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Non-Clonal Mast Cell Activation: A Growing Body of Evidence

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SYNOPSIS

Patients who present with typical features of mast cell activation with laboratory confirmation and without evidence of a clonal mast cell disorder or other medical condition should be initiated on medical treatment to block mast cells and their mediators. If a major response is achieved, a diagnosis of non-clonal mast cell activation syndrome (NC-MCAS) is likely and treatment should be optimized including management of any associated conditions. In this review, the latest evidence with regards to the diagnosis and treatment of NC-MCAS is presented.

Keywords

mast cell activation syndrome; tryptase; histamine; prostaglandin; mastocytosis; mast cell; flushing

Introduction

Over the last decade, recognition of a unique syndrome has emerged in clinical practices and in the literature. These patients present with a unique constellation of signs and symptoms suggesting primary mast cell activation such as systemic mastocytosis (SM) but without fulfilling the established criteria (**see** Figure 1). Furthermore, these patients do not have primary allergic disorders to better explain their presentation such as IgE-mediated allergy, chronic idiopathic urticaria, or idiopathic anaphylaxis (examples of secondary mast cell activation). Other medical inflammatory conditions, auto-immune diseases, malignant processes, and infections have been ruled out. Although objective markers for this disorder are lacking at this time, patients are diagnosed with idiopathic mast cell activation syndrome and have greatly benefitted from specific treatments that work to block the mast cell mediators. In this review, the diagnosis and treatment of non-clonal idiopathic mast cell activation syndrome (NC-MCAS) will be discussed.

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Background and Proposed Mechanisms

The mast cell is a complex immune cell that in its mature form resides in the tissues that interact with the external environment such as the air passageway, skin, and gastrointestinal tract. While best known for its central role in allergy, anaphylaxis, and asthma, mast cells primarily function in host defense to bacteria, parasites, and viruses (reviewed in (1). While a full explanation for the mechanisms that drive activation of mast cells is beyond the scope of this review, it is important to highlight the diversity of receptors and mediators that mast cells may release that characterize the diverse aspects of mast cell activation. Although mast cells exhibit plasticity in development and in response to various stimuli, they generally express the high affinity IgE receptor and low affinity IgG receptor, receptors for complement, proteinase-activating receptors, and pathogen-specific receptors such as toll-like receptors. Upon activation, mast cells release a variety of “pre-formed” mediators housed in the cytosol granules including proteases (tryptase, chymase), histamine, newly generated lipid mediators including prostaglandins and leukotrienes, and more than 30 cytokines and chemokines that may be synthesized and released (reviewed in (2)). These mediators that are released either in total (e.g. anaphylaxis) or piecemeal (3), carry out a wide array of pathophysiologic functions including dilation of blood vessels, stimulatory and inhibitory interactions with nerves, physiologic shifts in electrolytes and fluids, and serving as a chemoattractant for other immune cells (e.g. neutrophils).

The pathologic hallmark of NC-MCAS is inappropriate activation of mast cells to stimuli that otherwise would be tolerated if not in the activated or reactive state. This may occur due to altered threshold for activation, aberrant expression of receptors and mediators shifted towards an allergic immune response, or changes in the tissue environment that affect the expression and function of the mediators (4). There may also exist defects or changes in downstream signaling pathways for mast cell activation (reviewed in (5)). The genetic basis for NC-MCAS is not well understood but a team of investigators has identified many mutations in the KIT receptor (responsible for proliferation and retention of mast cells in the tissues) and alternative splicing variants in the CD117+ peripheral blood cells of patients with NC-MCAS (6).

Clinical Features

It has become apparent that there is a typical constellation of signs and symptoms of mast cell activation that suggest NC-MCAS and then a smattering of other features that may be more unique to an individual. Many of these classical symptoms have been long appreciated in patients with SM. These are necessary for the diagnosis (**see** Box 1) and include signs and symptoms involving the skin (flushing, pruritis, urticaria, sweating, localized swelling), the air passageway and lungs (rhinitis, throat tightness, wheezing, dyspnea), the gastrointestinal tract (intermittent abdominal pain and cramping, loose stools and diarrhea, abdominal bloating, nausea, reflux), the neurologic system (headaches, difficulty with concentration and memory (“brain fog”), tingling in the extremities), and the cardiovascular system (palpitations, fast heart rate, pre-syncope, hypotension, and syncope). More atypical signs and symptoms may exist in any other organ system such as various aches and pains, however patients and providers should hesitate to attribute all of their symptoms to mast cell

activation-especially when they are not relieved with medications that block the mast cell mediators or that occur in isolation of the other symptoms.

Although triggers for mast ell activation in an individual with NC-MCAS may be numerous particularly when in an activated state, there are a set of triggers commonly experienced in these patients. In a cross-sectional survey filled out by patients with mast cell disorders including those with SM, cutaneous mastocytosis, and NC-MCAS, heat was the most common trigger reported in 82%, followed by stress (81%), exercise (63%), alcohol (54%), medications (53%), and odors (48%) (7).

Several recent studies have attempted to identify clinical characteristics of patients with presumed NC-MCAS. In a population of 83 patients who presented to an Allergy clinic for further evaluation of “severe and systemic” mast cell activation symptoms, 39% did not have evidence for a clonal mast cell population on bone marrow biopsy and were labeled NC-MCAS (8). The authors in this study aimed to compare the clinical, biological, and molecular characteristics of this identified population with NC-MCAS compared with the patients diagnosed with a primary clonal form of mast cell disorder. When compared to the clonal mast cell disorder groups, the patients with NC-MCAS had significantly more urticaria and angioedema, were more often female, and were triggered more by drugs. In addition, the NC-MCAS patients were triggered less by insect stings, and had less pre-syncope and syncope. In keeping with the diagnostic criteria, patients with NC-MCAS also had lower tryptase levels, and no evidence of clonal mast cells as assessed by serum KIT mutations and presence of CD25 on bone marrow examination.

The clinical manifestations of a cohort of patients referred to a center with expertise in mast cell disorders and diagnosed with NC-MCAS (classic symptoms and signs of mast cell activation, an elevated mast cell mediator on laboratory testing, positive response to anti-mast cell mediator therapy, and without other medical conditions to explain the symptoms) were evaluated. In this select group of 18 patients, gastrointestinal symptoms were prominent with abdominal pain and diarrhea present in 17 (94%) and 12 (67%) of patients respectively. The skin manifestations of flushing and dermatographism were each present in 16 (89%) of patients while headache and poor concentration and memory were observed in 15 (83%) and 12% (67%).

The reported signs and symptoms of mast cell activation in NC-MCAS are remarkably similar to published cohorts of patients with SM ((9–12) and reviewed in (13)).

In the published cohort studies of NC-MCAS, there is a female predominance with peak age of diagnosis in the fifth and sixth decades although many of the patients had experienced signs and symptoms for many years prior to diagnosis (14). The vast majority of patients diagnosed with NC-MCAS are Caucasian but there is little published about the incidence in non-North American and European populations. The overall prevalence of NC-MCAS is unknown but is thought to be perhaps 10-fold higher than SM by many experts studying this disorder.

Diagnostic Guidelines

Although no consensus diagnostic criteria exist for NC-MCAS, proposed diagnostic criteria have been published (15; 16) and then discussed at a working conference of experts in 2012 (17). Important to the panel set of guidelines is the "accepted, objective, easily measureable, and commonly applicable parameters and criteria". By these guidelines and in order to satisfy the criteria, "typical" symptoms (as described above) must be present and intermittent or persistent and involving two or more organ systems. The objective piece for the diagnosis is a documented increase in easily and reproducibly measureable mediators over baseline during a period of increased symptoms attributable to mast cell activation. The preferred mediator is the mast cell specific serum tryptase and other acceptable mediators include 24 hour urine tests for metabolites to histamine and prostaglandin D2 (see diagnostic testing below). The third criterion is a major response (>50% reduction) in mast cell activation symptoms with medications that block the production or activity of mast cell mediators. It is noted that the medications used to treat mast cell activation may have actions on other cell types and factors so that medication response is only considered supportive to the diagnosis.

Important to the criteria port forth by Akin, Valent, and Metcalfe is the fourth criterion which is to rule out other causes of mast cell activation and those medical conditions that may present with overlapping signs and symptoms. There are two primary causes of mast cell activation that must be considered and ruled out before diagnosing a patient with NC-MCAS. One is SM, a proliferative mast cell disorder characterized by specific clonal mutations most often in the KIT gene (e.g. D816V) and defined by a set of criteria including one major and four minor criteria (18). The other is monoclonal mast cell activation syndrome where there are clonal populations of mast cells but without abnormal proliferation or clustering of mast cells, overall satisfying 1 or 2 minor and no major criteria for SM (19). Medical conditions that may be associated with evidence of secondary mast cell activation include atopic disease and allergy mediated by IgE, autoimmune disorders and autoimmune urticaria, neoplasms, drug allergies, chronic infections, and chronic inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease.

Although no sub-classifications of NC-MCAS currently exist, one possible sub-group of patients has been recently described who have elevated serum levels of alpha tryptase due to duplications and triplications in the specific tryptase gene (20). They exhibit many clinical features of NC-MCAS and this specific disorder is inherited with variable penetrance.

Diagnostic Testing

As mentioned, laboratory testing can help confirm the diagnosis of NC-MCAS. Detection of serum tryptase is an important screening tool in the evaluation of a patient with a suspected mast cell disorder and is a highly reliable and reproducible test. Mast cells in the tissue produce and constitutively release the alpha form of tryptase which can be detected by a commercial fluoro-immune enzyme assay. A specialized assay can detect the beta form of tryptase that is released from the granules upon anaphylaxis or certain types of mast cell activation (21). The median baseline alpha tryptase level for heathy human subjects is

approximately 5 ng/mL and most laboratories consider a level <11.4 ng/mL to be normal (22). A level >20 ng/mL is a minor criterion for the diagnosis of SM (18) and a baseline level >11.4 and <20 ng/mL is suggestive of a diagnosis of NC-MCAS. Elevation of serum tryptase is detected during or within four hours of a reaction (reviewed in (23)) and the expert panel on the diagnostic criteria of NC-MCAS agreed that a 20% +2 ng/mL increase from the baseline level constitutes mast cell activation (17). It is important to note that false positive elevations in serum tryptase may exist including chronic end stage kidney disease, and certain hematologic malignancies (reviewed in (24)).

Histamine metabolites in a 24 hour urine specimen (n'methyl histamine) is also a reliable marker of mast cell activation in certain patients albeit less specific than mast cell tryptase given that basophils also produce and release histamine. The third suggested laboratory test to confirm mast cell activation is prostaglandin D2 or its metabolite 11-beta prostaglandin F2-alpha in a 24 hour urine specimen.

In a study that showed the utility of the measurement of metabolites for histamine and prostaglandin to detect mast cell activation using urine assays, the authors found differences between a group of chronic urticaria patients with hypersensitivity to aspirin and food additives who were challenged compared with a group that was not sensitive to aspirin and food additives who were challenged (25).

Other laboratory assessments that have been used in MCAS include Chromogranin A, a member of the granin family of neuroendocrine secretory proteins. This test is not specific to mast cells and may be affected by cardiac and renal failure and medications namely proton pump inhibitors. Plasma heparin may be a strong marker of mast cell activation and was positive more often than the traditional markers mentioned above in a study of 257 MCAS and SM patients (26) but current clinical assays are not sensitive enough to detect the low levels that may be released. A urine test for the detection of leukotriene E4 is being developed which could also serve as a helpful diagnostic tool to detect mast cell activation (27).

The assessment of tissue biopsies is an important part of the diagnostic work up of patients with NC-MCAS, mainly to rule out other primary causes of mast cell activation and medical conditions such as inflammatory disorders and malignancies. Criteria have been established for the indications to perform a bone marrow biopsy on patients suspected of having a clonal mast cell disorder and these include individually or a combination of the following: presence of urticaria pigmentosa skin lesions, tryptase >15 ng/mL, unexplained anaphylaxis, REMA score >2 (28), and presence of typical mast cell symptoms. In the absence of any of these factors, the diagnostic yield of biopsies for clonal mast cells in the bone marrow or other organs is thought to be low. In the intestine, patients with NC-MCAS have normal findings at endoscopy and the mast cells on histology are single and dispersed and found in similar numbers compared with a healthy control population (14). In a study that compared 100 patients with IBS with 100 healthy controls and 10 patients with MCAS, there was no clinically meaningful difference in the numbers of mast cells in the intestinal mucosa between any of the groups. Future studies may help to determine whether there are subtypes of NC-MCAS which may indeed have significantly elevated mast cells as 30% of the NC-

MCAS patients had “increased mast cells “ (>25 per hpf) compared with 16% of controls (29).

A highly sensitive and specific, non-invasive screening test for primary clonal mast cell disorders is a peripheral blood test to detect the KIT D816V mutation (30). A positive result for this test when a clonal mast cell disorder is strongly suspected is a minor diagnostic criterion for SM (18).

Associated Conditions

Although not well reported in the literature, it is becoming apparent that there are certain conditions that present in association with NC-MCAS. What is not known is how or why these associations occur and how mast cell activation may or may not specifically play a role. One such condition is the postural orthostatic tachycardia syndrome (POTS). In a small study, patients with POTS and mast cell activation defined as elevated histamine levels and presence of flushing, had more adrenergic features of POTS compared to POTS subjects without mast cell activation and healthy controls (31). These included orthostatic tachycardia and elevated blood pressure in the upright position. Another condition that is frequently present in association with NC-MCAS is the connective tissue disorder Ehlers-Danlos syndrome (EDS), particularly the hypermobility subtype. In the cohort of patients with symptoms attributable to mast cell activation and inherited duplications of the tryptase gene leading to alpha hypertryptasemia, there was an associated prevalence of POTS and joint hypermobility (20).

In the current proposed guidelines for NC-MCAS, patients with anaphylaxis are best characterized as idiopathic anaphylaxis although there may be a spectrum of the disorders where some patients have prominent MCAS manifestations in between anaphylactic episodes and may be better characterized as NC-MCAS with anaphylaxis (reviewed in (32)).

Not surprisingly, allergic disorders and specific IgE-mediated allergies to environmental factors and foods are prominent in NC-MAS patients and should be weighed in the context of the presenting manifestations to decide whether secondary mast cell activation due to allergy is the more appropriate diagnosis. Furthermore, the presence of NC-MCAS may increase the severity of allergic reactions as was shown in a cohort of patients with NC-MCAS and allergy to amoxicillin (33).

Patients with NC-MCAS have numerous non-IgE mediated intolerances to foods and drugs that provoke various symptoms. A possible mechanism for the idiosyncratic, non-IgE mediated reactions to drugs was recently identified. Investigators showed that many basic secretagogues such as inflammatory peptides and drugs can activate the mast cell surface receptor Mrgprb2 that is the orthologue of the G-coupled receptor MRGPRX2 (34).

Treatment Options

The successful treatment of patients with NC-MCAS requires a multi-modal approach to address the multitude of triggers, reactions, and intermittent and chronic symptoms (**see** Box 2). It is possible that patients with NC-MCAS experience heightened reactivity states that

increase with each individual reaction, a state that may be highest around the time of diagnosis. Therefore, a key arm of treatment is an understanding of the triggers for each individual followed by strict avoidance. Unfortunately, there is no clinically validated test for the non-IgE mediated reactions that patients with NC-MCAS may experience. While there are a host of “classical” triggers (outlined above), an individual may experience unique triggers that are only identified after an exposure and subsequent reaction.

The next step in treatment management is the initiation and titration of medications that target mast cells and their mediators in order to break the cycle of reactivity. In general, a combination of medications are used in a step-wise approach and adjusted to maximal efficacy, tolerance, and safety for each individual. Due to the reactivity of NC-MCAS patients, it is advised to start with low doses of each new medication and titrate to the recommended daily maintenance doses. It is also important to note that in the United States there are no medications that are approved by the Food and Drug Administration for the treatment of NC-MCAS so the below recommendations are considered “off-label use”.

The first line medication is often the combination of non-sedating H1 antihistamines (e.g. cetirizine, loratidine, and fexofenadine) and H2 antihistamines (e.g. ranitidine and famotidine). The anti-vasodilatory effects of type one and two antihistamines may work best when used in combination. Their dosages are adjusted to the minimum effective amount so as to prevent tachyphylaxis and side effects such as sedation and dry mouth. It is important for NC-MCAS patients to have on demand treatment for significant reactions and could include short-acting H1 blockers such as a sublingual form of loratidine or traditional diphenhydramine.

While the H1 type of anti-histamines are considered first line agents in most published guidelines, there is little published evidence of efficacy; most trials were conducted several decades ago with small numbers of SM patients (reviewed in (35)). In a more recent trial, investigators enrolled 33 patients with systemic and cutaneous mastocytosis to receive the second generation-H1 antihistamine rupatadine versus placebo. They found significant improvements in itching, flushing, skin reactivity, headache, and tachycardia. Quality of life was also improved (36).

A key maintenance medication most often used in combination with antihistamines is cromolyn sodium. Although the exact mechanisms of action of this drug are not fully known, one study showed that cromolyn acts as an agonist for the G-protein-coupled 35 receptor expressed in human mast cells and alters calcium flux, a process thought to be necessary for the release of the cytosolic granule mediators once the mast cell is activated (37). This medication has been used with good effect to treat the gastrointestinal manifestations of SM including abdominal pain and cramping, loose stools and diarrhea, abdominal bloating, and nausea (38). A more recent study was designed to evaluate the ability of cromolyn to treat patients with diarrhea-predominant irritable bowel syndrome, a functional disorder of the gut with a similar intestinal symptom profile as mastocytosis and where mast cell activation is known to play a role (39–41). The authors determined that cromolyn reduced gastrointestinal symptoms and markers of mast cell activation such as luminal tryptase and ultrastructure changes showing degranulation of mast cells. Although

cromolyn is thought to have poor intestinal absorption, patients may report improvement in symptoms outside of the gastrointestinal tract and it may be considered to be a first line therapy. A case report details the added symptom benefit of inhaled cromolyn for symptoms attributed to mast cell activation (42).

Another medication that has been used for the treatment of anaphylaxis and extended to the treatment of NC-MCAS is ketotifen which is thought to have both antihistamine and mast cell-stabilizing properties. In a study to assess the effect of treatment with ketotifen on patients with IBS characterized by increased visceral hypersensitivity in the rectum, patients with IBS had improvement in the hypersensitivity as well as other symptoms of IBS and quality of life. The authors in this study however did not detect changes in the release of histamine or tryptase in the rectal biopsies so the exact mechanism of action of ketotifen was not determined (43). In one small blinded, placebo-controlled study comparing treatment with ketotifen with hydroxyzine over 12 weeks in patients with pediatric mastocytosis and mediator-related symptoms, seven of eight patients had greater reduction in symptoms with hydroxyzine (44).

If symptoms persist, other medications may be added in a step-wise approach. The cysteinyl leukotriene receptor blockers (e.g. montelukast) and 5-lipoxygenase inhibitors (e.g. zileutin) may be especially effective for pulmonary and airway symptoms in keeping with their primary indication in asthma.

Aspirin has been proposed as a treatment for NC-MCAS patients with elevated urine prostaglandin metabolites. In a small case series, baseline levels of prostaglandin were restored to normal and symptoms were prevented (45). To achieve therapeutic targets, high doses of aspirin were needed (325mg to 650mg daily but as high as 1950mg in one patient) which may limit their use due to bleeding risk and gastrointestinal toxicity. In another study of MC-MCAS patients at the Mayo Clinic, 9 patients with elevated prostaglandin levels were treated with aspirin therapy and 8 had normalization of urine prostaglandin levels and 6 out of 9 experienced symptom improvement (flushing and pruritis were the most common symptoms in this subset) (46).

Corticosteroids are given for refractory cases but ideally in short effective courses so as to limit steroid side effects. They may be used in the acute setting for severe reactions and before diagnostic studies or procedures where severe reactions are anticipated. All patients with NC-MCAS should be asked about episodes of anaphylaxis and prescribed injectable epinephrine if there is any suspicion. This is a potentially life-saving treatment.

Flavonoids including quercetin are compounds with anti-oxidant and anti-inflammatory properties that have been shown to inhibit the release of cytokines and proteases from cultured human mast cells (47). In a publication comparing the use of the flavonoid quercetin with cromolyn, quercetin more effectively blocked inflammatory cytokine release and reduced symptoms of contact dermatitis and photosensitivity in small, pilot, non-blinded clinical trial (48).

Lastly, omalizumab, a monoclonal antibody to IgE that may increase the threshold for mast cell mediator release, has had efficacy in refractory cases of patients presenting with mast

cell activation. In a small, non-blinded observational study of patients with SM, treatment with omalizumab resulted in a complete or major reduction in the physician global assessment of symptoms in over half of the patients. Treatment efficacy was best with skin manifestations and episodes of anaphylaxis at the various time points with a median duration of follow up of 17 months (49). While the experience with omalizumab for the treatment of NC-MCAS is less studied and published, there are reports of treatment success for this patient population (50).

There is very limited published data on response to medical therapies for NC-MCAS. In a non-blinded and non-placebo controlled trial using standardized treatment response criteria established for SM (14), 12 of 18 patients with NC-MCAS had a complete or major (>50%) regression in symptoms after 12 months of standard anti-mast cell medical therapy. There were no patients who had no regression in symptoms.

Other Treatments

Specific dietary interventions for the treatment of symptoms have not been studied in patients with mast cell disorders. In practice, the single most important dietary recommendation is to avoid known triggers. Other recommendations may include avoiding foods known to be high in histamine content and poorly tolerated, processed and preserved foods, inflammatory foods such as sugars and foods high in omega-6 fatty acid content, and alcohol. Several dietary factors that have been shown to suppress mast cell activation include vitamin C (reviewed in (51)) and curcumin (52). Gluten has been shown to stimulate mast cell activation (53) and many patients with NC-MCAS report improvement in symptoms with gluten avoidance.

Numerous studies have examined the relationship between depression, anxiety, and psychological stress with mast cell activation and mast cell disorders (reviewed in (54; 55)). To round out the treatment of patients with NC-MCAS, medical and behavioral therapy should be directed at the co-existing psychiatric symptoms. Patients are encouraged to pursue activities for stress reduction such as yoga, meditation, and exercise.

Conclusions and Future Perspectives

In this review, the characteristic clinical presentation of patients with NC-MCAS has been highlighted and that includes atypical features that may characterize an individual’s symptom profile. The greatest challenge for the treating provider is to correctly attribute signs and symptoms to the disorder and to appropriately work up any other features that may not fit or may overlap with other diseases. As emphasized in this review, objective markers for the disorder are lacking and every effort must be made to obtain confirmatory laboratory evidence and to rule out other conditions with appropriate testing. If the diagnosis is suspected and other more likely conditions have been ruled out, directed medical therapies targeting mast cell mediators can not only help to confirm the diagnosis but can provide relief to the significant burden of illness.

The development of objective markers of disease may lead to a diagnostic test or tests and established guidelines for treatment that may easily be followed by the wide array of

providers seeing these patients. Once established, clinical studies and clinical trials will be possible to build on the foundation of our current understanding of the disorder and its treatment. Drug discovery may also be advanced to include curative therapies that “reset” the hyperactive and inappropriate immune response. While there is a lot of work to be done, these future developments are obtainable, and begin with increased awareness among the medical and scientific research communities of the many complex features of NC-MCAS.

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KEY POINTS

1. Patients who present with typical features of mast cell activation with laboratory confirmation and without evidence of a clonal mast cell disorder or other medical condition should be initiated on medical treatment to block mast cells and their mediators.
2. If a major response is achieved, a diagnosis of non-clonal mast cell activation syndrome (NC-MCAS) is likely and treatment should be optimized including management of any associated conditions.
3. In this review, the latest evidence with regards to the diagnosis and treatment of NC-MCAS is presented.

Box 1

Typical Presenting Features of NC-MCAS

Typical Mast Cell Activation Symptoms

Skin-flushing, pruritis, sweating, urticaria

Air passageway- rhinitis, throat itching and swelling, dyspnea, wheeze

Gastrointestinal- abdominal pain, diarrhea, nausea, bloating

Cardiac- palpitations, tachycardia, pre-syncope

Neurologic- headache, paraesethesias, memory and concentration difficulties

Typical Mast Cell Activation Signs

Skin- dermatographism, flushing (face and chest)

Gastrointestinal- bloat, abdominal tenderness

Cardiac- tachycardia

Typical Mast Cell Activation Triggers

Heat and temperatures changes

Stress

Alcohol

Certain drugs- morphine, NSAIDs, antibiotics

Strong odors- perfumes, smoke, cleaning agents

Typical Demographics

Female

Age- 5^{th} and 6^{th} Decade

Caucasian

Typical Associated Conditions

POTS- adrenergic type

Ehlers-Danlos Syndrome- hypermobility type

Box 2

The Phases of Diagnosis and Treatment for Patients with NC-MCAS

Phase one

Establishing diagnosis- typical symptoms, lab tests, ruling out other conditions (provider)

Trial of medications to block mast cells and mediators (provider and patient)

Learning individual triggers for mast cell activation (patient)

Phase two

Adding mast cell blocking medications in a step-wise manner (provider)

Discerning which symptoms are due to mast cell activation and which are not (patient)

Managing how to avoid triggers- Environmental, diet (patient)

Phase three

Adjusting dosing of mast cell blocking medications (provider)

Adding in complementary therapies- stress reduction, exercise (provider and patient)

Reassessing any new symptoms or signs not typical of mast cell activation (provider)

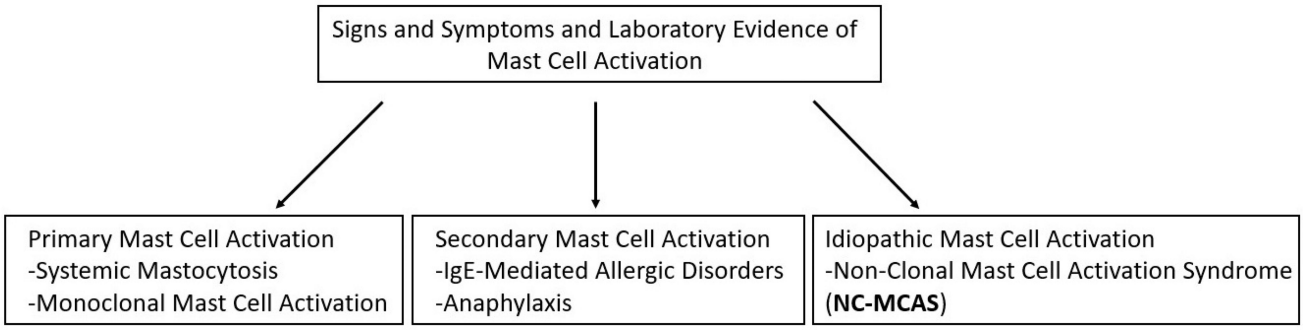

Figure 1.
Classification Schemes of Mast Cell Activation Disorders.