP levels during the attack are found mainly in patients with abdominal locations. In the absence of an attack, increased CRP levels may alert the physician to severe inflammation. Imaging may prove useful in the initial investigation of abdominal pain episodes. During an abdominal attack, endoscopy may show ascites and/or visceral edema and frequently edema of the intestinal wall [2]. Since intestinal swelling associated with acute HAE attacks could induce pancreatitis, serum amylase and lipase should be monitored, as management of the attack could vary depending on the results.

The therapies currently available for treatment of HAE attacks comprise C1-INH concentrate, hr-C1-INH, icatibant, and ecallantide [1]. As no specific biomarker of this condition has been identified, rapid improvement in symptoms after administration of specific therapy enables us to differentiate between abdominal attacks of HAE and other etiologies.

Although rare, HAE is associated with significant comorbidity, and a history of unnecessary abdominal surgeries is not unusual in abdominal attack of HAE. Health professionals should be aware of the existence of this entity to perform early diagnosis and institute appropriate therapy. Since HAE is a potential cause of acute abdomen (eg, acute pancreatitis), HAE-specific therapy should be considered a therapeutic option.

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Conflicts of Interest

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Previous Presentations

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Allergy to Strawberry in Children From the Mediterranean Area: Is It Really Allergy?

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Members of the *Rosaceae* family are the most frequent cause of allergic reactions to fruits in the Mediterranean area [1]. Strawberry, which belongs to the *Rosoideae* subfamily of *Rosaceae*, has an apparently unjustified poor reputation among the general population, as self-reported symptoms after ingestion of strawberry are very common [2,3]. However, few cases of true allergy have been reported in the literature [4-7].

The aim of our study was to make a descriptive analysis of pediatric patients with a history self-reported strawberry allergy and to investigate whether they had true allergy. Patients from the Pediatric Allergy Department of Hospital General Universitario Gregorio Marañón, Madrid, Spain were retrospectively analyzed on the basis of a clinical history of strawberry allergy, specific IgE (sIgE) to strawberry, and age under 17 years.

The data we recorded included demographic and clinical characteristics, specific IgE (sIgE) values to strawberry (ImmunoCAP 250, Thermo Fisher Scientific), skin prick test (SPT) results with a commercial strawberry extract (Leti), sensitization to profilin by prick and peach nonspecific lipid transfer protein (nsLTP) by prick (peach extract enriched with Pru p 3 [ALK-Abelló] or Pru p 3 [ImmunoCAP]), and tolerance to strawberry in oral food challenge (OFC). sIgE values to birch PR-10 (Bet v 1) were not analyzed, as sensitization to birch pollen is not common in our area. SPT wheals ≥3 mm and sIgE values ≥0.35 kU/L were considered positive.

Qualitative variables are expressed as a frequency and quantitative variables as median (IQR). Categorical variables were compared using the χ^2 test and Fisher exact test; quantitative variables were compared using the Mann-Whitney test.

The study population comprised 43 children with a clinical history of strawberry allergy. Of these, 29 (67%) had a positive SPT and/or sIgE result to strawberry (group 1) and 14 (33%) had negative results in both tests (group 2).

Median time between self-reported symptoms related to strawberry intake and the allergological work-up for assessment of tolerance was 4 (3-6) months and 6 (4-9) months.

Cofactors such as concomitant exercise, infectious disease, and nonsteroidal antiinflammatory drug intake were excluded in all patients.

Among patients belonging to group 1 (58.6% male, median age 9 [6-12] years), the most frequently reported symptoms were pruritus of the oral mucosa (oral allergy syndrome [OAS]) and cutaneous symptoms (48.3% and 37.9%, respectively). Three patients (10.3%) reported gastrointestinal symptoms and 1 anaphylaxis (3.4%). All patients also had concomitant atopic diseases: 23 patients (79.3%) were allergic to other foods (mostly other fruits [n=20], with peach the most frequently involved [39.3%] in fruit-allergic patients), 16 (55.1%) had rhinoconjunctivitis and/or bronchial asthma related to aeroallergens other than birch, and 13 (44.8 %) had atopic dermatitis.

Symptoms at onset in patients belonging to group 2 (57.1% male, median age 4.5 [2-12] years) comprised OAS (50%) and cutaneous symptoms (50%). All but 1 patient had at least another atopic disease: 7 (50%) had atopic dermatitis, 6 (42.8%) had at least 1 other food allergy (with fruits being the most frequently involved [n=4]), and 5 (35.7%) had rhinoconjunctivitis and/or bronchial asthma related to aeroallergens but not birch.

No statistical differences were observed regarding gender, age, or type of symptoms between groups. Patients in group 1 were more frequently allergic to other foods and fruits than those in group 2 (p=0.03 and 0.01 respectively), although no differences were observed for other atopic diseases.

The results of the allergological work-up are shown in the Table. Tolerance was assessed in 28 children (65.1%, 16 belonging to group 1 and 12 to group 2), with a dose proportionate to their age, and all but 1 tolerated strawberry (96.4%). There were no significant differences between patients belonging to group 1 in whom tolerance to strawberry was assessed and those in whom it was not regarding age, clinical symptoms, concomitant atopic diseases, sIgE values to strawberry, and SPT results with strawberry, profilin, and nsLTP. These data were not analyzed for patients belonging to group 2 owing to the small sample (12/14 tested for tolerance vs 2/14 not tested).

All but 1 child in group 1 (16/29 tested) tolerated strawberry (93.7%): 3 were not allergic to other fruits, 7 were allergic to peach, 3 to *Rosaceae* fruits other than peach, and 2 to fruits other than *Rosaceae*. The patient who did not tolerate strawberry had a clinical history of anaphylaxis with strawberry, a positive SPT and ImmunoCAP result to strawberry (2.47 kU/ L), and a positive SPT to profilin (sensitization to LTP not tested). This boy was also allergic to apple, house dust mite, and plane tree pollen. All children tested in group 2 tolerated strawberry.

Consistent with other studies carried out in southern Europe, most of the patients in our study who self-reported symptoms after strawberry consumption experienced mild symptoms (OAS and cutaneous symptoms) and were allergic to other fruits, mostly peach [4,5,7]. Moreover, 96% of the children in our study with symptoms after strawberry intake tolerated the fruit in a subsequent OFC, thus supporting the idea that true allergy to strawberry is not as frequent as it seems. Since this was independent of whether or not they were sensitized to strawberry, neither SPT nor CAP seem to have good sensitivity, although specificity was good, as all patients with negative results in both diagnostic tests tolerated strawberry.

The high percentage of patients sensitized to peach LTP (61.3% [19/31 tested]) and profilin (41.4% [12/29 tested]) could partly explain the patient's sensitization to strawberry due to cross-reactivity [4].

Our study suggests that true allergy to strawberry in our part of the Mediterranean area is rare. Therefore, we believe that, in our region, OFC should be considered in children who report mild symptoms (OAS and/or cutaneous symptoms) after strawberry intake, regardless of whether or not they are sensitized to strawberry, and even in those who are sensitized to LTP. Nevertheless, in patients with more severe symptoms, true allergy to strawberry might be considered.

Further studies involving more patients are needed in order to analyze whether severity of the symptoms and strawberry allergen sensitization profile are associated with true strawberry allergy.

Table. Result of the Allergological Work-up

	Group 1 (n=29)	Group 2 (n=14)	*P* Value
Strawberry sIgE			<.0001
≥0.35 kU/L, No. (%)	26 (89.7)	0 (0)	
Median (IQR) sIgE value, kU/L	2.53 (1.05-8)	NA	
<0.35 kU/L, No. (%)	3 (10.3)	14 (100)	
Strawberry SPT, No. (%)			.003
Positive	9 (31)	0 (0)	
Negative	9 (31)	14 (100)	
ND11 (37.9)	0 (0)		
Peach LTP			.03
Positive, No. (%)	17 (58.6)	2 (14.3)	
No. positive by SPT/No. tested by SPT	13/20	2/8	
No. with Pru p 3 ≥0.35 kU/L/No. tested for Pru p 3	11/15	0/2	
Median (IQR) sIgE value, kU/L	7.35 (2.04-15.6)	NA	
Negative, No. (%)	6 (20.7)	6 (42.9)	
ND, No. (%)	6 (20.7)	6 (42.9)	
Profilin by SPT, No. (%)			.21
Positive	12 (41.4)	0 (0)	
Negative	9 (31)	8 (57.1)	
ND	8 (27.6)	6 (42.8)	
OFC with strawberry, No. (%)			.98
Positive	1 (3.4)	0 (0)	
Negative	15 (51.7)	12 (85.7)	
ND	13 (44.8)	2 (14.3)	

Abbreviations: NA, not applicable; ND, not done; OFC, oral food challenge; SPT, skin prick test.

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Conflicts of Interest

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Anaphylaxis to Mepolizumab and Omalizumab in a Single Patient: Is Polysorbate the Culprit?

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The past decade has seen an increase in the use of biological agents such as mepolizumab and omalizumab for the treatment of severe asthma. These agents reduce the frequency of exacerbations, allow for reduced oral corticosteroid use, and increase quality of life. Their safety profile is generally very good. Beside local adverse effects, which are comparable in placebo-controlled clinical trials, there are very few reports on anaphylactic reactions to these biologics [1,2].

Pivotal studies indicate that the anti-IL-5 antibody mepolizumab is well tolerated, with no reports of anaphylaxis or treatment-related deaths [2]. The anti-IgE monoclonal antibody omalizumab binds to the constant region of free IgE only and, therefore, does not cause mast cell degranulation. However, omalizumab has been reported to cause anaphylaxis in <0.1% of patients, with reactions being delayed in many cases [3]. The mechanism for these reactions is, however, unclear [3]. Here, we report an anaphylactic response after 13 months of treatment with mepolizumab and following the subsequent first injection of omalizumab in a patient with severe asthma.

The patient was a never-smoking woman (born 1989) who, since childhood, had had allergic asthma due to sensitization to cat and dog dander, house-dust mite, and tree and grass pollen. Sublingual immunotherapy for chronic rhinosinusitis without polyps due to mite allergy was attempted but discontinued because of unwanted adverse effects. There were no other clinically relevant comorbidities. During the 12 months before starting mepolizumab, the patient experienced 4 serious asthma exacerbations despite using a high-dose inhaled corticosteroid (fluticasone 1500 µg), a long-acting ß mimetic, a long-acting muscarinic antagonist, and a leukotriene receptor antagonist. Her symptoms were severe, with nightly awakening (3-5 times/wk) and exercise-induced dyspnea after climbing about 20 stairs.

Before starting mepolizumab on November 1, 2017, the patient had a total blood IgE of 1109 kU/L, sIgE against grass pollen (class 4), tree pollen (class 5), and *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (class 6). Her eosinophil count was 540/µL (without oral corticosteroids). FEV_1 was 2.5 L (65% predicted). Following initiation of

mepolizumab (100 mg/mo), she was able to discontinue corticosteroids and experienced no exacerbations for 13 months. Her FEV_1 increased to 3.1 L (78% predicted).

On December 12, 2018, about 30 minutes after her 13th injection of mepolizumab 100 mg, the patient developed dry cough and dyspnea, with a fall in blood pressure to 90/60 mm Hg, a heart rate of 140 bpm, and respiratory distress. Her FEV_1 decreased from 2.4 L (62% predicted) to 1.6 L (41% predicted), and she hyperventilated (pO_2, 84 mm Hg; pCO_2, 22 mmHg). She was treated with 250 mg prednisolone intravenously and inhaled salbutamol and ipratropium bromide. She was hospitalized with a diagnosis of status asthmaticus and treated with inhaled adrenaline, subcutaneous terbutaline, and noninvasive intermittent ventilation therapy. Her laboratory results 8 days later were as follows: eosinophils, 0.3% (30/μL); C-reactive protein, 0.2 mg/dL; and tryptase, 6.7 μg/L.

The patient herself and the attending pulmonary physician assumed that this was probably not a reaction to mepolizumab but an asthma exacerbation that had occurred many times before the biologic. She was subsequently referred to us with a request to continue mepolizumab therapy for severe asthma in our center. Three weeks later, after discussion with the patient, we performed a prick test with undiluted mepolizumab. As the test was negative after 20 minutes, we injected mepolizumab 0.3 mL (about 35 mg) subcutaneously.

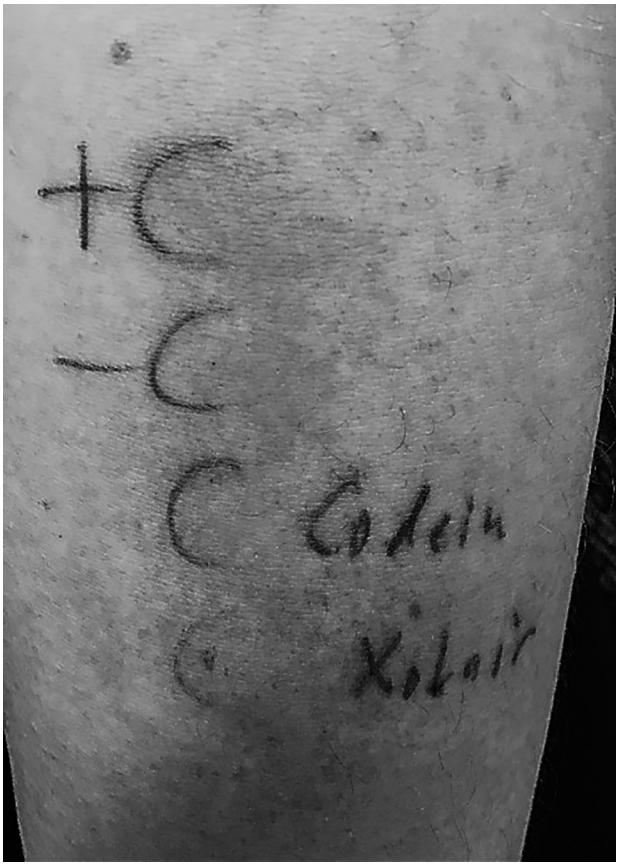

Figure. Skin prick test with histamine (0.1%), saline (0.9%), codeine (0.9%), and omalizumab (Xolair, undiluted) after 45 minutes.

Thirty minutes later, she developed dry cough, dyspnea, and wheezing, with a decrease in blood pressure. She was treated immediately with prednisolone 250 mg intravenously, terbutaline subcutaneously, salbutamol, and oxygen. After 20 minutes she recovered slowly and was not hospitalized.

Since the patient fulfilled the indication for omalizumab, we responded to her request to start taking the drug, although we wanted to clarify her tolerability in advance. On February 21, 2019, we performed skin prick tests with omalizumab, mepolizumab, benralizumab, and polysorbate (all undiluted). Given that all tests were negative after 15 minutes, we injected omalizumab 0.1 mL subcutaneously. However, about 10 minutes later, the test with polysorbate became positive, with a wheal of 4 mm, and the test with omalizumab became positive after about 45 minutes (Figure). About 20 minutes following the omalizumab injection, the patient developed a dry cough, dyspnea, dizziness, and obstruction with no signs of hyperventilation or any other stress-induced reaction. The reaction was moderate. Following inhalation of salbutamol and a subcutaneous terbutaline injection, the dyspnea resolved, and the patient's breathing returned to normal.

No cases of mepolizumab-induced anaphylaxis have been reported to date. In contrast, anaphylactic responses minutes following administration of omalizumab after more than a year of uneventful treatment have been described in 2 patients [4]. However, the authors concluded that this was not due to sensitization to the monoclonal antibody, as neither IgE nor IgG antibodies to omalizumab could be found. Instead, they concluded that polysorbate 20, an excipient in omalizumab, was the most likely cause of these reactions. Interestingly, polysorbate is also an excipient in mepolizumab.

Polyoxyethylene-sorbitan-20-monolaurate (also known as polysorbate 20 and Tween 20) is a solubilizing agent used ubiquitously in many medical preparations. With respect to the biologics used to treat asthma, polysorbate 20 is an excipient in omalizumab and benralizumab, as is polysorbate 80 in mepolizumab and dupilumab but not reslizumab. Polysorbate 20 and 80 have no differences as inducers of anaphylactic reactions. In a patient experiencing multiple anaphylactic responses to an intravenously administered vitamin product, polysorbate 80 was identified as the causative agent [5]. Furthermore, polysorbate 80 has been considered the causative agent in anaphylaxis to intramuscular corticosteroids [6] and in anaphylaxis in a teenager receiving omalizumab containing polysorbate 20 [7]. The fact that antipolysorbate IgE molecules were not found in any of these reports suggests that the response was nonallergic anaphylaxis. A clue to the possible mechanism has been suggested in experiments in beagle dogs, in which polysorbate 80 has been shown to activate the complement cascade, resulting in mast cell degranulation [8]. Polysorbates are structurally related to polyethylene glycols, which are also frequently used as excipients and which are reported as a cause of anaphylaxis [9].

We have since performed skin prick tests to polysorbate 20 in 8 healthy adults and 7 patients with severe asthma receiving mepolizumab or benralizumab for more than 3 months. All results were negative.

In conclusion, we show the development of hyperresponsiveness to mepolizumab 13 months after

successful treatment and apparent cross-reactivity with omalizumab. We believe that in both cases, the cause was a non–IgE-mediated anaphylactic response to the excipient polysorbate, which was used in both agents.

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Anaphylaxis in an 8-Year-Old Boy Following the Consumption of Poppy Seed

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Palabras clave: Anafilaxia. Semillas de amapola. Alergia alimentaria. Niño. Diagnóstico molecular.

The seeds of the poppy (*Papaver somniferum*) are traditionally used as ingredients in cakes and bread and for garnishing and are rarely considered a cause of food allergy [1]. The most common hypersensitivity reactions to seeds are those induced by sesame, with 0.1%-0.2% of the world's population being allergic. In contrast, few data are available regarding hypersensitivity to poppy seeds. The adverse effects associated with poppy seed consumption affect the gastrointestinal tract, the skin, and the respiratory system [2]. Anaphylactic reactions may occur, particularly in patients with concomitant allergy to hazelnuts and pollens. Poppy seeds can induce both immunological and nonimmunological hypersensitivity [3], and physical effort may also be a cofactor in reactions [4].

The aim of the present article is to raise awareness of poppy seed anaphylaxis in children. It is also the first case study to confirm sensitization to a 2S albumin from poppy seeds by means of molecular diagnosis tests.

An 8-year-old boy was admitted to our department following 2 incidents of anaphylaxis after consuming products containing poppy seeds. The first incident occurred at the age of 6 years. A few minutes after biting into a poppy seed cake, the child experienced generalized urticaria, runny nose, sneezing, conjunctival redness, wheezing, and shortness of breath. The second incident occurred 2 years later, when the same symptoms were observed a few minutes after consuming a poppy seed roll. The patient's medical history revealed that he had periodically reported discomfort in the mouth and redness of the conjunctiva after eating chocolate. Laboratory tests (ImmunoCAP ISAC) indicated an increased concentration of tIgE (733 kU/L) and sIgE for poppy seeds (28.3 kU_A/L) (Table). Sensitization to hazelnut (9.6 kU_A/L), soybean (0.91 kU_A/L), sesame seed (3.4 kU_A/L), and alder pollen (1 kU_A/L) were also demonstrated. The result of prick-by-prick testing was positive for fresh poppy seeds extracted in liquid nitrogen. Molecular diagnostics using the ALEX test identified the presence of sIgE for poppy extract (13.17 kU_A/L), Pap s 2S albumin (2.31 kU_A/L), and nut extract, as well as pumpkin, sunflower, and sesame seeds. Component-resolved diagnostics performed using the ISAC method identified allergy to hazelnut Cor a 9, sesame seed Ses i 1, and soybean Gly m 6 (Supplementary Table 1). Based on the clinical history and test results, the patient was diagnosed with anaphylaxis to poppy seeds.

Few descriptions of anaphylactic reactions to poppy seed have been published, especially those regarding children (Supplementary Table 2). Such reactions usually result from oral ingestion, although a case of anaphylaxis has also been described following inhalation [5]. Contact urticaria and swelling of the face after contact with a poppy flower (*Papaver rhoeas*) have also been demonstrated in the absence of allergy to poppy seed [6].

The course of poppy allergy can vary from mild oral allergy syndrome to anaphylactic reactions. Panasoff [7] reported the case of a 17-year-old boy who experienced anaphylactic reactions in the form of acute abdominal pain with generalized urticaria and hypotension after eating poppy seed cake. The author emphasized that only a trace amount of allergen was responsible for the symptoms. Similarly, the anaphylactic reactions observed in the present patient occurred after only 1 bite of cake.

As in most case reports [1,3,5-7] and in contrast with Kutting and Brehler [4], in the present case, physical effort

Table. Sensitization to Poppy Seed in the Present Case Assessed Using Different Methods

Allergen Test							
SPT[a]		asIgE[b,c]		CRD[d]			
Allergen Extract	Diameter	Allergen Extract	Concentration, kU_A/L		Allergen		Concentration, kU_A/L
Poppy seed	7 mm	Poppy seed[b] Poppy seed[c]	28.3 13.17	Poppy seed[d]	Pap s 2S Albumin	2S albumin	2.31

Abbreviations: SPT, skin prick test; asIgE, allergen specific IgE; CRD, component-resolved diagnosis.
[a]Prick by prick method, histamine diameter 3 mm, negative control diameter 0 mm.
[b]ImmunoCAP, allergen extract.
[c]ALEX, MacroArrayDX (extracts, kUA/L).
[d]ALEX; MacroArrayDX (allergens, kUA/L).

was not found to be a cofactor of reaction after ingestion of poppy seed.

Hazelnut allergy is commonly found to co-occur in patients with poppy seed allergy [1,3-5,7,8], and was also identified in the present case.

Among the previous descriptions of the methods used to diagnose poppy allergy, only Oppel et al [1] used an oral food challenge with ground poppy seed. Our case report is the first to describe the use of a molecular approach to diagnose allergy to poppy seeds.

The best-known allergens of poppy seed are Pap s 1, Pap s 2, and Pap s 34 kD, although reported data also support the possible role of other allergenic molecules, such as 2S albumin [3,9]. The main poppy allergen is believed to be a 45-kD glycoprotein, which, owing to its homologous structure, may cross-react with Bet v 1. Poppy seed also displays cross-reactivity with proteins present in wheat, rye flour, buckwheat, sesame, rice, and kiwi [2-3]. Varga et al [8] reported the case of a patient allergic to an 11S globulin who experienced anaphylaxis to buckwheat and showed symptoms of OAS after ingesting poppy seed. The presence of antibodies produced through contact with buckwheat or hazelnut allergens may cause a cross-reaction with the 11-S poppy globulin. It is also possible that the antibodies raised against 2S of poppy albumin may also cross-react with prolamins of other seeds, nuts, and legumes. Asero et al [10] reported cross-reactivity between sesame and poppy protein extracts (molecular mass, 10-12 kDa) and suggested that the major sesame allergens Ses i 1 or a Ses i 2 may cross react with poppy seed 2S albumin [10]. Although not yet registered in the official allergen database IUIS, a poppy seed 2S albumin is included in the ALEX microarray. It is noteworthy that in the ALEX macroarray, we can assess only sensitization to the whole poppy seed extract and to 2S albumin. The patient in the present report may by sensitized to other poppy seed allergens, since sIgE to the whole extract in ALEX was 13.17 kU/L, whereas sIgE to Pap s 2S was only 2.31 kU_A/L.

In the case we report, the main culprit allergen was poppy seed. Both the ImmunoCAP ISAC study and the ALEX study detected the presence of antibodies to the hazelnut 11S globulin Cor a 9, which is a marker of primary sensitization and is responsible for systemic reactions. However, the antibody concentration was low, and the patient had consumed hazelnut products on several occasions, reporting only oral allergy syndrome and minor conjunctival redness.

Although rare, allergy to poppy seed is often rapid, generalized, and potentially life-threatening. Poppy seeds should therefore be considered a causative agent in the diagnosis of anaphylaxis.

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Conflicts of Interest

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Erythema Multiforme Induced by Tramadol: An Allergy Assessment

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Erythema multiforme (EM) is a severe inflammatory skin disorder caused mainly by infections and rarely by drug hypersensitivity. Sulfamides, penicillins, and antiinflammatory drugs are the most common causes of drug-induced EM. A weak association between tramadol and Stevens-Johnson syndrome and toxic epidermal necrolysis has been reported [1]. We report a case of EM induced by tramadol confirmed with an allergy work-up.

An otherwise healthy 47-year-old nonatopic woman was taking acetaminophen 325 mg/tramadol 37.5 mg (Pazital) every 8 hours and etoricoxib 60 mg every 24 hours for low back pain. After 4 weeks of treatment, she experienced an eruption with symmetrical distribution of target lesions on the palms, soles, arms, and torso and then on the oral mucosa 3 days later. She was evaluated in the dermatology department and treated with oral antihistamines, prednisone, lidocaine, topic fusidic-acid/hydrocortisone-acetate (Fucidine), and 0.05%/0.1% betamethasone-dipropionate/gentamicin-sulfate (Diprogenta). The lesions resolved within 2 months without sequelae or hyperpigmentation.

A biopsy specimen was taken from the right palm, and a polymerase chain reaction assay was performed to detect human herpesvirus 6, 7, and 8. The result of the serology study was negative, and infection, stress, and other possible targets of EM were not suspected. Histopathology confirmed a diagnosis of drug-induced EM (Figure). The patient was referred to the allergy department.

We performed patch tests with acetaminophen 5% and 10%, tramadol 5%, and etoricoxib 10%, (petrolatum as vehicle). Two nonatopic patients were controls. We obtained negative results at 48 and 96 hours. A lymphocyte transformation test (LTT) was performed.

The LTT showed a mild positive result for Pazital, with a stimulation index (SI) of 2.25 and negative results (<2) for etoricoxib, acetaminophen, and tramadol. In addition, the patient reported having taken Pazital some weeks before the reaction and that this had led to micropapules on her palms that resolved spontaneously in 5 days after intake. One month after the reaction resolved, the patient took acetaminophen with ibuprofen and experienced palmar pruritus with no lesions. She interrupted drug intake and experienced no further symptoms. She subsequently tolerated ibuprofen.

With the test results and related history, we suspected acetaminophen as the most probable culprit drug and performed various dose-graded drug provocation tests (DPTs). The result for etoricoxib was negative. Unexpectedly, with tramadol, the patient experienced typical cutaneous lesions on the palms slightly over 1 hour after intake of 40 mg of tramadol (Supplementary figure). The result of the DPT with acetaminophen was negative.

After the positive DPT result with tramadol, we performed a new LTT with Pazital as previously reported [2]. We obtained an SI of 2.08 and 2.04 for Pazital, 4.56 (10 µg/mL) and 5.67 (25 µg/mL) for tramadol, and <2 for acetaminophen, thus confirming tramadol as the culprit agent.

There are no reported cases of EM due to tramadol. In the present case, the patch test and LTT results were not sufficient to confirm the diagnosis and we had completed the study with DPT. We finally obtained a positive LTT result after the positive DPT result.

EM is a well-characterized skin syndrome consisting of a polymorphous eruption of macules, papules, and characteristic target lesions that are symmetrically distributed with a propensity for the distal extremities and minimal mucosal

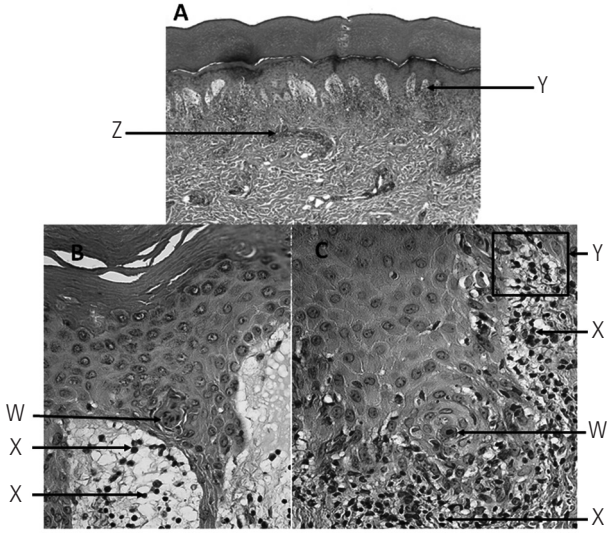

Figure. Histopathology image of an erythema multiforme skin lesion (original magnification, x4 [A] and x20 [B, C]). Necrotic keratinocytes throughout the epidermis (W). In the superficial dermis, note the inflammatory infiltrate characterized by lichenoid infiltrate rich in lymphocytes (X), with interface damage, lymphocytic exocytosis (Y), with blood extravasation (Z). A perivascular inflammatory infiltrate can be seen in the dermis, with no fibrinoid necrosis in the walls of the blood vessels.

involvement. The severity of EM varies, and the condition has been classified as EM minus (less severe) and EM majus (more severe) [3]. Our case fits the description of EM minus. We found few publications reporting drug-induced EM confirmed with biopsy and a positive DPT result, as reported here [4].

In their review of 37 cases of drug-induced EM from 2010 to 2016, Roujeau et al [5] reported that the diagnosis was considered definite/probable in 6 cases (16%), possible in 7 cases (19%), and 'no case' in 24 cases (65%). Therefore, 65% did not fulfill the published clinical criteria for EM, and none of the 6 cases of probable EM were supported by evidence of drug causality [5].

The novelty of the present case lies in the rapid onset of target lesions on the palms after taking tramadol in the DPT.

Given the rapid onset in the positive provocation test with tramadol, we might consider the reaction to be a fixed drug eruption (FDE) resembling EM. Nonetheless, we think that the reaction was EM. The morphology of targetoid lesions (Figure) is typical of EM. FDE can present with targetoid lesions that mimic EM (erythema multiforme–like FDE), although in FDE, these lesions have only 2 concentric zones of color with a darker, dusky hue in the center. This description differs from that of the present case, and the palms are not usually affected in FDE. Many atypical histologic reaction patterns have been described in FDE. In the present case, a lymphocytic infiltrate was involved in the dermo-epidermal junction, with no melanin incontinence (frequently found in repeated lesions of FDE) or residual lesions, as is usually the case in FDE [6].

Type IVb nonimmediate drug reactions correspond to a TH2-type immune response, where TH2 T-cells secrete IL-4 and IL-13, thus potentially accounting for the rapid onset of the skin lesions [7,8]. The activated T cells migrate to the tissue and kill tissue cells such as keratinocytes in a perforin/granzyme-B– and/or FasL-dependent manner [9]. Part of the activated T cells transform into effector memory T cells; when these are located on the skin (palms in the case we report) as tissue-resident memory CD8+ T cells, they can produce a faster response than the previous one in the next contact with the drug (skin-homing T cells) [2,7].

The LTT yielded positive results, probably owing to the proliferation of activated lymphocytes in the reaction as memory $CD8^+$ T cells, $\delta\gamma$ T cells, NK cells, and NKT cells [7,9]. The reproducibility of the LTT has been proven elsewhere [10], with a coefficient of variation <9% for phytohemagglutinin stimulation, thus illustrating the good quality of the technique. Therefore, our LTT result was interpreted as correct and can explain the timing of nonimmediate reaction.

We describe EM induced by tramadol assessed using an allergy study and with negative skin test results. The diagnosis was based on clinical data and confirmed by histopathology and LTT, after a positive DPT result. The rapid onset of target lesions on the palms after the DPT highlights the intriguing immunological nature of this entity.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

The data from this study were presented in part in poster form at the 43rd Spanish National Congress of Dermatology and Venereology (May 2015, Seville, Spain) and in poster form at the Meeting of the European Academy of Allergy and Clinical Immunology (June 2015, Barcelona, Spain).

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Cheilitis Associated With Sensitization to *Penicillium notatum* in a Clarinetist

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Palabras clave: Queilitis. *Penicillium notatum*. Dermatitis de contacto. Clarinete. Atopia.

Cheilitis is an inflammatory process affecting the lips. It could be due to various causes, such as extreme temperatures, malignant conditions (actinic cheilitis), nutritional deficiencies, infections, atopic dermatitis, and contact dermatitis [1]. Isolated cases of cheilitis due to contact dermatitis caused by sensitization to wood have been reported in wind instrument players [2-5]. Allergic contact dermatitis is the most frequently reported allergic condition affecting violinists and violists [6].

A 15-year-old boy consulted in 2017 for recurrent episodes of cheilitis. He had been treated with repeated cycles of a potent topical corticosteroid (clobetasol), and his clinical condition improved. Nevertheless, cheilitis relapsed when the treatment was stopped. He also reported that several months previously, he had experienced a self-limiting episode of labial angioedema while eating a pork loin sandwich. When specifically asked about his hobbies, he told us that he had played the clarinet since the age of 8 years using a wooden mouthpiece (*Arundo donax*). He also reported a personal history of allergic rhinoconjunctivitis due to sensitization to the fungus *Penicillium* and had rhinoconjunctivitis that was related to exposure to a fish tank in his bedroom. His symptoms resolved when the fish tank was removed. He had also been diagnosed with allergic rhinoconjunctivitis due to grass pollen allergy that had improved notably after 4 years of sublingual immunotherapy with a 5-grass extract. The physical examination was unremarkable, except for upper and lower lip cheilitis (Figure).

Skin prick tests with a locally adapted battery of aeroallergens were positive to Penicillium species and grass pollen. Specific IgE results (ImmunoCAP, Thermo Fisher Scientific) were as follows: *Penicillium notatum* (7.13 kU_A/L and 13.4 kU_A/L, 5 years ago and at present, respectively) and *Phleum pratense* (65.1 kU_A/L). Total IgE was 357 kU/L.

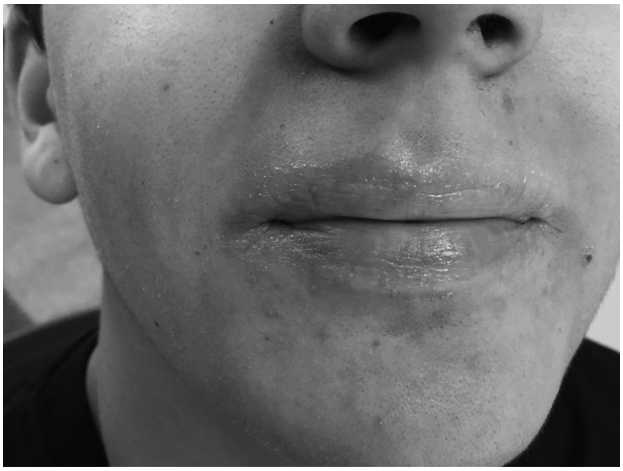

Figure. Upper and lower lip cheilitis.

Culture of the mouthpiece was performed by the Department of Medical Microbiology on blood agar plates and Sabouraud dextrose agar with chloramphenicol for the selective isolation of fungi. A fungus had grown at 48 hours and was identified as *P notatum* using matrix-assisted laser-desorption ionization–time-of-flight mass spectrometry [10]. The microbiologist did not know that the patient was sensitized to *P notatum*.

We advised the patient to change the mouthpiece for a plastic one and to wash it with a disinfectant solution after use. At his 1-year check-up, the patient reported that he had not experienced any further episodes of cheilitis.

We present the case of an atopic clarinet player who developed recurrent episodes of cheilitis. He had previously experienced rhinoconjunctivitis due to *P notatum*. We were able to demonstrate the growth of *P notatum* in the wooden mouthpieces that he used when playing the clarinet. Cheilitis due to contact dermatitis caused by the wood used in wind instruments has been reported by several authors [2-5]. Ruiz Hornillos et al [2] and McFadden et al [3] both reported a case of cheilitis in a clarinetist who used a cane reed nozzle. Inoue et al [4] reported a case with similar symptoms in a saxophonist, also due to a cane reed mouthpiece. None of those patients were sensitized to molds. Van der Wegen-Keijser et al [5] reported cheilitis in a saxophonist, although the mycological culture of the nozzle was negative for molds. In the present case, we were able to rule out the wood of the mouthpiece as the culprit factor because the patient had later been playing the same clarinet using a plastic mouthpiece that he disinfected after every use without relapse of cheilitis.

Concerning the mechanism of the reaction, it is clear that the fungus *P notatum* was present in the mouthpiece. It seems that the organic nature of the mouthpiece, together with the humidity provided by the saliva, provides a favorable substrate for the growth of the fungus. Nevertheless, we cannot say whether an IgE-mediated mechanism (protein contact dermatitis, as the patient was sensitized to *P notatum*, demonstrated by skin prick test and sIgE) or a type IV contact

mechanism is involved (as in other case reports with similar symptoms due to type IV sensitization to woods) [2-7]. Finally, the episode of lip angioedema when eating pork loin could be explained by the fact that processed cold meat is stuffed into casing with mold cultures to enhance flavor and aroma [8-9].

To the best of our knowledge, we report the first case of cheilitis due to *P notatum*.

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Conflicts of Interest

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Successful Adaptation of Bee Venom Immunotherapy in a Patient Monosensitized to Api m 10

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Bee venom immunotherapy (BVIT), although highly effective, does not protect 10%-15% of patients allergic to bee stings [1]. Even though the production of allergenic extracts is standardized, the real content of major components is not completely known, given the total content of allergenic proteins and the enzymatic activity of phospholipase A2 (Api m 1) and hyaluronidase (Api m 2).

To date, 12 allergens have been described as components of Apis mellifera venom (AMV). Api m 1, Api m 2, Api m 3, Api m 5, and Api m 10 are considered major allergens, and their specific IgE (sIgE) can be determined using commercially available techniques [1]. Api m 1 was the first described and is the most important; indeed, the presence of IgE to rApi m 1 is regarded as an unequivocal sign of sensitization to AMV. Nevertheless, undetectable sIgE to rApi m 1 does not exclude sensitization to AMV [2]. Therefore, sensitization to AMV can be extremely complex, and some of the many profiles defined have been associated with therapeutic failure [3]. In order to optimize the diagnosis of AMV allergy, it seems appropriate to consider determination of sIgE to the whole AMV extract, together with the available molecular compounds.

A 46-year-old part-time beekeeper who had reported large local reactions after bee stings and tolerance to wasp stings developed palmoplantar pruritus and generalized erythema with a sensation of oppression in the throat a few minutes after a honeybee sting on his right ear. He went immediately to the nearest hospital, where he experienced dizziness, tachycardia, and hypotension. He was successfully treated with intramuscular adrenaline, intravenous methylprednisolone, and dexchlorpheniramine. His REMA score was 2 [4]. The intradermal skin test performed with A mellifera, Polistes dominula, and Vespula species (ALK-Abelló SA) was negative consecutively at 1 µg/mL both 1 month after the sting reaction and 3 weeks later. sIgE and sIgG4 levels to whole AMV and its allergenic components (rApi m 1, rApi m 2, rApi m 3, rApi m 4 [manufacturer's prototype], rApi m 5, and rApi m 10; ImmunoCAP, Thermo Fisher Scientific) were quantified (Table). The basal tryptase value (ImmunoCAP) was 5.98 µg/L.

IgE-immunoblot was performed using a lyophilized preparation obtained from raw bee venom (In-House Reference [IHR], ALK-Abelló, Madrid, Spain) and the patient's serum (Supplementary Figure 1). The results showed specific recognition of 2 bands (50-55 kDa), which matched the main molecular variants of Api m 10 [5].

The basophil activation test (BAT) was performed by incubating 0.1 and 1 µg/mL of AMV (Pharmalgen, ALK-Abelló) with whole blood and staining with the CD63-FITC/ CD123-PE/anti-HLA-DR-PerCP cocktail (BD FastImmune, Becton, Dickinson) before starting BVIT and 1 year later (Table).

Table. sIgE and sIgG4 Levels and Percentage of CD63+ Basophils

	T0	T1	T2
sIgE, kU_A/L			
Apis mellifera	38.6	11.1	5.12
rApi m 1	0.08	0	0
rApi m 2	0.01	0	0
rApi m 3	3.55	1.32	1.32
Api m 4[a]	0	0	0
rApi m 5	1.10	0.91	0.5
rApi m 10	65	14.8	12.3
sIG4, mg/L			
Apis mellifera	163	7322	11735
rApi m 1	<1.00	3357	8231
rApi m 2	<1.00	1858	2129
rApi m 3	<1.00	145	276
Api m 4[a]	<1.00	341	1430
rApi m 5	38.4	98.8	286
rApi m 10	<1.00	<1.00	33.1
Basophils CD63+, %			
Negative control[b]	0.7	1.1	ND
Positive control[b]	49.3	36.0	ND
0.1 µg/mL AMV	9.3	7.1	ND
1 µg/mL AMV	75.8	22.1	ND

Abbreviations: AMV, *Apis mellifera* venom; T0, baseline; T1, 1 year after starting VIT; T2, 2 years after starting venom immunotherapy.
[a]Api m 4 (melittin sequence: H-GIGAVLKVLTTGLPALISWIKRKRQQ-OH from Schafer-N ApS) was coupled into CAPs, which were activated by Thermo Fisher Scientific Inc., to be able to quantify sIgE and sIgG4 levels.
[b]Phosphate-buffered saline and fMet-Leu-Phe were used as negative and positive controls, respectively

Sensitization was diagnosed based on the AMV sIgE level and a positive BAT result at 1 µg/mL of AMV (this high concentration was possibly adequate to provide enough Api m 10 to stimulate the basophils). Molecular sIgE and immunoblot results, together with clinical data, led to a final diagnosis of Müller grade IV anaphylaxis to honeybee venom, with major sensitization to Api m 10 (Table).

Before selecting the best therapeutic approach, 4 commercial extracts were analyzed to detect which most successfully inhibited sIgE of Api m 10 [6]. The best result (31% inhibition) was obtained when 20 µg of Pharmalgen AMV extract was reconstituted immediately and incubated with 100 µL of the patient's serum (InmunoCAP inhibition). Treatment with Pharmalgen AMV from the same test batch was then started without premedication and in a cluster schedule to reach the therapeutic dose in 4 weeks. An arbitrary dose of 300 µg was planned in order to protect this patient with double the risk of therapeutic failure (predominant sensitization to a very rare protein and beekeeping). No adverse events were recorded. Since then, the patient has been taking 300 µg monthly as a maintenance dose; tolerance has been good for the last 2 years. All vials were reconstituted immediately before use to avoid degradation of Api m 10, although Blank et al [7] demonstrated the stabilizing effect for Api m 10 of human serum albumin, which is used as a diluent in commercial therapeutic extracts.

A controlled sting challenge was performed 1 and 2 years after starting BVIT, according to Moreno et al [8], with negative results in both cases. Moreover, the patient experienced a field sting 15 months after starting BVIT, with no reaction. The result of the intradermal test with AMV remained negative. The progress of sIgE and sIgG4 levels, as well as BAT results, is shown in the Table.

Api m 10, a 23-kDa glycosylated protein, is considered a genuine and relevant major allergen, despite the fact that it only represents <1% of the venom dry weight. Some patients are exclusively or predominantly sensitized to Api m 10, which has been associated with failure of BVIT [5]. Nevertheless, studies performed to date do not include a molecular analysis of sensitization to honeybee venom components before starting BVIT [9,10] or propose a solution for treatment.

We report the case of a patient who was predominantly (almost exclusively) sensitized to Api m 10 and treated using an effective specific BVIT strategy. He tolerated 2 controlled in-hospital stings and a field sting without anaphylactic reactions. We observed the intended decrease in sIgE and increase in sIgG4 throughout BVIT, both to the whole venom extract and to its specific allergenic components, even though production of rApi m 10 sIgG4 was lower than that of rApi m 1 and rApi m 2 sIgG4. A progressive decrease in the percentage of $CD63^+$ basophils was also detected. The persistence of positive sIgE values and degranulated basophils with a negative response to a controlled-sting challenge suggests that the latter remains the gold standard for assessment of the effectiveness of BVIT.

The strategy used to achieve protection was the selection of a nonpurified AMV extract, which had previously showed the strongest IgE inhibition to Api m 10, and an arbitrary chosen triple maintenance dose to reach a potentially protective dose. BVIT in patients predominantly sensitized to Api m 10 is challenging owing to the low presence of this protein in the whole extract. We present a therapeutic approach based on 3 points: (*1*) molecular diagnosis using both whole venom extract and all commercially available molecular allergens; (*2*) tailored selection of the best available extract in terms of Api m 10 content; and (*3*) a high dose of BVIT.

Additional cases are necessary to validate these results, together with examination of other possibilities to improve the effectiveness of BVIT.

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Conflicts of Interest

Dr. Labrador-Horrillo reports personal fees from Alk-Abelló S.A. outside the submitted work.

Dr. Monsalve currently works at Alk-Abello S.A.

The remaining authors declare that they have no conflicts of interest.

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Usefulness of Omalizumab in Rapid Drug Desensitization in Patients With Severe Anaphylaxis Induced by Carboplatin: Open Questions

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Palabras clave: Fármacos quimioterápicos. Carboplatino. Omalizumab. Desensibilización rápida.

Carboplatin is an effective and well-tolerated chemotherapeutic agent used as first-line and subsequent treatment for ovarian cancer. Hypersensitivity reactions to chemotherapy have increased in frequency in the last 20 years, thus preventing the use of first-line therapies and causing a negative impact on patient survival and quality of life [1,2].

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody approved for the treatment of severe allergic asthma and recurrent chronic idiopathic urticaria. It has been studied as an add-on therapy in food allergy, oral immunotherapy for food allergy, atopic dermatitis, idiopathic anaphylaxis, and mastocytosis [3].

We present 2 cases of severe anaphylaxis to carboplatin in which omalizumab was used to prevent reactions during rapid drug desensitization (RDD).

The first patient was a 57-year-old woman diagnosed with ovarian adenocarcinoma who had initially been treated with 6 cycles of carboplatin and paclitaxel without complications. A local recurrence developed 1 year later, and the patient started carboplatin and gemcitabine. During the second cycle of carboplatin (eighth exposure), she developed palmar pruritus and generalized erythematous rash that resolved with dexchlorpheniramine and methylprednisolone. With the following cycle (ninth exposure), she developed palmar pruritus, generalized erythematous rash, nausea, and vomiting and reported a sense of impending doom. Her blood pressure was 60/30 mmHg and her heart rate was 40 bpm. She was treated with intravenous dexchlorpheniramine, methylprednisolone, and intramuscular epinephrine. She also had epigastric pain radiating to the back, with ST segment

elevation in leads V1 to V6, elevated troponin I (0.14 ng/ml), and normal creatinine kinase MB. The patient was asymptomatic after 24 hours without treatment.

She was referred to our department for an allergological work-up. We carried out skin prick testing (SPT) (10 mg/mL in saline solution) and intradermal testing (IDT) (1 and 10 mg/mL) with carboplatin. The result of IDT was positive at 10 mg/mL. Given the severity of the reaction and the positive IDT result, we considered RDD with omalizumab as an adjuvant. After giving her informed consent and with the approval of the institutional review board, the patient received a dose of 300 mg of subcutaneous omalizumab and another dose of 150 mg 7 days later and every 14 days thereafter. Twenty-four hours after the second dose, we performed a 16-step RDD in the intensive care unit, as previously described [1]. The patient finally tolerated 6 cycles with the same protocol, each without complications.

The second patient was a 61-year-old woman diagnosed with breast and endometrial cancer who had previously been treated with chemotherapy and radiotherapy and started treatment with carboplatin and paclitaxel for a recurrence. During the third cycle (17th exposure to carboplatin), she experienced general malaise, blurred vision, nausea, hypotension, and severe bronchospasm. The symptoms resolved with treatment.

We performed SPT and IDT with carboplatin, as described in the previous patient. IDT was positive. Omalizumab was prescribed as an adjuvant for RDD using the protocol described above. The patient gave her written informed consent, and the procedure was approved by the institutional review board.

We administered 4 cycles of a 16-step RDD protocol, and the patient reacted in all of them. The reactions appeared at steps 12 (first cycle), 14 (second cycle), and 16 (third and fourth cycles), and all of them involved the skin exclusively, with manifestations ranging from palmar pruritus and facial erythema to a generalized rash only once. All the reactions resolved with intravenous antihistamines and corticosteroids, and the patient was able to finish the 4 cycles.

RDD enables safe readministration of a drug to which a patient has become allergic. The procedure is usually safe and effective, although there is an inherent risk of a severe or even fatal anaphylactic reaction when a medication to which a patient had presented a severe hypersensitivity reaction is reintroduced [1]. Both patients presented severe life-threatening reactions with serious cardiovascular involvement. We recommended a 16-step desensitization with carboplatin in an intensive care unit. However, both patients and their oncologists refused the drug owing to the severity of the previous reactions. Given that carboplatin is the most appropriate drug in patients with ovarian cancer, we decided to administer omalizumab as an adjuvant treatment in order to diminish the risk of a severe reaction during RDD. One patient tolerated RDD without experiencing a reaction, and the other presented mild skin reactions. We do not know whether they would have tolerated the RDD if omalizumab had not been administered as an adjuvant.

To our knowledge, there are only 6 publications on the beneficial effect of omalizumab as an adjuvant in drug desensitization protocols: 1 case report with insulin [4], 12 patients with aspirin [5,6], and 3 cases with chemotherapeutic agents [7-9]. The Table summarizes the latter 3 cases, together with the 2 cases we report.

Omalizumab dosing in allergic asthma is based on the patient's weight and total IgE, whereas in urticaria a 300-mg dose is given. All the patients desensitized to aspirin with add-on omalizumab had asthma, and the dose was calculated as for the asthma indication and administered every 2-4 weeks for 16 weeks prior to desensitization [5,6]. However, when clinicians consider using omalizumab as an adjuvant in RDD to chemotherapy, they do not know what dose to administer and cannot pretreat patients for several months, because continuing

Table. Characteristics of Patients Who Received Omalizumab as Adjuvant Therapy During Rapid Desensitization to Chemotherapy Drugs

Authors	Cases	Patient	Drug Allergy	Symptoms	Dose of Omalizumab	No. of Doses of Omalizumab Before RDD	No. of RDD Cycles	Tolerance
Cahill et al [8]	1	68 y (sex not specified)	Oxaliplatin	Anaphylaxis	150 mg/2 wk	2 doses	4	Mild reaction
Ojaimi et al [7]	1	Female 63 y	Carboplatin	Anaphylaxis	300 mg/2 wk	3 doses	4	No reaction
Prieto et al [9]	1	Female 61 y	Oxaliplatin	Anaphylaxis	300 mg/2 wk	1 dose	6	No reaction
Sánchez-Morillas et al	2	Female 57 y	Carboplatin	Anaphylaxis	300 mg once. After 7 d, 150 mg/2 wk	2 doses	6	No reaction
		Female 61 y	Carboplatin	Anaphylaxis	300 mg once. After 7 d, 150 mg/2 wk	2 doses	4	Mild reaction

Abbreviations: RDD, rapid drug desensitization.

with the chemotherapy regimen is more urgent. Consequently, the dose given is decided arbitrarily.

In all the cases reported in the Table, omalizumab was administered every 2 weeks, albeit at variable doses. Ojaimi et al [7] and Prieto-García et al [9] administered 300 mg, whereas Cahill et al [8] administered 150 mg. We administered 300 mg followed 7 days later by 150 mg/2 wk. The patients described by Ojaimi et al and Prieto-García et al and patient #1 in the present report tolerated all RDD cycles with omalizumab without reactions. In contrast, the patient reported by Cahill et al and patient #2 in the present report experienced mild reactions. While more data are needed, it seems that the 300-mg dose is more effective than the 150-mg dose. The number of doses of omalizumab administered before RDD varies from 1 to 3.

In the light of currently available data, we suggest that omalizumab 300 mg given every 2 weeks, and with at least 1 dose given before starting RDD, enables patients with severe anaphylaxis to platinum drugs to receive them safely. Adding omalizumab increases the treatment cost of gynecological cancer, although when platinum-based treatment is avoided, the second-line chemotherapy agents seem to be associated with reduced survival [2].

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Dr. Sánchez-Morillas reports personal fees from the Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica, ALK, and Stallergenes.

Dr. Casado Herráez reports participating on advisory boards for Pharmamar, Lilly, Merck (MSD), EISAI, and Roche International and receiving consultancy fees from Pharmamar, Roche, and Lilly.

Dr. Rubio Pérez has no conflicts of interest to declare.

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Drug-Induced Enterocolitis Syndrome Due to Amoxicillin-Clavulanic Acid With Good Tolerance to Penicillin

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Palabras clave: Síndrome de enterocolitis inducida por fármacos. Amoxicilina-clavulánico. Provocación con medicamentos. Proteína catiónica del eosinófilo.

Drug-induced enterocolitis syndrome (DIES) is a non–IgE-mediated hypersensitivity reaction caused by a medication. To our knowledge, there are very few reported cases, and they all involve aminopenicillins [1-5]. We report a new case with the intention of raising awareness of this clinical entity to facilitate accurate diagnosis and management.

An 18-year-old man came to our clinic with vomiting in relation to intravenous infusion of amoxicillin-clavulanic acid and metamizole during surgery for acute appendicitis when he was 9 years old. The allergological study we describe below was carried out with the written consent of the patient.

Skin prick tests (SPT) and intradermal tests (IDT) were performed with penicilloyl-poly-lysine (PPL), minor determinant (MD), and clavulanic acid at commercially available concentrations (Diater), as well as with penicillin G (10 000 IU/mL), amoxicillin (20 mg/mL), amoxicillin-clavulanic acid (20/4 mg/mL), cefuroxime (2 mg/mL), ceftazidime (2 mg/mL), and meropenem (1 mg/mL). The results of the skin tests were negative, and the patient underwent a drug provocation test (DPT) with amoxicillin-clavulanic acid. Two and a half hours after receiving a therapeutic dose of 500/125 mg (cumulative dose, amoxicillin 875 mg/clavulanic acid 218.75 mg), he experienced epigastric pain, dizziness, and nausea and vomited once. A bolus of physiological saline solution, ranitidine, and ondansetron were administered intravenously, with complete resolution of symptoms in 2.5 hours.

Metamizole was assessed on a different day. SPT at 400 mg/mL and IDT at 4 and 10 mg/mL yielded negative results, and the patient underwent DPT with metamizole, which was well tolerated.

Given the suspicion that the digestive symptoms during the DPT with amoxicillin-clavulanic acid were nonspecific, SPT and IDT were repeated for ß-lactams 3 weeks later. Once again, the results were negative. DPT was performed with amoxicillin-clavulanic acid. One and a half hours after receiving a therapeutic dose of 500/125 mg, the patient experienced abdominal pain, profuse diarrhea, nausea, and repetitive vomiting. Two boluses of physiological saline, ranitidine (50 mg), ondansetron (8 mg), and methylprednisolone (60 mg) were administered intravenously. Loperamide (4 mg) was also given orally. The patient developed marked pallor and dizziness. His vital signs remained stable at all times. Three hours after the onset of symptoms, and despite all the medications given, profuse diarrhea persisted. A blood sample revealed no relevant abnormalities other than a hemoglobin concentration of 18 g/dL, which was consistent with dehydration secondary to loss of liquids. The patient was transferred to the emergency room, where he only received another bolus of physiological saline. His condition gradually improved, and he was discharged after 2.5 hours of observation.

A blood test performed at a follow-up visit 2 days later revealed hemoglobin 15.4 g/dL, tryptase 3.2 µg/dL, negative serum specific IgE for amoxicillin, ampicillin, cefaclor, and penicillin G and V, and total IgE of 496 kU/L (ImmunoCAP, Thermo Fisher Scientific). Analysis of stool samples taken 24 and 48 hours after the DPT with amoxicillin-clavulanic acid were sent for determination of eosinophil cationic protein (ECP) and revealed 77.4 and 50 µg ECP/g feces, respectively. Six weeks later, measurement of ECP in a further 2 stool samples taken on 2 different days yielded results of 1.8 and 2.1 µg ECP/g feces, respectively.

Finally, in order to rule-out cross reactivity with other ß-lactams, a DPT was performed with penicillin V and G, both of which were well tolerated.

DIES is an uncommon and probably underreported non–IgE-mediated hypersensitivity reaction provoked by drugs. Its clinical presentation is very similar to that of food protein–induced enterocolitis syndrome (FPIES) [1-5]. Extrapolating the criteria of the 2017 International Consensus Guidelines for FPIES [5] to the present case shows that the patient fulfils the major criterion (vomiting in the 1- to 4-hour period after ingestion of the suspected drug and absence of classic IgE-mediated allergic skin or respiratory symptoms) and 5 of the 9 minor criteria (repetitive vomiting after ingestion of the same drug, marked pallor, need for emergency department visit, need for intravenous fluid support, and diarrhea in the 24 hours following ingestion of the suspected drug) [6]. Increased neutrophil count is a common finding after positive food challenge in FPIES and has also been described in 4 of the reported cases of DIES. Neutrophils usually peak 6 hours after ingestion of the trigger [6]. In the present case, the patient's blood was collected 3 hours after taking a therapeutic dose, possibly prior to the peak.

To our knowledge, out of the few cases of DIES reported [1-5], this is the second to involve amoxicillin-clavulanic acid [3]. DPT was carried out successfully with penicillin in only 2 of the published cases [2,5] and with cefpodoxime in 1 [5]. We confirmed that the patient tolerated penicillin, thus enabling us to prohibit only aminopenicillins and cephalosporins with the same side chain as amoxicillin (cefaclor, cefalexin, cefadroxil, and cefprozil) and to allow all other ß-lactam antibiotics.

In all of the reported cases, the DPT was performed close in time to the initial reaction, although in the case we

report, there was a 9-year interval between the first reaction and the positive DPT. In FPIES, periodic re-evaluations are recommended to assess whether the patient is still reactive. Rates of resolution of FPIES vary considerably, although many resolve after a few years [6]. While we do not know whether this applies to DIES, persistence over time was observed in the present case.

It is noteworthy that all the reported cases of DIES involve amoxicillin with or without clavulanic acid [1-5]. Compared with penicillin, these drugs increase the motility of the small intestine [9] and are associated with a higher frequency of gastrointestinal adverse effects, including diarrhea [10]. However, the gastrointestinal symptoms reported in the present case are suggestive of DIES with a specific underlying immune mechanism. This is supported by the fact that onset was after intake of the first therapeutic dose, the severity of the reaction, and the presence of elevated ECP in stool. These findings are consistent with the activation of eosinophils in FPIES reported elsewhere [7,8].

In summary, we report a case of DIES induced by amoxicillin-clavulanic acid in an adult patient with good tolerance to penicillin. Assessing tolerance to penicillin is important in the management of such uncommon cases in order to avoid unnecessary restrictions of all ß-lactam antibiotics.

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Conflicts of Interest

Dr. Sánchez-Morillas reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica and from Alk-Abelló outside the submitted work.

Dr. González-Gutiérrez reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica and from GSK and Teva outside the submitted work.

Dr. Cimarra reports personal fees from Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica and from Novartis and ALK outside the submitted work.

Dr. Cerecedo reports personal fees from Diater, Leti, ALK, Stallergenes, and Sociedad Madrid-Castilla La Mancha de Alergología e Inmunología Clínica outside the submitted work.

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The remaining authors declare that they have no conflicts of interest.

Previous Presentation

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