

### Bovine Amniotic Fluid: A New and Occupational Source of Galactose- $\alpha$ -1,3-Galactose

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In 2009, Commins et al [1] reported a series of patients with delayed anaphylaxis, angioedema, and urticaria after consumption of red meat or dairy products. In 2011, the first cases showing the same features were reported in Spain [2]. Since then, several additional sources of galactose- $\alpha$ -1,3-galactose ( $\alpha$ -gal) have been reported, namely, mammalian innards [3], gelatin-containing foods and drugs [4-6], and bioprosthetic aortic valves [7]. Here, we report the cases of 3 cattle workers who presented with allergic symptoms after assisting the veterinarian during calving.

The first patient was a 36-year-old woman who, at the time she was evaluated at our hospital in April 2014, had a 10-year history of recurrent urticaria and angioedema (every 10-15 days). Her total IgE concentration was 25.9 IU/mL (ImmunoCAP, Thermo Fisher Scientific). IgE (kU<sub>A</sub>/L) to  $\alpha$ -gal was 4.21 for bovine thyroglobulin, 3.28 for beef, 2.81 for pork, 3.97 for lamb, 0.69 for bovine serum albumin, and <0.10 for chicken. The patient was instructed to follow a mammalian meat-free diet and to return for a check-up in March 2016. During the 2-year interval, the patient remained asymptomatic, except when touching the placenta or amniotic fluid during calving, which induced immediate urticaria on the exposed skin areas.

The second patient was a 53-year-old man who consulted with a 3-month history of recurrent urticaria and abdominal symptoms in December 2013. His total IgE concentration was 346 IU/mL. IgE to  $\alpha$ -gal was 51.1 for bovine thyroglobulin, 29.3 for beef, 26.7 for pork, 11.4 for lamb, 0.48 for bovine serum albumin, and <0.10 for chicken. The patient initiated a mammalian meat-free diet and was re-evaluated a year later. He had presented a new episode after consuming pork. Moreover, he noticed pruritus and wheals when assisting during calving and suspected that it was caused by contact with the amniotic fluid and placenta.

The third patient was a 56-year-old woman diagnosed with  $\alpha$ -gal allergy in November 2015 because of an anaphylactic reaction after consuming veal and taking naproxen. We ruled out nonsteroidal anti-inflammatory drug allergy/intolerance by performing an oral challenge test with naproxen. The total IgE concentration was 44.5 IU/mL. IgE to  $\alpha$ -gal was 21.7 for bovine thyroglobulin, <0.1 for beef, <0.1 for pork, 0.87 for lamb, 0.43 for rabbit, 0.14 for bovine serum albumin, and <0.10 for chicken. The patient started a mammalian meat-free diet and was reevaluated in April 2016. She had remained asymptomatic but experienced 3 episodes of wheals and chest tightness with dyspnea immediately after contact with amniotic fluid when assisting during calving.

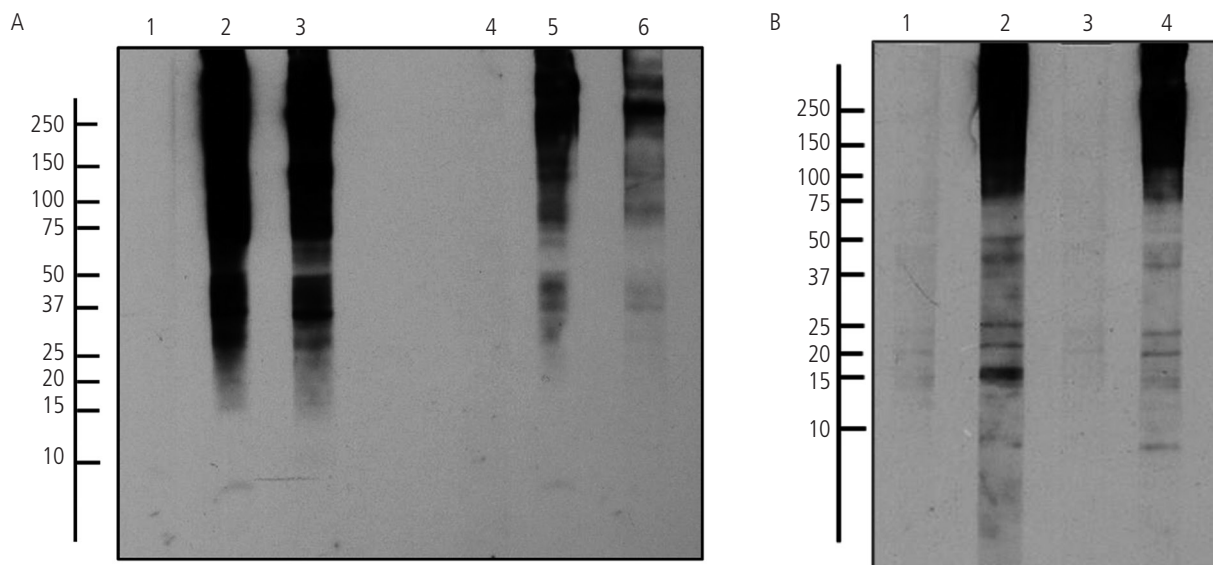
A test to assess inhibition of IgE binding to  $\alpha$ -gal was performed with the sera of patients 2 and 3 using a preparation of bovine amniotic fluid as the inhibitor. Two samples of amniotic fluid were provided by the patients. Both samples were centrifuged for 30 minutes at 12 500 rpm, and the protein concentration was determined using the Bradford protein assay. Two hundred microliters of serum was incubated with 200  $\mu$ L of amniotic fluid at a protein concentration of 2 mg/mL or with 200  $\mu$ L of buffer for 3 hours at room temperature. Specific IgE to  $\alpha$ -gal was subsequently determined. As an assay control, specific IgE against the pollen of *Phleum pratense* (g6) was also determined in a serum pool from grass-allergic patients (control serum) after incubation with the amniotic fluid or buffer under the conditions described above.

Preincubation of the patients' serum with the amniotic fluid inhibited over 95% of the binding of specific IgE to  $\alpha$ -gal, with no inhibition of specific IgE to grass in the control serum, thus indicating the presence of  $\alpha$ -gal in the amniotic fluid and explaining the allergic reaction experienced by the patients after contact with the fluid during calving.

An immunoblotting assay was performed to confirm the presence of  $\alpha$ -gal in the various proteins present in bovine amniotic fluid (Figure).

The 2 amniotic fluid preparations were analyzed using SDS-PAGE, and the proteins were transferred to nitrocellulose strips. Some of the strips were incubated with the serum from patients 2 and 3, and later with a human anti-IgE antibody (Figure, A). At the same time, other strips were incubated with anti- $\alpha$ -gal monoclonal antibody IgM (Enzo Life Science) and later with a second sheep antibody specific for mouse IgM (Figure, B). Finally, adhesion of human IgE antibody and anti- $\alpha$ -gal monoclonal antibody to the proteins of the amniotic fluid was detected using a chemiluminescence reaction.

IgE immunoblotting indicated the presence of IgE in serum, which recognized different proteins of the amniotic fluid with molecular weights ranging between 15 kDa and >250 kDa (Figure, A). Anti- $\alpha$ -gal monoclonal antibody immunoblotting indicated the presence of  $\alpha$ -gal in the proteins of the amniotic fluid, with a pattern that was similar to that obtained with the IgE immunoblotting using the patients'



**Figure.** A, SDS-PAGE immunoglobulin E immunoblotting results for amniotic fluid samples. Amniotic fluid #1: lane 1, negative control (buffer); lane 2, serum from patient #2; lane 5, serum from patient #3. Amniotic fluid #2: lane 4, negative control (buffer); lane 3, serum from patient #2; lane 6, serum from patient #3. Molecular mass markers are shown on the left. B,  $\alpha$ -gal-immunodetection experiment using anti- $\alpha$ -gal anti-IgM against amniotic fluid samples. Amniotic fluid #1 with buffer (negative control) (lane 1) and with IgM anti- $\alpha$ -gal antibody (lane 2). Amniotic fluid #2 with buffer (negative control) (lane 3) and with IgM anti- $\alpha$ -gal antibody (lane 4). Molecular mass markers are shown on the left.

serum. These results confirm the presence of  $\alpha$ -gal in various proteins of the amniotic fluid, with a relatively wide range of molecular weights.

We report the cases of 3 known  $\alpha$ -gal-allergic patients who experienced allergic reactions on exposure to amniotic fluid when assisting during calving. Patients 1 and 2 experienced contact urticaria limited to exposed areas, while patient 3 also experienced dyspnea, probably due to inhalation of amniotic fluid proteins. The severity of the symptoms prevented the patients from continuing to assist the veterinarian during calf delivery. The laboratory results enabled us to identify several proteins in the amniotic fluid that were recognized by the IgE of the patients' serum, pointing to  $\alpha$ -gal as the etiologic agent.

We report a new source of  $\alpha$ -gal that must be borne in mind when making recommendations to persons assisting during calving. The occupational origin of these cases could have legal implications.

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#### Conflicts of Interest

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## Chemotherapy in Mastocytosis: Administration Issues, Hypersensitivity, and Rapid Drug Desensitization

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Mastocytosis comprises a heterogeneous group of mast cell (MC) disorders characterized by abnormal expansion, proliferation, and accumulation of clonal MCs in various tissues [1-4]. The manifestations (ranging from pruritus to fatal anaphylaxis) are due to release of mediators, which is occasionally induced by medications, hymenoptera stings, and other stimuli [1-4]. Mastocytosis patients have an increased risk of anaphylaxis, with reported prevalences of between 22% and 49% in adult patients [5]. Recent publications [1,5] focus on drug hypersensitivity in MC activation disorders such as mastocytosis. However, no data have been reported on tolerance to intravenous chemotherapy in patients with mastocytosis. Moreover, in the case of hypersensitivity to chemotherapy drugs, no data have been published on rapid drug desensitization (RDD).

Previous studies by our group [6-8] show how all patients referred to our Desensitization Program cohort at Ramon y Cajal University Hospital (RCUH), Madrid, Spain undergo a systematic prospective protocol comprising a detailed clinical history, skin testing, in vitro testing (including baseline serum tryptase determination), risk stratification, drug provocation test (DPT), and RDD. We searched our database over a 5-year period (between January 2009 and January 2014) for patients with a diagnosis of mastocytosis who had received chemotherapy.

We included patients who were referred for assessment after a drug hypersensitivity reaction (DHR) to chemotherapy and were already diagnosed with mastocytosis (or were diagnosed with mastocytosis as a result of the DHR). We also included patients diagnosed with mastocytosis who had not previously experienced a DHR but who were referred to our program for assessment of the administration of chemotherapy.

As in our previous studies [6-8], trained personnel performed and assessed skin testing in adequate settings, and patients were classified according to their risk.

Patients with a diagnosis of mastocytosis and a previous DHR were considered high-risk patients (ie, susceptible to

anaphylaxis beyond medical control) and therefore excluded from DPT [6-8]. Their next administration of the culprit drug was performed by means of RDD, which was started only after signature of the informed consent document by the patient and confirmation of the indication by the referring oncologist for the culprit drug to be administered as first choice [6-8].

A different protocol was applied for patients with a diagnosis of mastocytosis who had not experienced a previous DHR but were referred to our program for assessment of administration of chemotherapy. Even if patients had not experienced a previous DHR, we found the increased risk of anaphylaxis associated with mastocytosis to be an important factor; therefore, these patients received their first administration according to the manufacturer's instructions, although in a controlled environment. No additional premedication was used for the procedure (except for standard premedications recommended in the manufacturer's/institutional protocol) [6].

Controlled first administrations and first RDDs were both performed in a medical intensive care unit [6-8]. The previously published standard 10-step RCUH protocol was followed for RDD [7]. The only premedication prior to RDD was that included in the manufacturer's instructions and that prescribed by the referring oncologists [6-9]. No additional premedications were used. DHRs were classified (Brown classification) and treated according to our local protocols [7]. Patients who experienced breakthrough reactions during RDD also received acetylsalicylic acid (provided the patient had known tolerance to nonsteroidal anti-inflammatory drugs) and montelukast as premedication for their subsequent procedures, since these drugs have shown effectiveness in preventing mast cell mediator-related symptoms during RDD [7,9].

A total of 309 patients were assessed during the 5-year study period. We found 4 patients who fulfilled the eligibility criteria. Two patients (patients 1 and 2) were assessed after experiencing a DHR and were classified as probable for mastocytosis according to the validated score of the Spanish Mastocytosis Network (REMA) [4]. They were assessed as part of our Mastocytosis Program and diagnosed with mastocytosis.

The other 2 patients (patients 3 and 4) had previously been diagnosed with mastocytosis and were referred for assessment of administration of chemotherapy. The Table shows further patient characteristics.

We report the outcomes of 4 patients diagnosed with mastocytosis who received treatment with intravenous chemotherapy (paclitaxel, cisplatin, and oxaliplatin). All 4 patients experienced a DHR during standard administration of chemotherapy (3 during their first administration). Two patients were diagnosed with mastocytosis after their DHR based on the REMA score (patients 1 and 2). All 4 patients were able to receive their programmed therapy by means of RDD. Most RDDs (75%) did not involve breakthrough reactions. All breakthrough reactions were mild (Brown classification). This safety profile is similar to that reported previously [7]. However, all patients experienced a breakthrough reaction during their first RDD, which was controlled in subsequent RDDs by adding acetylsalicylic acid and montelukast as premedication (RDD protocol otherwise unaltered).

Table. Patient Characteristics: Diagnosis, Hypersensitivity Reactions to Chemotherapy, Allergy Workup, and Outcome of Rapid Drug Desensitization

Patient	Gender	Disease	Age	BST, ng/mL	REMA Score	Bone Marrow Biopsy		MIS
1	Male	Colorectal cancer	67	26.9	7	Multifocal dense infiltrates of MCs in bone marrow >25% aberrant MCs CD25/CD2 +	D816V Mut. +	No
2	Female	Colorectal cancer	62	39.6	5	Multifocal dense infiltrates of MCs in bone marrow >25% aberrant MCs CD25/CD2 +	D816V Mut. +	No
3	Female	Breast cancer	75	11.6	2	Multifocal dense infiltrates of MCs in bone marrow >25% aberrant MCs CD25/CD2 +	D816V Mut. +	No
4	Female	Lung cancer	66	24.0	3	Multifocal dense infiltrates of MCs in bone marrow >25% aberrant MCs CD25/CD2 +	D816V Mut. +	No
	Culprit Drug	No. of Uneventful Culprit Drug Exposures Before First DHR	Symptoms During Initial DHR	Severity Initial DHR (Brown Classification)	Elapsaed Time From Drug Infusion To Initial DHR	Tryptase, ng/mL, 60 Min After Onset Of DHR	Skin Tests <sup>a</sup>	Breakthrough Reactions During RDD
1	Oxaliplatin	20	Dizziness, dyspnea, diaphoresis, abdominal/back pain	2 (moderate)	20 min	Unknown	Positive (ID 0.5 mg/mL)	Yes, mild (first RDD)
2	Oxaliplatin	1	Dizziness, nausea, vomits	2 (moderate)	60 min	Unknown	Negative	Yes, mild (first RDD)
3	Paclitaxel	0	Erythema, chest/back pain	2 (moderate)	10 min	20.8	Negative	Yes, mild (first RDD)
4	Cisplatin	0	Erythema, dizziness, throat tightness	2 (moderate)	5 min	25.6	Negative	Yes, mild (first RDD)

Abbreviations: BST, baseline serum tryptase; D816V Mut, KIT mutation D816V; DHR, drug hypersensitivity reaction; ID, intradermal test; MC, mast cell; MIS, mastocytosis in the skin; REMA, Spanish Mastocytosis Network; RDD, rapid drug desensitization.

<sup>a</sup>The skin test concentrations used by our group are described in other publications [6,7]: oxaliplatin (0.5 and 5 mg/mL), paclitaxel (1 and 6 mg/mL), cisplatin (0.1 and 1 mg/mL).

Following the manufacturer's instructions for paclitaxel, patient 3 received premedication with antihistamines and corticosteroids; however, it was not until the addition of acetylsalicylic acid and montelukast to RDD that she could tolerate paclitaxel. Defining best premedication protocols for these patients is an issue to be addressed in future publications.

Even if the mechanisms of RDD have only been investigated in normally functioning MCs [10], we describe patients with mastocytosis who respond to RDD much like any other patient.

Previous data [10] show how patients need repeated exposure to platins before sensitization and that the positive



skin testing results observed suggest IgE-dependent mechanisms (patient 1). DHRs to taxanes occur on early exposures, and the results of skin testing are usually negative, suggesting non-IgE-dependent mechanisms (patient 3). Patients 2 and 4 experienced a DHR during their first session with platin. However, although such a reaction is atypical, patients with mastocytosis also tend to present DHRs to other drugs on first exposure, without necessarily having become sensitized [1,5]. In any case, RDD was successful for these different patient phenotypes.

Ours is the first publication to address the safety of intravenous chemotherapy and RDD in patients at risk of severe anaphylaxis due to mastocytosis. Even if more studies with a higher number of patients are necessary to design specific protocols, our data are based on a systematic approach to this unexplored issue, thus enabling us to draw a series of conclusions. Patients with mastocytosis benefit from management by expert allergists and access to safe facilities before receiving their first cycle of chemotherapy. Even if the prevalence of mastocytosis is low (1.29% in the study population), it may be useful, in terms of safety, to screen for this condition in chemotherapy-reactive patients (easily identified by baseline serum tryptase measurements and the REMA score in study protocols). Moreover, RDD is a safe and effective therapeutic approach for chemotherapy-reactive patients with mastocytosis receiving their first-choice treatments (in the setting of a desensitization program with RDD experts and appropriate facilities).

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#### Conflicts of Interest

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## Protein Contact Dermatitis to Chrysanthemum

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Weed pollen grains and leaves belonging to the Asteraceae family contain a variety of protein allergens (eg, pectate lyase, defensin, and lipid transfer protein) and haptens (sesquiterpene lactones) that induce type I or IV allergies in susceptible people [1,2]. *Chrysanthemum*, a member of the Asteraceae

family, is a common cause of occupational contact dermatitis among gardeners and florists [3].

We report the case of a 40-year-old horticultural worker from Lyon, France who worked mainly with chrysanthemum flowers (*Chrysanthemum grandiflorum*). The patient had developed multiple cutaneous manifestations progressively over 10 years. The initial manifestation was immediate localized pruritus after direct skin contact with the plants. Some years later he experienced eczema at the same sites and also through airborne contact at different sites in association with rhinoconjunctivitis. Symptoms disappeared completely from December to March when the patient was no longer exposed to the plants and recurred gradually when the chrysanthemum plants began to grow again.

Patch tests (Chemotechnique Diagnostics) based on the European Baseline and Plant Series were performed with various species (eg, *Achillea millefolium*, *Anthemis nobilis*, *Chamomilla*, *Arnica montana*, *Chrysanthemum cinerea*), alantolactone,  $\alpha$ -methylene butyrolactone, other compounds (eg, oils), and organic substances (eg, lichen acid mix, parthenolide, *Tanacetum*, *Taraxacum*, and turpentine oil). The results were negative. Photopatch tests with the recently proposed European series complemented with sesquiterpene lactone mix and lichen acid mix (Chemotechnique Diagnostics) were also negative [4].

Patch tests with large pieces of *C grandiflorum* (2×2 cm) were positive after 72 hours (++) according to International

Table. Characteristics of Tests Applied: Patch, Photopatch, Skin Prick, and Specific IgE

	Patch Tests	Photopatch	Prick Tests	Specific IgE, kU <sub>A</sub> /L
European standard series	(-)			
Plant series	(-)	(-)		
European Photopatch Baseline Series		(-)		
Codeine phosphate			6 mm	
Negative control			0 mm	
<i>Chrysanthemum grandiflorum</i>	(++)		Flower: 5 mm leaf: 6.5 mm	
<i>Artemisia vulgaris</i>			4 mm	13.10
<i>Ambrosia eliator</i>			3 mm	17
<i>Chrysanthemum leucanthemum</i>				15
<i>Taraxacum vulgare</i>				14.30
<i>Xanthium commune</i>				17.20
<i>Matricaria chamomilla</i>				15.80
<i>Solidago virgaurea</i>				16
<i>Iva ciliata</i>				16
<i>Helianthus annuus</i>				18.70
nAmb a 1				0.96
nArt v 1				0.20
nArt v 3				0.12
rPar j 2				0.22
nSal k 1				5.98

(-), negative; (++) , strong infiltrate, numerous papules, vesicles present.

Contact Dermatitis Research Group values, as were prick-to-prick tests with *chrysanthemum*. The result of prick-to-prick tests with chrysanthemum performed in 10 asymptomatic controls were all negative.

The prick test results were also positive for mugwort and ragweed pollens and for specific IgE to different weed pollens (Thermo Fisher Scientific) (Table).

The finding of eczematous skin manifestations and immediate itching together with positive patch and prick-to-prick test results led us to diagnose protein contact dermatitis to chrysanthemum. It was noteworthy that the skin lesions appeared to be due to both contact and airborne dermatitis. This is an unusual finding [5]. The lesions were temporally limited to the period of exposure to chrysanthemum, thus confirming imputability.

Contact allergy confirmed based on negative patch test results does not indicate sensitization to a traditional Asteraceae hapten but rather to IgE sensitization to proteins of this family. In addition, sensitization does not seem to involve mugwort or ragweed allergens (Amb a 1, Art v 1), both of which are commonly implicated in rhinoconjunctivitis caused by these plants [6]. In contrast, sensitization to nSal k 1 was detected, although *Salsola kali* is not present in the area where the patient lives [7]. We therefore propose 2 hypotheses: (1) proteins from the pectin methylesterase family may play a role in protein contact dermatitis to *chrysanthemum*; or (2) positivity to nSal k 1 results from glycosylated fragments in nSal k1 [8].

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## Reversible Hypogammaglobulinemia in 2 Pediatric Patients With Primary Immunodeficiency

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**Key words:** Primary immunodeficiency. Common variable immunodeficiency. Nijmegen breakage syndrome. Immunoglobulin recovery.

**Palabras clave:** Inmunodeficiencia primaria. Inmunodeficiencia común variable. Síndrome de rotura de Nijmegen. Recuperación de inmunoglobulinas.

Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency in adults [1]. It is characterized by recurrent infections with bacteria, viruses, or, less commonly, opportunistic microbes. Most patients with CVID have an IgG level <5 g/L and reduced or undetectable IgA and/or IgM levels. CVID may occur as early as 2 years of life, and approximately 20% of patients become symptomatic before they reach adulthood.

Nijmegen breakage syndrome (NBS) is a rare DNA repair disorder characterized by microcephaly, immunodeficiency, and predisposition to cancer [2]. In immunodeficient patients with NBS, class switch recombination is severely impaired, leading to profound hypogammaglobulinemia or a pattern resembling the hyper IgM syndrome.

In the late 1980s, reversible hypogammaglobulinemia was reported in 4 patients with CVID after infection by the human immunodeficiency virus (HIV) [3-6].

We report on 2 HIV-negative pediatric patients with CVID and NBS who experienced spontaneous recovery of serum immunoglobulin levels.

Patient 1 was a 12-year-old boy with lower-back pain, acute diarrhea, and a mildly swollen, painful knee joint (PCR with *Mycoplasma* species obtained from joint fluid was negative). Throat and stool cultures were negative for enterovirus. No specific treatment for arthritis was given. His past medical history revealed that he had had recurrent otitis media and aphthous stomatitis. Clinical examination revealed normal weight (38 kg) and height (142 cm); neck and peripheral lymph nodes were not palpable. Other physical findings were normal.

The results of the laboratory investigations were as follows: hemoglobin, 134 g/L; red cell count,  $4.9 \times 10^{12}/L$ ; and white cell count,  $16.5 \times 10^9/L$ , with 63% neutrophils and 24% lymphocytes (absolute lymphocyte count,  $3970/mm^3$ ). Serum protein was normal (64 g/L), as was albumin (46 g/L). Immunologic investigations revealed significantly decreased concentrations of IgA (0.07 g/L [reference range, 0.42-2.95 g/L]), IgM (0.06 g/L [0.41-2.55 g/L]), and IgG (1.40 g/L [5.03-17.10 g/L]). Serum anti-B isohemagglutinin

was not detected. Phenotypic analysis of peripheral blood lymphocytes revealed normal counts for CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> cells. The B-cell count was slightly decreased ( $190/mm^3$ ). IgM-IgD<sup>+</sup>CD27<sup>+</sup> B-cell counts were decreased (1.8% [7.2%-30.8%]), and naive IgD<sup>+</sup>IgM<sup>+</sup>CD27<sup>-</sup> B-cell counts were normal (18.4% [17%-30%]). The results of serology tests for HIV and for *Salmonella*, *Yersinia*, *Campylobacter*, *Brucella*, and *Mycoplasma* species were negative, as were those for Epstein-Barr virus, cytomegalovirus, and herpes simplex virus. The results of PCR-based DNA assays for HIV, Epstein-Barr virus, and cytomegalovirus were negative. Mutation analysis of the *btk* gene ruled out X-linked agammaglobulinemia.

A diagnosis of CVID was established at 12 years of age based on significantly decreased Ig levels (3 classes) and failure to produce specific antibodies after immunization with hepatitis B and pneumococcal vaccines [7]. Monthly intravenous immunoglobulin (IVIG) replacement therapy (400 mg/kg) was started, and protective IgG trough levels of 5-6 g/L were achieved. Two years later, a spontaneous increase in serum IgM (0.88 g/L) was detected, whereas the concentration of IgA remained low (0.08 g/L). We stopped IVIG, and, during the following year, IgG levels returned to normal (>7 g/L). Six years later, serum IgG and IgM levels remained normal, while the IgA concentration remained low. The patient was immunized with tetanus toxoid, hepatitis B vaccine, and pneumococcal polysaccharide vaccine, resulting in protective titers of antitetanus (0.3 IU/mL, protective >0.1 IU/mL), HBs antibody (17 mIU, protective >10 mIU), and pneumococcal antibodies (>1.3 µg/mL).

Patient 2 was a 25-year-old woman of Slavic origin who had been assessed at 8 years of age for immunodeficiency [8].

Immunologic investigations revealed low serum IgA (0.22 g/L [0.34-2.74 g/L]), increased IgM (3.10 g/L [0.38-2.51 g/L]), and decreased IgG (1.7 g/L [4.62-16.82 g/L]). There were no specific antibody responses to vaccines (tetanus, polio, pneumococcus). The phenotypic analysis of peripheral blood lymphocytes was normal, and lymphocyte proliferative responses to mitogens in vitro were normal. The diagnosis of NBS was later confirmed by analysis of mutations in the NBS1 gene. IVIG was started at 400 mg/kg/month.

At 10 years of age, examination of the patient revealed fever, lymph node enlargement, hepatosplenomegaly, and mediastinal mass. A diagnosis of T-cell lymphoblastic lymphoma/leukemia was established, and treatment for acute lymphoblastic leukemia was introduced [8]. The patient achieved full hematologic remission.

After being successfully treated for cancer, the patient was lost to follow-up. She did not receive IVIG for 3 years. Investigations performed at 15 years of age revealed low serum IgA (0.23 g/L) but normal IgM (2.16 g/L) and normal IgG (7.70 g/L) concentrations. Serum IgG subclasses were normal (IgG1, 6.061 g/L; IgG2, 1.984 g/L; IgG3, 0.386 g/L; IgG4, 0.186 g/L). Phenotypic analysis of blood lymphocytes revealed normal counts for CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>+</sup>, and CD19<sup>+</sup> B cells, and testing for anti-HIV antibodies and qualitative PCR for HIV DNA were both negative. Eight years after cessation of chemotherapy, the patient's IgM and IgG concentrations returned to normal, and she was doing well, without infections.



Recovery of antibody production was originally reported in 4 men who have sex with men with CVID after acquisition of HIV infection [3-6]. By contrast, HIV infection was excluded in the 2 cases we report.

Webster et al [5] and Jolles et al [6] showed definite evidence that HIV infection in CVID may result in synthesis of IgM and IgG and that reversion of immunoglobulin production may persist for longer than 10 years [5,6]. The same authors stressed that recovery of immunoglobulin synthesis is unusual, because they had also observed severe, persistent hypogammaglobulinemia in another 2 HIV-infected patients with CVID [9]. In HIV-infected individuals who recovered IgG synthesis, serum IgA levels remained low, as was the case in the patients we report.

Other possible causes of secondary immunodeficiency (eg, HIV, drugs, malignancy, protein-losing enteropathy) were ruled out in patient 1. Furthermore, given the age of the patient, transient hypogammaglobulinemia of infancy seems unlikely. A recovery of immunoglobulin production in transient hypogammaglobulinemia of infancy is usually detected from 9 to 18 months of life, but rarely after 4 years of life.

Approximately 80% of patients with NBS are hypogammaglobulinemic at presentation, while normal immunoglobulin concentrations or IgG subclass deficiency may be detected in the remaining 20% [10]. Immunodeficiency in NBS is progressive, in contrast to our observations.

We are not able to speculate that chemotherapy in patient 2 had an impact on repair of a defective class-switch mechanism in NBS. It seems that robust immune reconstitution in NBS can be only achieved with successful stem cell transplantation.

We report on a rare phenomenon, spontaneous recovery of IgG and IgM synthesis in HIV-negative patients with CVID. The cause of normalization of immunoglobulin levels remains unknown, although the potential role of other epigenetic factors such as viruses cannot be excluded.

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#### Conflicts of Interest

The author declares that he has no conflicts of interest.

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## Pregnancy and Postpartum in Hereditary Angioedema With C1 Inhibitor Deficit in Women Who Have No Access to Therapy

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**Key words:** Hereditary angioedema. Pregnancy. Breastfeeding. Childbirth.

**Palabras clave:** Angioedema hereditario. Embarazo. Leche maternal. Nacimiento.

Hereditary angioedema (HAE) is an autosomal dominant inherited disease that results from a quantitative and/or functional defect in C1 inhibitor (C1-INH). Laboratory diagnosis is confirmed based on levels and/or functional activity of C1-INH [1,2]. The disease is characterized by attacks of subcutaneous edema affecting mainly the hands and feet, as well as the genitals, trunk, face, and tongue. Gastrointestinal edema and laryngeal edema are also present, and laryngeal edema in particular can lead to asphyxia and death if not treated [3]. The main reported triggering factors include trauma, stress, and hormones [4]. Prophylactic drugs include attenuated androgens, antifibrinolytics, and plasma-derived C1 inhibitor (pdC1-INH).

Data on HAE during pregnancy, delivery, and postpartum are limited, and there are no data from developing countries [5-7]. Thus, we evaluated patients during the period prior to the availability of specific therapy in Brazil.

A questionnaire was completed during pregnancy and postpartum by women aged  $\geq 18$  years referred from the Brazilian Association of Patients with Hereditary Angioedema (ABRANGHE). The diagnosis of HAE with C1-INH deficit was confirmed based on laboratory findings. Patients who were treated with other therapies and had diseases that might influence pregnancy were excluded. Only pregnancies from the previous 10 years were included. The responses were evaluated using a descriptive analysis, and quantitative data were evaluated using nonparametric statistical tests. The protocol was approved by the local ethics committee, and all patients provided their informed consent before completing the questionnaire.

After application of the inclusion and exclusion criteria, a total of 13 women and 22 pregnancies were available for analysis. The mean ages at the onset of symptoms and diagnosis were 15.3 (2-26) and 25.6 (2-40) years, respectively. We believe that this reflects difficulties in access to diagnostic tests and the late demand for specialized care.

Caballero et al [7] showed that the most common triggering factors for HAE were emotional distress and physical trauma.

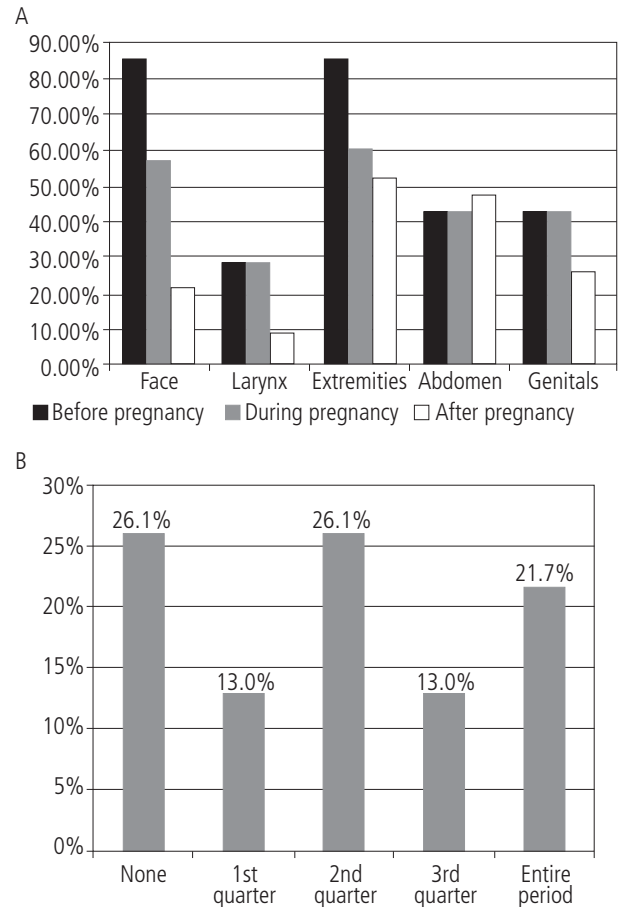


Figure. A, Symptoms before, during, and after pregnancy in the patients evaluated. B, Frequency of attacks during pregnancy according to the gestational period.

Our findings confirm that in pregnancy, emotional stress is the most common triggering factor (65.2%), followed by trauma (33.3%). The extremities were the part of the body most frequently affected by edema both before pregnancy (85%) and during pregnancy (61%) (Figure, A). Most attacks occurred in the second trimester (26.1%), followed by the third and first trimesters (both 13%) (Figure, B). In addition, the severity of the attacks did not vary across trimesters, and attacks were less intense than before pregnancy. Czaller et al [8] reported more attacks during the third trimester, affecting mainly the extremities and the abdomen, and found that severity may vary from pregnancy to pregnancy in the same woman. Of note, given that the patients in our study did not have access to appropriate therapy, the course of the pregnancy was not modified or controlled with specific drugs such as C1 inhibitors.

Four patients (17%) received prophylaxis for short periods. Two patients received tranexamic acid, and the other 2 patients received antihistamines (prescribed by nonspecialists). Tranexamic acid should be administered with caution owing to its adverse effects [1,9]. Six women (26%) were treated for attacks: 2 received fresh frozen plasma, and the other 2 were prescribed allergy drugs. Given the small number of patients

who received treatment for attacks, it was not possible to compare how long it took to reduce symptoms with each of the medications.

During pregnancy, pdC1-INH is the only HAE therapy that can be used without restriction [9], although it was not available in Brazil. pdC1-INH should be administered prior to cesarean delivery and is also highly recommended for vaginal delivery in patients with additional risk factors or severe C1INH-HAE symptoms during pregnancy or previous deliveries. Therefore, therapy should always be available on demand in the delivery room and during hospitalization [11].

Control of HAE during labor requires special consideration because it may be exacerbated [10]. None of our patients reported attacks during labor or the immediate postpartum. All deliveries were by cesarean section. During breastfeeding and postpartum, emotional stress continued to be an important triggering factor (14 pregnancies [60.8%]), as did trauma (8 women [34.7%]). Symptoms mainly affected the abdominal area, as previously reported by Czaller et al [8].

A family history of HAE was identified in 71.4% of the patients analyzed. The babies were affected by HAE in only 2 pregnancies. One of the mothers reported mild attacks (4 times during pregnancy) and a spontaneous abortion, while the other only experienced 1 attack of moderate intensity.

In theory, spontaneous abortion and premature labor are more likely in symptomatic patients because of the action of bradykinin in the contraction of smooth muscle in the uterus [9]. In support of this fact, the patients in the present study reported 5 spontaneous abortions (21.7%), which is a higher rate than in the general population in Brazil (ie, approximately 14%). These findings may be associated with inadequate therapy.

Our observations are relevant and reflect the situation in populations without access to specific care during pregnancy and postpartum throughout the world. This situation will likely change in the future, once appropriate drugs are approved for these patients. Nevertheless, it remains noteworthy that there is no specific medication for long-term prophylaxis or attacks in several Latin American countries.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

#### Previous Presentations

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Hotel Margitszget, Budapest, Hungary, May 28-31, 2015 "Machado AMRG, Pires, RMG, Martins, RO, and Grumach AS. Hereditary angioedema with C1 inhibitor deficit during pregnancy, childbirth and postpartum (breastfeeding) in Brazil".

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## Fixed Eruption by Multiple Plant Foods

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Palabras clave: Erupción fija. Alimentos vegetales. LTP.

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. Nonallergic adverse reactions to foods may be the result of food intolerance or adverse physiologic reactions [1].

The most frequently reported clinical manifestations of food allergy are acute urticaria and/or angioedema, oral allergy syndrome, and anaphylaxis. However, isolated digestive and respiratory symptoms are less common.

The diagnostic approach to food allergy starts with the clinical history, by which the clinician attempts to identify the food involved and its relationship with the patient's symptoms. This assessment must be supported by the detection of food-specific IgE antibodies by skin prick test (SPT) and/or serum determination. Finally, food challenge is the definitive, or gold standard, test [1,2].

We report the case of a 20-year-old man who complained about the appearance of skin lesions after eating certain plant foods. The patient was a high school student living in an urban house without pets who first came to our allergy department in March 2014. No drug allergies were reported. During childhood, he had been diagnosed with allergic rhinitis and asthma and treated with sublingual immunotherapy for 3 years. At the date of the consultation, his disease was well controlled with montelukast 10 mg, formoterol/budesonide 4.5 mg/160 mg, and rupatadine.

He also reported urticaria due to almond and peanut (diagnosed in 2003), and his mother had allergic rhinitis.

The patient had consulted for the appearance 1 year earlier of 2 itchy purple and erythematous skin lesions that have persisted ever since. They were located beside his left eye and on his left elbow extensor surface, covering part of the arm. He thought they were exacerbated by daily eating of fruit and vegetables at school. The suspected foods were apple, strawberry, pear, kiwi, banana, tomato, lettuce, corn, onion, and nuts (not almonds or peanuts).

Physical examination confirmed the presence of the previously described skin lesions and no other pathological findings.

The outcomes of the complementary test were as follows:

- SPT with inhalant allergens was positive for *Dermatophagoides pteronyssinus*, *Dermatophagoides*

*farinae*, *Alternaria* species, cat dander, and pollen from olive and *Artemisia* species.

- SPT with foods was positive to peach and the panallergen lipid transfer protein (LTP). SPT was negative to hazelnut, peanut, almond, walnut, pistachio, sunflower seed, apple, banana, pineapple, melon, kiwi, strawberry, pear, tomato, celery, and paprika.
- Spirometry revealed an obstructive pattern with a positive bronchodilator test result.
- The results of the blood count, biochemistry, and thyroid, and complement study were normal.
- Autoimmunity testing proved to be negative for antinuclear antibodies.
- Total IgE was 859 kU/L.
- Specific IgE findings (kU<sub>A</sub>/L CAP system, Thermo Fisher Scientific) were as follows: LTP, 58; apple, 2.9; strawberry, 3.1; pear, 1.9; kiwi, 5.7; banana, 6.8; tomato, 15.4; lettuce, 12.4; corn, 9.8; walnut, 49.8; hazelnut, 1.7; sunflower seeds, 0.0; peanut, 2.1; and almond 1.8.

The patient was prescribed a plant food-free diet (rosaceae fruits, vegetables, and nuts) for 2 weeks, after which the lesions disappeared, leaving slight brown pigmentation on the left elbow.

Patch testing with peach (both skin and flesh directly without petrolatum) performed 1 week later on the residual lesion resulted in localized itchy mild erythema at 48 hours.

All suppressed foods were subsequently reintroduced into the diet, and the skin lesions reappeared after a week. These were more intense than the previous ones.

Analysis of the biopsy specimen (Figure) revealed a

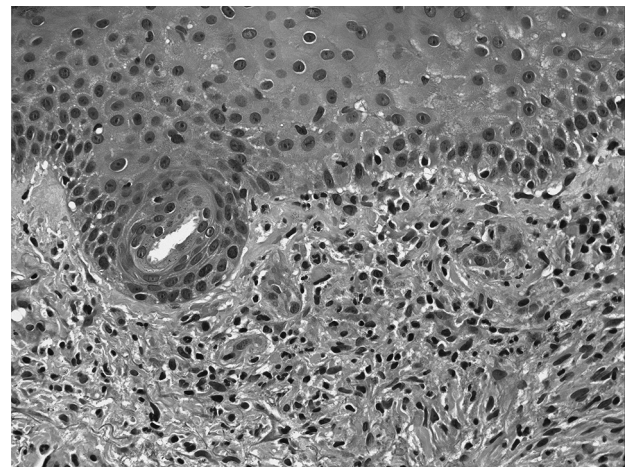


Figure. Histopathology of the biopsy specimen.

perivascular dermal lymphocytic infiltrate with mild basal spongiosis and abundant eosinophilic leukocytes. Such findings were consistent with fixed eruption.

A new avoidance diet was started, excluding only foods to which the patient was sensitized. The symptoms disappeared in 5 days.

All foods were then reintroduced one by one, with each



taken for 7 days, as follows:

- 1st provocation: walnut. Lesions exacerbated after 24 hours.
- 2nd provocation: tomato. Similar symptoms after 48 hours.
- 3rd provocation: lettuce. Negative after 7 days.
- 4th provocation: banana. Positive after 48 hours.
- 5th provocation: corn. Positive after 24 hours.
- 6th provocation: kiwi. Positive after 48 hours.
- 7th provocation: pear (without peel). Negative after 7 days.
- 8th provocation: strawberry. Negative after 7 days.
- 9th provocation: apple (without peel). Negative after 7 days.
- 10th provocation: hazelnut. Positive after 48 hours.

The patient remains asymptomatic (no skin lesions) with a diet free of walnut, tomato, banana, corn, kiwi, and hazelnut (in addition to almond and peanut).

The exact immunological mechanisms involved are unknown. Late symptoms reoccurred with oral challenges, and the positive peach patch test result suggests a delayed type IV hypersensitivity mechanism. However, specific IgE has been demonstrated against LTP and other vegetables, with no immediate symptoms after food intake; therefore, the causative mechanism could be a mixed IgE-mediated and non-IgE-mediated mechanism. We consider LTP to be the culprit allergen owing to its presence in all the foods that produced positive provocation test results and their high level of specific IgE.

Exposure to the plant food would enhance the release of cytokines, with the subsequent recruitment of intraepidermal lymphocytes infiltrating the skin at the site of the fixed eruption lesions.

Although fixed eruption due to plant foods has been reported [3-7], this is the first case involving multiple plant foods and with LTP as the suspected causative agent. To date, LTP has been involved in a wide variety of manifestations, ranging from oral allergy syndrome to anaphylaxis [8-9], but not in this kind of delayed cutaneous reaction.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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## Omalizumab as Third-Line Therapy for Urticaria During Pregnancy

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Palabras clave: Urticaria. Omalizumab. Angioedema. Terapias.

Chronic spontaneous urticaria (CSU) is characterized by the development of wheals (hives), angioedema, or both that last 6 weeks or more. Treatment aims to relieve symptoms and to improve quality of life [1]. H<sub>1</sub>-antihistamines are the first choice of treatment, although symptoms persist in up to 25% of patients, even with high doses [2]. Omalizumab is an anti-IgE monoclonal antibody that was approved as add-on therapy for refractory CSU in 2014. We report on the use of omalizumab during pregnancy in 2 women with CSU not controlled with high doses of antihistamines.

A 29-year-old white woman presented with a 15-year history of CSU. Her symptoms started when she was 14 years old, with periods of remission, but have been persistent since she was 20. She experienced daily generalized urticaria involving the face, extremities, and trunk, with occasional swollen joints. The results of the physical examination were unremarkable, except for wheals on the extremities.

She had no personal history of atopy or other significant medical conditions. Over the years, other possible causes of chronic urticaria were ruled out.

The results of the laboratory work-up (thyroglobulin and thyroid peroxidase antibody, thyroid function, complement, and erythrocyte sedimentation rate) were unremarkable. The antinuclear antibody titer was 1/1280 (fine speckled pattern). Total serum IgE level was 180 IU/mL. Direct immunofluorescence of a skin biopsy specimen showed no evidence of urticarial vasculitis.

Nonsteroidal anti-inflammatory drugs were avoided. Her condition was refractory to combinations of maximal doses of antihistamines, antileukotrienes, and H<sub>2</sub>-blockers.

In April 2012, omalizumab was introduced at 300 mg every 4 weeks, with a significant improvement in symptoms within 3 days. All the other drugs were gradually withdrawn during the following days. Two months later, she was not taking any other drug and had no symptoms of urticaria. After 6 months, urticaria was clinically controlled with a 150-mg dose. No specific tools were used to assess disease activity or control.

One year later, she decided to stop taking omalizumab. She was in remission for 8 months without treatment. When

the symptoms of urticaria reappeared, omalizumab was reintroduced at the same dose (150 mg).

In June 2014, she became pregnant, and after a long discussion about the risks and benefits of using off-label omalizumab during pregnancy, the patient, her family, and her doctors decided to continue treatment. During her pregnancy, she took four 150-mg doses of omalizumab and had no complaints other than those typical of pregnancy. In February 2015, she gave birth to a full-term male by elective cesarean section (3555 g, 50.5 cm). No congenital abnormalities were observed at birth. The boy was breastfed until 9 months, and is currently 2 years old with normal physical and mental status for age.

One year later, she became pregnant again and continued to take omalizumab (3 doses [150 mg] during the pregnancy). In October 2016, she gave birth to a full-term healthy male by elective cesarean section (4150 g, 51.0 cm). The boy is now 6 months old and healthy, is still being breastfed, and has no developmental abnormalities.

The other patient was a 32-year-old white woman with a 3-month history of wheals and pruritus with angioedema affecting the eyelids, lips, and tongue. Her symptoms were not associated with any specific trigger. At her first visit, she had been taking levocetirizine 10 mg/day, epinastine 20 mg/day, and doxepin 20 mg/day, with partial control of symptoms. She had a previous history of rhinitis and insect sting allergy. The patient also reported a past episode of diclofenac-induced urticaria and now avoids all nonsteroidal anti-inflammatory drugs except paracetamol. She had no family history of urticaria or any other allergy.

Her laboratory data showed an antinuclear antibody titer of 1/320 (fine speckled pattern) and unremarkable thyroglobulin and thyroid peroxidase antibody titers. The results for thyroid function tests, complement, serology (viruses), and erythrocyte sedimentation rate were also unremarkable. Total IgE was 255 IU/mL, and specific IgE was 0.4 kU<sub>A</sub>/L to fire ant and <0.35 kU<sub>A</sub>/L to honey bee.

Treatment was adjusted to levocetirizine 20 mg/day, and a short course of prednisolone 40 mg/day was proposed. Urticaria was controlled with systemic corticosteroids, but the symptoms relapsed after the drug was stopped, with an Urticaria Activity Score (UAS7) of 18 after 2 weeks. The patient started omalizumab 300 mg every 4 weeks in December 2014, and urticaria was controlled 3 months later (UAS7, 0). She became pregnant and, after being informed of the potential risks and unknown safety of omalizumab during pregnancy, she decided to stop the drug. However, 3 months later, she relapsed (UAS7, 22), and a 300-mg dose of omalizumab was administered, with a complete response in 1 week. Another 300-mg dose of omalizumab was administered 12 weeks later when the urticarial symptoms reappeared.

In November 2015, she gave birth to a full-term male by elective cesarean section (50 cm and 3500 g). No congenital abnormalities were observed. The boy is still being breastfed, and his physical and mental development is normal. The patient is currently taking omalizumab 300 mg every 8 weeks, after a failed attempt at reducing the dose to 150 mg.

CSU is often a challenging disease in pregnancy. International guidelines suggest the treatment algorithm

**Table.** Publications on Omalizumab Use for Urticaria During Pregnancy

Authors	Number of Patients	Number of Pregnancies	Safety	Efficacy
Viera dos Santos et al [4]	1	1	No adverse reactions	Complete control
Ghazanfar et al [5]	1	2	No adverse reactions	Complete control
Cuervo-Pardo et al [6]	4	4	No adverse reactions	Complete control
González-Medina et al [7]	2	2	No adverse reactions	Complete control

used in nonpregnant patients, including nonsedating H<sub>1</sub>-antihistamines in up to 4-fold doses as the first and second line, and omalizumab as the third line for recalcitrant urticaria [1]. According to the United States Food and Drug Administration, omalizumab is classed as a category B drug based mainly on the results of the Xolair Pregnancy Registry (EXPECT), a postmarketing prospective observational study of asthmatic patients treated with omalizumab [3]. Few publications report on administration of omalizumab to treat urticaria during pregnancy (Table) [4-7]. Although omalizumab has not been approved for use during pregnancy, it can be considered a safe and efficient alternative for patients who are refractory to antihistamines.

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## Acute Localized Exanthematous Pustulosis Due to Bemiparin

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**Palabras clave:** Bemiparina. Agudo. Localizado. Exantema. Pustulosis.

Nonimmediate allergic reactions to drugs are the most common reactions induced by specific immunologic mechanisms and can be induced by all commercially available drugs. These reactions can appear hours, days, or even weeks after drug intake and elicit a broad spectrum of mainly clinical manifestations, including acute generalized exanthematous pustulosis (AGEP) [1]. Acute localized exanthematous pustulosis (ALEP) is considered a possible variant of AGEP [2]. The pathophysiological mechanisms of AGEP and ALEP remain uncertain, although 90% of cases of AGEP are induced by drugs, even topical drugs [3].

The second-generation, low-molecular-weight heparin (LMWH) bemiparin is a sodium salt of depolymerized porcine intestinal mucosa that produces significant elevation in plasma levels of the tissue factor pathway inhibitor, which increases the anti-Xa effect and is responsible for favorable antithrombotic activity [4].

We report the case of a 65-year-old woman with no history of psoriasis, cutaneous drug reaction, autoimmune diseases, immune suppression, or heart disease. After undergoing a procedure to remove osteosynthesis material, the patient was prescribed bemiparin (2500 IU/d administered subcutaneously for 6 days), cefazolin (2 doses of 1 g each with a 12-hour interval between doses), and metamizole 500 mg. After 24 hours, the patient developed an erythematous eruption at the injection site (abdomen), which extended 12 hours later to the palms of both hands in the form of pustules (Figure), the dorsum of the hands, and lateral areas of both feet. No fever, arthralgia, or other general symptoms were recorded. All drugs were withdrawn and treatment with prednisone 30 mg/d was prescribed for 1 week. Tapering doses of prednisone were administered for 1 additional week. Fifteen days later, the patient started treatment with prednicarbate topical for 10 days, and despite the previous treatment, the skin lesions persisted for 6 weeks. The skin on her palms eventually began to peel.

The results for complete blood count, biochemistry, determination of Ig, and protein profile were normal.

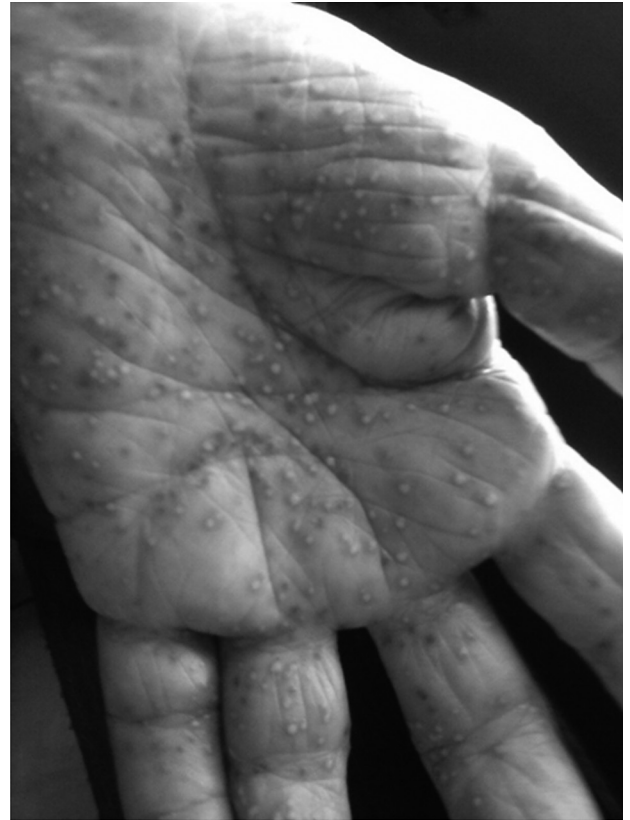


Figure. Acute localized exanthematous pustulosis due to bemiparin.

The results for viral culture, PCR, and bacterial and fungal cultures of skin lesions were negative.

Histological analysis of the biopsy specimen of the cutaneous lesions revealed subcorneal pustules, necrotic keratinocytes, edema in the upper dermis, and mild perivascular infiltrate with scarce neutrophils and eosinophils. There were no signs of vasculitis or acantholysis.

After confirming the diagnosis of ALEP, we performed the allergy study. Patch tests performed 2 months after the onset of symptoms with metamizole, cefazolin, bemiparin, enoxaparin, and nadroparin (20% in water and petrolatum) were positive only for bemiparin (water and petrolatum, reading at 48 and 96 hours), and eruptions were observed on the area tested. The results of challenge testing with enoxaparin, metamizole, and cefazolin were all negative, with good tolerance. The result of the subsequent challenge test with bemiparin, however, was positive, and 2 days after taking 1000 IU, the patient complained of generalized itching and cutaneous eruption on her back and palms, which persisted for up to 7 days.

Allergic reactions to heparins, especially immediate reactions, are uncommon; delayed skin lesions to subcutaneous heparin are the most common type of hypersensitivity reaction [5].

ALEP is a rare and localized variant of AGEP. Until 2 years ago, only 21 cases of ALEP had been reported in the literature; 15 cases were related to drug administration [6], and 6 pediatric cases occurred in springtime, with no associated drug administration in any case [7].



Our evaluation of the patient and specific assessment of the skin rash with pustules 1-2 days after ingestion of several drugs led us to suspect that one of the drugs could be the causative agent; therefore, we withdrew all pharmacological treatment [2], since this type of reaction is mainly drug-induced. The latency period was 1-2 days, which could indicate that the patient was probably sensitized to bemiparin. However, although the patient had been treated with LMWH, she did not remember whether the heparin prescribed previously was bemiparin or not. As with the delayed skin allergy to LMWH, the skin eruption began in the abdomen, where bemiparin was injected [4]. When we performed the challenge test with bemiparin, the patient did not develop rash or erythema at the injection site. She did develop a rash with pustules on the back and palms, although the incubation period was longer, possibly because the dose of bemiparin was smaller.

ALEP usually resolves within a few days after withdrawal of the causative drug [2]. In the present case, we were unable to identify the causative mechanisms leading to the indolent course of the pustular eruption, although there is at least 1 case in the literature in which the reaction took several weeks to resolve [8].

ALEP was diagnosed based on the morphology of the skin lesions and the absence of symptoms and was later confirmed by the histological analysis of the biopsy specimen.

We performed the differential diagnosis with other, similar pustular skin eruptions, such as pustular psoriasis, which was ruled out by the absence of a history of psoriasis and the different varieties of IgA pemphigus (especially the subcorneal pustular dermatosis subtype). We were able to diagnose ALEP based on the absence of recurrences of pustular cutaneous lesions and the positive allergy test results (patch tests and positive challenge tests with bemiparin, with recurrence of rash after challenge with bemiparin). Negative results in the microbiological studies ruled out an infectious cause.

The allergy study [9] confirmed that the causative drug was bemiparin and not cefazolin or metamizole, although both  $\beta$ -lactam antibiotics [6] and some nonsteroidal anti-inflammatory drugs (eg, ibuprofen) are involved in the etiology of ALEP [10].

Cross-reactivity has been demonstrated in delayed allergy to LMWH [4]. However, in the case we report, a patient with ALEP tolerated enoxaparin; therefore, at least with this heparin, there was no cross-reactivity. This observation is important, since the patient can be prescribed enoxaparin if she needs it in the future.

We report the first case of ALEP due to bemiparin in a patient who tolerated enoxaparin.

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#### Conflicts of Interest

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## Palpebral Edema and Eosinophilia

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Key words: Edema. Eosinophilia. Myalgia. Trichinosis.

Palabras clave: Edema. Eosinofilia. Mialgia. Triquinosis.

Acute angioedema is very common, and underlying causes can be highly heterogeneous. It is more a symptom than a specific disease and is caused by drugs, physical factors, allergic and pseudoallergic reactions, and infections. In Spain, angioedema induced by helminths or other parasites it is uncommon. We report the case of a patient with palpebral edema and eosinophilia due to *Trichinella* infection.

The patient was a 50-year-old woman who presented at our allergy unit with a 1-month history of palpebral edema, nonpruritic macular erythematous eruption, fever, and intense myalgia. A complete blood count showed marked eosinophilia (26.8%), with an eosinophil count of  $1.98 \times 10^9/L$ . We suspected trichinosis and questioned the patient to determine her epidemiological history. She said that she had eaten boar meat sausage and that her husband and daughter had eaten the same sausage and had also experienced myalgia and fever.

We performed a skin prick test with a series of common aeroallergens and foods (Bial Aristegui). Positive results were obtained for grass pollen and *Cupressus arizonica*. A complete blood count taken 13 days after the first determination showed eosinophilia to be 38.4% and an eosinophil count of  $2.75 \times 10^9/L$ . Biochemistry revealed the following values: creatinine phosphokinase (CPK), 872 IU/L (normal range, 10-170); aspartate transaminase (AST), 39 IU/L (5-32); alanine transaminase (ALT), 51 IU/L (5-31); C-reactive protein, 51.4 mg/L (0-9); and total IgE, 92.6 IU/mL (0-100). One month later, the result of indirect immunofluorescence to detect IgG antibodies to *Trichinella* was indeterminate (1/20). However, the same test was performed 14 days later and revealed an elevated antibody titer ( $>1/160$ ). At that time, the titer for IgG to *Trichinella* according to ELISA was 2.56 (positive  $\geq 1.10$ ). Determinations performed 45 days later (complete blood count, CPK, ALT, AST, and C-reactive protein) all yielded normal values. Serum specific IgE was positive for *Cynodon dactylon* (0.54 IU/mL), *Lolium perenne* (5.02 IU/mL), *Olea europaea* (0.69 IU/mL), and *Cupressus sempervivens* (0.47 IU/mL).

The patient was treated with albendazole 400 mg twice daily for 10 days and was asymptomatic after 15 days. The local health authorities were informed and participated in the evaluation.

Eosinophilia is prominent in specific infectious diseases. Helminths are multicellular, metazoan organisms, and infections with a diversity of helminth parasites elicit

eosinophilia. Helminth parasites elicit  $T_H2$ -like lymphocyte responses, and IL-5 production accounts for eosinophilia. While eosinophilia may indicate the presence of helminth infections, the absence of blood eosinophilia does not exclude such infections [1].

Trichinosis, or trichinellosis, is an infection by the nematode *Trichinella spiralis*. Most cases of trichinosis in Spain [2-4] affect people who have consumed uncooked boar meat or pig meat from slaughters that have not been inspected by the public health authorities. The disease is acquired by consumption of raw or undercooked meat with viable larvae of the parasite. Diagnosis is based on symptoms, compatible epidemiology, and positive serology for trichinosis [5].

The *Trichinella* life cycle is maintained in animals that are fed other animals (eg, pigs, horses) or that eat other animals (eg, bears, foxes, boars) whose striated muscle contain encysted infective larvae (eg, rodents). Humans become infected by eating raw, undercooked, or underprocessed meat from infected animals, most commonly pigs, boar, and bear. The larvae encyst in the small bowel, penetrate the mucosa, and mature in 6 to 8 days.

Mature females release living larvae for 4 to 6 weeks and then die or are expelled. Newborn larvae migrate through the bloodstream and lymphatic system but ultimately survive only within striated skeletal muscle cells. Larvae fully encyst in 1 to 2 months and remain viable for several years as intracellular parasites. Dead larvae are eventually resorbed or calcify. The cycle continues only if encysted larvae are ingested by another carnivore.

*Trichinella* infections may result in a broad spectrum of clinical forms ranging from asymptomatic to fatal. Interestingly, trichinosis is thought to be one of the causes of death of Wolfgang Amadeus Mozart [6]. *Trichinella* infections are usually asymptomatic or mild. During the first week, the patients may experience nausea, abdominal cramps, and diarrhea. Systemic symptoms and signs appear 1 to 2 weeks after infection and include facial or periorbital edema, urticaria [7], nonspecific skin rashes [8], myalgia, persistent fever, headache, and subconjunctival hemorrhages and petechiae. Eye pain and photophobia often precede myalgia. Symptoms due to muscle invasion may mimic polymyositis [9]. The muscles of respiration, speech, mastication, and swallowing may be painful. Eosinophilia usually begins when newborn larvae invade tissues, peaks 2 to 4 week after infestation, and gradually declines as the larvae encyst. The intensity of the eosinophilia is dependent on the number of larvae, the species of *Trichinella* involved, the susceptibility of the host to infection, and the time at which the treatment (in particular, treatment with anthelmintics) was started [10]. Symptoms and signs gradually resolve, and most disappear by about the third month, when the larvae have become fully encysted in muscle cells and eliminated from other organs and tissues. Vague muscle pains and fatigue may persist for months.

In the case we report, the clinical findings, compatible epidemiology, and positive serology results confirmed the diagnosis, rendering further tests unnecessary.

Since trichinosis is a notifiable disease, we contacted the health authorities, which informed us that there had not been an outbreak of trichinosis in the area where the patient resides.

In summary, physicians must be aware of trichinosis and should include it in their differential diagnosis when examining patients with palpebral edema and eosinophilia.

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#### Conflicts of Interest

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#### Scoliid Wasp Sting: A New Cause of Anaphylaxis

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**Palabras clave:** Anafilaxia. Veneno de himenóptero. Alergia a veneno de insecto. Antígeno 5.

Insect venom can cause potentially life-threatening allergic reactions. Stinging insects of the order Hymenoptera are the main cause of insect-related systemic allergic reactions, including anaphylaxis [1]. The 3 clinically relevant families that comprise this order are bees, vespids, and ants [2]. Within the Vespidae family, species of the genera *Vespa*, *Polistes*, and *Vespa*, which are found all over Europe, are the wasps that most frequently sting humans. The Scoliidae family comprises more than 500 wasps worldwide. The wasps are black, often with yellow or orange markings and a fairly large and stout body and distinctively corrugated wing tips. Scoliid wasps are parasitoids of soil-inhabiting scarab beetle larvae. They are solitary insects and not social nest builders, as are other wasps such as yellow jackets. For this reason, they rarely sting humans and are not aggressive unless provoked. The scoliids found in Italy belong to the species *Scolia* and *Megascolia* [3]. To the best of our knowledge, there are no reports of anaphylaxis induced by scoliid wasp sting in the literature.

We present the case of a 59-year-old man who experienced an anaphylactic reaction after a scoliid wasp sting. He was stung in the hand in a public park while trying to turn the insect away. Ten minutes later, he developed generalized urticaria, angioedema, and dyspnea. He arrived at the emergency department about 30 minutes after the sting. At the initial evaluation, he was awake but restless. His blood pressure was 70/50 mmHg, heart rate 86 bpm, and oxygen saturation 89% while breathing room air. He was treated with intramuscular adrenaline, oxygen, and intravenous antihistamines and corticosteroids. His serum tryptase level 2 hours after the onset of the reaction was elevated (13.0 µg/L). Treatment was successful, and the patient was discharged after 24 hours in observation.

The patient's past medical history revealed chronic hepatitis C infection (genotype 1b) and previous intravenous drug abuse; he was not taking medication and did not report any prior anaphylactic reactions due to Hymenoptera stings. He had previously been stung by wasps without experiencing systemic or large local reactions.

The patient was able to capture and provide the stinging insect, which was identified as a wasp of the genus *Scolia* (Vespoidea superfamily, Scoliidae family), *Scolia flavifrons*.

We performed tests for serum specific IgE antibodies, skin prick tests, and intradermal tests with venom from honeybee (*Apis mellifera*), yellow jacket (*Vespula* species), European hornet (*Vespa crabro*), and European paper wasp (*Polistes dominulus*). Skin tests (ALK-Abelló, Anallergo) were carried out according to international guidelines [1]; venom from *S flavifrons* was not used because it was not available. The skin prick test showed negative results, while the intradermal test at 0.1 µg/mL was positive only to yellow jacket (wheal diameter of 5 mm). Antigen-specific serum IgE, and specific IgE against the components Api m 1, Pol d 5, Ves v 1, and Ves v 5 was determined by ImmunoCAP (Thermo Fisher Scientific) with positive results for *Vespula* species, *P dominulus*, rVes v 5, and rPol d 5 (Table). The serum tryptase level 2 weeks after the sting was within the normal range (4.18 µg/L). The basophil activation test (BAT) was then performed with yellow jacket venom (Pharmalgen, 1 µg/mL) using a commercially available Flow-CAST kit (Bühlmann) according to the manufacturer's instructions. The BAT yielded a positive result (activated cells, 21.6%).

Besides the vespids that commonly cause allergic reactions, ie, *Vespula* species, *Polistes* species, and *Vespa crabro*, other wasps of the *Vespa* genus have been reported to be responsible for anaphylaxis, including *Vespa affinis* [4] and, more recently, *Vespa velutina*, which is becoming increasingly common in Europe [5]. In the case of *Vespa magnifica*, unusual reactions with renal failure have been reported [6]. Since scoliid wasps are solitary insects that are not particularly aggressive, they do not usually sting humans under natural conditions. To our knowledge, allergic reactions to scoliid wasp stings have not yet been reported; moreover, no venom proteins have been identified, and standardized extracts of venom for diagnosis are not currently available. Likewise, specific immunotherapy with scoliid venom is obviously not possible. IgE cross-reactions between vespid venoms are well known [7] and could explain the presence of serum specific IgE to yellow jacket and paper wasp in the case we report. The positive BAT result with yellow jacket venom provides

further confirmation. Antigen 5 is a major allergen of vespid venoms. However, antigen 5 of several hymenoptera species is highly cross-reactive, thus rendering it unfeasible in many cases for determining sensitization to various venoms [7,8]. To date, the only antigen 5 allergens available for routine molecular diagnostics are Ves v 5 (*Vespula* species) and Pol d 5 (*P dominulus* venom). The presence of serum specific IgE against antigen 5 from other vespids (Ves v 5 and Pol d 5) in the case we report could be due to the previous wasps stings, but also to the presence of an as yet uncharacterized antigen 5 in scoliid wasp venom leading to in vitro cross-reactivity with the homologous allergens of these vespids commonly causing allergic reactions. We do not know whether immunotherapy with the available extracts of other vespid venoms could prove effective for treating the patient reported here, since there is no possibility of treatment with the specific venom of scoliid wasp. However, based on the statement in the 2005 EAACI guidelines on prevention and treatment of Hymenoptera venom allergy (when venom from *V crabro* was not yet available), which state that since it can be assumed that most patients with allergic reactions to *V crabro* were first sensitized by *Vespula* stings, immunotherapy with *Vespula* venom alone is sufficient [9]. Given that no new data were produced to modify this issue in more recent reports [10], such an approach could also be valid for reactions to scoliid wasps.

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#### Conflicts of Interest

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Table. Results of In Vitro Specific IgE

	Value, kU <sub>A</sub> /L
Honey bee ( <i>Apis mellifera</i> )	0.38
Yellow jacket ( <i>Vespula</i> species)	33.7
European hornet ( <i>Vespa crabro</i> )	0.59
European paper wasp ( <i>Polistes dominulus</i> )	16.2
MUXF3 CCD	0.00
rApi m 1 (Phospholipase A2)	0.00
rVes v 5 (Antigen 5)	28.3
rVes v 1 (Phospholipase A1)	0.45
rPol d 5 (Antigen 5)	14.6



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### Initial False-Negative Specific IgE to Gelatin in Gelatin-Induced Anaphylaxis

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**Palabras clave:** Anafilaxia. Gelatina. IgE específica. Anafilaxia perioperativa.

When an early reintervention (<4 weeks) is necessary after perioperative anaphylaxis, skin testing is insufficiently sensitive to identify the culprit drug(s) and to rule out potential allergy to other drugs [1]. In this situation, specific IgE (sIgE) determination can help to identify the culprit drug(s) and guide treatment choices early after the event [2,3]. Serum sIgE is not consumed during anaphylaxis [4], presumably because the reaction is mediated by mast cell- and basophil-bound IgE. The ideal timing for determination of sIgE is not well defined for most drugs. Current practice consists mostly of sampling at the time of the reaction and, in the case of inconsistent results, repeat sampling at the allergy work-up 4-6 weeks later. Guidelines indicate that determination of sIgE against neuromuscular blocking agents at the time of the reaction is equivalent to testing at a later stage [5]. Laroche et al [6] observed no difference in the titer of sIgE to neuromuscular blocking agents at the time of the reaction and 8 weeks later. Similarly, the results of 10 of 11 skin tests [7] and 6 of 8 skin tests [8] confirmed that chlorhexidine-allergic patients had detectable sIgE for chlorhexidine when samples were taken at the time of the reaction. However, these findings cannot be extrapolated to other allergens. Moreover, sIgE titers for chlorhexidine decline over time, sometimes to below the limit of detection, whilst retaining the capacity to elicit symptoms upon re-exposure [7,8]. However, the limit of detection in the above-mentioned studies [7,8] was 0.35 kU<sub>A</sub>/mL, and it is unclear whether a limit of 0.10 kU<sub>A</sub>/mL would have altered these findings. The cause of the declining titer of sIgE to chlorhexidine is unknown, although it may result from a lack of stimulation through repeated exposure. The purpose of this study was to evaluate the influence of the timing of sampling on the result of sIgE to gelatin in the context of perioperative anaphylaxis.

We present the case of a 62-year-old man who experienced anaphylaxis 15 minutes after receiving a gelatin-containing plasma expander during general anesthesia for hip surgery. Decontamination was performed with chlorhexidine. Induction

was with propofol, lidocaine, sufentanil, rocuronium, and dexamethasone 2.25 hours before the event, and cephazolin was administered 1.75 hours before. The 500-mL gelatin infusion was stopped after near complete infusion. Treatment was started with epinephrine, norepinephrine, promethazine, hydrocortisone, and saline fluid expansion. Serum tryptase increased transiently (95.7 ng/dL 1.5 hours after the reaction vs 6.0 ng/dL at baseline). The results of ImmunoCAP (Thermo Fisher) for sIgE to gelatin, galactose- $\alpha$ -1,3-galactose, ethylene oxide, latex, and chlorhexidine were negative ( $<0.10$  kU<sub>A</sub>/mL) in the samples obtained 1.5 hours after the event; these findings were independently confirmed at a later stage in the same sample. However, repeat sampling after the event demonstrated positive values for gelatin at day 16 (15.40 kU<sub>A</sub>/mL) and day 96 (4.85 kU<sub>A</sub>/mL) and for chlorhexidine at day 16 (0.22 kU<sub>A</sub>/mL) and negative values for galactose- $\alpha$ -1,3-galactose, ethylene oxide, and latex. On day 18, the patient underwent a new intervention under general anesthesia and without gelatin-containing plasma expanders. The procedure was unremarkable. An allergy work-up 4 weeks after the event revealed positive skin tests for the 4% gelatin-containing plasma expander (3-mm and 5-mm wheal diameter after skin prick testing at 1:10 and 1:1, respectively) and negative skin tests for chlorhexidine (skin prick test at 5 mg/mL and intradermal test at 0.002 mg/mL), latex (skin prick test), and cephazolin (skin prick test at 300 mg/mL and intradermal test at 30 mg/mL). The allergy work-up showed that anaphylaxis was due to gelatin allergy. We reasoned that the initial sIgE for gelatin was a false negative owing to competition between the intravascular high-molecular-weight gelatin infusion and the gelatin ImmunoCAP assay, rather than a boosting phenomenon. Therefore, a modified inhibition assay was performed to mimic the postevent procedure by incubating patient serum obtained at day 16 for 1.5 hours at room temperature with a serial dilution of the gelatin-containing plasma expander (Figure). We observed near-complete inhibition of sIgE (50% inhibitory concentration, 0.02%) at the expected plasma gelatin concentration at the time of

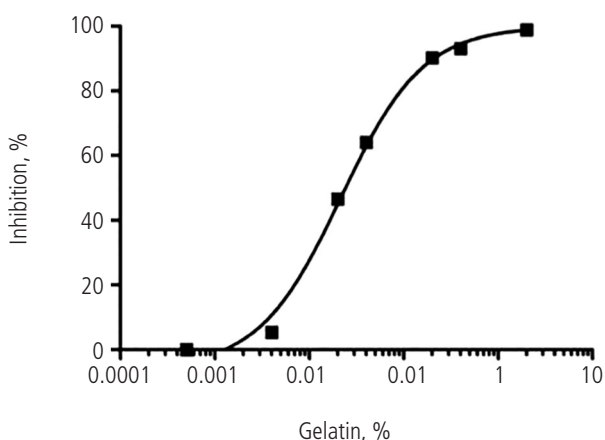


Figure. Modified ImmunoCAP-inhibition assay for gelatin sIgE determination. Data were plotted using GraphPad Prism (nonlinear fit, log(agonist) vs response).

initial sampling (a plasma gelatin concentration of ~0.8% was assumed based on infusion of 500 mL of 4% Gelofusine plasma expander with a half-life of 2.5 hours in 2.5 L of intravascular plasma volume). No pre-event sample could be obtained to assess pre-existing sensitization. Of note, the patient tolerated red meat products throughout the follow-up despite the bovine origin of the gelatin in the plasma expander.

We found that the sIgE titer decreased over time, as demonstrated for chlorhexidine. In addition, we hypothesize that the false-negative sIgE result at the time of the event may have been caused by competition between the highly concentrated high-molecular-weight intravascular allergen and the ImmunoCAP coated allergen. Our findings indicate that determination of sIgE should be repeated if it is negative in samples taken at the time of the event despite a high index of suspicion. In the case of gelatin, resampling is deemed relevant at an early stage, especially if early reintervention ( $<4$  weeks after the initial event) is necessary.

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#### Previous Presentations

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