

Clinical Communications

Systemic mastocytosis presenting as IgE-mediated food-induced anaphylaxis: a report of two cases

Alicia Prieto-García, MD, PhD^a,

Alberto Álvarez-Perea, MD^a, Almudena Matito, MD, PhD^{b,c},

Laura Sánchez-Muñoz, MD, PhD^{b,c},

Jose Mario Morgado, MSc^{b,c}, Luis Escribano, MD, PhD^{c,d},

and Iván Álvarez-Twose, MD^{b,c}

Clinical Implications

- Patients with anaphylaxis should be evaluated for an underlying clonal mast cell (MC) disease, regardless of the cause. The Spanish Network on Mastocytosis score provides a clinical and noninvasive tool to assay the risk of a clonal MC disease in patients with anaphylaxis who lack skin mastocytosis.

TO THE EDITOR:

Anaphylaxis is a common manifestation in patients with systemic mastocytosis (SM), particularly in adults with indolent SM without skin involvement (ISM[−]),^{1,2} with an estimated prevalence of 20% to 49%.^{3,4} The association between ISM[−] and hymenoptera venom anaphylaxis^{1,2,5} is well established. In contrast, IgE-mediated anaphylaxis secondary to drugs or foods has been reported in patients with SM^{1,3,4} only sporadically. We report 2 patients presenting with IgE-mediated food-induced anaphylaxis as the manifestation of an underlying ISM[−].

CASE REPORTS

Patient 1

A 43-year-old man with a long-lasting history of fish allergy, because of which he was following a fish-free diet, was referred due to 4 anaphylactic episodes after the accidental intake of foods containing fish sauce or bouillon. Previous symptoms of fish allergy consisted of flushing and throat tightness with hake, sole, and harvest fish, and perioral erythema, lip angioedema, and throat itching with anchovy and sardine. In turn, anaphylactic episodes were characterized by generalized flushing, chest and throat tightness, dyspnea, desaturation, dizziness, hypotension, and loss of consciousness. In all these episodes, the patient was treated with epinephrine, antihistamines, and corticosteroids, achieving a complete resolution within 30 minutes.

Patient 2

A 69-year-old man who suffered from 3 episodes of anaphylaxis was referred for allergy evaluation. The episodes consisted of palmar pruritus and erythema, followed by generalized itching erythema, nausea, vomiting, hypotension, and loss of consciousness. These symptoms started 30-60 minutes after the ingestion of shrimp or prawns and resolved in 30-60 minutes after the administration of epinephrine, antihistamines, and corticosteroids. The patient did not eat shellfish between or after the mentioned episodes.

The absence of hives at the time of anaphylaxis in both cases is remarkable. Both patients tolerated all other foods, and no additional hidden food allergen or cofactors of anaphylaxis were identified. Physical examination did not reveal skin lesions, adenopathy, or organomegaly. Complete blood count and differential, routine biochemistry, thyroid function tests, complement, immunoglobulins and 24-hour urine catecholamines, and 5-OH-indoleacetic acid were normal in both cases.

Allergy evaluation of patient 1 showed positive skin prick tests (SPTs) to commercial extracts of hake (16 × 10 mm), sole (8 × 6 mm), and anchovy (5 × 5 mm) and negative test to *Anisakis simplex*, salmon, and sardine (histamine 6 × 7 mm, saline negative). Specific serum IgE antibodies (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden) were detected against cod (0.51 kU/L), salmon (0.38 kU/L), and hake (0.58 kU/L), whereas they were negative (<0.1 kU/L) against sardine, sole, swordfish, mackerel, tuna, and *A. simplex*. Total serum IgE was 32.6 kU/L and serum baseline tryptase (sBT) (ImmunoCAP Tryptase System, Thermo Fisher Scientific) was 20.2 µg/L.

In patient 2, SPTs were positive to shrimp and lobster (4 × 4 mm) but negative to clam, squid, and to the relevant aero-allergens, dust mites, and cockroach (histamine 10 × 6, saline negative). No specific serum IgE was detected against shrimp, lobster, prawn, tropomyosin, *A. simplex*, and *echinococcus*. Total serum IgE and sBT were 55.8 kU/L and 19.6 µg/L, respectively.

Confirmation of food allergy by oral challenge was not performed considering the severity of the reactions as well as the multiple anaphylactic episodes always related to the same food in each case.

The Spanish Network on Mastocytosis (REMA) score^{6,7} was applied in each case. This model scores gender (male +1, female −1), absence (+1), or presence (−2) of itching/urticaria/angioedema, presence of presyncope and/or syncope (+3), and serum basal tryptase levels <15 mg/mL (−1) or >25 ng/mL (+2) as predictors of a clonal mast cell disease (c-MCD). The resulting score value ≥2 in both patients translated into a high probability of a systemic c-MCD. Accordingly, a complete bone marrow (BM) study was performed, including cytomorphological evaluation, flow cytometry immunophenotyping of bone marrow mast cells (BMMCs), and the screening for the *KIT* D816V mutation on fluorescence-activated cell sorting (FACS)-purified BMMCs and on eosinophils, neutrophils, lymphocytes, and CD34+ hematopoietic progenitor cells, following the recommendations of the REMA.⁸ This analysis revealed the presence of spindle-shaped CD25+ and D816V *KIT*-mutated MCs, such pathological features being restricted to only a subset (approximately 30%) of all BMMCs in patient 2. Of note, hematopoietic cells other than CD25+ MCs displayed a wild-type *KIT* gene. Immunohistochemical examination of BM biopsies showed MC aggregates in patient 1, and apparently normal numbers of BMMCs without compact MC aggregates in patient 2 (Figure 1). Altogether, these findings were consistent with the diagnosis of SM in both patients. Abdominal ultrasound and dual-energy X-ray absorptiometry scan demonstrated osteopenia in patient 2 and no other relevant abnormalities in either patient.

Both patients were warned to strictly avoid those foods involved in their previous reactions and to always carry an

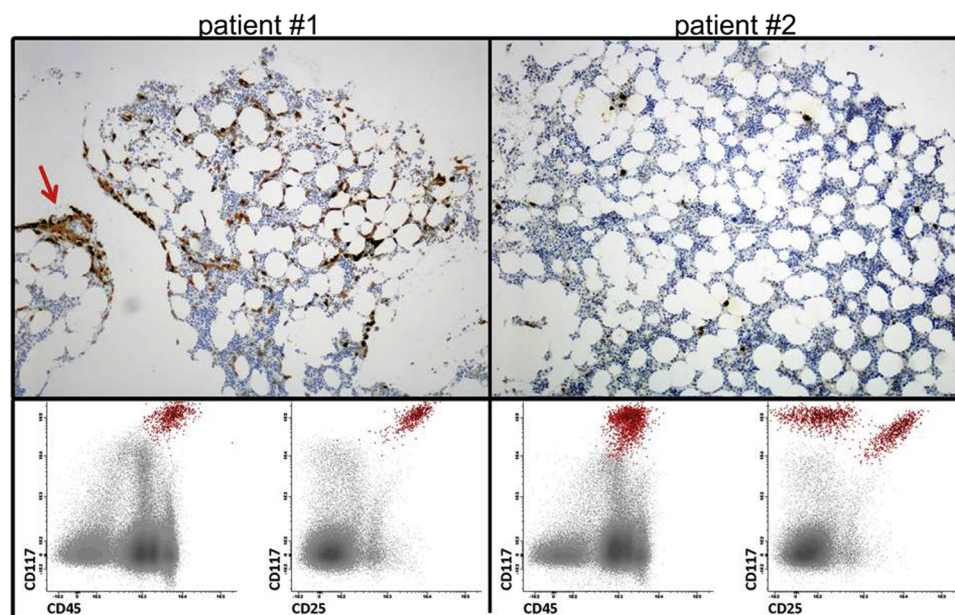


FIGURE 1. BM sections showed increased numbers of interstitial MCs and MC aggregates (red arrow) in patient 1, but scattered MCs in the absence of aggregates in patient 2 (upper panels, tryptase stain, $\times 400$). BM aspirate analysis by flow cytometry showed 0.09%/0.16% of BMMCs (red dots) in patients 1 and 2, respectively. Expression of CD25 was detected in all BMMCs in patient 1, whereas in only 30% from patient 2. *BM*, bone marrow; *MC*, mast cell.

epinephrine autoinjector. No further anaphylactic episodes were observed during a follow-up period of 3 years.

DISCUSSION

Anaphylaxis is a severe complication of SM that frequently presents as the first manifestation of an as-yet undiagnosed ISMs⁻. Hymenoptera sting is by far the most frequent trigger of anaphylaxis in patients with ISMs⁻,^{1,2,5} whereas other common triggers of anaphylaxis among the general population such as drugs or food are much less frequently observed.^{1,3,4,9} A recent study by the REMA that included the largest cohort of patients with mastocytosis associated with anaphylaxis reported so far showed food as a triggering factor in 36/271 (13%) cases, fish and/or seafood being the only triggers identified in only 6 (2%) of these patients.¹ Despite this, a precise description of the clinical characteristics as well as the results of the allergy evaluation of patients with mastocytosis and food-induced anaphylaxis was not specified in the latter study.

It should be emphasized that the absence of skin involvement in patients with ISMs⁻ presenting with anaphylaxis may obscure the diagnosis of the underlying c-MCD unless otherwise suspected, particularly when allergy to the culprit trigger is demonstrated. Here we present 2 paradigmatic cases of IgE-mediated food-induced anaphylaxis who were further diagnosed with ISMs⁻ once they were selected for a BM study based on the results of the REMA score, a point-based model that provides the risk of having an underlying c-MCD in patients with systemic MC-mediator release symptoms who lack mastocytosis in the skin.^{6,7} Of note, the REMA score has proven to be more efficient than sBT levels alone for the identification of patients with ISMs⁻; accordingly, it has

been incorporated to the updated consensus guidelines for the study of patients with systemic MC activation disorders developed by the European Competence Network on Mastocytosis (ECNM).¹⁰ It should also be noted that patients with ISMs⁻ typically show a low BMMC load that often results in the absence of BMMC aggregates, just slightly increased (even normal) sBT levels, and the coexistence of normal and neoplastic BMMCs,^{1,2,6} as demonstrated in one of our patients. This translates into the need for the systematic usage of highly sensitive diagnostic methods such as multiparameter flow cytometry immunophenotyping of BMMCs and molecular analysis of *KIT* mutations in FACS-purified BMMCs, to prevent the misdiagnosis of ISMs⁻ in suspected patients.⁸

^aServicio de Alergia, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

^bInstituto de Estudios de Mastocitosis de Castilla La Mancha, Hospital Virgen del Valle, Toledo, Spain

^cSpanish Network on Mastocytosis (REMA), Toledo, Spain

^dDepartamento de Medicina, Servicio General de Citometría, Centro de Investigación del Cáncer/IBMCC (USAL/CSIC), IBSAL, Universidad de Salamanca, Salamanca, Spain

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Corresponding author: Alicia Prieto García, MD, PhD, Servicio de Alergia, Hospital General Universitario Gregorio Marañón, Dr. Esquerdo, 46, 28007 Madrid, Spain.

E-mail: alicia.prieto@salud.madrid.org.

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