Mast Cell Activation Syndrome

The mast cell is a potent immune cell known for its functions in host defence responses and diseases, such as asthma and allergies. They are immune cells of the myeloid lineage and are present in connective tissues throughout the body. The activation and degranulation of mast cells significantly modulates many aspects of physiological and pathological conditions in various settings. With respect to normal physiological functions, mast cells are known to regulate vasodilation, vascular homeostasis, innate and adaptive immune responses, angiogenesis, and venom detoxification. On the other hand, mast cells have also been implicated in the pathophysiology of many diseases, including allergy, asthma, anaphylaxis, gastrointestinal disorders, many types of malignancies, and cardiovascular diseases. (1)

This review discussion is simply to point out current knowledge of the diversity of problems associated with mast cell activation, and an analysis of current and evolving management. The implications to specific problems, especially fibromyalgia, POTS and dysautonomia are discussed in the separate article on Mast cell Activation Management. In respect to the work by Lawrence Afrin, and the reproduction of his findings, this article follows closely the layout in his article: Presentation, Diagnosis and Management of Mast Cell Activation Syndrome. (5)

Managing POTS using a detailed timeline and working out activators and drivers to the syndrome does provide a way of tackling MCAS by reducing the impact of the drivers themselves rather than depending on medication. By looking at diet, mechanical, environmental factors such as trauma, emotional stress, vascular compression, posture, and spine drivers with activation of pain pathways, symptoms can be dramatically improved. The impact of high-level acupuncture must not be forgotten, as this does appear to turn down the inflammatory responses, while the mechanical and other causes are worked through.

“Mast cells play a key role in homeostatic mechanisms and surveillance, recognizing and responding to different pathogens, and tissue injury. An abundance of mast cells reside in connective tissue that borders with the external world (the skin as well as gastrointestinal, respiratory, and urogenital tracts.) Situated near nerve fibres, lymphatics, and blood vessels, as well as coupled with their ability to secrete potent mediators, mast cells can modulate the function of local and distant structures (eg other immune cell populations, fibroblasts, angiogenesis), and mast cell dysregulation has been implicated in immediate and delayed hypersensitivity syndromes, neuropathies, and connective tissue disorders.” (2)

Mast cells are involved in many immune reactions and diseases through:

1. The expressions of several receptors,
2. Production of various mediators such as histamine, cytokines, and chemokines,
3. Direct interactions with immune cells.

Besides allergic diseases, mast cells have been also assumed to be involved in autoimmune diseases such as bullous pemphigoid, rheumatoid arthritis, and multiple sclerosis. Moreover, several studies reported the involvement of mast cells in collagen disease. Mikita et al in 2017 reviewed recent findings about the role of mast cells especially in systemic lupus erythematosus and systemic sclerosis and found that in these diseases, mast cells seem to be involved in local inflammation and tissue damage partially in the targeted organ rather than the development of autoimmunity including production of autoantibodies. (3)

In the past years, accumulating evidence established the contribution of the mast cell to cardiovascular diseases as well, in particular, by its effects on atherosclerotic plaque progression and destabilization. Through its release not only of mediators, such as the mast cell–specific proteases chymase and tryptase, but also of growth factors, histamine, and chemokines, activated mast cells can have detrimental effects on its immediate surroundings in the vessel wall. This results in matrix degradation, apoptosis, and enhanced recruitment of inflammatory cells, thereby actively contributing to cardiovascular diseases. (4)

First recognized in 1991 and finally labeled in 2007, Mast Cell Activation Syndrome (MCAS) is a large collection of diseases resulting from inappropriately activated mast cells. If differs from the rare and very dangerous “mastocytosis” as it is not proliferating, but due to the marked diversity of biological effects caused by the inflammatory mediators released by the mast cells, MCAS typically presents as chronic, persistent or recurrent, or slowly progressive multisystem inflammatory problem. It is usually acquired early in life by the interaction of environmental with inherited risk factors. Virtually all of the syndrome’s manifestations are non-specific, leading to decades of mysterious illnesses and often incorrect diagnoses. “A large menagerie of mutations in mast cell regulatory elements has been found in MCAS patients, with no clear patterns, or genotype-phenotype correlations apparent,” driving the heterogenicity of the clinical presentations. All of the body’s systems can be affected, and there is often great difficulty in detecting definite measureable evidence to confirm this. (5)

Systemic mastocytosis usually drives significantly elevated levels of Tryptase, while MCAS usually has normal tryptase, although other indicators eg histamine, specific prostaglandins and other markers may be altered. Therapies against MCAS generally aim to control symptoms by inhibiting abnormal mediator production and release, and managing the consequences of these. Unlike systemic mastocytosis, lifespan on people with MCAS is usually normal, although quality of life can be severely affected. But systemic mastocytosis, which is a rare, is the tip of the iceberg of mast cell diseases.

Although symptoms can appear at any age, most commonly as a child or adolescent, sometimes in a neonate or infant, the diagnosis is unsuspected due to the non-specific nature of the symptoms. (5) Most patients live their lives without the underlying diagnosis being made. There are usually seen as chronically multi-systemically ill, perhaps being recognized as having an inflammatory disease, but with typical testing unable to localize the actual cause. History will usually provide a “trigger point” but in depth history will usually show earlier unrecognized symptoms. These can be as varied as gastrointestinal dysfunction, presenting with diarrhoea, or constipation, or disorders of erythropoiesis. Successful management of these requires a detailed timeline of disorders that track back to infancy.

Fatigue and malaise are the most common complaints in MCAS. (5) Most patients remain functional, but some are severely impaired. Low-grade temperature dysregulation is not uncommon, as are lymph node swelling, weight loss, unexplained weight gain, loss of appetite, fluctuating oedema, but it is the gain in adipose tissue that accounts for weight increase in most MCAS.(5) Again, there is often an identifiable acute stressor in the months prior to the weight gain. These patients may have bariatric surgery sometimes with complications of poor wound healing, and while there is initial weight loss, the other symptoms usually remain, and the weight gain slowly starts to return. (5) Mast cells are programmed to site themselves at environmental interfaces- lungs, gut, skin, bladder, nose and sinuses etc, so there can be a wide range of pathology in aberrant mast cell activation.

Dermatological Manifestations

Pruritis is a common complaint, which can be episodic or constant, often unpredictably migratory, and sometimes controlled with simple anti-histamines, but it too can be disabling. It can be generalized, eg aquagenic pruritis,or localized, or migratory. (5) Drug reactions can be from dyes and fillers in medications rather than the medication itself, and in these times of generic substitution, this can create difficulties localizing driving forces. Symptoms can vary with environmental changes, with reactions as complex as close exposure to venetian blinds, or UV light. This can be complicated by things such as reactions to pollens and similar environmental triggers.

Skin changes such as xerosis, fragility and telangiectasia, unpredictable migratory patchy rashes are common, as are warts and spontaneous folliculitis. Unexplained painful sensitive skin is not uncommon, nor is dermatographism. Wound healing is often impaired, with unexpected scarring. Striae may occur, especially in younger patients, often seen about the trunk, abdomen, axillae and sometimes costo-vertebral angles. (5)

Opthalmological Manifestations

Most commonly symptoms reflect generally non-infectious inflammation, the most common dry, itchy eyes. Chronic or episodic excessive lacrimation, scleritis, blepharitis, conjunctivitis also occur, as can lid tremors and tics. Not infrequently patients complain of acute episodes of inability to focus, lasting minutes to hours, often with flares of other symptoms especially fatigue. (5)

Otological, Oral and Sinonasal Manifestations

Otological symptoms are usually also of non-infectious inflammation, with otitis media especially in children, painful and/or itchy canals is not uncommon. Patients can experience hearing aberration, tinnitus, hyperacuris with often little to explain symptoms. (5)

Some of the highest concentrations of mast cells are in the sinonasal passages. A chronic sense of congestion is often reported. There may be intermittent ulcerations, sores, olfactory intolerances, and unprovoked, often severe epistaxes are not uncommon.(5)

Intermittent oral or labial discomfort to pain is not uncommon, focal sometimes migratory, or diffuse, abnormal taste, ulcerations, or a diffuse burning discomfort can be found with negative biopsies for Sjogren's Syndrome, the latter usually in response to a stressor, and leading many patients to be mistakenly diagnosed as having psychiatric illness.

Chronic or intermittent angioedema of the oral tissues are sometimes seen. Dental decay in spite of good dental hygiene is not uncommon, but the connection between stressor and dental problem is usually not seen due to the slower pace of development of the dental problems.

Pulmonary Findings

One of the major inflammatory mediators produced by mast cells is prostaglandin D2 (PGD2), a strong bronchoconstrictor, 10- times more potent than histamine, so the most common complaint is irregularly episodic dyspnoea, sometimes accompanied by wheezing, but where chest imaging and pulmonary function testing is usually unrevealing. They may be diagnosed as "reactive airways disease." Mast cell activation may be part of the progression of emphysema and chronic obstructive pulmonary disease, as well as pulmonary hypertension. (5)

Cardiovascular Findings

Current evidence points towards a key role for mast cells as effector cells in atherosclerosis and acute cardiovascular syndromes. The many mechanisms involved include secretion of the proteases chymase and tryptase, histamine, growth factors and cyto- and chemokines eg TNF-α, interferon-γ, interleukin-6 and interleukin-8 by activated mast cells. Mast cell activation leads to increased plaque progression and destabilization. (4)

Cardiac, vasomotor, and vasculospastic issues occupy the entire spectrum of possible abnormalities. Palpitations are very frequent, resting tachycardia quite common, sometimes bradycardia. There can be unpredictable episodes of both hypotension and hypertension, unlike phaeochromocytoma with its tachycardia and hypertension. Noradrenalin is a known potent vasoconstrictor, and the mast cell provides one of the cellular sources of this. PGD2, whose dominant source is the mast cell, is more potent a vasoconstrictor than noradrenalin in certain vascular beds, but can act as a vasodilator in others. (5)

Presyncope is common, but frank syncope fairly uncommon. Episodes are described as sudden-onset "lightheadedness, weakness, dizziness and occasionally vertigo." Tilt table testing may suggest postural orthostatic tachycardia syndrome (POTS). (5)

Chest pain is sometimes described. Two uncommon chest pain syndromes are thought to be associated with mast cell activation- Kounis Syndrome (allergic angina or allergic myocardial infarction) in the absence of obstructive coronary lesions is thought to be from mast cell activation, and requires identification of the allergic insult. Takotsubo syndrome (acute stress-

induced cardiomyopathy with a hyperkinetic cardiac base, hypokinetic mid-ventricle and apex, and left ventricular apical ballooning) is seen in 2% of suspected acute coronary syndromes. 75% of Takotsubo cases have elevated plasma catecholamines. (5)

Mast cell activation syndrome-driven coronary and peripheral arteriosclerosis producing true vaso-occlusive pain can be aggressive even at a young age. (5)

Oedema is commonly found, often with normal cardiac function, and this can be episodic in nature, and move from one limb to the other, or elsewhere in the body eg periorbital. (5)

Gastrointestinal Findings

Oesophagitis is common, often refractory to acid reduction therapy. Gastritis and small and large bowel enteritis are common, manifest as migratory abdominal pain, diarrhoea, constipation, often alternating. Chronic or intermittent nausea and vomiting is common. These are usually diagnosed as Irritable Bowel Syndrome. Selective micronutrient malabsorption, especially iron, but including copper and B vitamins is common. Lawrence Adfrin (5) advocates H1/H2 histamine receptor blockade. (5)

Inflammation and/or fibrosis in pancreatic exocrine glands and/ or pancreatic ducts is thought to be part of the MCAS-driven inflammatory disease, where 40% of causes of chronic pancreatitis are “idiopathic” and increasingly thought to be auto-immune. (5)

Around 50% of MCAS patients have evidence of hepatic damage, with fibrosis the most common pathological finding. Cholestasis and portal hypertension are uncommon, but when the latter is present, is reflected in gastroesophageal varices and splenomegaly. (5)

Elevated levels of mast cell inhibitors are commonly not detectable unless the patient is markedly symptomatic. Occasionally mast cells are seen in biopsies from the GI tract and labelled “mastocytic enterocolitis.” 40% of patients with “gastroesophageal reflux disease” are refractory to maximal dose PPI, remaining symptomatic despite no significant acid production, therefore it is not acid production causing their symptoms. Biopsies are usually normal, or mild to moderate chronic inflammation, raising the possibility that these are a manifestation of mast cell disease. (5)

Genitourinary Findings

Interstitial cystitis and chronic recurrent prostatitis are common presentations, with sterile mast cell –driven dysuria. Vaginitis may also be present, as can renal inflammation and/or fibrosis. Acute and chronic renal failure can occur from obstructive uropathies, and if these are intermittent with no identifiable stones, obstructive ureteral angioedema may be occurring. (5)

Inflammatory mediators can cause aching and pain, often vague in location, and often causing chronic low back pain. (5)

Aberrant mast cell activation has been recognized to be a primary issue in endometriosis, affecting 15 to 20% of women in reproductive years. (5) Miscarriages in MCAS, especially if associated with an abnormal prothrombin time or partial thromboplastic time should be checked for MCAS-driven antiphospholipid antibody syndrome. (5)

Musculoskeletal and Joint Findings

Premature osteopenia/osteoporosis is frequently found, and occasionally osteosclerosis. This is thought to be from excessive RANKL-stimulated osteoclast activity with increased bone resorption. (5)

Diffuse, diffusely migratory aching and arthralgia is common, which may attract duagnoses or osteoarthritis, seronegative rheumatoid arthritis, fibromyalgia and polymyalgia rheumatica. It can be centered in bones or soft tissue with no radiological abnormality. There has been some evidence that mast cell dysfunction is associated with complex regional pain syndrome. (5)

Excessive joint laxity /hypermobility is sometimes seen suggesting Ehlers-Danlos Syndrome, but with negative testing for known mutations. This group also is subject to POTS. (5)

MCAS-driven pain often responds poorly to traditional analgesics, both non-steroidal or narcotics, and both of these can trigger flares of symptoms, and some respond to MC-directed treatment eg anti-histamines, cromolyn and bisphosphonates. (5)

Neuropsychiatric Findings

Mast cells are situated in proximity to nerves as well as environmental interfaces, and it is becoming apparent that inflammation is a significant factor in the development of neurologic and psychiatric disorders. (5)

Headaches are common, often disabling, including migraine where mast cell degranulation has been implicated. Vasomotor instability can be the principle symptom, leading to diagnoses of dysautonomia and POTS. Not uncommonly there are increased sensory and/or motor nerve activity reflected in paraesthesiaes and tics. Sometimes essential resting tremors are present, and acute presyncope can occur. While EMGs and nerve conduction tests are usually normal, occasionally testing suggests “chronic demyelinating polyneuropathy (CIDP), sometimes accompanied by a modest monoclonal gammopathy of undetermined significance, which is felt by Lawrence Afrin to be MCAS-driven. (5)

Afrin also believes that mast cells are involved in the development of multiple sclerosis and amyotrophic lateral sclerosis, with PGD2 inducing motor neurone loss through demyelination and enhanced astrogliosis. He describes symptom improvement with PGD2 receptor blockade. He also describes evidence of mast cell involvement in Alzheimers disease. (5)

Obstructive sleep apnoea is common in MCAS, as is sleep abnormality. (5)

Afrin describes episodic cognitive dysfunction (brain fog) as the most common psychiatric issue in MCAS, particularly affecting short-term memory and word-finding. Some patients find their overwhelming fatigue is the issue. Mood disorders, irritability, anger, depression, bipolar affective disease, attention deficit disorder, anxiety and panic attacks are not uncommon. (5)

Stressful events often trigger acute and chronic flares of MCAS, and makes a diagnosis of PTSD common. (5)

Mast cell activation appears to play a role in the etiology of autism spectrum disorders (ASD), with most ASD patients having food intolerance and other allergic symptoms. (5)

Endocrine / Metabolic Findings

TSH elevation is common, and hyperthyroidism less commonly. Elevated anti-thyroid antibodies are often detectable, sometimes high levels of titre are detected with no apparent thyroid disease.(5)

Elevated ferritin is known to be released by hepatocytes and macrophages, but elevated ferritin can also be released from mast cells, often misinterpreted as haemochromatosis. (5)

Obesity and diabetes mellitus are both clearly associated with mast cell disease, with both recognized as being inflammatory. Metabolites of PGD2 figure in at least one key adipose management pathway, so lipid abnormalities are common in MCAS. Statin-resistant lipid elevation can sometimes be corrected by MCAS-targetted therapy. (5)

Haematological Findings

MCAS is classified as a haematological disease presents with few to no significant haematological abnormalities in most cases. Part of the answer is that mast cells spend little of their lifespan in the marrow, leaving the marrow early, circulating briefly then residing for the

remainder of their relatively long lifespan of several months to years, in peripheral tissues. The clinical presentation of MCAS is entirely dependent on which mediators are being aberrantly released. (5)

Serum tryptase levels are more reflective of the total body load of mast cells and their activation state. But as MCAS id a relatively non-proliferative disease, most patients have normal tryptase levels. Afrin believes that levels 20% above baseline as highly suggestive of MCAS. (5)

The most common abnormality in peripheral blood is monocytosis, usually relative rather than absolute elevation, and often considered diagnostically insignificant. Persistent eosinophilia or "reactive lymphocytes" may also be seen. Thrombocytosis or thrombocytopaenia may also be present. The heterogenicity of these abnormalities across the MCAS population is thought by Lawrence Afrin to be likely due to the mutational heterogenicity of the disease. In thrombocytosis JAK2 analysis associated with the classic BCR/ABL-1 negative chronic myeloproliferative neoplasms may be positive or negative. There is a propensity for MCAS patients to develop haematological malignancies of any kind, he feels it possible for a JAK-2 positive MPN to have developed secondary to mast cell disease. (5)

MCAS patients may have increased or decreased red cells. Erythrocytosis is usually modest but can be misdiagnosed as polycythaemia vera, but have little response to phlebotomy. As hydroxyurea helps control some aberrant mast cells this may provide better responses. The erythrocytosis of MCAS is typically macrocytic, but the mechanism unclear. Anaemia is the most common erythrocytic abnormality seen, and can be macrocytic, microcytic, or normocytic. In the more severe macrocytosis, B12 deficiency is the most common cause, and ideally patients should be assessed for anti-intrinsic factor Ab and anti-parietal cell Ab. A deteriorating microcytic anaemia in a MCAS patient is most commonly iron but copper deficiency is possible as well. In iron-deficiency, once chronic bleeding has been excluded is often corrected by H1/H2 histamine receptor blockade. PPIs are commonly used to treat the reflux symptoms from the MCAS disease and can inhibit acid production sufficiently to affect iron absorption. (5)

Copper deficiency is usually the result of selective copper malabsorption, but possible zinc toxicity (which causes copper toxicity) should be checked. (5)

The bone marrow is usually normal in MCAS patients, but can show a non-specific, mild myeloproliferative/myelodysplastic appearance. (5)

Coagulopathic Findings

The bleeding most commonly seen by Lawrence Afrin in MCAS patients is "easy bruising" and intermittent unprovoked epistaxes. Surprisingly, menses may be normal. Some only have abnormal bleeding in surgical and non-surgical trauma, where bleeding is confined to the traumatized site. Thromboembolism is not rare, often without any coagulation system abnormality. (5)

Immunologic Findings

Both cellular and humoral immune abnormalities are common in MCAS, leading to impairments in any or all of the primary functions of the immune system. Leading to increased susceptibility to infection, increased development of auto-immune disease, impaired healing and increased risk of malignancies of all types. Acute, subacute and delayed hypersensitivity reactions can be seen. (5)

Investigations

- FBC, differential
- E's &LFTs
- Se magnesium
- Immunoglobulins (if problems with infections
- PTT, PT (if bleeding, bruising, thromboembolic events
- Se Tryptase (highly specific mast cell mediator)

- Se Chromogranin A (mast cell product- but also altered by heart failure, renal insufficiency, PPI usage, neuroendocrine malignancy)
- Plasma histamine (less specific than tryptase as also released by basophils)
- Chilled plasma PGD2

Management of Mast Cell Activation Syndrome

Avoidance of triggers, desensitization when specific unavoidable environmental abnormalities are present, and prophylactic therapies (eg bisphosphonate therapy for osteoporosis) can limit morbidity. Because of potential circulation of released mediators, and potential interaction of released mediators with elements of the nervous and hormonal/endocrine systems, the dysfunctional mast cells releasing the mediators causing symptoms may or may not be located proximately to the affected site. This therapies aim to:

1. Reduce mast cell production and release of mediators
2. Interfere with released mediators
3. Counter the effects of the released mediators.

The extreme underlying mutational heterogenicity of the disease almost certainly leads to extreme heterogenicity in patterns of mediator production and release, in turn leading to extreme heterogenicity of clinical presentation and responsiveness to therapeutic agents.In view of the disease complexity and the inherent propensity to react adversely to potentially any new exposure, it is important to make only change in therapy at a time.

Virtually all commercial products have various fillers and dyes which may be inert in normal people but can affect MCAS patients. In patients who react to wide ranges of fillers and dyes, products can usually be compounded. (5)

Medications:

1. Inhibition of mediator production
    a. Corticosteroids may be helpful but limited by toxicities
    b. NSAIDs and aspirin. NSAIDs can be helpful, but these can also trigger flares of activation.

2. Inhibition of mediator release (mast cell stabilization)
    a. Benzodiazepines to address end organ receptors as well as mast cells, added to potential improvement from reduced anxiety in some inflammatory bowel disease. Also may be helpful in the emergency management of the disease, especially the shorter half-life products eg loraxepam, clonazepam or alprazolam.
    b. Tricyclics eg doxepin have H1 receptor blocking effects that can be added to traditional antihistamines.
    c. SSRIs may benefit the associated depression but also can affect mast cells via surface serotonin reuptake transporters. However adding antihistamines to SSRIs brings the risk of serotonin syndrome.
    d. Zolpidem also targets the benzodiazepine receptor, independent of whether other benzodiazepines are in use. Helpful in the associated insomnias, but not in other MCAS symptoms. No role in emergency management.
    e. Cromolyn (Intal) can stabilize mucosal mast cells- for dosage regime see page 199 of “Presentation,Diagnosis and Management of Mast Cell Activation Syndrome.”
    f. Oral Ketotifen-originally marketed as an inhibitor of anaphylaxis, it inhibits release and/or activity of mast cell and basophil mediators including histamine, neutrophil and eosinophil chemotactic factors, arachidonic acid metabolites, prostaglandins and leukotrienes. (6) It is available in Australia as Zaditen eye drops, and would have to be compounded to be taken orally with a dose of 1 mg twice daily increasing weekly as tolerated.
    g. Quercetin is a flavonoid that is poorly absorbed but is thought to inhibit lipooxygenase and cyclooxygenase reducing production of inflammatory

mediators eg leukotrienes and histamine. It seems to have general anti-inflammatory effects and impedes PGD2-driven flushing. General dosing is 500 to 1000 mg twice daily.

h. Allergen-driven cross-linking of multiple IgE molecules bound to mast cell-surface IgE receptors is a major route of mast cell activation. Omalizumab (Xolair) is a humanized monoclonal antibody which reversibly binds the Fc portion of IgE hindering IgE binding with its mast cell-surface receptor.
i. Rarely hydroxyurea and immunosuppressants

3. Blockade of released mediators
    a. Histamine H1 and H2 blockade to address end organ receptors as well as mast cells
    b. Leukotrienes are synthesized and released by mast cells –Selective leukotriene receptor antagonists eg Singulair 10 mg 1-2times daily may help-limited in hepatic involvement.
    c. Bisphosphonates are helpful in excessive bone resorption. Prolia has demonstrated efficacy in osteopenic/osteoporotic situations, and should be effective in the MCAS-associated osteoporosis.
    d. Tumour necrosis factor (TNF) alpha is a well-established mast cell mediator product, and TNF-alpha antagonists eg etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicabe) are approved for use in a variety of systemic inflammatory diseases increasingly suspected to be of aberrant mast cell orogin (eg rheumatoid arthritis, psoriatic arthritis and inflammatory bowel disease). There have been no trials in any other mast cell diseases.

4. Other:
    a. Pancreatic enzyme supplements may be helpful in chronic pancreatitis where there is chronic diarrhoea, weight loss, and micronutrient malabsorption. (5)

Conclusion

The diversity of problems associated with mast cell activation has significant implications many complex medical problems such fibromyalgia, POTS, dysautonomia and auto-immune disease, and may be important in real cause of diseases such as diabetes, hypertension, cardiomyopathy, COPD, vascular disease and auto-immune disease just to name a few.

These are all inflammatory processes with multiple causes, most importantly genetic, and it is injury, lifestyle and similar factors which steers you into whatever disease you may develop, dependent on your individual DNA. Medicine is a constantly evolving science, and I have no doubt further research will unlock even more causes, or at least provide better explanations for the disease processes.

1. Krystel-Whittemore, M., Dileepan, K., Wood, J.G. Mast Cell: A Multi-Functional Master Cell, 2016. https://www.frontiersin.org/articles/10.3389/fimmu.2015.00620/full

2. Seneviratne,S.L., Maitland, A., Afrin A.: Mast Cell Disorders in Ehlers-Danlos Syndrome. 2017, American Journal of Medical Genetics Part C, 175C: 226- 236

3. Mikita, n., Inaba, Y.,Yoshimasu, T., Kanazawa, N., Furukawa, F.: Mast Cells in Collagen Diseases. 2017. https://www.researchgate.net/publication/319359864_Mast_cells_in_collagen_diseases

4. Bot, I., Shi, G., Kovanen, P.,Mast Cells as Effectors in Atherosclerosis. 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4304944/

5. Afrin, L. Presentation,Diagnosis and Management of Mast Cell Activation Syndrome. 2013. Nova Science Publishers,Inc.

6. Sokol,K.,Amar, N., Starkey, J., and Grant, A.: Ketotifen in the management of chronic urticaria: resurrection of an old drug. 2013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4309375/