Severe Congenital Neutropenia With a Novel ELANE Mutation in 2 Mexican Patients

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Neutropenia is a condition defined by low absolute numbers of peripheral neutrophil granulocytes (<1500 neutrophil granulocytes/mL). It is classified as severe when the neutrophil count is less than 500/mL of peripheral blood. Patients develop severe bacterial infections, without pus, that affect the lungs, skin, and deep tissues. In most cases neutropenia is acquired, but in recent years, several genetic causes have been identified [1].

ELANE was the first gene identified as a genetic cause of neutropenia in patients with cyclic neutropenia and it was later associated with severe congenital neutropenia (SCN) [2,3]. It can be sporadic or inherited in an autosomal dominant pattern. To date, over 80 mutations have been implicated in cyclic neutropenia and SCN [4]. In this paper we describe what are to our knowledge the first 2 cases of SCN with *ELANE* mutations in Mexico. The outcomes were different and we identified a novel mutation.

The first case was a 13-month-old girl who developed perianal ulcers that rapidly progressed to necrotizing fascitis and septic shock; *Pseudomonas aeruginosa* was isolated from tissue cultures. The complete blood count revealed hemoglobin, 6.1 g/dL; hematocrit, 18.5%; leucocytes, 5700 × 10^3 μL; neutrophils, 500 × 10^3 μL; lymphocytes, 4000 × 10^3 μL; and platelets, 256 000. The patient's clinical condition improved after surgical debridement and colostomy, antibiotic therapy with meropenem, and vancomycin and filgrastim. Serum immunoglobulins included IgG 1460 mg/dL, IgA 256 mg/dL, and IgM 223 mg/dL. The bone marrow aspiration revealed myeloid maturation arrest, and anti-neutrophil HN1a antibodies were negative. SCN was suspected and diagnosis was confirmed by *ELANE* gene sequencing of genomic DNA. We detected a novel mutation consisting of deletion of 3 base pairs of exon 2 [c.193-195delGTC], with a loss of valine without a shift in the reading frame [p-Val65del] in the heterozygous state. We started treatment with topical and subcutaneous filgrastim (dose up to 15 mcg/kg/d). However, the patient once again developed occipital ulcers, with severe neutropenia (neutrophils, 100 × 10^3 μL). Hematopoietic stem cell transplantation (HSCT) was performed when the infant was 2 years old. The conditioning regimen used was busulfan, cyclophosphamide, and antithymocyte globulin, and the patient received stem cells from an unrelated cord blood donor. On day 3 after HSCT, she developed sepsis; the primary focus was the infected colostomy, and the patient died on day 16.

The second case involved a 2-month-old boy with delayed separation of the umbilical cord (at 1 month). He had suppurative otitis media secondary to *P aeruginosa* that responded unfavorably to ceftazidime. The complete blood count revealed severe neutropenia (100 cells × 10^3/μL). The computed tomography scan showed signs of severe left otomastoiditis, which was treated with vancomycin, cefepime, and left radical mastoidectomy. We also started treatment with granulocyte colony-stimulating factor (G-CSF) at an initial dose of 3 mcg/kg/d, but this was increased up to 100 mcg/kg/d because the neutrophil count did not improve. SCN was suspected, and a molecular study of genomic DNA identified an *ELANE* mutation of exon 5, heterozygous state, with a C to G substitution at the nucleotide position [c.614C>G], and consequently replacement of proline (P) with arginine (R), at residue 205 [p.Pro205Arg]. This mutation, which has been previously reported, confirmed the diagnosis of type 1 SCN. At 7 months old, the infant underwent HSCT using cord blood from an unrelated donor, with a CD34 cell dose of 3.4 x 10^5/kg. The conditioning regimen was busulfan, cyclophosphamide, and antithymocyte globulin, and there were no complications. The patient received prophylaxis with antimicrobial agents and for graft-vs-host disease (GVHD). The engraftment was evaluated on day 25, and the neutrophil count was 2200/mm^3. On day 33, the patient was discharged. The patient showed mixed chimerism (57%) on day 60, and neutrophil counts of between 100 and 1200 × 10^3/μL. On day 240, his neutrophil count had dropped to 200 x 10^3/μL, and anti-HLA type I and II titers were positive. The engraftment was therefore considered a failure, and the patient is currently is being prepared for a second HSCT.

SCN is a rare hematologic disorder associated with severe infections and risk of progression to acute myelogenous leukemia [5]. In 60% to 80% of cases, it is caused by mutations in the *ELANE* gene, and most cases are sporadic [5,6]. We observed the same situation in our patients. No other relatives

were affected, and like Horwitz et al [7], we concluded that de novo mutations in *ELANE* are fairly common.

To our knowledge, the mutation we identified in case 1 has not been previously reported. The mutation in case 2, by contrast, was reported by Ancliff et al [1] in 2001.Neither of these patients had a mutation on exon 4, which is where mutations have been most frequently reported in SCN [4]. Neither of the patients had the G815R mutation either, which is known to have worse outcomes, because of poor response to G-SCF and progression to myelodysplastic syndrome and acute myeloid leukemia [8]. We therefore consider that molecular diagnosis is important in SCN, because it can facilitate the detection of cases that require aggressive intervention and guide genetic counseling, as, while most cases are sporadic, there is evidence of an autosomal dominant inheritance pattern [9].

The curative treatment for SCN is HSCT [10]. Unfortunately, one of our patients died due to infectious complications in the first few days posttransplantation. The second patient is alive but experienced engraftment failure. Connelly et al [10] described groups of patients at high risk of death from sepsis and of myelodysplastic syndrome. These patients include those who require high doses of G-CSF but only partially respond (patient 2 in our case), those who have a detectable clone harboring a mutation associated with myelodysplastic syndrome, and those who have the constitutional Gly185Arg *ELANE* mutation. High-risk patients should be considered for transplant using the best available donor in the best clinical conditions.

There are still many gaps in our knowledge of SCN, but ongoing and future investigations will provide us with more knowledge about the relationship between phenotype and genotype that will help to properly classify and provide adequate treatment to patients with SCN.

To our knowledge we have reported the first 2 Mexican cases of SCN with reported mutations in the *ELANE* gene.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Anaphylaxis After Oxaliplatin Allergy Skin Testing

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Palabras clave: Oxaliplatino. Pruebas de alergia. Intradérmica. Desensibilización.

Oxaliplatin (L-OHP) is a chemotherapeutic drug used in combination with fluorouracil and leucovorin in the treatment of colorectal cancer and other malignancies such as ovarian, breast, head and neck and lung cancer, non-Hodgkin lymphoma and melanoma.

The prevalence of hypersensitivity reactions is estimated at between 12% [1] and 19% [2]. The few cases reported suggest that these reactions are IgE-mediated: the clinical presentation is consistent with an allergic reaction, the reactions appear after several courses of therapy, the symptoms begin within 60 minutes of perfusion with small amounts of the drug, and the skin tests are positive.

Patients tend to react to the drug during the sixth or seventh infusion of oxaliplatin [1,2], with a cumulative dose of 500 to 600 mg/m^2. The reaction consists of flushing and swelling of the face and hands, itching, sweating, and lacrimation; this may worsen with dyspnea, wheezing, laryngospasm, psychomotor agitation, tachycardia, precordial pain, hypotension, or diffuse erythema.

Several studies have conducted skin tests to demonstrate an IgE-mediated reaction to oxaliplatin using concentrations of 0.1, 1, 5, and 10 mg/mL for the prick tests and 0.001, 0.01, 0.1, 0.5, 1, and 5 mg/mL for the intradermal tests [1-5]. The maximum concentration defined for a positive test was 10 mg/mL for the prick test and 0.1mg/mL for the intradermal test. The 1-mg/mL concentration used in intradermal testing caused an irritant reaction, without hypersensitivity, in 36% of the volunteers [2].

We report the case of a 45-year-old woman with metastatic colorectal cancer treated with oxaliplatin, 5-fluouracil, and leucovorin every 3 weeks. A few minutes after starting the seventh infusion of oxaliplatin, she developed generalized pruritus (particularly affecting the palms and soles), lacrimation, rhinorrhea, dyspnea, and hypotension. Infusion was stopped and adequate treatment administered. The patient showed good tolerance to 5-fluouracil and leucovorin afterwards.

Skin testing was conducted following the European Academy of Allergy and Clinical Immunology recommendations at a concentration of 5 mg/mL for the prick test and 0.05 mg/mL and 0.5 mg/mL for the intradermal test (volar surface of the forearm). The tests were performed in the intensive care unit (ICU), following informed consent.

The prick test was negative and the wheal induced by the first intradermal test with 0.05 mg/mL was smaller than that produced by histamine (10mg/mL in the prick test). We therefore performed the 0.5-mg/mL intradermal test, which gave a clear positive result (16 x 10mm wheal), 20 minutes later (Figure). Within 15 minutes, the patient began to experience itching of the eyes and nose, palpebral swelling, generalized pruritus (especially on the palms, soles and genitals), chest erythema, and restlessness. She received intramuscular epinephrine, and intravenous

dexchlorpheniramine and hydrocortisone, and recovered within minutes. She did not experience any delayed reaction.

With a diagnosis of oxaliplatin hypersensitivity, and after considering the options and talking to the patient, we decided that desensitization with oxaliplatin was the best option considering the patient's condition.

We followed the 12-step desensitization protocol developed by Dr Castells [4,6], with a target dose of 100 mg administered over an estimated time of 277 minutes, with monitoring in the ICU. The patient was given montelukast 10 mg and acetylsalicylic acid 250 mg on the day of desensitization and 2 days beforehand to increase safety and tolerability [7]. She was also given intravenous dexchlorpheniramine and ranitidine 20 minutes before starting the desensitization.

Five minutes after the twelfth step in the protocol was started, the patient started to feel mild itching on her palms and soles. We stopped the infusion, and administered intravenous

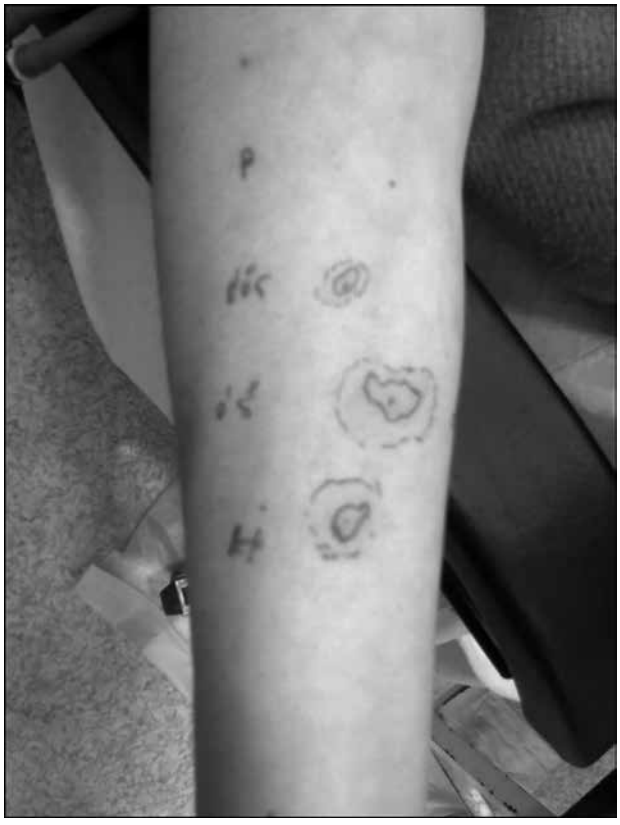

Figure. Intradermal test with oxaliplatin at concentrations of 0.05 mg/mL and 0.5 mg/mL, compared with histamine.

dexchlorpheniramine. After 30 minutes, we restarted the infusion where we had stopped and the patient did not experience any other symptoms.

The patient has undergone 4 infusions under this protocol and has tolerated them well. She has completed the treatment she needed and clinical response to date has been good.

With this report we would like to stress the importance of performing drug allergy tests in an appropriate place to treat any possible reactions and of carefully considering the concentrations used. As far as we know, this is the first report in the literature on an anaphylactic reaction due to oxaliplatin skin testing. An oxaliplatin concentration of 0.5 mg/mL may elicit systemic allergic reactions during intradermal tests. The 12-step protocol seems to be a very good option for patients allergic to chemotherapeutic agents, and has proven safe and useful, even for highly sensitive patients.

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Conflicts of Interest

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Long-Term Prophylaxis With C1-Inhibitor Concentrate in Patients With Hereditary Angioedema

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Key words: Hereditary angioedema. C1 inhibitor deficiency. Long-term prophylaxis. Plasma human C1 inhibitor concentrate. Self-administration.

Palabras clave: Angioedema hereditario. Déficit de C1 inhibidor. profilaxis a largo plazo. Concentrado plasmático de C1 inhibidor.

Hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH) is an uncommon condition inherited in an autosomal dominant manner. Symptoms are caused by extravasation of plasma as the result of the release of bradykinin [1]. Patients may benefit from long-term prophylaxis (LTP) when attacks are frequent or severe [2]. Attacks can be prevented with attenuated androgens or antifibrinolytics [2]. Nevertheless, the most rational treatment option is the administration of the deficient C1 inhibitor. Purified plasma-derived C1 inhibitor concentrate (pdhC1INH) has been available for many years, and has proven effective in the treatment of acute attacks [2], but it was only recently approved for use as LTP [3].

We present the cases of 5 patients diagnosed with HAE-C1-INH type I treated with off-label pdhC1INH. The patients had clinically uncontrolled disease, unacceptable adverse effects, or a contraindication for the administration of conventional LTP. Written informed consent for off-label use was obtained and the study was approved by the local ethics committee (PI-722).

HAE-C1-INH was diagnosed based on clinical history and laboratory criteria [1]. Clinical and laboratory evaluations were performed regularly, together with screening for viral safety and abdominal ultrasound. Adverse drug reactions were evaluated for pdhC1INH therapy. Hepatitis B virus vaccination was advised. LTP with pdhC1INH (Berinert, CSL-Behring) was initiated at 1000 U per week. A customized regimen based on documented edema attacks was designed for each patient. The characteristics of the patients and treatment are summarized in the Table.

Patient 1 developed adverse effects related to attenuated androgens (hair loss, hirsutism, weight gain, menstrual irregularities, increase in liver enzymes, steatohepatitis I/IV). Most of these effects resolved 6 months after withdrawal. The steatohepatitis disappeared a year later and alkaline phosphatase values returned to normal after 2 years. A central venous access was established, which allowed the patient to self-inject for 2 years. The catheter was removed after an episode of sepsis. The patient was successfully trained in intravenous self-administration.

Patient 2 was diagnosed with hormone-dependent centrilobular breast cancer, initially treated with trastuzumab. Stanozolol was contraindicated and tranexamic acid failed to prevent the edema attacks. Clinical control was achieved with pdhC1INH 1000 U per week. Tamoxifen was initiated as adjuvant chemotherapy but the patient's condition worsened. Doses were rescheduled every 5 days. Two years later, the patient successfully initiated self-administration.

Patient 3 developed adverse effects (weakness, nausea, vomiting, and steatohepatitis I/IV) after the joint administration of stanozolol and tranexamic acid; the effects disappeared a few months after withdrawal of treatment. A central venous access was established for home self-infusion of pdhC1INH, which was successful. The patient, however, was subsequently diagnosed with fibromyalgia-like syndrome, and experienced an increase in the frequency of the attacks. A definite dose of 1000 U every 48 hours was established, leading to good control. The central venous access was removed 5 years later, and the patient was trained in intravenous self-infusion with a pump, as she reported headache with fast pdhC1INH infusion.

Patient 4 developed persistent nausea and vomiting and was experiencing a mean of 3 episodes per month while on regular prophylaxis (Table 1). LTP with pdhC1INH was initiated and a dose of 2000 U per week was achieved within 2 months; the patient reported no symptoms.

Patient 5 developed attenuated androgen-related adverse events (weight gain, increase in lactase dehydrogenase levels, and hirsutism). He was later diagnosed with antiphospholipid syndrome and myelodysplastic syndrome (refractory anemia with excess blasts) and underwent allogenic bone marrow transplantation plus immunosuppressive therapy. AFs were contraindicated. Many complications (chronic graft-vs-host disease, hemorrhagic cystitis, pneumomediastinum, intestinal perforation) due to concomitant therapies led to a worsening in HAE-C1-INH. He is currently under control with 1000 U every 4 days and experiences attacks only under stressful situations.

LTP with pdhC1INH resulted in a significant improvement in the frequency and severity of attacks in our series of patients. The effectiveness of replacement therapy was first described in 1989 [4]. Since then, there have been many reports of patients benefiting from weekly injections of pdhC1INH [5-7]. One clinical trial reported a decrease in the number, severity, duration of attacks, and the need for rescue injections with pdhC1INH versus placebo [3]. Furthermore, an international group of experts have published recommendations on the use of pdhC1INH for LTP in all groups of patients [8].

Four of the 5 patients in our series were able to self-administer intravenous pdhC1INH, which has led to improved quality of life, as has been previously observed [5,9].

Concerns remain about the viral safety of plasma-derived products. Consistent with previous data [6], no proven viral transmission was documented after a mean of 5.5 years under replacement therapy in our patients.

We did not observe an increase in the number or severity of attacks in our patients, despite the frequent treatment with pdhC1INH concentrate. Nevertheless, patient 2 experienced an increase in disease activity, which coincided with the

Table. Patient Characteristics, Disease Severity, and Long-Term Prophylaxis With Pdhc1INH Concentrate (Berinert, CSL-Behring)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y/sex	30/F	40/F	51/F	38/F	41/M
Previous treatments	AA/AF	AA/AF	AA/AF	AA/AF	AA
Reason for discontinuation	LE/AEs	CI/LE	LE/AEs	LE/AEs	LE/AEs
Mean attacks per month before pdhc1INH, No.	33 12 abdominal 4 genital 15 peripheral 1 facial 1 laryngeal	4 2 abdominal 2 peripheral	6 3 abdominal 2 peripheral 1 genital	4 3 abdominal 1 peripheral	8 4 abdominal 4 peripheral
Mean attacks per month after pdhc1INH, No.	1-2 (with triggerings)	<1	1	<1	1-2 (with triggerings)
Initial dose	1000 U/wk	1000 U/wk	1000 U/wk	1000 U/4 d	1000U/48 h
Final dose	1000 U/72 h	1000 U/5 d	1000 U/48 h	1000 U/4 d	1000U/4 d
Time to optimal dose, y	3	1	4	1	1
Total time with pdhC1INH treatment, y	7	4	6	5	1.5
Tolerance	Local heat with first dose Good	Good	Headache with rapid infusion Good	Good	Good
Viral screening testing[a]	Negative	Negative	Negative	Negative	Negative

Abbreviations: AAs, attenuated androgens; AEs, adverse effects; AFs: antifibrinolytics; LE, lack of efficacy; CI, contraindication.
[a]Hepatitis A virus (HAV), HBV, HVC, parvovirus B19, HIV-1, HIV-2.

administration of tamoxifen. Tamoxifen displays partial agonist/antagonist properties that mimic estrogen action and has been reported to worsen clinical course in HAE-C1-INH. This may explain the increased frequency of the attacks in our patient.

One major concern regarding LTP with pdhC1INH concentrate is its high cost. Nevertheless, in addition to the direct costs of the medication for the treatment of acute attacks and chronic management, additional direct and indirect costs have to be considered. Emergency visits and hospital stays account for approximately 48% of the total cost of treating a HAE-C1-INH patient; this is the largest component of the total cost and can be as high as 68% for patients with severe disease [10]. Treatment with pdhC1INH concentrate leads to remarkable improvements in health-related quality of life [10] and disease control. Accordingly, it also substantially reduces emergency visits, hospital stays, and loss of productivity, thereby contributing to a decrease in other costs. In addition, having pdhC1INH concentrate available for on-demand treatment has not been found to result in a significant increase in the number of self-administrations when compared to the number of doses previously required by patients [6].

To conclude, patients with severe HAE-C1-INH who experience unacceptable adverse effects from treatment with attenuated androgens or antifibrinolytics and/or who do not respond to conventional prophylactic treatments, despite high doses, may benefit from pdhC1INH replacement therapy, which has proven to be efficacious, safe, and well-tolerated.

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Conflicts of Interest

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Adalimumab Desensitization Protocol in a Patient With a Generalized Urticarial Reaction and Angioedema Following Adalimumab Administration

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Adalimumab is a human-derived recombinant monoclonal antibody. For adults with rheumatoid arthritis, the recommended dose is 40 mg administered subcutaneously. The most common adverse effects associated with adalimumab are injection site reactions, although the prevalence of immediate and delayed allergic reactions is relatively low [1]. Some authors have reported immediate systemic reactions with significant skin involvement [1,2-4] and in some cases, an immunologic mechanism has been suggested due to the strength of the positive skin-prick response and intradermal test results with immediate readings [1,5]. Nonetheless, the presence of serum-specific IgE (sIgE) to adalimumab has not been demonstrated [1].

We report the case of a 37-year-old woman with a history of allergic rhinitis triggered by house dust who 8 years previously had been diagnosed with rheumatoid arthritis. Having responded poorly to a number of conventional therapies, she commenced biologic therapy with a subcutaneous dose of 40 mg adalimumab every 2 weeks. Twelve days after the first dose, she experienced localized erythema and edema at the injection site, which later developed into generalized urticaria and bilateral eyelid angioedema. She was treated with parenteral corticosteroids and antihistamines.

We recorded positive skin prick test (SPT) responses to house dust mites, cat and dog dander, and olive and grass pollen, and a negative response to latex. Bearing in mind the humanized nature of the antibody and its expression in Chinese

hamster ovary cells, we performed SPT and evaluation of sIgE for hamster epithelium, with negative results.

The SPTs with adalimumab were carried out at least 8 weeks after the initial adverse reaction, using the commercial formulation Humira (adalimumab 50 mg/mL). For intradermal testing, we employed a concentration of 1/100. Histamine prick (10 mg/mL) and saline solution were used as positive and negative controls respectively. A positive reaction was defined as a wheal with a diameter at least 3 mm larger than that produced by a negative control. SPT and intradermal tests were positive in immediate readings, producing wheal sizes of 3 x 3 mm and 11 x 8 mm respectively. The intradermal test was negative after 24 and 48 hours. These concentrations proved to be nonirritant in 10 control individuals not previously treated with adalimumab. A patch test with the undiluted drug was applied to the upper back and to the original injection site, producing negative results. Intradermal testing with Humira excipients, mannitol 18 mg/mL, and polysorbate 80 0.4 mg/mL, were also negative. No anti adalimumab IgG antibodies were detected in serum samples.

Given the initial therapeutic success with adalimumab and the failed response to standard treatments, signed informed consent was obtained and adalimumab therapy was restarted using a desensitization protocol. Premedication consisted of oral dexamethasone 20 mg and parenteral dexchlorpheniramine 5 mg 1 hour before administration of adalimumab. The desensitization protocol commenced with an initial subcutaneous dose of 0.003 mg, which was gradually increased to a cumulative dose of 40.333 mg (see Table), with 15-minute intervals between doses. The procedure lasted 2 hours and the patient experienced no local or systemic reactions. Two weeks later, a full-strength, divided dose of adalimumab was administered in both arms; this was repeated after a further 2 weeks and was well tolerated. The patient is currently receiving a full-strength, single dose of 40 mg adalimumab every 2 weeks, with no premedication and good tolerance.

To date, authors have reported varying latency periods before the onset of skin reactions following adalimumab administration. In the majority of cases, the reaction is delayed (1-24 hours) and localized at the injection site; the remaining reports describe immediate, generalized urticaria, with or without angioedema [2-4], sometimes accompanied by other systemic symptoms [5,6].

The clinical manifestations of mast cell degranulation immediately following the administration of adalimumab may be IgE-mediated. There have been no reports to date of the detection of sIgE to adalimumab in the diagnosis of reactions to this drug and skin tests (prick and intradermal with immediate readings) continue to be the method used to identify mast cell–sensitizing sIgE. The utility of skin testing in patients with immediate hypersensitivity reactions to monoclonal antibodies was established by Brennan et al [8]. Benucci et al [9] described injection-site reactions with positive skin tests at immediate reading and anaphylactic reactions in patients with adalimumab hypersensitivity, although the presence of sIgE to adalimumab was not detected.

In the case of delayed hypersensitivity reactions, some studies suggest the involvement of anti-adalimumab IgG antibodies. Steenholdt et al [7] report a case in which adalimumab-specific IgE antibodies were not found but anti adalimumab IgG antibody concentrations were high, leading the authors to conclude that the latter were the probable cause of the reaction, since no anti-adalimumab antibodies (IgG or IgE) were detected at repeat assessments prior to adalimumab injection [7]. In our study, the concentration of adalimumab-specific IgE antibodies was not determined but no anti-adalimumab IgG antibodies were present.

Our patient experienced a local reaction at the injection site and a generalized skin reaction (urticaria and angioedema) 12 days after the initial dose of adalimumab. Allergy test results suggested an IgE immune-mediated response. Negative skin tests with hamster epithelium and Humira excipients precluded their involvement in the allergic reaction. The timing of the onset of the reaction, 12 days after the initial administration of adalimumab, may be accounted for by the half-life of the drug, which averages 2 weeks, and this may also explain why this is a hypersensitivity reaction despite the fact that onset did not occur following the initial administration of the drug.

Puxeddu et al [10] report that of 6 patients treated with adalimumab who experienced hypersensitivity reactions, only 1 positive intradermal test response was recorded, suggesting the involvement of an IgE-mediated mechanism.

Table. Adalimumab Desensitization Protocol

Dose	Concentration, mg/mL	Volume, mL	Administered Dose, mg	Cumulative Dose, mg	Time, min
1	0.05	0.06	0.003	0.003	0
2	0.33	0.09	0.03	0.033	15
3	2	0.15	0.3	0.333	15
4	10	0.1	1	1.333	15
5	50[a]	0.04	2	3.333	15
6	50[a]	0.1	5	8.333	15
7	50[a]	0.2	10	18.333	15
8	50[a]	0.44	22	40.333	15

[a]Commercial formulation Humira (40 mg adalimumab in 0.8 mL).

To date, there have only been 2 published reports of adalimumab desensitization protocols [5,6]. The first, by Rodriguez-Jimenez et al [5], involved a patient with urticaria and rhinitis with a positive skin prick test, who required 6 hours to achieve the therapeutic dose of adalimumab. The second, by Quercia et al [6], describes a patient with anaphylactic shock and negative skin tests, in whom the therapeutic dose was reached in 2 hours. Our study provides a third instance of a successful and effective rapid adalimumab desensitization protocol, with the patient achieving the full, cumulative therapeutic dose in 2 hours. In our case, as previously described by other authors [5,6,8], the subsequent doses were administered every 2 weeks with no further requirement for desensitization procedures; this could be due to the relatively long half-life of adalimumab that would enable the maintenance of the desensitized state.

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Conflicts of Interest

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Successful Intravaginal Desensitization in a Woman With Seminal Plasma Anaphylaxis After Artificial Insemination Failure

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Human seminal plasma allergy (HSPA) is a rare condition. The clinical response varies from weak reactions such as vaginal itching to life-threatening anaphylactic shock [1-3]. Prevention is based on sexual abstinence and condom use, both of which are unacceptable solutions for couples trying to achieve pregnancy. Desensitization and artificial insemination have been reported to be effective in this situation [2-6].

A 32-year-old woman was referred for postcoital systemic urticaria, generalized edema, vomiting, diarrhea, dyspnea, and shock. These symptoms occurred several minutes after sexual intercourse with her husband. The couple had been married for 5 years. Initially, there were no symptoms after coitus without barrier contraception. However, they used condoms for 2 years because they did not want a pregnancy. For the last 3 years, coitus has been followed by mild symptoms such as vaginal itching. These symptoms worsened gradually until the patient began to experience severe symptoms such as generalized urticaria, edema, dyspnea, vomiting, and shock. She and her husband denied taking medication before intercourse, and the patient denied intercourse with partners other than her husband. The symptoms did not occur when a condom was used. As the patient wanted to achieve pregnancy, artificial insemination was attempted at another hospital. However, severe systemic reactions recurred several minutes after insemination with washed semen.

The patient had a 5-year history of asthma and allergic rhinitis. Skin prick tests with 55 common inhalant allergens (Allergopharma) revealed sensitization to dog dander only. She had kept a dog 2 years before the allergic symptoms developed, and her symptoms were aggravated when she came into contact with dogs. However, she did not receive immunotherapy against dog dander. Her total serum IgE concentration was 73.1 kU_A/L, the concentration of specific IgE to dog dander was 15.0 kU_A/L (CAP-system, Pharmacia), and the result of the methacholine challenge test was positive (PC_{20}, 7.68 mg/mL). Skin prick tests with dilutions of her husband's seminal plasma revealed a positive response with a 3 × 3 mm wheal (flare 6 × 8 mm) at a 1:100 dilution and a 4 × 3 mm wheal (flare 15 × 15 mm) at a 1:10 dilution. The positive control (1 mg/mL of histamine) resulted in a 3 × 3 mm wheal, and the negative control (0.9% saline) did not induce any reaction. The skin prick test was considered positive when the mean wheal diameter was equal to or greater than that produced by histamine. The level of serum-specific IgE to the husband's seminal plasma, measured using the Human IgE ELISA Ready-SET-Go kit (eBioscience) was 62.5 ng/mL. SDS-PAGE immunoblotting was carried out with her husband's seminal plasma and that of a healthy control using 2-mercaptoethanol. Immunoblot staining revealed specific IgE and its binding components in both the seminal plasma proteins of her husband and those of the healthy control (Figure). Immunoblotting showed IgE-binding bands of 12, 15, 18, 34, and 62 kDa in her husband's 2-mercaptoethanol-treated samples.

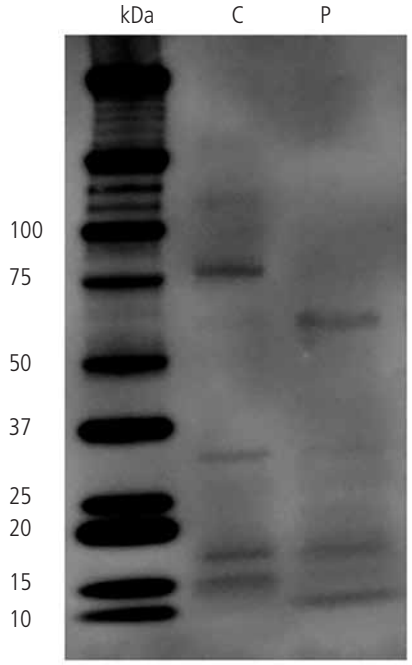

Figure. IgE immunoblotting of seminal plasma from the patient's husband and a healthy control. Immunoblotting was carried out with 2-mercaptoethanol–treated samples under reducing conditions. P indicates the husband's seminal plasma; C, control seminal plasma.

Intravaginal desensitization was attempted by depositing 1 mL of 10–5 vol/vol of her husband's diluted semen and 10-fold incremental increases in this concentration at 45-minute intervals, as described elsewhere [2]. No allergic reactions were observed during or after desensitization. She reported no allergic reactions after coitus with her husband on the following day. We advised her to have sexual intercourse every 2 or 3 days to maintain the desensitization state as suggested in the previous report [2]. She complied by having regular sexual intercourse for 1 month. The patient did not experience any allergic symptoms during this period and became spontaneously pregnant.

Hypersensitivity reactions to human seminal plasma range from local swelling to generalized systemic reactions [1,2]. Barrier methods, such as condoms, are usually recommended

to prevent HSPA. However, this method is unacceptable for patients want to achieve pregnancy. It is possible to become pregnant by means of artificial insemination using sperm washed of seminal plasma or by intravaginal desensitization [2-6]. Both options have been widely recommended for patients with HSPA who want to achieve pregnancy. However, artificial insemination is not a completely reliable means of preventing allergic reactions, and severe allergic reactions have been reported immediately after artificial insemination [7]. In the case we report, the patient experienced a systemic reaction after coitus, and the attempted artificial insemination failed for the same reason. The patient was successfully treated by local intravaginal desensitization. Achievement of pregnancy after intravaginal desensitization suggested that this approach could be recommended as an initial step in severe HSPA.

Several seminal plasma allergens have been characterized, and their molecular masses have been reported to range from 12 kDa to 75 kDa [2,3,6,8,9]. In our patient, immunoblotting revealed IgE-binding bands at 12, 15, 18, 34, and 62 kDa. Basagana et al [10] found that proteins from dog dander cross-react with human prostate-specific antigen and seminal plasma and suggested that allergy to dog dander might indicate a risk of developing HSPA. The authors reported the presence of a 34-kDa IgE-binding band in immunoblotting using a 2-mercaptoethanol–treated sample. This finding is consistent with those of the present report, where the patient was allergic to dog dander allergy and immunoblotting showed a band of 34 kDa. However, the other bands in our patient's sample suggested that additional protein components could be considered IgE-binding portions that induce allergic reactions.

Many patients with HSPA are allergic to the seminal plasma of different male partners [2]. In our case, common and specific antibodies to both the husband's and the control's seminal plasma were identified. We did not perform a skin prick test with the seminal plasma of the healthy control for ethical reasons (risk of infection or sensitization). However, our findings suggested that the seminal plasma of the healthy control could have induced allergic reactions in the patient.

Our results suggest that intravaginal desensitization is a safer method for preventing allergic reactions and achieving pregnancy than insemination with washed semen, especially in cases of severe allergic reactions such as anaphylaxis.

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Conflicts of Interest

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Occupational Rhinitis Due to Inhalation of Chicken Meat Protein

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Key words: Allergy to chicken meat. Butcher. occupational rhinitis. Glyceraldehyde 3-phosphate dehydrogenase.

Palabras clave: Alergia a carne de pollo. Carnicero. rinitis ocupacional. Gliceraldehido 3-fosfato deshidrogenasa.

Occupational rhinitis is 2-4 times more common than occupational asthma. Degree of exposure is considered the main risk factor for developing this type of reaction [1].

Occupational allergy due to inhalation of animal protein has been reported in workers in animal facilities and laboratories, as well as in animal farm workers [1]. There have been few reports of occupational allergy in butchers due to inhalation of meat protein [2] or to animal dander handled during the course of their work, since the allergen involved in such cases was not identified.

We report the case of a 58-year-old white man who worked as a butcher. He had a 4-year history of symptoms of nasal congestion, sneezing, and copious rhinorrhea, mainly in the morning, with a good response to topical intranasal corticosteroids, which he used intermittently.

During a 4-month period without working, the patient was asymptomatic. When he returned to work, his symptoms reappeared, generally when he was handling meat, mainly chicken. His condition was not accompanied by bronchial or cutaneous symptoms, even though he did not wear gloves. He reported good tolerance to ingestion of meat, whether from birds or mammals, raw or cooked.

Prick tests were performed with extracts of mite, pollen, fungus spores, animal dander, feathers, and egg proteins (Bial-Aristegui and Laboratorios Leti); the results were negative for all extracts. Prick by prick tests were performed with raw chicken, beef, pork, and lamb; the results were positive.

Protein extracts were made from both raw and cooked meats (rabbit, pork, lamb, beef, chicken, duck, turkey, ostrich, and quail [Bial-Aristegui]) by delipidation, homogenization in phosphate-buffered saline, centrifugation, dialysis, and lyophilization. Prick tests were performed with these raw and cooked extracts; positive results were obtained with raw meat extracts and negative results with cooked meat extracts.

A nasal challenge test was performed using anterior active rhinomanometry according to the recommendations of the Rhinoconjunctivitis Committee of the Spanish Society of Allergy and Clinical Immunology [3]. The test involved instillation of the allergen solution on the inferior turbinate using a syringe (0.1 mL) and assessment of nasal airflow resistance. We obtained positive results for raw chicken extract at a concentration of 2 mg/mL, measured as a 100% increase in airway resistance, and negative results for raw beef extract at a concentration of 10 mg/mL. In 5 healthy controls, a nasal challenge test with chicken extract was negative, reaching a concentration of 10 mg/mL.

Total serum IgE levels were 98 IU/mL. Serum specific IgE levels were measured using the enzyme allergosorbent test against raw and cooked meat extracts (HYTEC Specific IgE EIA kit, HYCOR Biomedical Ltd). Determination of specific IgE was negative to cooked meat extracts (<0.35 kU_A/L) and positive to raw meat extracts from chicken (5.6 kU_A/L, class 2), pork (0.6 kU_A/L, class 1), beef (0.7 kUA/L, class 2), rabbit (0.7 kU_A/L, class 2), and lamb (0.8 kU_A/L, class 2). Specific IgE against α-gal was negative (<0.35 kU_A/L) (ImmunoCAP, ThermoFisher).

SDS-PAGE immunoblotting revealed an IgE-binding band with a molecular mass of 36-37 kDa in all the assayed raw meat extracts (Figure). No bands were detected when the assay was performed with cooked meat extracts.

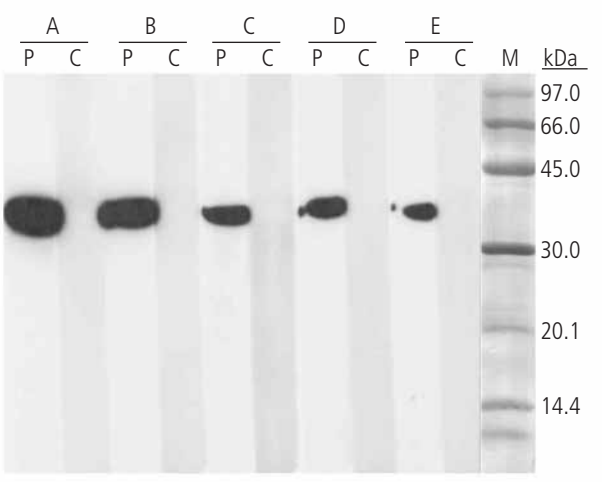

Figure. SDS-PAGE immunoblotting results. A, Raw chicken meat extract. B, Raw beef meat extract. C, Raw pork meat extract. D, Raw lamb meat extract. E, Raw rabbit meat extract. Lane P, patient serum; Lane C, control serum (pool of sera from nonatopic patients); Lane M, molecular mass marker.

The IgE-binding bands detected in the extracts from raw beef, pork, and chicken were extracted from the gel, and proteins were identified by mass spectrometry using tandem mass spectrometry (MS/MS), as previously described [4]. The sequence of internal peptides was obtained. Analysis of protein databases revealed the IgE-binding band to be glyceraldehyde 3-phosphate dehydrogenase (GPDH) in all 3 extracts.

We recommended the patient to avoid handling chicken meat, although this was not possible for him because his butcher's shop was a family business. His symptoms only appear when he has been cutting chicken continuously for 2 or 3 hours and resolve with topical intranasal corticosteroids.

Meat allergy is very rare despite high consumption. It is mainly reported for cooked meat. The literature contains a few cases of occupational asthma induced by handling compounds used in the manufacture of meat products such as anis [5], cochineal extract, and carmine [6]. A case caused by the inhalation of proteins of mammalian meat was not accompanied by allergy due to ingestion [2].

In the case we report, the patient had symptoms of occupational rhinitis without bronchial involvement that were triggered by sensitivity to chicken meat protein. The patient tolerated meat from poultry and mammals, and the sensitizing protein was GPDH.

The allergenic character of inhaled GPDH has been described for various allergens, such as wheat [7], latex [8], and the spores of fungi (*Aspergillus versicolor*) [9]. Furthermore, in a study on occupational allergy to fish proteins in fish processing factory workers [10], serum specific IgE was detected for sardine GPDH, thus proving the ability of this protein to act as an inhaled sensitizing agent. We observed that the protein was present in the meat of birds and mammals and report these as new allergenic sources. Sensitization was by inhalation, as demonstrated in the studies cited above.

In conclusion, we report the case of a butcher with occupational rhinitis caused by inhalation of chicken meat proteins. The patient tolerated ingestion of meats. GPDH was the sensitizing protein and was probably the cause of the allergic symptoms and cross-reactivity with other meats.

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Conflicts of Interest

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Bradykinin-Mediated Hereditary Angioedema (Non–Estrogen-Dependent) Without C1 Inhibitor Deficiency

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Hereditary angioedema (HAE) is a genetic disorder characterized by spontaneous and recurrent episodes of edema without urticaria. The affected areas include the skin of the extremities, face, genitals, and torso, as well as the digestive tract mucosa, larynx, and internal organs [1,2]. The prevalence of HAE varies, although it has been estimated to affect between 1 in 10 000 and 1 in 50 000 individuals worldwide, with no differences between the sexes or ethnic groups [3,4]. HAE is a rare disease with a nonspecific clinical presentation that is often misdiagnosed and underdiagnosed. It is classified into 3 groups. Type I (80-85%) is characterized by decreased or absent values of a functional C1 inhibitor (C1-INH) protein. Type II (15-20%) is associated with normal or increased levels of dysfunctional C1-INH that reduces C1-INH activity. Type III is independent of C1-INH deficiency and affects mostly women; 80% of cases are caused by a mutation in the coagulation factor XII gene, *F12* [1].

We report the case of a woman aged 40 years with a history of recurrent thrombophlebitis. In 2008, she presented episodes of urticarial rash and angioedema on the face, hands, and feet, with recurrences approximately every 2 weeks for 2-3 months (April-August). In September 2009, she presented abdominal distension of very rapid onset (minutes) accompanied by abdominal pain (mainly in the hypochondrium), dyspnea without pathological chest sounds or cough, hoarseness and occasional hypoxemia. The frequency of these episodes was similar to that of the episodes reported during the previous year. No association with menstruation or contraceptive treatment was identified. The patient also presented daily areas of peripheral edema related to microtrauma. In 2008, she was diagnosed with hypogammaglobulinemia (IgG2, 96-181 mg/dL). She received treatment with γglobulin from 2010-2011. After some months of improvement, the abdominal episodes began to appear weekly. These were treated with intramuscular adrenaline, corticosteroids, and intravenous antihistamines, with remission of abdominal distension at between 2 and 8-10 days. She continued to take oral corticosteroids between outbreaks.

The patient has a 9-year-old daughter and a 7-year-old son, both of whom have recurrent angioedema.

A complement study performed on several occasions included quantification of C1-INH (24-45 mg/dL) and activity during asymptomatic periods and acute episodes. The other analyses performed included complete blood count, blood chemistry, creatinine, coagulation, antinuclear antibodies, albumin, protein profile, parasites in stool, sputum culture, urine sediment, antibodies to hepatitis (A, B, and C), HIV, rheumatoid factor, celiac profile, thyroid function, baseline tryptase, and tryptase in acute episodes. The results were normal for all the analyses. The results of the allergy workup were negative, as were those of the chest radiographs and cranial computed tomography scan. Abdominal ultrasound performed during the acute phase revealed normal findings.

Given the patient's lack of response to adrenaline, corticosteroids, and antihistamines, a bradykinin mechanism was suspected in the absence of quantitative and functional alteration of C1-INH. The patient was evaluated at the Angioedema Unit of La Paz University Hospital, Madrid, Spain and was shown to be a homozygous carrier of the C677T mutation in the *MTHFR* gene with elevated plasma homocysteine (9-9.89 µmol/L). None of the mutations described were detected in exon 9 of the *F12* gene.

In July 2011, the patient began on-demand treatment with icatibant, with which the attacks resolved in less than 45 minutes in most cases (Figure); however, on 3 occasions, it was necessary to administer 3 doses in 24 hours to control the attack.

Figure. Sudden episode of abdominal angioedema and successful recovery after receiving icatibant. Time elapsed: 36 minutes.

Given the high demand for this drug, prophylactic treatment with C1-INH 1000 IU/5 d was administered over a period of 7 weeks, with little benefit.

In addition to on-demand treatment with icatibant, the patient currently receives prophylactic treatment with tranexamic acid and nadroparin calcium. The initial dose of tranexamic acid was 1000 mg/8 h, which was reduced every 15 days. Nadroparin calcium was initially administered in prophylactic doses (0.4 mL/24 h), although when the patient presented superficial thrombophlebitis it was increased to therapeutic doses (0.8 mL/24 h). Overall, she experienced some improvement. She had 3 acute episodes during the first 8 weeks of treatment. Further reducing the dose of tranexamic acid led to an increase in the frequency of episodes, so the current dose is set at 1000 mg/12 h in combination with nadroparin calcium (0.6 mL/24 h). Nevertheless, minor symptoms persist almost daily.

Angiotensin-converting enzyme inhibitors, exogenous estrogens, and dipeptidyl peptidase-4 were contraindicated.

The patient we report had frequent episodes of acute abdominal and upper airway edema. Given the lack of response to adrenaline, corticosteroids, and antihistamines, a bradykinin mechanism was suspected in the absence of quantitative and functional alteration of C1-INH. Therefore, on-demand treatment was started with off-label icatibant, a blocker of bradykinin B21 receptors, whose efficacy confirmed the pathogenesis [5]. The family history points to an as yet unidentified genetic alteration, since mutations in exon 9 of the *F12* gene associated with HAE without C1-INH deficiency have been ruled out.

Given the high frequency of attacks, various prophylactic treatment strategies have been tested [6]. Furthermore, since the patient is a homozygous carrier of the C677T mutation in the *MTHFR* gene with elevated plasma homocysteine (an inherited cause of thrombophilia) and given her history of thrombophlebitis, at first we avoided androgens and antifibrinolytics because of the increased risk of thrombosis. We started treatment with off-label C1-INH because it inhibits expression of kallikrein [7], although little benefit was obtained. The patient is currently receiving treatment with tranexamic acid and nadroparin calcium to reduce the risk of thrombosis and because it has been reported to be effective in the acute and prophylactic short-term treatment of hereditary angioedema due to C1-INH deficiency [8]. To date, this prophylactic strategy has been moderately effective.

We report the case of a patient with bradykinin-mediated angioedema and no quantitative or functional C1-INH deficiency. The case is unrelated to hyperestrogenemia and the patient does not carry the genetic alterations described in the literature in association with estrogen-dependent hereditary angioedema. The presence of the same symptoms in her children, a prepubertal girl and a boy, are exceptional in the literature on type III hereditary angioedema. Consequently, we suspect an as yet unidentified mutation that is probably autosomal dominant.

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Conflicts of Interest

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Venom-Dependent Vibration-Induced Anaphylaxis: A New Hazard Following Large Local Reactions From Hymenoptera Stings

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Palabras clave: Anafilaxia con picadura de insecto. Angioedema vibratorio. Urticaria física. Anafilaxia inducida por vibración dependiente de veneno. Mastocitos.

Large local reactions (LLRs) caused by insect stings are frequent in adults [1] and are usually induced by an IgE-dependent late-phase reaction [2]. A number of cases of acquired cold urticaria/anaphylaxis after LLRs have been reported, whereas cases of delayed anaphylaxis caused by insect stings have proved to be merely anecdotal [3-5].

Although vibratory angioedema is a rare disorder, cases resulting from mast-cell degranulation have been reported [6,7]. We evaluated serum tryptase level (as a marker of mast cell degranulation [8]) and vibration sensitivity in a patient who experienced severe anaphylaxis 18 hours after a wasp sting.

The patient was a 49-year-old man, the owner of a men's clothing factory, who was stung by a wasp on his right forearm. Two hours later, he developed an LLR with mild local pain and itching.

The following morning, 17 hours after the sting, the symptoms appeared to have resolved, so the patient decided to go to his factory to personally test a new, high-speed (3600-rpm) buttonholing machine. He had been working on the machine for about 30 minutes when he felt a notable increase in the swelling at the site of the LLR along with generalized itching and dyspnea. Less than 10 minutes later the patient lost consciousness and was taken to the emergency department. Anaphylaxis resolved within an hour after administration of intramuscular epinephrine and intravenous fluids. The patient was discharged 24 hours later with an epinephrine autoinjector. Of note, the patient's serum tryptase levels were 75 µg/L at admission and 3.6 µg/L at discharge. The LLR resolved completely within 4 days.

We evaluated the patient for the first time 2 weeks after the anaphylaxis episode. The patient had a history of many previous insect stings—the most recent only 5 weeks before the current episode—although the reactions were always mild and local. The results of the physical examination and standard laboratory tests were normal. Skin testing and serum specific IgE (1.5 kU_A/L; ImmunoCAP, Thermo Scientific) revealed isolated sensitization to wasp venom (*Polistes* species). The patient refused to undergo a bone marrow biopsy to investigate silent mastocytosis and a specific immunotherapy protocol including regular assessment of vibration sensitivity. However, he did agree to undergo a series of vibratory challenge tests (VCTs) in several sessions. His right forearm was exposed to a vortex mixer at 1200 rpm for 10 minutes [6], and his whole body was exposed to the vibratory forces of the buttonholing machine for 60 minutes. Serum tryptase was measured 1 hour before each VCT, and the patient was observed for 6 hours after. We recorded tryptase levels 1 hour and 6 hours after a VCT devoid of clinical manifestations or 1 hour after onset and 4 hours after resolution of any de novo symptom.

Fifteen minutes after the vortex VCT, the patient reported generalized pruritus. Two minutes later, an erythematous and itchy wheal (6 cm) developed at the site of the previous LLR. Both the pruritus and the wheal cleared up within 1 hour after taking a 10-mg cetirizine tablet.

Seven days later the patient was retested using the buttonholing machine. After 30 minutes, erythematous itchy wheals developed on his forearms at the site of the previous sting and at the site of the skin test with wasp venom we had performed on left forearm. Therefore, the test was stopped. A few minutes later, the patient developed rash with urticarial wheals and pruritus on his trunk and legs. His blood pressure was normal, with no other complications. The rash resolved 1 hour after an intramuscular injection of chlorphenamine maleate (10 mg). No other signs or symptoms of disease were observed during the following 10 hours of hospital observation. The results of appropriate diagnostic tests for other physical urticarial syndromes were negative [6]. Therefore, we advised the patient not to operate the buttonholing machine. The results of both VCTs were negative 5 weeks after the initial positive result. The serum tryptase levels recorded during the VCTs are shown in the Table. Based on the clinical and experimental data collected, we advised the patient to avoid activities likely to induce significant body vibrations for at least 8 weeks after an insect bite.

The onset of anaphylaxis 18 hours after the wasp sting casts doubt on the possibility of a delayed systemic reaction, which could have been triggered directly by the sting. Moreover, the temporal relationship between the onset of anaphylaxis and exposure to the buttonholing machine, the clinical VCT findings, and the values of the associated serum tryptase levels (Table) suggest that the vibrations played a prominent role in triggering symptoms, which essentially resulted from widespread mast cell degranulation [7,8]. The patient's hypersensitivity to vibrations was only recorded in conjunction with the LLRs but not with the small reactions induced by previous stings. In addition, it took only a short time to resolve. The coincidence of the cutaneous effects of the VCT at both sites of the previous contacts with wasp venom (ie, with the sting and during the skin test), as well as the patient's decreasing hypersensitivity to vibrations, which is proportional to the time elapsed from the wasp sting, suggest that transient vibratory hypersensitivity is venom-dependent. The patient's specific IgE to wasp venom and his exposure to 2 stings in less than 2 months may have determined the transient altered response of mast cells to vibratory stimuli through as yet unknown pathways [5,9,10]. Delayed cold anaphylaxis 12

Table. Serum Tryptase Levels Before and After Vibratory Challenge Tests in a Patient With a Recent Story Of Venom-Dependent Vibration-Induced Anaphylaxis After a Wasp Sting

Days Since the Last Wasp Sting	Type of VCT	Clinical VCT Findings (See Text)	Serum Tryptase Levels, µg/L		
			One hour before VCT	One hour after the onset of clinical VCT findings[c]; 1 hour after the negative VCT[d]	Four hours after the resolution of clinical VCT findingse; 6 hours after the negative VCT[f]
A) 23	Vortex Vibrator 15 min	Positive[a]	4.2	12.6[e]	6.7[e]
B) 30	BH-M 30 min	Positive[a]	4.6	14.5[e]	8.4[e]
C) 58	Vortex Vibrator 15 min	Negative[b]	3.4	5.8[d]	4.8[f]
D) 65	BH-M 60 min	Negative[b]	3.2	6.0[d]	4.8[f]

BH-M, buttonholing-machine; VCT, vibratory challenge test.
[a]Onset of symptoms during or immediately after the execution of the VCT. Of note, delayed negative outcomes on the A and B challenges could be due to treatment given for the immediate reaction.
[b]No outcomes until 6 hours after the execution of the VCT.

days after a hymenoptera sting accompanied by long-lasting chronic cold urticaria was recently reported [4]. However, there are no reports of vibration-induced anaphylaxis or transient hypersensitivity to vibrations after hymenoptera stings.

The main clinical finding in the case we report is that patients with LLR can develop life-threatening anaphylaxis induced by early but transient hypersensitivity to vibration. To prevent the dangerous consequences of this reaction, physicians should investigate the possibility that it could occur and advise patients to avoid exposure to vibrations for at least 8 weeks after the onset of an LLR.

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