

Pre-emptive Evaluation of Venom Allergy in a Patient with Systemic Mastocytosis

Theo GÜLEN¹⁻³ and Cem AKIN⁴

¹Department of Respiratory Medicine and Allergy, K85, Karolinska University Hospital Huddinge, SE-141 86 Stockholm, ²Department of Medicine Solna, Immunology and Allergy Unit, Karolinska Institutet, ³Mastocytosis Centre Karolinska, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, and ⁴Department of Internal Medicine, and Division of Allergy and Clinical Immunology, University of Michigan Health System, Ann Arbor, Michigan, USA. E-mail: Theo.gulen@sil.se; Theo.Gulen@ki.se
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Systemic mastocytosis (SM) is a clonal disorder of mast cells (MCs) characterized by the accumulation and activation of these cells in at least one extracutaneous organ (1, 2). Anaphylaxis is a well-known feature of SM; in particular, venom allergy represents an increased risk of severe anaphylactic reactions to insect stings in these patients (3, 4). Although the overall prevalence of venom-induced anaphylaxis (VIA) is approximately 25% in patients with SM (4), there is no data available to suggest whether pre-emptive evaluation of venom allergy in patients with mastocytosis can reduce the risk of future episodes of VIA. There are also no consensus recommendations about whether to start venom immunotherapy based on positive blood or skin testing in patients with mastocytosis who have not experienced VIA. We present here an instructive case of indolent SM in a patient who experienced VIA, despite the absence of pre-sensitization to venom.

CASE REPORT

A 75-year-old woman presented with a history of reddish-brown spots on her legs, abdomen and chest. The skin lesions were not itchy, but had increased in size over the years. She had consulted a dermatologist for the first time in 2005 and a skin biopsy was taken. However, she was not informed whether the biopsy findings were consistent with urticaria pigmentosa (UP). She subsequently consulted another dermatologist and a new investigation was initiated due to suspicion of mastocytosis. The patient was referred to a local haematologist where she underwent a bone marrow biopsy. She was then referred to the Mastocytosis Center in Karolinska University Hospital Huddinge.

The patient underwent a comprehensive evaluation at the respiratory medicine and allergy clinic at Karolinska University Hospital Huddinge in May 2010. She had no history of pollen or animal dander-induced allergic symptoms and did not report any symptoms of asthma or allergic rhinitis. She had no known drug or food hypersensitivities. She had been stung by a wasp during the early 1990s, but she had had only a local reaction. Furthermore, she did not report any mast cell mediator-related symptoms, such as palpitations, dizziness, hypotension, or symptoms related to the gastrointestinal system. She had never experienced anaphylaxis or syncopal episodes. Her skin lesions did not urticate on exposure to cold, heat, physical exertion, stress, drugs, or intake of alcohol or food. A skin prick test (SPT) with commercial extracts (ALK-Nordic, Kungsbacka, Sweden) was performed, but did not reveal any immunoglobulin E (IgE) sensitization to pollen, animal dander, dust mites, honeybee or *Vespa* venoms.

Physical examination was unremarkable, except for reddish-brown pigmented spots on the skin of the patient's trunk, abdomen, shoulders and legs. Histopathological evaluation of her bone-marrow biopsy revealed the presence of atypical morphology, with spindle-shaped MCs, and presence of aberrant MCs expres-

sing CD25. The bone marrow aspirate was also positive for *KIT* D816V mutation and her baseline serum tryptase (sBT) levels were elevated (30 ng/ml; ref. value <11.4 ng/ml). No other haematological disorder was found. Therefore, these findings fulfilled the diagnosis of indolent SM with UP and the patient was re-referred to her local hospital.

The patient, however, re-contacted the allergy clinic to report an anaphylactic reaction she had after a wasp sting on her right hand in September 2012. A few minutes after the sting, she had lost consciousness, and by the time the ambulance arrived, the patient was unconscious and had difficulty in maintaining her blood pressure. She was immediately given adrenaline, antihistamines and glucocorticoids and taken to the local hospital. In the emergency room, the patient remained unconscious, with low blood pressure (approximately 70 mmHg systolic), and unresponsive to stimuli. She also had expiratory wheezing. She was given a further 0.5 mg intramuscular (i.m.) adrenaline and intravenous (i.v.) hydration. Her systolic blood pressure then began to increase towards 75 mmHg, but still had expiratory wheezing, generalized urticaria and facial angioedema. Electrocardiography (ECG) revealed an irregular rhythm and sharp ST elevations inferiorly. She was admitted to the intensive care unit (ICU) for further observation and discharged after 24 h. Her tryptase levels were not measured during the anaphylactic episode.

At a follow-up visit in February 2013 a new SPT was undertaken. She now tested 2+ (5 × 6 mm) for *Vespa* venom, but negative for honeybee venom. In addition, the specific IgE for wasp was 0.83 kU/l (reference <0.10 kU/l), but negative for bee venom. Analysis of the venom-specific component revealed rVes5 0.12 kU/l and rVes1 0.94 kU/l (reference values <0.10 kU/l). Her total IgE level was 15 kU/l and sBT 38 ng/ml. The patient confirmed that she had not had any insect stings between her initial visit in May 2010 and September 2012. In March 2013, venom-specific immunotherapy was started with wasp extract (ALK-Abelló, Horsholm, Denmark) according to a 7-week traditional schedule, in which patient was received incremental, weekly doses of venom extract subcutaneously until a maintenance dose of 100 000 standard quality units (SQ-U/ml) was reached. The achieved maintenance dose (100,000 SQ-U/ml) was then given every 4–6 weeks. Up to June 2017 the patient had not experienced any side-effects during uposing or maintenance treatment, and she had not had any new Hymenoptera stings since September 2012.

DISCUSSION

Although venom allergy represents a particular risk for exceptionally severe anaphylactic sting reactions in patients with mastocytosis, the precise mechanisms behind these reactions have not been fully elucidated. It is possible that the high MC load, reflected by higher levels of sBT, is responsible for this association. This idea is supported by a study showing a linear correlation between sBT levels and risk of severe VIA (5). However, the majority of the study patients (> 91%) had normal levels of sBT (<11.4

ng/ml). Furthermore, later studies challenged this notion by revealing the risk of VIA in patients with SM initially increased parallel with MC load, but after sBT levels reaching a plateau the risk declined (6, 7). Thus, higher levels of sBT (> 11.4 ng/ml) *per se* in patients with SM cannot alone explain the increased susceptibility, as this correlation appears to be bell-shaped (6, 7). In addition, the presence of non-IgE-mediated MC activation mechanisms induced by the properties of venom toxin in patients with SM might also contribute (8, 9).

In the light of current knowledge, the potential mechanism behind VIA reactions in patients with SM is thought to be IgE-mediated, since, in most patients, evidence of allergen-specific IgE can be found by either SPT or venom-specific IgE testing. The value of pre-emptive venom allergy evaluation in patients without anaphylactic reactions has been questioned, as some of these reactions can be life threatening. In a recent study, we sought to explore this issue by performing a comprehensive allergy work-up including skin tests for venom allergens in 122 patients with newly diagnosed SM (7). Interestingly, no patients without a prior VIA have yet tested positive with venom SPT. This observation is in line with the current report. Although this patient historically experienced a local reaction after a wasp sting, the previous SPT did not show any IgE sensitization to venom. However, it is possible that if *in-vitro* testing had been carried out at the initial evaluation specific IgE to wasp venom would have been identified, since the discrepancy between venom skin test results and *in vitro* tests is well-known in the literature (10). In addition, component-resolved diagnostics may provide useful information to distinguish relevant from irrelevant sensitization (11). Nevertheless, further investigations were not indicated in the current case, since no prior anaphylactic reaction was reported at that time (12).

At present, wasp venom immunotherapy is not recommended in sensitized mastocytosis patients with no history of an anaphylaxis episode. Moreover, there is no consensus among experts whether to prescribe adrenaline to all patients with SM or only to those SM patients who are at increased risk of anaphylaxis. Our current approach is to make individual recommendations based on a comprehensive allergy work-up, since there is a wide variation between SM patients regarding potential triggers. In the current case, if venom testing had been positive at the initial stage, we would have recommended that the patient carried an adrenaline pen.

In conclusion, there is a clear distinction between patients with mastocytosis and those without mastocytosis regarding the risk of severe VIA. Currently, there is no data regarding the rate of venom sensitization prior to VIA in patients with mastocytosis and its potential impact on the subsequent severe systemic reactions.

This case clearly illustrates that the severity of venom-induced reactions cannot be determined in advance by

pre-emptive skin prick testing in patients with mastocytosis. Furthermore, non-IgE-mediated MC activation mechanisms might also involve (8, 9). Hence, there is a need to develop a risk predictive tool to identify patients with mastocytosis who have a high risk of anaphylaxis (7).

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The authors have no conflicts of interest to declare.

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