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The Role of KIT Mutations in Anaphylaxis

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Abstract

Purpose of Review Gain of function KIT mutations are detected in clonal mast cell diseases, namely mastocytosis and monoclonal mast cell activation syndrome. Timely diagnosis and treatment of these disorders are crucial because of their association with severe and life-threatening anaphylaxis. KIT mutations also have implications for targeted therapies of mast cell disorders. This review article strives to serve as an overview of the role of clonal mast cell disorders in anaphylaxis while elucidating current and future therapies.

Recent Findings Clonal mast cell disease has been increasingly diagnosed in patients with severe hymenoptera allergy and those with recurrent unexplained anaphylaxis. The current state of knowledge of the epidemiology, pathophysiology, diagnosis, and treatment of mastocytosis with a particular focus on anaphylaxis and its triggers which are described in this context. Novel and forthcoming treatments are discussed including the relevance of KIT mutation status.

Summary This review provides an overview of the role of KIT mutations in mastocytosis and anaphylaxis, and highlights emerging therapies for mastocytosis, targeting these mutations.

Keywords Mastocytosis · Anaphylaxis · KIT mutation · C-KIT · Hymenoptera

Introduction

Anaphylaxis is an acute and life-threatening multisystem syndrome caused by sudden release of mast cell mediators into systemic circulation [1, 2]. Signs and symptoms can include cutaneous (erythema, pruritus, urticaria, and/or angioedema); respiratory (wheezing, coughing, bronchospasm, laryngeal edema); cardiac (arrhythmias, dizziness, palpitations), gastrointestinal (hyperperistalsis, nausea, vomiting); and neurologic (headache, feeling of impending doom, and unconsciousness) findings [3]. The prevalence of anaphylaxis is estimated to be as high as 2% in the USA based on stringent clinical diagnostic criteria [4]. The prevalence appears to be rising in developed countries [5–7]. Factors affecting the incidence are geographic location, sex, atopy, and socioeconomic status, although a precise definition of risk factors have been lacking [8]. Overall, anaphylaxis is under-recognized [9], underreported [10], and under treated [9].

Anaphylaxis may be "allergic" or IgE-dependent, "immunologic" or IgG-mediated, or immune complex/complement-mediated or non-immunologic [11]. IgE is unequivocally involved in conferring immunological specificity to effector cells [12, 4, 13]. It binds to the high-affinity receptor FcεRI on mast cells. In anaphylaxis, there is cross-linking of FcεRI-bound IgE, which induces activation of mast cells and causes release of mediators, such as histamine, tryptase, chymase, and heparin [3], as well as de novo synthesis of many inflammatory mediators, such as leukotrienes, prostaglandins, and cytokines [13]. H1 and H2 receptors are directly activated by histamine. H1 receptors mediate itching, rhinorrhea, tachycardia, and bronchospasm, whereas both H1 and H2 receptors mediate HA, flushing and hypotension [14].

Anaphylaxis can also occur in a mechanism independent of IgE. It is known that some patients can experience anaphylaxis despite having low or undetectable levels of circulating allergen-specific IgE [15]. Conversely, allergen-specific IgE can be found in many people who do not develop clinical symptoms even when exposed [16]. Therefore, presence of specific IgE alone does not predict anaphylaxis. This suggests that abnormalities in activation pathways or numbers of effector cells (mast cells) may also contribute to the susceptibility and severity of anaphylaxis.

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Role of Mast Cell in Anaphylaxis

Mast cells are widely accepted as the most important player in IgE-dependent anaphylaxis [12]. They express high-affinity IgE receptor (FcεRI), though differences in their degranulation may influence clinical outcome with or without the presence of IgE [17, 18]. The key role that mast cells play in anaphylaxis is illustrated by the high occurrence of anaphylaxis in patients with mastocytosis, defined as a heterogeneous grouping of neoplasms with clonal expansion of mast cells in one or more organ systems, typically including the skin and hematopoietic system [19•]. Estimated prevalence of mastocytosis in Middle Europe is 0.005–0.01% or 0.5–1 per 10,000 [20]. The lifetime prevalence of anaphylaxis has been reported to be approximately 30%, and the incidence at least six times greater in patients with mastocytosis compared to general population [21]; anaphylaxis is also more severe in those with mastocytosis compared to those without [22•].

Mastocytosis and related diagnostic criteria have been refined and updated by the consensus group and the World Health Organization (WHO) [23••]. Mastocytosis can be divided into sub-variants of cutaneous mastocytosis (CM), in which no systemic involvement is found, systemic variants (SM), and localized MC tumor. In systemic mastocytosis (SM), neoplastic MCs infiltrate organs, including the bone marrow, spleen, liver, and gastrointestinal system. Bone marrow is involved in virtually all patients with SM [24]. Skin involvement in CM is usually found in patients with indolent SM (ISM), is less frequently detected in aggressive SM (ASM), and is rarely seen in MC leukemia (MCL). The diagnosis of systemic mastocytosis requires a tissue (most often bone marrow) biopsy. WHO diagnostic criteria for systemic mastocytosis are shown in Table 1. A limited histopathologic variant presenting with mast cell activation symptoms/anaphylaxis and 1 or 2 clonality criteria (KIT D816V mutation and/or CD25 expression on mast cells) has been termed monoclonal mast cell activation syndrome [25].

Table 1 World Health Organization's updated classification of mastocytosis in 2016

Cutaneous mastocytosis (CM)

- Maculopapuplar CM = urticaria pigmentosa
- Diffuse CM
- Mastocytoma of the skin

Systemic mastocytosis (SM)

- Indolent SM
- Smoldering SM
- SM with associated hematologic neoplasm[a]
- Aggressive SM
- Mast cell leukemia

[a] The previous term SM with clonal hematologic non-mast cell-lineage disease and the new term SM with associated hematologic neoplasm can be used synonymously

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KIT Mutations

Mast cells are hematopoietic stem cells-derived tissue resident-granulated cells found close to blood vessels, nerves, and mucosal surfaces. The major growth and differentiation factor for the mast cell lineage is stem cell factor, which binds KIT, a transmembrane receptor with intrinsic tyrosine kinase activity [26]. The c-*KIT* proto-oncogene is necessary for the development and survival of mast cells through the Stat5-P13Akt signaling pathway [27, 28]. Upon binding its ligand, stem cell factor, KIT induces autophosphorylation and downstream signal transduction, which leads to differentiation, proliferation, and antiapoptotic effects in mast cells [29, 30].

The pathophysiology of mastocytosis is driven by an activating KIT mutation in neoplastic mast cells [31], which is present in more than 95% of patients with systemic mastocytosis [32]. In adults with SM, KIT mutations primary affect exon 17 encoding for phosphotransferase domain, usually D816V [33]. Other less frequent mutations affect exons 2, 8, 9, and 10 encoding for the extracellular or transmembrane domains, or exons 13, 14, and 17 encoding for kinase domain. These atypical mutations have been described in childhood onset cutaneous mastocytosis (extracellular forms) or advanced systemic disease (atypical exon 816 mutations). The majority of mastocytosis mutations are sporadic somatic mutations that affect the mast cell progenitors and are not present in germ cells. In cases of rare familial mastocytosis (representing < 1% of all cases), these patients usually do not have KIT mutations or have rare mutations, such as K509I, N835I, N835K, A533D, M835K, S841I, or K839E [34].

The degree of KIT D816V mutation status in SM can be highly variable given the differing degrees of mast cell infiltration in affected organs. One review illustrated that the rate of KIT mutation varied among skin, bone marrow, and blood, from 81 to 95% [32].

Anaphylaxis and Mastocytosis

There are many risk factors for anaphylaxis in those with mastocytosis. In children, risk is proportional to the extent and density of skin lesions and serum tryptase level [35]. Adults with mastocytosis are at greater risk for anaphylaxis than children with a prevalence between 22 and 49% [35–37]. Prevalence is higher in males and those with higher IgE [36]. Similar to children, those with higher baseline serum tryptase level are also at higher risk for anaphylaxis [35].

Idiopathic anaphylaxis (IA) is a form of anaphylaxis with unknown etiology but similar symptoms to other forms of anaphylaxis [38]. While the causes of the majority of cases of anaphylaxis can be identified, over 8% of anaphylaxis events are idiopathic [39]. IA is increased in patients with mastocytosis [37, 36], with 14–42% of patients having clonal mast cell disorder in different series (mastocytosis or monoclonal mast cell activation syndrome) [40•, 41]. A sensitive peripheral blood allele-specific quantitative PCR was able to identify the presence of KIT D816V mutation and predicted bone marrow disease in patients with IA and a clonal disorder with a 100% positive predictive value [41]. There was no evidence of a hyper-responsive mast cell phenotype in patients with IA in patients without clonal mast cell disorder [41].

Hymenoptera venom allergy has a strong association with clonal mast cell disease; in patients with mastocytosis and anaphylaxis, 19–30% reported hymenoptera stings as a culprit [35, 42]. On the other hand, several studies reported elevated baseline tryptase levels in patients with hymenoptera venom allergy correlating with severity of the reaction [43, 44]. One study from Italy found that as many as 12% of patients with systemic reactions to venoms have elevated baseline tryptase levels (> 11.4 ng/ml), and the majority of these patients had clonal mast cell disease [45]. Another study confirmed elevated basal tryptase levels in 12.0% of the hymenoptera allergic patients and elevation of tryptase was most significantly correlated with the severity of anaphylaxis ($P < 0.001$) [46]. Up to 15% of patients with mastocytosis and systemic reactions to hymenoptera venom may be negative to skin prick and specific IgE, which is more frequent than the general public [47•] . Venom immunotherapy (VIT) is recommended for patients with SM with IgE-mediated allergy, and is considered safe and effective [48–50]. Omalizumab has been used successfully to help tolerate desensitization for VIT [51–53].

Perioperative periods are also a potent risk factor for anaphylaxis. Mast cell disease was identified in 4% of patients with perioperative anaphylaxis [54]. Conversely, 0–2% of patients with mastocytosis experienced anaphylaxis while undergoing procedures requiring general anesthesia [55•] .

Procedures that occur under anesthesia can increase release of mast cell mediators, which are likely multifactorial from stress, tissue manipulation, and medications including neuromuscular blockers, analgesics (opioids and NSAID), and hypnotics [56–59]. These procedures, therefore, are considered higher risk in patients with mastocytosis based on reports of severe reactions, including death [60–64]. Reactions are more likely to occur in patients who have had anaphylaxis before or are undergoing a procedure under general anesthesia [61]. Most agree that patients with prior episodes of anaphylaxis should be pretreated with medications [65, 61, 58], and some authors focus on treating anxiety, which could cause worsening mast cell mediator release [61]. To date, there is no placebo controlled trials to examine the effects of pre-treating all patients.

Food allergies are much less frequently reported as the presenting symptoms of mastocytosis [66, 35]. The rate of food allergy does not appear to differ greatly in patients with mastocytosis compared to the general population [36]. Allergy to mammalian meat is a recently identified etiology of anaphylaxis triggered by exposure to a mammalian oligosaccharide, galactose-α-1,3-galactose (α-gal) [67], after sensitization from a tick bite [68], and has been reported as a cause of anaphylaxis in mastocytosis [69, 70].

Unlike traditional food allergies, anaphylaxis to mammalian meat may occur in a delayed fashion, up to 6 h after consumption [67]. It has been suggested that a screening tryptase should be obtained in those with severe α-gal anaphylaxis [71].

Several physical anaphylaxis conditions exist, including temperature and exercise-induced forms. Exercise-induced anaphylaxis is characterized by symptoms of anaphylaxis at the beginning, during, or after exercise [72]. It should be suspected based on history, and its diagnosis can be confirmed with a positive exercise challenge, but negative exercise challenge does not exclude this disorder [73]. The condition is thought to be related to release of mediators by mast cells as with most IgE-related anaphylaxis. However, the mechanism is less clear than in general anaphylaxis. Our personal experience suggests that there is likely an overlap in EIAn and clonal mast cell disorders; however, their precise relationship is not well-documented.

Most frequent symptoms of anaphylaxis in patients with mastocytosis are cardiovascular, with skin lesions being surprisingly infrequent [74, 35, 37]. A scoring system based on gender, tryptase levels, and symptoms of anaphylaxis was proposed to predict patients with a high likelihood of having mastocytosis [75].

Diagnostic and Therapeutic Considerations

To screen for systemic mastocytosis, an algorithm was developed based on clinical signs and symptoms, and tryptase levels that is capable of predicting the existence of clonality with a sensitivity of 92% and a specificity of 81%. A score ≥ 2 suggests that ISM should be ruled out [76]. Patients with idiopathic anaphylaxis and venom-induced anaphylaxis with normal tryptase levels at baseline need evaluation for the *KIT* D816V mutation in peripheral blood. If results are positive, a bone marrow biopsy is warranted [77].

Once mastocytosis is diagnosed, the goal of treatment is either symptomatic management or cytoreductive therapy. Current treatments for symptomatic management are with antihistamines (H1 and H2 receptor blockers), antileukotrienes, and mast cell stabilizers. Data have shown that antihistamines can increase quality of life in patients with mastocytosis [78]. H1 and H2 receptor antagonists are helpful for dermatologic

and GI symptoms of mastocytosis [79]. Patients with predominantly GI complaints, such as abdominal cramping, vomiting, or diarrhea, may benefit from cromolyn [80]. Leukotriene inhibitors, such as montelukast, have limited data but are frequently used as an adjunctive therapy. It has been shown to be effective for patients with dermatologic complaints [81, 82]. In terms of cytoreductive therapy, patients were typically treated with cladribine or interferon-alpha until midostaurin was approved. Although chemotherapy, such as cladribine, can induce a response of 50% in patients with SM, ASM, or MCL, and can also drastically reduce anaphylactic episodes, it can have significant toxicities including lymphopenias and opportunistic infections [83]. Therefore, targeted therapies to reduce mast cell burden and activation have been investigated.

The most studied targeted drugs specific to mast cell proliferation are KIT tyrosine kinase inhibitors [84]. Midostaurin, a tyrosine kinase inhibitor, is the only FDA-approved therapy for patients with advanced subtypes of mastocytosis [85]. Unlike previous tyrosine kinase inhibitors such as imatinib, midostaurin inhibits not only the wild-type form of its targets but also their mutant forms, including D816V mutant [26]. It is shown to reduce organ damage and disease progression [86••], and is found to have durable effect and is safe at 10 year follow-up [87]. In addition, midostaurin also seems to reduce symptoms in patients with severely symptomatic indolent mastocytosis [88]. BLU-285 compound or avapritinib is another novel tyrosine kinase inhibitor that selectively inhibits KIT exon 17 mutants, including KIT D816V. It also inhibits STAT3 and AKT phosphorylation in vitro in human MC line [89]. It seems to be well-tolerated and demonstrated significant clinical and biologic activities in all advanced SM subtypes, including in those who did not respond to midostaurin [90]. The effects of tyrosine kinase inhibitors on anaphylaxis in clonal mast cell disease remain to be explored.

Omalizumab (anti-IgE antibody) seems not only to be a promising treatment for patients with chronic urticaria and allergic asthma but also reduces anaphylaxis in clonal and non-clonal mast cell disorders [91, 92]. Mechanisms of omalizumab action in these patients remain to be elucidated [93••, 51].

Conclusions

Mast cells play an important role in IgE-dependent anaphylaxis, which is a life-threatening condition. Those with mastocytosis, a group of neoplasms with clonal expansion of mast cells, are at a particularly elevated risk of anaphylaxis. Mastocytosis is driven by an activating KIT mutation in mast cells, which is present in majority of people with the disorder. This group of individuals is more prone to experience anaphylaxis in many situations, such as during peri-operative periods, with bee stings, foods, and medications, as well as physical factors, such as temperature and exercise. The identification of KIT mutation is instrumental in guiding therapies. Many symptoms of mastocytosis can be controlled with anti-histamines, and most novel-targeted therapies currently involve KIT tyrosine kinase inhibitors.

Compliance with Ethical Standards

Conflict of Interest Elise Coulson and Sherry Zhou declare that they have no conflict of interest. Cem Akin has consultancy agreements with Novartis and Blueprint Medicines.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391–7. https://doi.org/10.1016/j.jaci.2005.12.1303.
2. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010;126(3):442–77. https://doi.org/10.1016/j.jaci.2010.06.022.
3. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. J Allergy Clin Immunol. 2002;110(3):341–8.
4. Wood RA, Camargo CAJ, Lieberman P, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. J Allergy Clin Immunol. 2014;133(2):461–7. https://doi.org/10.1016/j.jaci.2013.08.016.
5. Poulos LM, Waters A-M, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. J Allergy Clin Immunol. 2007;120(4):878–84. https://doi.org/10.1016/j.jaci.2007.07.040.
6. Lieberman P, Camargo CAJ, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. Ann Allergy Asthma Immunol. 2006;97(5):596–602. https://doi.org/10.1016/S1081-1206(10)61086-1.
7. Sicherer SH, Muñoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. J Allergy Clin Immunol. 1999. https://doi.org/10.1016/S0091-6749(99)70224-1.
8. Lieberman P. Epidemiology of anaphylaxis. Curr Opin Allergy Clin Immunol. 2008;8(4):316–20. https://doi.org/10.1097/ACI.0b013e3283036a69.
9. Banerji A, Rudders S, Clark S, Wei W, Long AA, Camargo CAJ. Retrospective study of drug-induced anaphylaxis treated in the emergency department or hospital: patient characteristics, management, and 1-year follow-up. J Allergy Clin Immunol Pract. 2014;2(1):46–51. https://doi.org/10.1016/j.jaip.2013.08.012.

10. Alvarez-Perea A, Ameiro B, Morales C, et al. Anaphylaxis in the pediatric emergency department: analysis of 133 cases after an allergy workup. J Allergy Clin Immunol Pract. 2017;5(5):1256–63. https://doi.org/10.1016/j.jaip.2017.02.011.
11. Khan BQ, Kemp SF. Pathophysiology of anaphylaxis. Curr Opin Allergy Clin Immunol. 2011;11(4):319–25. https://doi.org/10.1097/ACI.0b013e3283481ab6.
12. Galli SJ, Tsai M. IgE and mast cells in allergic disease. Nat Med. 2012;18(5):693–704. https://doi.org/10.1038/nm.2755.
13. Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. J Allergy Clin Immunol. 2017;140(2):335–48. https://doi.org/10.1016/j.jaci.2017.06.003.
14. Kaliner M, Sigler R, Summers R, Shelhamer JH. Effects of infused histamine: analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. J Allergy Clin Immunol. 1981;68(5):365–71.
15. Golden DBK, Tracy JM, Freeman TM, Hoffman DR. Negative venom skin test results in patients with histories of systemic reaction to a sting. J Allergy Clin Immunol. 2003;112(3):495–8.
16. Simons FER, Frew AJ, Ansotegui IJ, et al. Risk assessment in anaphylaxis: current and future approaches. J Allergy Clin Immunol. 2007;120(1 Suppl):S2–24. https://doi.org/10.1016/j.jaci.2007.05.001.
17. Bryce PJ, Falahati R, Kenney LL, et al. Humanized mouse model of mast cell-mediated passive cutaneous anaphylaxis and passive systemic anaphylaxis. J Allergy Clin Immunol. 2016;138(3):769–79. https://doi.org/10.1016/j.jaci.2016.01.049.
18. Buka RJ, Crossman RJ, Melchior CL, et al. Anaphylaxis and ethnicity: higher incidence in British South Asians. Allergy. 2015;70(12):1580–7. https://doi.org/10.1111/all.12702.
19.• Volertas S, Schuler CF 4th, Akin C. New insights into clonal mast cell disorders including mastocytosis. Immunol Allergy Clin N Am. 2018;38(3):341–50. https://doi.org/10.1016/j.iac.2018.04.014 **Good overview of mastocytosis.**
20. Valent P. Mastocytosis: a paradigmatic example of a rare disease with complex biology and pathology. Am J Cancer Res. 2013;3(2):159–72.
21. Broesby-Olsen S, Farkas DK, Vestergaard H, et al. Risk of solid cancer, cardiovascular disease, anaphylaxis, osteoporosis and fractures in patients with systemic mastocytosis: a nationwide population-based study. Am J Hematol. 2016;91(11):1069–75. https://doi.org/10.1002/ajh.24490.
22.• Worm M, Francuzik W, Renaudin J-M, et al. Factors increasing the risk for a severe reaction in anaphylaxis: an analysis of data from The European Anaphylaxis Registry. Allergy. 2018;73(6):1322–30. https://doi.org/10.1111/all.13380 **Shows increase risk of anaphylaxis in patients with mastocytosis.**
23.•• Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420–7. https://doi.org/10.1182/blood-2016-09-731893 **Describes the current classification and emerging treatments of mastocytosis.**
24. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. J Invest Dermatol. 1991;96(3):2S–4S.
25. Akin C. Mast cell activation syndromes. J Allergy Clin Immunol. 2017;140(2):349–55. https://doi.org/10.1016/j.jaci.2017.06.007.
26. Bibi S, Arock M. Tyrosine kinase inhibition in mastocytosis: KIT and beyond KIT. *Immunol Allergy Clin North Am* 2018;38(3):527–543. https://doi.org/10.1016/j.iac.2018.04.007.
27. Yarden Y, Kuang WJ, Yang-Feng T, et al. Human proto-oncogene c-kit: a new cell surface receptor tyrosine kinase for an unidentified ligand. EMBO J. 1987;6(11):3341–51.
28. Harir N, Boudot C, Friedbichler K, et al. Oncogenic Kit controls neoplastic mast cell growth through a Stat5/PI3-kinase signaling cascade. Blood. 2008;112(6):2463–73. https://doi.org/10.1182/blood-2007-09-115477.
29. Komi DEA, Rambasek T, Wohrl S. Mastocytosis: from a molecular point of view. Clin Rev Allergy Immunol. 2018;54(3):397–411. https://doi.org/10.1007/s12016-017-8619-2.
30. Akin C. Anaphylaxis and mast cell disease: what is the risk? Curr Allergy Asthma Rep. 2010;10(1):34–8. https://doi.org/10.1007/s11882-009-0080-8.
31. Cruse G, Metcalfe DD, Olivera A. Functional deregulation of KIT: Link to mast cell proliferative diseases and other neoplasms. *Immunol Allergy Clin North Am* 2014. https://doi.org/10.1016/j.iac.2014.01.002.
32. Kristensen T, Vestergaard H, Moller MB. Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. J Mol Diagn. 2011;13(2):180–8. https://doi.org/10.1016/j.jmoldx.2010.10.004.
33. Orfao A, Garcia-Montero AC, Sanchez L, Escribano L. Recent advances in the understanding of mastocytosis: the role of KIT mutations. Br J Haematol. 2007. https://doi.org/10.1111/j.1365-2141.2007.06619.x.
34. Arock M, Sotlar K, Akin C, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia. 2015. https://doi.org/10.1038/leu.2015.24.
35. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. Allergy. 2008;63(2):226–32. https://doi.org/10.1111/j.1398-9995.2007.01569.x.
36. Gonzalez de Olano D, de la Hoz Caballer B, Nunez Lopez R, et al. Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish network on mastocytosis (REMA). Clin Exp Allergy 2007;37(10):1547–1555. https://doi.org/10.1111/j.1365-2222.2007.02804.x.
37. Gulen T, Hagglund H, Dahlen B, Nilsson G. High prevalence of anaphylaxis in patients with systemic mastocytosis - a single-centre experience. Clin Exp Allergy. 2014;44(1):121–9. https://doi.org/10.1111/cea.12225.
38. Nwaru BI, Dhami S, Sheikh A. Idiopathic anaphylaxis. Curr Treat options allergy. 2017;4(3):312–9. https://doi.org/10.1007/s40521-017-0136-2.
39. Ahanchian H, Behmanesh F, Azad FJ, et al. A survey of anaphylaxis etiology and treatment. Med Gas Res. 2018;8(4):129–34. https://doi.org/10.4103/2045-9912.248262.
40.• Akin C, Scott LM, Kocabas CN, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "idiopathic" anaphylaxis. Blood. 2007;110(7):2331–3. https://doi.org/10.1182/blood-2006-06-028100 **First demonstration of clonal mast cell disease with KIT mutations in patients formerly diagnosed with idiopathic anaphylaxis.**
41. Carter MC, Desai A, Komarow HD, et al. A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. J Allergy Clin Immunol. 2018;141(1):180–188.e3. https://doi.org/10.1016/j.jaci.2017.05.036.
42. Niedoszytko M, De Monchy J, Van Doormaal JJ, Jassem E, Oude Elberink JNG. Mastocytosis and insect venom allergy: diagnosis, safety and efficacy of venom immunotherapy. Allergy Eur J Allergy Clin Immunol. 2009. https://doi.org/10.1111/j.1398-9995.2009.02118.x.
43. Haeberli G, Brönnimann M, Hunziker T, Müller U. Elevated basal serum tryptase and hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. Clin Exp Allergy. 2003. https://doi.org/10.1046/j.1365-2222.2003.01755.x.
44. Ruëff F, Przybilla B, Biló MB, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase-a study of the European Academy of Allergology and Clinical Immunology Interest Group

on Insect Venom Hypersensitivity. J Allergy Clin Immunol. 2009. https://doi.org/10.1016/j.jaci.2009.08.027.

45. Bonadonna P, Perbellini O, Passalacqua G, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. J Allergy Clin Immunol. 2009. https://doi.org/10.1016/j.jaci.2008.11.018.
46. Stoevesandt J, Hain J, Kerstan A, Trautmann A. Over- and underestimated parameters in severe Hymenoptera venom-induced anaphylaxis: cardiovascular medication and absence of urticaria/angioedema. J Allergy Clin Immunol. 2012. https://doi.org/10.1016/j.jaci.2012.03.024.
47.• Alvarez-Twose I, Gonzalez de Olano D, Sanchez-Munoz L, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. J Allergy Clin Immunol 2010;125(6):1269–1278.e2. https://doi.org/10.1016/j.jaci.2010.02.019**. Guidance on when to suspect clonal mast cell disease in anaphylaxis.**
48. Haeberli G, Bronnimann M, Hunziker T, Muller U. Elevated basal serum tryptase and hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. Clin Exp Allergy. 2003;33(9):1216–20.
49. Bonadonna P, Zanotti R, Caruso B, et al. Allergen specific immunotherapy is safe and effective in patients with systemic mastocytosis and Hymenoptera allergy. J Allergy Clin Immunol. 2008;121(1):256–7. https://doi.org/10.1016/j.jaci.2007.10.014.
50. Bonadonna P, Gonzalez-de-Olano D, Zanotti R, et al. Venom immunotherapy in patients with clonal mast cell disorders: efficacy, safety, and practical considerations. J Allergy Clin Immunol Pract. 2013;1(5):474–8. https://doi.org/10.1016/j.jaip.2013.06.014.
51. Sokol KC, Ghazi A, Kelly BC, Grant JA. Omalizumab as a desensitizing agent and treatment in mastocytosis: a review of the literature and case report. J Allergy Clin Immunol Pract. 2014;2(3):266–70. https://doi.org/10.1016/j.jaip.2014.03.009.
52. da Silva EN, Randall KL. Omalizumab mitigates anaphylaxis during ultrarush honey bee venom immunotherapy in monoclonal mast cell activation syndrome. J Allergy Clin Immunol Pract. 2013;1(6):687–8. https://doi.org/10.1016/j.jaip.2013.07.004.
53. Bonadonna P, Zanotti R, Pagani M, et al. How much specific is the association between hymenoptera venom allergy and mastocytosis? Allergy. 2009;64(9):1379–82. https://doi.org/10.1111/j.1398-9995.2009.02108.x.
54. Guyer AC, Saff RR, Conroy M, et al. Comprehensive allergy evaluation is useful in the subsequent care of patients with drug hypersensitivity reactions during anesthesia. J Allergy Clin Immunol Pract. 2015. https://doi.org/10.1016/j.jaip.2014.11.011.
55.• Carter MC, Metcalfe DD, Matito A, et al. Adverse reactions to drugs and biologics in patients with clonal mast cell disorders: a Work Group Report of the Mast Cells Disorder Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2019; **Provides an excellent summary of adverse drug reactions in patients with mastocytosis.**
56. Marone G, Stellato C. Activation of human mast cells and basophils by general anaesthetic drugs. Monogr Allergy. 1992;30:54–73.
57. Genovese A, Stellato C, Marsella CV, Adt M, Marone G. Role of mast cells, basophils and their mediators in adverse reactions to general anesthetics and radiocontrast media. Int Arch Allergy Immunol. 1996;110(1):13–22. https://doi.org/10.1159/000237305.
58. Dewachter P, Castells MC, Hepner DL, Mouton-Faivre C. Perioperative management of patients with mastocytosis. Anesthesiology. 2014;120(3):753–9. https://doi.org/10.1097/ALN.0000000000000031.
59. Carter MC, Metcalfe DD, Matito A, et al. Adverse reactions to drugs and biologics in patients with clonal mast cell disorders: a Work Group Report of the Mast Cells Disorder Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. December 2018. https://doi.org/10.1016/j.jaci.2018.10.063.
60. Bridgman DE, Clarke R, Sadleir PHM, Stedmon JJ, Platt P. Systemic mastocytosis presenting as intraoperative anaphylaxis with atypical features: a report of two cases. Anaesth Intensive Care. 2013;41(1):116–21.
61. Matito A, Morgado JM, Sanchez-Lopez P, et al. Management of anesthesia in adult and pediatric mastocytosis: a study of the Spanish network on mastocytosis (REMA) based on 726 anesthetic procedures. Int Arch Allergy Immunol. 2015;167(1):47–56. https://doi.org/10.1159/000436969.
62. Vaughan ST, Jones GN. Systemic mastocytosis presenting as profound cardiovascular collapse during anaesthesia. Anaesthesia. 1998;53(8):804–7.
63. Ten Hagen A, Doldersum P, van Raaij T. Anaphylactic shock during cement implantation of a total hip arthroplasty in a patient with underlying mastocytosis: case report of a rare intraoperative complication. Patient Saf Surg. 2016;10:25. https://doi.org/10.1186/s13037-016-0113-x.
64. Ishii K, Miyoshi H, Akiyama D, et al. Anesthetic management of patients with systemic mastocytosis. J Clin Anesth. 2018;50:61. https://doi.org/10.1016/j.jclinane.2018.06.047.
65. Hermans MAW, Arends NJT, Gerth van Wijk R, et al. Management around invasive procedures in mastocytosis: an update. *Ann Allergy Asthma Immunol* 2017;119(4):304–309. https://doi.org/10.1016/j.anai.2017.07.022.
66. Prieto-Garcia A, Alvarez-Perea A, Matito A, et al. Systemic mastocytosis presenting as IgE-mediated food-induced anaphylaxis: a report of two cases. J Allergy Clin Immunol Pract. 2015;3(3):456–8. https://doi.org/10.1016/j.jaip.2015.01.011.
67. Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol. 2009;123(2):426–33. https://doi.org/10.1016/j.jaci.2008.10.052.
68. Commins SP, James HR, Kelly LA, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. J Allergy Clin Immunol. 2011;127(5):1286–93.e6. https://doi.org/10.1016/j.jaci.2011.02.019.
69. Roenneberg S, Böhner A, Brockow K, et al. α-Gal-a new clue for anaphylaxis in mastocytosis. J Allergy Clin Immunol Pract. 2016. https://doi.org/10.1016/j.jaip.2015.11.027.
70. Carter MC, Ruiz-Esteves KN, Workman L, Lieberman P, Platts-Mills TAE, Metcalfe DD. Identification of alpha-gal sensitivity in patients with a diagnosis of idiopathic anaphylaxis. Allergy Eur J Allergy Clin Immunol. 2018. https://doi.org/10.1111/all.13366.
71. van Nunen S. Tick-induced allergies: mammalian meat allergy, tick anaphylaxis and their significance. Asia Pac Allergy. 2015;5(1):3–16. https://doi.org/10.5415/apallergy.2015.5.1.3.
72. Romano A, Di Fonso M, Giuffreda F, et al. Food-dependent exercise-induced anaphylaxis: clinical and laboratory findings in 54 subjects. Int Arch Allergy Immunol. 2001;125(3):264–72. https://doi.org/10.1159/000053825.
73. Hanakawa Y, Tohyama M, Shirakata Y, Murakami S, Hashimoto K. Food-dependent exercise-induced anaphylaxis: a case related to the amount of food allergen ingested. Br J Dermatol. 1998;138(5):898–900.
74. Alfaya Arias T, Soriano Gomis V, Soto Mera T, et al. Key issues in Hymenoptera venom allergy: an update. J Investig Allergol Clin Immunol. 2017;27(1):19–31. https://doi.org/10.18176/jiaci.0123.
75. Alvarez-Twose I, González-De-Olano D, Sánchez-Munoz L, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. Int Arch Allergy Immunol. 2012. https://doi.org/10.1159/000329856.

76. Alvarez-Twose I, Gonzalez-de-Olano D, Sanchez-Munoz L, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. Int Arch Allergy Immunol. 2012;157(3):275–80. https://doi.org/10.1159/000329856.
77. Castells M. Diagnosis and management of anaphylaxis in precision medicine. J Allergy Clin Immunol. 2017;140(2):321–33. https://doi.org/10.1016/j.jaci.2017.06.012.
78. Mullol J, Bousquet J, Bachert C, et al. Update on rupatadine in the management of allergic disorders. Allergy. 2015;(70 Suppl):1:1–24. https://doi.org/10.1111/all.12531.
79. Kettelhut BV, Berkebile C, Bradley D, Metcalfe DD. A double-blind, placebo-controlled, crossover trial of ketotifen versus hydroxyzine in the treatment of pediatric mastocytosis. J Allergy Clin Immunol. 1989;83(5):866–70.
80. Escribano L, Akin C, Castells M, Schwartz LB. Current options in the treatment of mast cell mediator-related symptoms in mastocytosis. Inflamm Allergy Drug Targets. 2006;5(1):61–77.
81. Turner PJ, Kemp AS, Rogers M, Mehr S. Refractory symptoms successfully treated with leukotriene inhibition in a child with systemic mastocytosis. Pediatr Dermatol. 2012;29(2):222–3. https://doi.org/10.1111/j.1525-1470.2011.01576.x.
82. Tolar J, Tope WD, Neglia JP. Leukotriene-receptor inhibition for the treatment of systemic mastocytosis. N Engl J Med. 2004;350(7):735–6. https://doi.org/10.1056/NEJM200402123500723.
83. Barete S, Lortholary O, Damaj G, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood. 2015;126(8):1009–1016; quiz 1050. https://doi.org/10.1182/blood-2014-12-614743.
84. Ustun C, Gotlib J, Popat U, et al. Consensus opinion on allogeneic hematopoietic cell transplantation in advanced systemic mastocytosis. Biol Blood Marrow Transplant. 2016. https://doi.org/10.1016/j.bbmt.2016.04.018.
85. Kasamon YL, Ko C-W, Subramaniam S, et al. FDA approval summary: midostaurin for the treatment of advanced systemic mastocytosis. Oncologist. 2018;23(12):1511–9. https://doi.org/10.1634/theoncologist.2018-0222.
86.•• Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374(26):2530–2541. https://doi.org/10.1056/NEJMoa1513098. **Multicenter study of multitargeted tyrosine kinase inhibitor midostaurin in advanced mastocytosis, which led to FDA approval of the drug for advanced mastocytosis.**
87. DeAngelo DJ, George TI, Linder A, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. Leukemia. 2018;32(2):470–8. https://doi.org/10.1038/leu.2017.234.
88. van Anrooij B, Oude Elberink JNG, Span LFR, et al. Midostaurin in patients with indolent systemic mastocytosis: an open-label phase 2 trial. J Allergy Clin Immunol. 2018;142(3):1006–1008.e7. https://doi.org/10.1016/j.jaci.2018.06.003.
89. Evans E, Gardino A, Hodous B, et al. Blu-285, a potent and selective inhibitor for hematologic malignancies with KIT exon 17 mutations. Blood. 2015.
90. Drummond MW, DeAngelo DJ, Deininger MW, et al. Preliminary safety and clinical activity in a phase 1 study of Blu- 285, a potent, highly-selective inhibitor of KIT D816V in advanced systemic mastocytosis (SM). Blood Conf 58th Annu Meet Am Soc Hematol ASH 2016 United States Conf start 20161203 Conf end 20161206. 2016.
91. Hinojosa T, Lewis DJ, Vangipuram R, et al. The efficacy of omalizumab in cutaneous mastocytosis: a case series. *Dermatol Ther*. January 2019:e12848. https://doi.org/10.1111/dth.12848.
92. Peterson MR, Coop CA. Long-term omalizumab use in the treatment of exercise-induced anaphylaxis. Allergy Rhinol (Providence). 2017;8(3):170–2. https://doi.org/10.2500/ar.2017.8.0204.
93.•• Broesby-Olsen S, Vestergaard H, Mortz CG, et al. Omalizumab prevents anaphylaxis and improves symptoms in systemic mastocytosis: efficacy and safety observations. Allergy. 2018;73(1):230–8. https://doi.org/10.1111/all.13237 **Showed omalizumab effectivley decreased episodes of anaphylaxis and improved symptoms in patients with SM.**