

Trousseau syndrome, developmental delay, partial complex epilepsy, hydrocephalus with ventricular-peritoneal shunt, gastroesophageal reflux disease, poor feeding, fundoplication and G-button placement, and horseshoe kidney.

The patient had craniofacial dysmorphism, consisting of macrocephaly, trigonocephaly, broad nasal bridge, small nose, and triangular-shaped upper lip. She had global developmental delay. Neurologic examination demonstrated nystagmus, spasticity and clonus, palmar and plantar grasp reflexes, no purposeful movements bilaterally, abnormal Babinski reflex, and no tracking with her eyes. She has a ventricular-peritoneal shunt on the right side.

The patient was hospitalized at 11 months for presumed viral pneumonia and at 23 months for severe pneumonia and respiratory distress that required mechanical ventilation. Parainfluenza virus 3 and *Pseudomonas aeruginosa* were identified from tracheal aspirates. The patient had no history of recurrent otitis media, sinusitis, oral or cutaneous candidiasis, or skin abscesses. The patient had a history of multiple kidney and bladder infections, most commonly with *Escherichia coli*.

As indicated in Table 1, the patient had persistent lymphopenia (decreased CD3⁺ count of 816–955 cells/mm³ (37%–39%) (reference range, 1,400–3,700 cells/mm³ [53%–75%]). Memory CD4⁺CD45RO⁺ cell counts were increased 55% to 58% (reference range, 7%–20%). CD56⁺ natural killer (NK) cell counts ranged from decreased (64–181 cells/mm³) to normal (130–720 cells/mm³). CD19⁺ B-cell counts were normal, but CD27⁺ memory B cell counts were 0%. Lymphoproliferative responses to the mitogens phytohemagglutinin, concanavalin A, and pokeweed mitogen were normal. Lymphoproliferative responses to *Candida albicans*, tetanus toxoid, and alloantigens were decreased. The patient was anergic to *Candida albicans* and tetanus toxoid. T-cell receptor V β spectra-type analysis revealed a normal repertoire of the V β family. The NK cell cytotoxicity to K562 cells was decreased. Serum IgG and IgA levels were normal, but IgM levels were decreased (32–48 mg/dL; reference range, 49–202 mg/dL). Antibody titers were normal to diphtheria toxoid, tetanus toxoid, and *Haemophilus influenzae* type B. Antibody titers were decreased to 2 of 7 serotypes in the conjugated *Streptococcus pneumoniae* vaccine (Prevna; Wyeth Pharmaceuticals, Madison, New Jersey). After a diagnosis of immunodeficiency, treatment with trimethoprim-sulfamethoxazole and intravenous immunoglobulin was started.

Because of decreased T-cell counts and function and decreased NK cell function, gene analysis of Janus kinase 3 (*JAK3*) was performed. Gene sequencing revealed a 452C > G (pro151arg) heterozygous missense mutation in exon 4. Schumacher et al⁵ reported this mutation previously in patients with the *JAK3* form of severe combined immunodeficiency (SCID). A second intronic mutation was identified, 3096+18 A > G heterozygous mutation, which was thought to not be associated with immunodeficiency. The CD3 ϵ gene (*CD3E*), which maps to chromosome 11q23, was sequenced to be normal. Cytogenetic studies demonstrated chromosome 11q23 terminal deletion.

JAK3 is associated the common γ chain (γ) cytokine receptors of interleukin 2 receptor (IL-2R), IL-4R, IL-7R, IL-15R, and IL-21R. IL-7R is critical for T-cell development, and IL-15R is critical for NK cell development.^{5–7} Thus, mutations of either γ or *JAK3* genes, which result in absence of protein expression and function cause a T⁺B⁺NK[−] phenotype of SCID.^{5–7} Our patient had a pro151arg missense mutation, which may have allowed for some *JAK3* protein expression and function. Variable phenotypic expression of mutated genes has been reported for many of the different

genetically defined types of classic SCID, such as *RAG1*, *IL-2RG*, *ADA*, *JAK3*, and *CD3E*.⁸ These variant types result in a moderate combined immunodeficiency or atypical SCID, as seen in our patient. The *JAK3* gene is mapped to chromosome 19p13.1, whereas Jacobsen syndrome is mapped to deletion of 11q23. Combined immunodeficiency has been reported previously in Jacobsen syndrome. This is the first report, to our knowledge, to identify the *JAK3* type of combined immunodeficiency in a patient with Jacobsen syndrome.

DOUGLAS R. LOTZ, MD
ALAN P. KNUTSEN, MD

Department of Pediatrics
Division of Allergy & Immunology
Saint Louis University
St Louis, Missouri
knutsenm@slu.edu

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OMALIZUMAB MONOTHERAPY FOR BEE STING AND UNPROVOKED “ANAPHYLAXIS” IN A PATIENT WITH SYSTEMIC MASTOCYTOSIS AND UNDETECTABLE SPECIFIC IgE

Venom immunotherapy (VIT) is not recommended by current guidelines for individuals with a confirmed history of sting anaphylaxis without specific IgE demonstrable in vivo or in vitro.¹ Such patients may develop life-threatening sting reactions; occult mastocytosis is often the underlying disorder.² A patient with mastocytosis; IgE-negative, sting-induced, and unprovoked anaphylaxis; and a favorable response to omalizumab is described herein.

A 48-year-old man was evaluated twice in 10 years for 3 near-fatal bee sting reactions and 3 unprovoked anaphylaxis events of similar severity. In 5 of the 6 episodes, he had developed immediate (≤ 10 minutes) generalized erythema, dizziness, loss of consciousness, and urinary and fecal incontinence. On arrival at the hospital (approximately 15 minutes), the patient was still unconscious, edematous, and cyanotic, and his blood pressure and pulse rate were unobtainable. Each time he had recovered after prolonged resuscitation.

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tation measures, including intensive care unit hospitalization during the latest sting anaphylaxis, 2 months before evaluation. The rest of his medical history and physical examination, with special focus on mastocytosis signs and symptoms, was noncontributory.

Intradermal skin tests with all Hymenoptera venoms (to 1 $\mu\text{g/mL}$) (Pharmalgen; ALK-Abelló, Hørsholm, Denmark) and RAST (ImmunoCAP; Phadia, Uppsala, Sweden) were negative for venom specific IgE (the tests were performed 3 and 4 months after the second venom anaphylaxis and 2 and 3 months after the third). Allergy evaluation did not reveal atopic sensitization, including foods. The rest of the workup, with emphasis on hematopoiesis, organomegaly, organ dysfunction, and lytic bone lesions, was negative. The clinical diagnosis of indolent systemic mastocytosis (SM) was confirmed by (1) multiple mast cell aggregates (>15 cells) in bone marrow and intestinal biopsy samples (tryptase+, CD117+, and CD25 not being available to us at the time); (2) 30% spindle-shaped mast cells, and (3) elevated serum tryptase levels (ImmunoCAP).

DNA was extracted from bone marrow (BioRobot EZ1; Qiagen Inc, Valencia, California), and 100-ng samples were amplified in mutation-specific polymerase chain reaction (PCR) for the detection of c-kit's exon 17 point mutation D816V. The PCR products were directly analyzed by means of agarose gel electrophoresis. C-kit exon 17 was amplified from bone marrow samples; PCR products were directly sequenced using a genetic analysis system with high-precision DNA fragment sizing and accurate identification of changes and mutations in one sequence (Beckman Coulter CEQ8000; Beckman Coulter Inc, Brea, California) and compared with the c-kit germline sequence. No c-kit mutation was detected using either approach.

The probability of a lethal sting reaction and omalizumab's relevant actions and preliminary data supporting its efficacy against unprovoked³ and VIT-induced anaphylaxis in SM^{4,5} lead to a trial of omalizumab monotherapy. The patient gave written informed consent.

Treatment consisted of 300-mg monthly doses (greater than that recommended for IgE [118 IU/mL] and weight [79 kg]). Serial tryptase measurements were performed in a blinded manner 1 hour before the first (baseline), second, and fifth omalizumab courses; every 3 months up to the 18th monthly course; and every 6 months thereafter. An in-hospital bee sting challenge was also planned. Patient and family were advised to use the adrenaline autoinjector promptly while rushing to the closest medical facility in case of "anaphylaxis."

Thirty monthly omalizumab courses have been administered uneventfully; the patient has tolerated, without any reaction, 3 field stings (1 bee sting and 2 unknown Hymenoptera stings), 100 μg of bee venom subcutaneously, and a controlled bee sting challenge. Unprovoked anaphylaxis has not recurred, and tryptase levels have slowly decreased by 33.7% (Fig.1).

The management of venom anaphylaxis without demonstrable specific IgE remains problematic; a law suit against a prominent allergist for not offering VIT to an "IgE-negative" venom reactor who succumbed to a subsequent sting illustrates the magnitude of the problem.⁶

A search of the literature did not identify any references about omalizumab's probable action on non-IgE-mediated mast cell activation. At the clinical level, such action is suggested by 2 case reports³ and is supported by this patient's course regarding sting-induced and unprovoked anaphylaxis.

By interacting with circulating IgE, omalizumab reduces Fc ϵ R-I on mast cells, leading to their "stabilization" in 4 months. Reducing mast cell-bound monomeric IgE might further stabilize mast cells and reduce their numbers through increased apoptosis^{7,8}; however, there is no evidence for the latter in humans.

The serum tryptase changes observed in this patient (33.23% total reduction with 25 monthly treatments, 10.3% after the first dose) (Fig 1) of different magnitudes were also present in (1) a previously published patient with mastocytosis^{4,5} (55.3% in 26

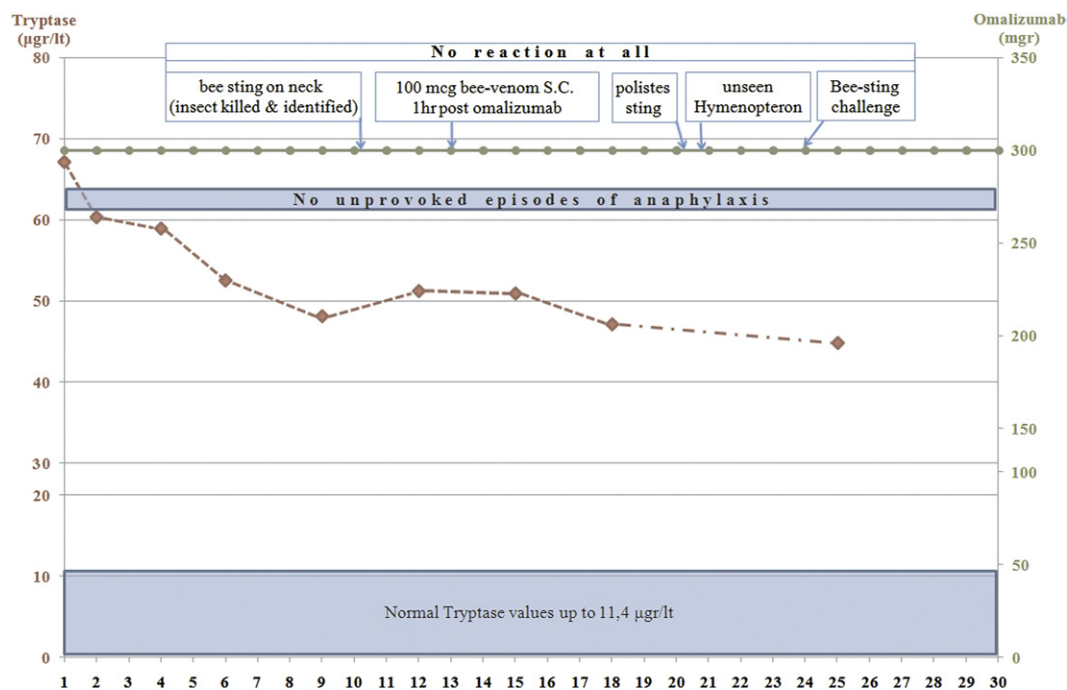


Figure 1. Clinical response to omalizumab monotherapy of a patient with systemic mastocytosis, life-threatening bee sting, and unprovoked "anaphylaxis." SC indicates subcutaneously.

months [from 42.1 to 18.8 ng], 19.2% after the first dose [from 42.1 to 34 ng]) and (2) an incompletely (distance obstacles) studied patient (13.3% after the first dose [from 82 to 71.9 ng]). Two patients with mastocytosis reported by Carter et al³ did not exhibit such tryptase changes. The patients with SM (all Greek nationals) seem to lack c-kit D816V mutations, but they fulfill the World Health Organization diagnostic criteria for indolent SM.

In conclusion, this case study suggests that omalizumab monotherapy might be efficacious in preventing unprovoked and sting-induced “anaphylactoid” reactions in patients with SM without c-kit exon 17 mutations. Controlled trials evaluating omalizumab’s effect on anaphylaxis in mastocytosis need to confirm these preliminary findings.

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KALLIOPI KONTOU-FILI, MD, PhD*
CHRISTOS I. FILIS, MD†
CHRISTINA VOULGARI, MD, PhD‡
PANAYIOTIS G. PANAYIOTIDIS, MD, PhD§

*Euroclinic Hospital of Athens
†Private practice
‡Elpis Municipal Hospital of Athens
§Department of Hematology
University of Athens Medical School
Athens, Greece
kontoufk@otenet.gr

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A CASE OF GENERALIZED URTICARIA CAUSED BY ARROWROOT INGESTION

Arrowroot (*Pueraria lobata*) is a popular plant in Asian countries, including Korea, Japan, and China. Arrowroot has been considered an herbal medicine for centuries.¹ In the food industry, it has been processed as starch or used as food supplements. Allergic reactions to arrowroot have rarely been reported, and immunologic investigations have not yet been performed.² We report a case of generalized urticaria induced by ingestion of fresh arrowroot.

A 26-year-old man visited our allergy clinic because of whole-body acute urticaria that developed 2 hours after drinking a bottle of arrowroot juice. The juice had been squeezed from a bundle of raw

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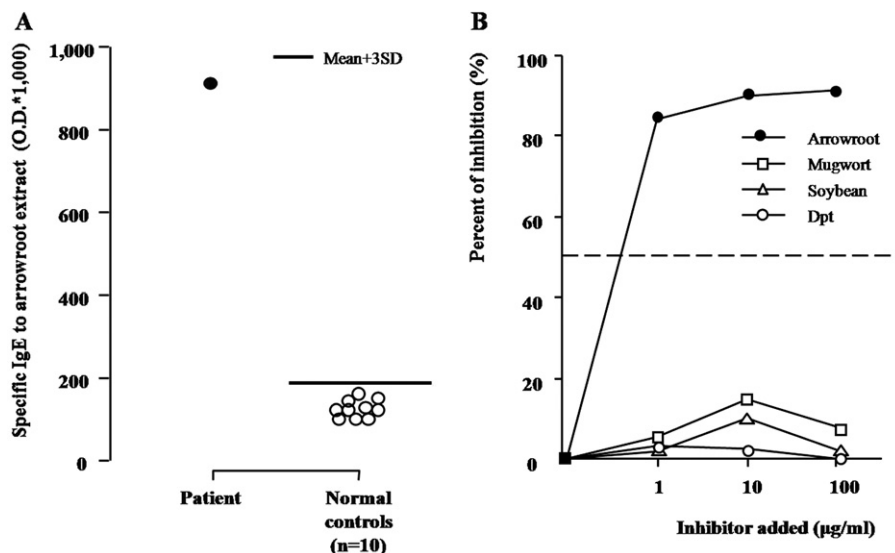


Figure 1. Arrowroot extract specific IgE serum levels determined using enzyme-linked immunosorbent assay (ELISA) from the patient and the 10 healthy controls. A, Horizontal bar indicates the positive cutoff value determined from the mean absorbance value of healthy controls $\pm$ 3 SDs. B, Arrowroot IgE ELISA inhibition test with serial additions of arrowroot, mugwort, soybean, and *Dermatophagoides pteronyssinus* extracts.