Adult-Onset Mast Cell Activation Syndrome Following Scombroid Poisoning a case report and review of the literature

Isabelle Brock (✉ research@connective-tissue-issues.com )
   Indiana University School of Medicine https://orcid.org/0000-0003-4144-9763

Nicole Eng
   University of Pittsburgh School of Medicine

Anne Maitland
   Mount Sinai School of Medicine: Icahn School of Medicine at Mount Sinai

Research Article

Keywords: mast cell, mast cell activation syndrome, scombroid poisoning, histamine, tryptase, epithelium, tolerance, immune homeostasis

DOI: https://doi.org/10.21203/rs.3.rs-415528/v1

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Abstract

Mast Cell Activation syndrome (MCAS) is a clinical condition, defined by the combination of 1) typical symptoms, 2) laboratory abnormalities and 3) response to treatment. Patients present with episodic symptoms of aberrant mast cell activation, such as abdominal cramping, asthma, hypotensive episodes, tachycardia, anaphylaxis, unexplained arrhythmias, and neurologic/psychiatric symptoms. Both clonal and nonclonal mast cell activation syndromes have been described, with a greater prevalence of nonclonal MCAS among the pediatric and adult population. Numerous extrinsic triggers of mast cell activation (MCA) are described, but recent reports point to nonatopic triggers, as the predominant, extrinsic stimulants of MCA in the adult population. The etiology of MCAS is unclear, though recent studies point to the disruption of the epithelium by infection, toxic exposures or physical trauma, and perturbation the tight regulation of these innate immune cells, associated to the epithelial borders. Here we describe a geriatric patient with adult onset MCAS, following a significant toxic exposure, scombroid poisoning. We also review the relevant literature regarding MCAS diagnosis and management as well as potential mechanisms for this hypersensitivity syndrome in adults.

Background

Mast Cells are closely associated with epithelium, serving as sentinels, responsible for the recognition of tissue injury and coordination the initial inflammatory response. Upon detection of the contents of injured cells, mast cells then tailor the release of pre-formed and newly produced chemical mediators to the detected challenge via an array of pathogen receptors. In addition to Immunoglobulin E (IgE) receptor triggered mast cell activation (MCA), commonly referred to allergic or atopic disorders, non-IgE mediated mast cell activation follows engagement of Toll Like Receptors (TLRs), IgG receptors, and complement receptors. Upon containment of the extrinsic challenge, acute inflammation is downregulation and repair of the injured tissue ensues. The mast cell compartments must return to a baseline steady state, to remain tolerant towards self antigens as well as harmless entities, including and environmental conditions, in order to prevent unnecessary immune activation and chronic hypersensitivity disorders.

Over the past half century, an increasing number of patients are experiencing episodes of aberrant mast cell activation, not associated with allergen specific mast cell disease or systemic mastocytosis. This led to proposed diagnostic criteria of mast cell activation syndrome (MCAS). MCAS is a heterogeneous disorder, defined by a combination of 1) recurrent symptoms, typical of MCA, 2) an increase of validated mast cell derived mediators, and 3) response to treatment with mast cell stabilizing or MC mediator targeted therapies. Onset of MCAS ostensibly reflects the loss of tolerance, in the mast cell compartment, to nonthreatening entities as well as nonhazardous, environmental conditions. The etiology of chronic mast cell dysregulation and associated intolerance to self-antigens or harmless entities is not well understood, but a growing number of studies point to exposures to the epithelial borders, which leads to inappropriate or excessive mast cell activation or impaired resolution of acute inflammation, following neutralization of the identified pathogen.
Here we present a case of adult onset MCAS, following scombroid poisoning. Scombroid toxicity is usually a self-limited illness, but there are individuals who have been shown to have severe symptoms or persistent illness, following histamine fish poisoning. We describe a 74-year-old woman, with a history of drug induced urticaria, who developed a constellation of hypersensitivity illnesses, consistent with the diagnosis of MCAS, after ingestion of tainted fish. We also review the literature, describing the diagnostic criteria for MCAS as well as the proposed mechanisms leading to loss of tolerance in the mast cell compartment.

Case Presentation

A 74-year-old Caucasian woman, with a past medical history of coronary artery disease, breast cancer with bilateral mastectomy, an acoustic neuroma, menopause, hypothyroidism and chronic musculoskeletal complaints, presented to the emergency department (ED) with intense redness of her face and hands, burning sensation involving her face and neck, palpitations a “pounding headache”, difficulty breathing, dysphagia, and a rapid heart rate. Her illness began shortly after eating a tuna burger, from a local fish market. She denied previous incidents of food intolerance or anaphylaxis. In the past, the patient had only used prescription or over-the-counter antihistamines for drug induced urticaria, to opiate pain relievers and NSAIDs. Both pain relievers had been avoided for years.

Upon arrival in the emergency department (ED), her vital signs were a body temperature of 97.0° F (36.1° C), a pulse of 120 bpm, a blood pressure of 123/55, an oxygen concentration of 99% on room air, and a respiration rate of 16 breaths per minute. She also reported chest pain, with a level of 5/10. On physical exam, she was found to have an erythematos facial rash and complained of diffuse itch. The patient was administered prednisone 60 mg and diphenhydramine 50 mg, with relief of her headache, rash, chest pain and pruritis. In addition, an electrocardiogram revealed sinus tachycardia, at 107 bpm, without any signs of acute ischemia. No other laboratory tests were ordered. Two samples of the tuna steak were obtained from the local fish market, which sickened four adults with scombrotoxinism. Both samples contained a histamine level of 500 ppm and 4850 ppm, which is greater than the threshold deemed nontoxic by federal regulation, less than 50 ppm. Since both the patient and her husband exhibited allergic like reactions to the tuna burger, scombroid poisoning was suspected.

Unlike her husband, who was treated and recovered from this episode of scombrotoxinism, the patient experienced persistent urticaria as well as angioedema, with the diagnosis of new onset dermatographism, following completion of the 5-day course of oral prednisone and diphenhydramine, from the initial ED visit. Despite the use topical corticosteroids as well as daily levocetirizine 5 mg, loratadine 40 mg daily, and fexofenadine 180 mg, the patient experienced daily symptoms, for the next 6 weeks. The patient then returned to the local emergency department for persistent facial swelling and difficulty swallowing, following ingestion of crab cakes for dinner, which had been tolerated in the past. The patient reported difficulty swallowing, sensation of food getting stuck, increased throat clearing, nasal congestion, as well as numbness and tingling of the tongue, lips and throat. In the local ED, the patient was found to have a body temperature of 98.2° F (36.8°C), a pulse of 106 bpm, a blood pressure
of 140/65, oxygen concentration of 98% on room air, and a respiration rate of 18 breaths per minute. On physical exam, an erythematous facial rash was reported and the patient was evaluated by an otolaryngologist in the ED, given new onset dysphagia. The otolaryngologist reported erythema of the laryngeal mucosa. The patient was discharged, with a course of famotidine 20 mg, prednisone 40 mg and diphenhydramine 25 mg.

Following her second visit to the ED, in two months, the patient underwent an evaluation by a local allergy specialist. Recurrent urticaria was noted, and laboratory tests revealed the following: a total serum Immunoglobulin E (IgE) of 16 IU/ml; total complement level within normal limits; undetectable serum IgE for insect venoms, tuna and crab; undetectable autoantibodies to nuclear antigen (ANA); a negative recommended avoidance of all seafood.

The patient sought another opinion with our practice, regarding chronic urticaria and new onset shellfish allergy, one month after her last ED visit and 6 months after scombroid poisoning. She had continued her regimen of thrice daily histamine receptor-1 blockade as well as famotidine 20 mg twice daily. In addition to the recurrent flushing, rhinitis complaints, dyspepsia and episodic dysphagia, the patient cited chest tightness at rest, in the evening, and on exertion. Spirometry revealed an obstructive pattern consistent with reversible airway disease, which exhibited a modest improvement, following administration of levalbuterol 0.63 mg/3 ml. Another set of laboratory tests were ordered, with the following results: a serum tryptase of 4.8 and a serum IGE 17 IU/mL, which was comparable to previous results, but a plasma histamine level of 13 nmol/L was detected, with a normal range: 0–8 nmol/L. The patient maintained a limited diet, given her history of new onset shellfish allergy, carried an epinephrine autoinjector as well as short acting beta agonist inhaler, for the anaphylaxis and asthma, respectively. The patient opted for treatment with omalizumab, for chronic urticaria, and was prescribed 300 mg, administered every 4 weeks, since she was still symptomatic, despite thrice daily antihistamines, twice daily leukotriene modifiers, oral and inhaled cromolyn preparations.

Following her first dose of omalizumab, the patient complained of increased pruritis, flushing and chest tightness, prompting another ED visit. The patient required epinephrine administration, for a grade two, drug induced anaphylactic event. Following another course of oral corticosteroids and diphenhydramine, the patient underwent a graded challenge to omalizumab. Over a 3-month period, omalizumab 150 mg, administered every 2 weeks, was successfully reintroduced. As recently reported, the addition of omalizumab, to standard of care for patients with MCAS.

The diagnosis of MCAS in this patient, following scombroid poisoning, is supported by detection of increased mast cell derived mediators. Following anaphylaxis, to crab meat and then to the 1st administration of omalizumab, we tested for validated markers of mast cell activation, within a few hours of each suspected MCA event (table 1). An elevated serum histamine level was detected following ingestion of crab meat and her first omalizumab administration. After her 3 episode of anaphylaxis, the serum histamine returned to baseline, but the serum tryptase also reduced, to 2.2 mcg/ml, from her previous recorded values, which ranged from 4.8–5.2 mcg/ml. Along with the constellation of recurrent
symptoms of mast cell activation, including chronic urticaria, asthma, and susceptibility to anaphylaxis, and a partial response to histamine and leukotriene blockade, the detection of an elevated plasma level, following to episodes of anaphylaxis, as well as a reduction of the serum tryptase of greater than 2 mcg/ml and > 20%, the patient was diagnosed with non-clonal mast cell activation syndrome (MCAS). (Table 2).

Upon reaching the maintenance dose of omalizumab 150 mg, every 2 weeks, the patient was able to expand her diet and reduce her daily medical regimen to control her asthmatic condition and chronic spontaneous urticaria. In addition to omalizumab, the patient is maintained on daily levocetirizine, chlorpheniramine, zafirlukast and famotidine. Moreover, her quality of life was restored, including less disrupted sleep, resumption of outdoor exercise, re-introduction of food stuffs, except seafood, and less frequent urticarial outbreaks.

**Discussion**

Over the past half century, there has been a rise in classic mast cell activation disorders, such as rhinitis, food hypersensitivity, anaphylaxis, urticaria, and asthma, as well as less known MCAD, such as neuropsychiatric and musculoskeletal syndromes. A growing number of pediatric and adult patients are experiencing recurrent episodes of MCA, not associated with allergen-specific mast cell activation disease or systemic mastocytosis. This led to proposed diagnostic criteria of mast cell activation syndrome, which include the following: (1) systemic mast cell activation involving 2 or more organ systems, in parallel; (2) an increase in validated mast cell markers, during symptomatic episodes; and (3) have a major response to medications that block MCA or inhibit the action of MC derived mediators (Table 2). The diagnosis of mast cell activation syndrome (MCAS) is appropriate, when all three criteria are met\(^1\,^2\).

Mechanisms contributing to rise of mast cell activation disorders, including mast cell activation syndrome (MCAS), has not been established. Studies have implicated environmental exposures, of modern living, leading to excessive mast cell initiated, acute inflammation or impaired resolution of inflammation, following neutralization of the offending agent. This case report demonstrates the onset of MCAS in a 74-year-old woman, following exposure to a toxin, scombrotxin.

Scombroid poisoning, or histamine fish poisoning, is a toxic event with symptoms and treatment that mimic anaphylaxis. Scombroid poisoning results from consumption of mishandled fish. Histamine and other decomposition products are generated in time-temperature abused raw fish by bacterial, enzymatic conversion of free histidine. The onset of scombroid poisoning is typically from 10 min to 1 h following consumption of poisonous fish. The symptoms are variable and include peppery or metallic taste, oral numbness, headache, dizziness, palpitations, rapid and weak pulse (low blood pressure), difficulty in swallowing, and thirst. Scombroid poisoning often mimics allergen-specific IGE triggered mast cell activation, with symptoms such as hives, rash, flushing, facial swelling, nausea, vomiting, abdominal cramps and diarrhea. Less specific symptoms such as anxiety are less frequently observed\(^10\).
Recovery is usually complete within 24 h, but in rare cases can last for days. For example, serious cardiovascular compromise and respiratory complications have been observed, and in a few unusual cases hospitalization, including treatment for anaphylaxis. There are two reports of patients developing chronic mast cell activation disorders, following scombroid poisoning: after ingesting decomposed tuna, a 21-year old woman, with a history of intermittent asthma, developed not well controlled asthma, requiring multiple ED visits and 5 daily medications, to control new onset, severe persistent asthma. Another woman, without a history of MCADs, was diagnosed with adult-onset rhinitis and asthma, following scombroid poisoning.

Scombroid poisoning is associated with elevated histamine levels in the outbreak-associated samples. However, there is not a clear dose-response relationship between oral administration of histamine and the magnitude of toxicity associated with scombroid poisoning. Interestingly, several studies point to the impact of “histamine releasing factors” on the epithelium and closely associated mast cells, by enteric, gram negative bacteria, found in the fish cutis and intestines. This includes such as Escherichia coli, Klebsiella species, Pseudomonas aeruginosa, and Morganella morganii. As reported in animal models of anaphylaxis and asthma, loss of tolerance in the mast cell compartment can be induced with exposure to chemical adjuvants and microbial derived substances, such as aluminum hydroxide and lipopolysaccharide, respectively. Combined with signals of tissue injury, called alarmins or damage associated molecular patterns (DAMPs), the microbial derived substances are potent stimulants of mast cell activation.

With this patient, the reportedly high levels of histamine detected in the two samples of tuna from this seafood market, greatly exceeded the level of histamine deemed toxic by the FDA, more than 50 mg/100 g of tuna (50 ppm). Such high levels of histamine ostensibly reflect the burden of scrombotoxins, which in turn induced epithelial damage and delivered large quantities of histamine in the poisoned diners of the tainted fish. That is, the combination of histamine and histamine release factors, scombrotoxins, may have either severely disrupted the epithelium border and consequently a pronounced MCA event, or interfered with the processes, which resolve inflammation, after the acute insult has been neutralized. Three of the four adults with scombroid poisoning had a full recovery within 24 hours, with conservative medical management. In contrast, our patient, with a distant history of drug induced urticaria, required daily medication for adult onset spontaneous inducible urticaria/angioedema, hypersensitivity gastroenteritis, and moderate persistent asthma, starting in the seventh decade of life. In addition to diet restriction, including avoidance of seafood, gluten, cow's milk, soybean and nuts, she must carry an epinephrine autoinjector and short acting beta agonist inhaler, given her history of anaphylaxis and intrinsic asthma exacerbations, following scombroid poisoning.

Conclusion

In summary, we describe the clinical presentation of a presentation with MCAS, following scombroid poisoning. The diagnosis is appropriate given her combination of 1) typical symptoms, 2) laboratory
abnormalities and 3) response to treatment. Following scombroid poisoning, adult onset chronic urticaria/angioedema evolved into susceptibility of anaphylaxis, chronic hypersensitivity gastroenteritis, and moderate persistent asthma; symptomatic episodes were associated with an elevation in validated mast cell markers, both serum tryptase as well as histamine; and, her symptoms came under better control with the addition of omalizumab, the anti-Immunoglobulin E monoclonal antibody, to her daily regimen of cromolyn anti-histamines and leukotriene blockade. Despite the rise of immediate hypersensitivity disorders, it is not uncommon for MCAS to be diagnosed late, as observed with our patient. This leads to delayed recommendations for more effective treatment prescriptions of medications with adverse effects, both of which may contribute to progressive disease. As recently described, the greatest hurdle to diagnosis and management of MCAS is to correctly attribute appropriate symptoms to this disorder and timely measurement of validated mast cell activation markers. The latter will differentiate MC activation disorders from other syndromes, with overlapping symptomatology.\textsuperscript{3,17} This case also lends insight into potential etiologies and risk factors for development of MCAS.

Mast cell dysregulation can be due to a mutation affecting homeostasis of the mast cell compartment, clonal MCAS (mastocytosis, hyper alpha tryptasemia) or extrinsic factors driving aberrant MCA. Although the etiology of this newly recognized hypersensitivity syndrome is unknown, the course of events leading to this adult-onset MCAS in this patient points to the disruption of the epithelial barrier by scombrotoxins. This, in turn, disrupted the tight regulation of this tissue based, innate immune cell population, and increased susceptibility to mast cell activation events. Animal models and epidemiological studies support this theory of recurrent or severe injury the epithelium of susceptible children and adults leading to development of immediate and delayed hypersensitivity syndromes: disruption of the epithelial barrier leads to loss of regulation of the mast cell compartment. This, in turn, lends to increased susceptibility of unnecessary inflammation, from impaired barrier function, and implicates the use of therapeutics targeting epithelial-mast cell interactions in preservation or restoration of immune homeostasis.\textsuperscript{15,18}

**Declarations**

**Ethics approval -** consent to participate was given by the patient

**Consent for publication -** Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review upon request.

**Availability of data and material -** The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.
Competing interests - Isabelle Brock has no conflicts to declare. Anne Maitland receives compensation as part of the speakers’ bureau of Sanofi Pharmaceuticals, Regeneron and Genentech. There is no conflict of interest with the observations reported in this manuscript and Dr. Maitland’s affiliation.

Funding - This work received no funding.

Authors’ contributions – both authors have contributed in equal parts to all parts of the study and manuscript

Acknowledgements – none

Abbreviations

Mast Cells (MC), Mast Cell Activation Syndrome (MCAS), Toll-Like Receptors (TLR), Immunoglobulin receptors (IgR), complement receptors (CR), acute respiratory distress syndrome (ARDS), pathogen associated molecular pattern (PAMPs), postural orthostatic tachycardia syndrome (POTS), hypermobile type Ehlers Danlos Syndrome (hEDS), primary immunodeficiency (PID), angiotensin-converting enzyme 2 (ACE2), damage-associated molecular patterns (DAMPs)

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**Tables**

Tables 1-2 are not available with this version.

**Supplementary Files**

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- [ScombroidCAREchecklistEnglish2013.pdf](#)