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Anesthesia for the Patient with Mast Cell Activation Disease

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by

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ABSTRACT

Title: Anesthesia for the Patient with Mast Cell Activation Disease

Background: Mast cell activation disease involves the accentuated increase of mast cell activation and release of chemical mediators, occurring unpredictably to a variety of triggering stimuli making perioperative management difficult as both anesthesia and surgery are responsible for triggers of rapid activation of mast cells in patients with mastocytosis.

Purpose: To review the challenging presentation, treatment, knowledge, and anesthetic considerations for patients with mast cell activation disease and to have an updated source of research of the recent advancements for success during the perioperative period.

Process: Research was conducted to extend our understanding of the disease and how to predict the association between the immediate drug hypersensitivity and mast cell degranulation. Reports were investigated for anesthetic medication used for patient with mastocytosis undergoing procedures requiring anesthesia, the medication side effects reported, and suggested prophylaxis techniques.

Results: Preoperative prophylaxis regimes as well as pretreatment for conditions of intraoperative stress (anesthesia and surgery) need to be conducted to prevent possible cardiovascular collapse with adult mastocytosis. Immediate reaction occurring in patients with mastocytosis should be highly investigated for future documentation of the mechanism of the reaction.

Implications: There are currently no official guidelines for intraoperative management of mast cell activation disease and no known studies have been found to predict mast cell degranulation in this patient population. Extended research is needed for perioperative antidotes for the anaphylaxis-like incidences in mastocytosis patients.

Keywords: Mast cell activation disease; Systemic mastocytosis; Mast cell activation syndrome; drug hypersensitivity; anaphylaxis; C-KIT mutation.

Background

Mast cell activation disease (MCAD) is a condition involving hematopoietic tissue called mast cells, and the enhanced release of mast cell mediators. Mast cells are found in all human tissues and secrete over 200 known mediators including histamine, tryptase, chemokines, and cytokines, playing an important role in our innate and adaptive immunity (Molderings et al., 2016). Mediators are secreted by mast cells through multiple intercellular pathways in response to allergic, microbial, and nonimmune triggers in the environment, all which play a role in the body's defense mechanisms, growth, and healing (Afrin & Khoruts, 2015).

The term mast cell activation disease is caused by altered mutated genes and encompasses three similar classes: systemic mastocytosis (SM), idiopathic systemic mast cell activation syndrome, and mast cell leukemia (Molderings, 2015). This complex disease can also impersonate other conditions such as "anaphylaxis, leukemia, basophil activation, and other cardiac conditions leading to profound hypotension" (Klein & Misseldine, 2013, p 589).

In patients without the disease, mast cells usually serve to detect and act upon "environmental changes and bodily insults and respond by releasing large and variable assortments of molecular mediators which directly and indirectly influence behavior in other local and distant cells and tissues, to respond to changes and insults so as to maintain, or restore, homeostasis" (Afrin & Molderings, 2014, p 2).

History

Mast cells were first discovered in the late 19th century and classification systems and diagnostic criteria for mastocytosis were first proposed in the 1980s (Afrin & Molderings, 2014). It was not until the 20th century that the rare systemic mast cell disease was discovered, and just a quarter century ago when the transmembrane tyrosine kinase receptor (KIT), and somatic D816V

mutation was revealed (Afrin & Molderings, 2014). Mast cells are "myeloid lineage cells that arise from bone marrow precursors, more specifically from CD34+ and KIT+ hematopoietic progenitors" (Pardanani, 2012, p 1117). It was first thought that mast cell disease was neoplastic in nature and that symptoms were due to pure inappropriate mediator release, and it was only recently that the KIT mutation was most likely responsible for the immunohistochemical changes that manifest the symptoms of the disease (Afrin & Molderings, 2014). Ultimately, the umbrella term "mast cell activation disease" was proposed, suggesting there are known several variants to the disease.

Epidemiology

Mastocytosis is a rare disease and exact prevalence remains unclear although predictions have been estimated to affect < 200,000 people in the United States (Brockow, 2014). The disease occurs both in children and adults with equal gender distribution, and can occur at any age, although most patients have an onset occurring in less than two years of age, or between the ages of 20 to 50 years of age (Brockow, 2014). There are two main differences of mastocytosis; with cutaneous mastocytosis primarily occurring in children, while SM primarily occurring in the adult population. Indolent SM is the most common form occurring in adults and is assumed present in 90% to 95% of all patients with mastocytosis (Brockow, 2014). The risk factors for anaphylaxis in patients with mastocytosis involves a higher basal level of serum tryptase and has been reported to be present in 22% to 49% of patients (Brockow, 2014). SM in adults also correlates with excess mortality and morbidity occurring within 5 years after diagnosis is confirmed, and "inferior survival is associated with advanced age, history of weight loss, anemia, thrombocytopenia, hypoalbuminemia, and excess bone marrow blasts" (Pardanani, 2012, p 1122).

Case Report

A 40-year-old woman was scheduled for a hysterectomy, dilation and curettage, with an intrauterine device insertion for abnormal uterine bleeding. Preoperative vital signs included blood pressure of 134/79, heart rate of 89, respiratory rate of 16, pulse oxygen saturation of 98 percent, and a temperature of 36.9 degrees Celsius. The patient had a known history of mast cell activation syndrome, as well as multiple past allergic shock states, hypertension, obstructive sleep apnea, morbid obesity, anxiety, hypermenorrhea, and left ovarian cyst. The patient was 5'4 and 112 kilograms, with no known allergies. Her home medications included EpiPen (epinephrine injection USP), Zyrtec (cetirizine), Allegra (fexofenadine), Singular (montelukast), Zantac (ranitidine, Hcl), Requip (ropinirole Hcl), and labetalol.

The patient was medicated with 2mg midazolam, 25mg diphenhydramine, 10mg dexamethasone, and 40mg of 1% lidocaine. Induction medications included 150mcg fentanyl, 14mg etomidate, and 30mg rocuronium. A dexmedetomidine infusion was also initiated at 0.5mcg/kilogram/hour. With the patient's history, epinephrine was diluted down into a 10mcg/ml syringe to have on standby. Following intubation, lungs sounds were diminished, ventilatory tidal volumes were decreased, and oxygen saturations were 70% on 100% FiO2. A bronchospasm was diagnosed based on rapid increase in peak inspiratory pressure with an increased height and a "shark-fin" appearance on the capnography waveform, as well as diminished breath sounds with wheezing. Positive pressure was immediately administered, sevoflurane gas was increased to 8%, FiO2 was increased to 100%, and 10 puffs of Albuterol was administered via the endotracheal tube. The patient's low oxygen saturations and diminished tidal volumes resolved within 2 minutes and vital signs normalized. At this time, the decision was made to keep the patient on a deepened anesthetic with sevoflurane at 2.8% in addition to

the administration of 125mg of solumedrol for anti-inflammatory properties.

For the next 45 minutes, surgery and anesthesia remained uneventful until peak inspiratory pressures increased and oxygen saturations started to decrease. Once again, a bronchospasm was observed with the same manifestations as previously. There were no obvious causes of stress besides current surgical stimulation. Treatment remained the same as before and symptoms spontaneously resolved within 1 minute. Preparing for the end of the case began with the decision to extubate deep with sevoflurane at 1.5 MAC with the dexmedetomidine infusion continuing. The patient neuromuscular blockade was antagonized with 0.6mg of glycopyrrolate and 4mg of neostigmine, and albuterol was given endotracheally for prophylaxis. After adequate reversal was confirmed with train of four monitoring, and spontaneous breathing was evaluated and confirmed with adequate tidal volumes and regular rate, an oral airway was placed, and the patient was then extubated deep with no signs of bronchospasm. The post anesthesia care unit (PACU) was called and notified of highly irritable airway, and respiratory therapy was referred for the patient to be placed on CPAP therapy upon arrival. With 10L oxygen via simple mask, the patient was delivered safely to the PACU and no bronchospasm occurred during recovery.

Discussion

Diagnosis of MCAD

The World Health Organization (WHO) has a diagnostic classification consensus criterion for diagnosing MCAD. According to the WHO (2008) guidelines for the diagnosis of mastocytosis, “Major criterion involve multifocal, dense aggregates of mast cells (15 or more) in sections of bone marrow or other extracutaneous tissues and confirmed by tryptase immunohistochemistry or other special stains” (Afrin & Molderings, 2014, p 4). Tryptase “identifies virtually all cells regardless of maturation or activation stage, or tissue of localization;

however, neither tryptase nor CD117 immunostaining are able to distinguish between normal and neoplastic mast cells" (Pardanani, 2012, p 1118). Minor criteria include "atypical or spindled appearance of at least 25% of the mast cells in the diagnostic biopsy, expression of CD2 and/or CD25 by mast cells in marrow, blood, or extracutaneous organs, KIT codon 816 mutation in marrow, blood, or extracutaneous organs, and persistent elevation of serum total tryptase >20ng/ml" (Afrin & Molderings, 2014, p 4). Diagnosis of MCAD is confirmed with one major criterion and one minor criterion together, or any three minor criteria. Tryptase is a mast cell enzyme protease that acts as a "surrogate for mast cell activation, with a test specificity of 98% and a sensitivity of approximately 83% to 93% for diagnosing SM at tryptase levels greater 20 ng/mL" (Bains & Hsieh, 2010, p 5).

Presentation of MCAD

MCAD has more than 200 mast cell mediators and the clinical presentation involves a wide array of findings and varies greatly among individuals. According to Afrin, Spruill, Schabel, & Young-Pierce (2014), potential constitutional manifestations include fatigue, sweats, flushing, pallor, pruritus, poor healing, and chemical/physical sensitives. Ophthalmologically, the eyes may become irritated easily and blepharospasm may occur, while otologic symptoms involve tinnitus, hearing loss, and epistaxis. Adenopathy, adenitis, and splenitis are common symptoms involving the lymphatic system (Afrin, Spruill, Schabel, & Young-Pierce, 2014).

Common gastrointestinal disturbances include organ inflammation, dyspepsia, reflux, nausea and vomiting, angioedema, malabsorption, and ascites, while genitourinary symptoms may include chronic kidney disease, endometriosis, infertility, and miscarriage (Afrin, Spruill, Schabel, & Young-Pierce, 2014). Neurological and psychiatric manifestations in patients with MCAD may include headache, sensory/motor neuropathies, seizure disorders, mood

disturbances, anxiety, and sleep disruption (Afrin, Spruill, Schabel, & Young-Pierce, 2014). Abnormal electrolytes, impaired glucose control, dyslipidemia, and delayed puberty are endocrinologic and metabolic possible disturbances (Afrin, Spruill, Schabel, & Young-Pierce, 2014).

Hematologically, there is usually no histologic evidence of mast cell abnormalities in the bone marrow, although anemia, bleeding disorders, thromboembolic disease, and easy bruising/bleeding can occur (Afrin, Spruill, Schabel, & Young-Pierce, 2014). Patients with MCAD have immunologic compromise leading to the hypersensitivity reactions that can be detrimental in the disease process including the increased risk of malignancy and autoimmunity, as well as increased infection risk and decreased immunoglobulins (Afrin, Spruill, Schabel, & Young-Pierce, 2014).

The respiratory system, if irritated, may cause airway inflammation, cough, dyspnea, wheezing, obstructive sleep apnea, and pulmonary hypertension (Afrin, Spruill, Schabel, & Young-Pierce, 2014). Lastly, cardiovascular symptoms may include syncope, hypertension or hypotension, palpitations, edema, chest pain, atherosclerosis, and vascular anomalies (Afrin, Spruill, Schabel, & Young-Pierce, 2014). Aggressive disease involves "hepatomegaly with ascites or portal hypertension, splenomegaly with hypersplenism, gastrointestinal malabsorption with hypoalbuminemia and weight loss, and osteoporosis with pathologic fractures, lytic bone lesions, and cytopenia" (Bains and Hsieh, 2010, p 6).

Mast Cell Pathogenesis

Mast cells are formed in the bone marrow first as pluripotent stem cells, where they differentiate and mature into the adult form with the help of stem cell factor (Valent et al., 2003).

From the bone marrow, mast cell progenitor cells then migrate into the vessels, peripheral tissues, and nerves where growth and differentiation occur, as well as where the binding of surface tyrosine kinase occurs (Klein & Misseldine, 2013). Differentiation is not complete until mast cells reach peripheral tissues, involving most solid tissues including the lung, heart, and central nervous system (Klein & Misseldine, 2013).

Mast cells have secretary granules that contain proteases, which are the major proteins that comprise them, with the major protease being tryptase (Carter, Metcalfe, & Komarow, 2014). Surface tyrosine kinase is a "c-kit proto-oncogene product that is expressed on the surface of pre-committed myelopoietic progenitor cells, mast cell-committed progenitor cells, as well as mature mast cells" (Valent et al., 2003, p 695). The total tryptase is "comprised of mature tryptase stored in granules and released only upon activation, and immature (pro) tryptase, which is constitutively secreted by the mast cell" (Carter, Metcalfe, & Komarow, 2014, p 183).

Surface tyrosine kinase receptors, known as mast cell markers, include CD34, CD13, CD117 (C-KIT), and CD25 markers to which point mutations can exits at the "C-KIT locus (Asp816Val, or codon 816) codes for an abnormal cell membrane receptor protein for stem cell factor, producing clonal mast cell lines that lack normal growth and differentiation" (Klein & Misseldine, 2013, p 589). It is the surface KIT expression that is exhibited at high levels of maturation, and the "interaction between the KIT and stem cell factor has been shown to promote the proliferation, maturation, adhesion, chemotaxis, and survival of mast cells" (Pardanani, 2012, p. 1119). These mutations are able to be detected in the bone marrow where the C-KIT mutation can be found in 90% of adults with SM (Klein & Misseldine, 2013). The mutated mast cells have granules that store and generate a number of vasoactive mediators (histamine, tumor necrosis

factor-α (TNFα), vascular endothelial growth factor (VEGF), leukotrienes, prostaglandin D_2, and other biologically active molecules (interleukins, proteases, heparin) (Valent et al., 2003).

Treatment

Treatment for SM involves ongoing monitoring, suppression of symptoms, and avoidance to the triggers of extreme mast cell mediator release. Mediators that cause the origin of symptoms include "histamine, proteoglycans (heparin), tryptase, acid hydrolases, leukotrienes, prostaglandins, platelet activating factor, interleukins and tumor necrosis factor" (Scherber & Borate, 2018, p 16). The disease is highly variable in presentation and treatment is individualized to the patient's disease symptoms. Avoidance of emotional stress, excessive physical trauma, infections, and medications such as contrast, radioactive dyes, opioids, NSAIDS, and anticholinergics is suggested (Scherber & Borate, 2018).

Patients with asthma or allergic conditions must always have an epinephrine pen on hand. For symptom control of pruritus' and flushing, first line treatment includes the use of H1-antagonists (cetirizine 5-10mg/day), along with other treatments including leukotriene antagonists (Montelukast 10mg/day), NSAIDs (aspirin), Psolaren plus UVA photochemotherapy, and Omalizumab (150mg SC every 2 weeks) (Scherber & Borate, 2018). First line treatment for symptoms of abdominal pain, diarrhea, and nausea include the use of H2-agonists (ranitidine 150mg BID), with other treatments including proton pump inhibitors (omeprazole 20mg/day), Cromolyn (100-200mg QID), and corticosteroids (prednisone 0.5-1mg/kg/day) (Scherber & Borate, 2018).

Symptoms of headache, cognitive impairments, and depression can be treated with H1- and H2-antagonists as well as sodium cromolyn (Scherber & Borate, 2018). With patients who

experience anaphylactoid reactions, treatment consists of administering intramuscular epinephrine 0.3mg of 1:1,000, although the patient must be competent in the administration of the injectable epinephrine pen, followed by seeking medical attention immediately (Bains & Hsieh, 2010). For recurrent hypotension episodes, first line treatment using epinephrine is advocated, although other treatment methods include H1- and H2-antangonists, corticosteroids, and cytoreductive therapy (Scherber & Borate, 2018). Candidates for cytoreductive therapy is "only indicated in patients with target organ damage due to SM, typically patients with aggressive systemic mastocytosis, SM with associated clonal hematologic non–mast cell lineage disease, and mast cell leukemia disease categories" (Bains & Hsieh, 2010, p 6).

Lastly, osteoporosis symptoms may be treated with bisphosphonate and purine nucleoside analogs (Scherber & Borate, 2018). To current date, Midostaurin, a "tyrosine kinase inhibitor, has a response rate of 60% in patients with advanced SM which is effective against KIT- D816V" (Scherber & Borate, 2018, p 18). Pharmacotherapies also used for mastocytosis therapy include interferon (IFN)-α, "commonly regarded as the first-line cytoreductive therapy in symptomatic SM and shown to improve skin, gastrointestinal, and systemic symptoms associated with MC degranulation, as well as an impact on skeletal disease through its ability to improve bone density" (Pardanani, 2012, p 1123). For all subtypes of SM, 2-chlorodeoxyadenosine, a cytoreductive agent, is another successful therapy for patients who experience intolerance to IFN-α (Padrdanini, 2012). Other agents currently being studied for the treatment of SM include Imatinib, Masitinib, Dasatinib, and Hydroxycarbamide (Scherber & Borate, 2018).

Differential Diagnosis

Systemic mastocytosis and the disease symptoms may have common manifestations of other cofounding disease processes. Mast cell activation can endocrinologically be similar to the

effects of a pheochromocytoma, autoimmune vasculitis, carcinoid syndrome, and neurological fibromyalgia (Scherber & Borate, 2018). Its digestive symptoms may be diagnosed as celiac disease, irritable bowel disease, as well as simple intolerance to gluten (Scherber & Borate, 2018).

To diagnose mastocytosis, the presence of typical clinical symptoms including vomiting, malabsorption, abdominal pain, diarrhea, nausea, blisters, myalgia, pruritus, ascites, fevers/chills, migraines, anorexia, bone pain, and asthma are common (Scherber & Borate, 2018). Additionally, serum total tryptase must be increased "by at least 20% above baseline, 2ng/ml during or within 4 hours after a symptomatic period and must have the response of clinical symptoms to mast cell blocking agents such as cromolyn" (Scherber & Borate, 2018, p 12). Serum tryptase levels can be elevated in diseases such as "myeloid neoplasms, acute myeloid leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, refractory anemia, and hypereosinophilic syndrome, and thus, elevated tryptase levels are only indicative of SM in the absence of other hematologic malignant neoplasms" (Bains & Hsieh, 2010, p 5). If the patient's history and symptoms are consistent with mastocytosis or the common differential diagnosis' the KIT D816V analysis should be evaluated for possible clonality as the cause of their symptoms (Scherber & Borate, 2018). Systemic mastocytosis is a "disorder of clonal proliferation of mast cells and the diagnosis is established by detection of mast cells with abnormal morphologic features and immunophenotypes in the bone marrow or other extracutaneous organs and specific mutations in its growth factor (c-KIT) receptor" (Bains & Hsieh, 2010, p 4).

Triggers

For people with mast cell disease, anesthesia is a risk for patients undergoing surgical procedures due to the stress response from surgery as well as the medications needed to induce

and maintain anesthesia. Mast cell degranulation triggers include heat, friction, opioids, anesthetics, contrast, vaccines, non-steroidal anti-inflammatory drugs, insect bites, anxiety, and stress (Scherber & Borate, 2018). Other 'triggering' factors include medications (some antibiotics, amphotericin B, tramadol, and ketorolac), alcohol or radiographic contrast media (Valent et al., 2003).

Intraoperative drugs noted to take part in mast cell degranulation include aspirin, thiamine, polymyxin-B, quinine, dextromethorphan, anticholinergic preparations, alpha-adrenergic blockers, d-tubocurarine, metocurine, doxacurium, etomidate, enflurane, isoflurane, and lidocaine (Bains & Hsieh, 2010). Anesthetic drugs that have been known to have experimental histamine release and mast cell degranulation include alfentanil, cisatricurium, codeine, fentanyl, ketamine, meperidine, midazolam, morphine, Propofol, rocuronium, succinylcholine, sufentanil, thiopental, and vecuronium (Klein & Misseldine, 2013).

It is known that some foods, as well as mechanical stress, pressure, physical exertion, and thermal stress can cause histamine release (Klein & Misseldine, 2013). Examples of stress inducing effects in the operating room include patient anxiety, cold room temperature, bright lights, hemodynamic stress of induction medications, direct laryngoscopy, surgical stimulation, emergence from anesthesia, and extubation. Degranulation signs can be as discrete as a small rash or flushing, to bronchospasm, profound hypotension, and cardiovascular collapse. Cardiovascular symptoms include tachycardia, syncope and anaphylaxis, while respiratory symptoms include irritable lower respiratory tract rhinitis, and lymphadenopathy (Bains & Hsieh, 2010).

Preoperative management

Due to perioperative immediate reactions as a result of mast cell degranulation, a thorough preoperative plan should be in place. Anaphylaxis due to a "massive mast cell mediator release is present in a significant portion of SM patients (22–49%) and can be elicited by either known or unknown triggers through diverse mechanisms involving IgE- or non-IgE mediated pathways" (Matito et al., 2015, p. 48). The severity of reactions that occur in the operating room depend on the "cardiovascular homeostasis disturbances, as profound vasodilatation following mast cell degranulation with subsequent histamine release may, at the extreme, result in life-threatening conditions" (Renauld et al., 2011, p 458).

Suggested prophylaxis regimens found throughout the medical literature suggest that anti-histamines and steroids be administered, a baseline tryptase level should be acquired, and identification should be provided to the patient with MCAD with a medical alert bracelet (Klein & Misseldine, 2013). If diagnosis is suspected, a thorough preoperative "physical examination and determination of serum tryptase level, complete blood count, and hepatic enzyme levels are recommended" (Klein & Misseldine, 2013, p 590). Currently there are no guidelines for preoperative prophylaxis regimes, only case reports found in recent literature.

Preparation for cardiovascular collapse is essential for safety, especially in a known mastocytosis patient undergoing anesthesia for a surgical case. It is important that the anesthesia practitioner is aware that patients with mastocytosis "experience both immune (IgE-related) and non-immune anaphylaxis, and the overall incidence of anaphylaxis in patients with mastocytosis has been reported to be higher than in the general population" (Klein & Misseldine, 2013, p 591). The most substantial mediator is histamine. The prophylactic use of H1-receptor and H2-receptor antagonists are given to prevent preformed histamine release. Histamine is known to act

on four different histamine receptors, which all cause capillary membrane permeability, urticaria, swelling hypotension and vasodilation, gastrointestinal and bronchial smooth muscle contraction, mucous and edema formation, pruritus, and gastric acid production (Carter, Metcalfe, & Kamarow, 2013). H_1 receptors "modulate bronchial and GI smooth muscle contraction and may be blocked by antihistamines such as diphenhydramine (Benadryl) and cetirizine (Zyrtec), while stimulation of gastric acid secretion by parietal cells is regulated by H_2 receptors and is inhibited by H_2 antagonists like ranitidine (Zantac)" (Carter, Metcalfe, & Kamarow, 2013, p 183).

Glucocorticoids are used as mast cell stabilizers and have anti-inflammatory properties for the preoperative patient with mastocytosis (Klein & Misseldine, 2013).

Measuring a baseline tryptase level preoperatively is also recommended to evaluate the degree of elevation. As discussed previously, "mast cell degranulation occurs secondary to a variety of non-immune triggers specific for each patient, including psychological, traumatic (tourniquet), and physical (rubbing, extreme temperatures) agents", suggesting that surgery itself can lead to mast cell triggered mediator release (Renauld et al., 2011).

Intraoperative Management

Continue to maintain the avoidance of triggers that will cause mast cell mediator release. There are documented anesthetic drugs that are considered initiators of mast cell degranulation and activation in patients with mastocytosis. As discussed previously, anesthetic drugs that have been known to have experimental histamine release and mast cell degranulation include alfentanil, cisatricurium, codeine, fentanyl, ketamine, meperidine, midazolam, morphine, Propofol, rocuronium, succinylcholine, sufentanil, thiopental, and vecuronium (Klein & Misseldine, 2013). Other intraoperative drugs noted to take part in mast cell degranulation

include aspirin, thiamine, polymyxin-B, quinine, dextromethorphan, anticholinergic preparations, vancomycin, alpha-adrenergic blockers, d-tubocurarine, metocurine, doxacurium, etomidate, enflurane, isoflurane, and lidocaine (Bains & Hsieh, 2010).

Matito et al., (2014) reviewed 501 mastocytosis patients who underwent anesthetic techniques including general, regional, and local anesthetic techniques, and found that, in adult mastocytosis patients who "underwent anesthetic procedures, the frequency of anaphylaxis was 0.6% and mast cell mediator release symptoms was 7% respectively and despite this, anesthetic procedures are considered high-risk in SM patients since severe reactions (e.g. systemic hypotension/anaphylactic reactions and coagulopathy) can result in death in individual patients that have been recurrently reported" (Matito et al., 2015, p 53).

Histamine is largely responsible for most mastocyte degranulation and will respond to H_1- and H_2-histamine receptor antagonists. Although mast cell degranulation is unpredictable with occurrence, other "'antimediator' drugs that are beneficial include glucocorticoids, cromolyn sodium, acetylsalicylic acid (aspirin) and leukotriene antagonists" (Valent et al., 2003, p 705). Although aspirin is often contraindicated in patients with mast cell disease due to its ability to cause mast cell degranulation, it is a cyclo-oxygenase inhibitor, which can help if the culprit of degranulation is prostaglandin D2. Gadolinium, an intravenous contrast agent, has typically been considered safe in patients with mast cell degranulation, although if radiocontrast medium needs to be administered, "all patients should be premedicated with steroids and antihistamines before receiving iso-osmolar radiocontrast media" (Bains & Hseih, 2010, p 6).

Intraoperative Crisis Management

Aggressive treatment is needed during a mast cell degranulation crisis and epinephrine should always available and ready for use. In patients with mastocytosis, prompt administration

of epinephrine is indicated for treatment of severe spontaneous hypotensive episodes. Treatment is aimed at opposing the effects of mediators in the body that have been released while in turn, stabilizing the mast cell membrane (Vaughan & Jones, 2002). There has been known episodes of unpredictable profound hypotension in patients with SM, and most reasonably caused by mast cell mediators histamine and prostaglandin D2 (Vaughan & Jones, 2002). Any reaction, from isolated flushing to anaphylaxis should be investigated in order to identify the mechanism of the reaction and performing an IgE specific assay is recommended to rule out if the reaction was from the disease process or drug/agent-induced IgE-mediated mechanism (Klein & Misseldine, 2013). Epinephrine has been known to have added benefit not only for cardiovascular symptoms, but the beta-2 adrenoceptors can be used to prevent degranulation on the mast cell (Vaughan & Jones, 2002). In patients with SM, bronchospasm is said to usually not occur, although due to where mast cells populate and their exposure to the external environment (skin, gastrointestinal, and respiratory tracts), risks are present for severe mast cell degranulation (Renauld et al., 2011).

Postoperative Management

Continuing treatment including antihistamines, leukotriene antagonists, and steroids has not been found as an added benefit in the postoperative period, as it does in the preoperative period, however extended post anesthesia management and monitoring is still recommended in patients with mastocytosis (Klein & Misseldine, 2013). It is also highly suggested that an "immediate reaction occurring in patients with mastocytosis should be investigated extensively, including measurement of serum tryptase levels and skin tests, in order to document the mechanism of the reaction, either histamine release due to the disease itself or due to concurrent drug/agent-induced IgE-mediated mechanism" (Renauld et al., 2011, p 456).

Conclusion

The effect that anesthesia and surgery have on potential mast cell mediator release in patients with mastocytosis is poorly investigated. With perioperative anaphylaxis incidences being much higher in patients with mastocytosis, anesthesia practitioners need evidence-based research guidelines to avoid and control mast cell mediator-associated symptoms. Currently, there is limited data and no official guidelines for intraoperative management of mast cell activation disease. Extended research is needed to assist in predicting and treating the anaphylaxis-like incidences that can occur with this disease.

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Anesthesia for the Patient with Mast Cell Activation Disease

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Introduction

- Mast cell activation disease involves mast cell activation and degranulation with the enhanced release of chemical mediators.
- Occurs unpredictably to a variety of triggering stimuli (allergic, microbial, nonimmune) making perioperative management difficult as both anesthesia and surgery are responsible for triggers of rapid activation of mast cells in patients with mastocytosis.
- Epidemiology: Estimated <200,000 people in the US are effected and occurs is both children and adults
- Mastocytosis: Umbrella term comprising of systemic mastocytosis (all forms), mast cell leukemia, and cutaneous mastocytosis.
- Classification systems and diagnostic criteria for mastocytosis were first proposed in the 1980s and mast cells were first discovered in the late 19th century

Pathogenesis

- Mast cells are formed in the bone marrow first as pluripotent stem cells, where they differentiate and mature into the adult form with the help of stem cell factor.
- From the bone marrow, mast cell progenitor cells then migrate into the vessels, peripheral tissues, and nerves were growth and differentiation occur as well as the binding of surface tyrosine kinase
- Differentiation is not complete until the cells reach peripheral tissues involving most solid tissues including the lung, heart, and central nervous system
- Mast cells have secretary granules that contain proteases, which are the major proteins that comprise them, with the major protease being tryptase

Pathogenesis

- Surface tyrosine kinase receptors
  - mast cell markers
    - CD34, CD13, CD117 (C-KIT), and CD25
    - Point mutations can exits at the "C-KIT locus (Asp816Val, or codon 816)
    - Codes for an abnormal cell membrane receptor protein for stem cell factor, producing clonal mast cell lines that lack normal growth and differentiation
- The mutated mast cells have granules that store and generate a number of vasoactive mediators
  - Histamine, tumor necrosis factor-α (TNFα), vascular endothelial growth factor (VEGF), leukotrienes, prostaglandin D_2 interleukins, proteases, heparin.
- These mutations are able to be detected in the bone marrow where the C-KIT mutation can be found in 90% of adults with systemic mastocytosis

Diagnosis of Systemic Mastocytosis

Systemic mastocytosis
Presence of at least 1 major and 1 minor criterion or 3 minor criteria in the bone marrow or other extracutaneous organ:
Major
Multifocal dense infiltrates of MCs (>15 MCs in aggregates)
Minor 1. MC infiltrates contain >25% spindle-shaped cells or other atypical morphologic features 2. c-KIT D816V mutation 3. Expression of CD2 and/or CD25 on CD117 $^{+}$ MCs 4. Serum tryptase levels >20 ng/mL (not valid if patient has concomitant hematologic disorder)

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Triggers

Category	Examples
Physical stimuli	Heat, cold, friction, pressure, excessive sunlight, intense exercise
Emotional factors	Stress, anxiety
Drugs	Aspirin, NSAIDs, thiamine, alcohol, morphine, codeine, polymyxin-B, amphotericin B, quinine, dextromethorphan, anticholinergic preparations, vancomycin, α-adrenergic blockers
General anesthesia	Succinylcholine, d -tubocurarine, metocurine, doxacurium, atracurium, mivacurium, rocuronium, etomidate, thiopental, enflurane and isoflurane, lidocaine
Venoms	Snakes, stinging insects
Polymers	Dextran
Miscellaneous	Radiocontrast media

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Selected Mast Cell Mediators and Effects

- **Histamine**
  - Hypotension, shock, tachycardia, pruritis, urticaria, gastric hypersecretion, abdominal pain
- **Prostaglandin- D2**
  - Flushing and syncope
- **Heparin**
  - Hemorrhage (surgical and gastric)
- **Thromboxane**
  - Bronchoconstriction and vasoconstriction
- **Leukotrienes**
  - Vasoconstriction/vasodilation, increased capillary permeability
- **Tryptase**
  - Fibrinolysis

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Treatment

Symptom	Initial therapy
Pruritus	H 1 antihistamines
Flushing	H 1 antihistamines
Recurrent anaphylaxis	H 1 and H 2antihistamines, self-injectable epinephrine
PUD	PPI
Diarrhea, nausea, vomiting, abdominal pain	H 2 antihistamines
Malabsorption	Cromolyn
Osteoporosis	Calcium and vitamin D
Bone pain	Non-NSAID analgesia
Neurologic symptoms	H 1 and H 2antihistamines

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Case Information

- Surgical Procedure
  - Hysterectomy, dilation and curettage, intrauterine device insertion for abnormal uterine bleeding
- Age: 40
- Gender: Female
- Weight: 112kg
- ASA: 2
- No known allergies

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Pre-operative Evaluation

- Past Medical History
  - history of mast cell activation syndrome, multiple past allergic shock states, hypertension, obstructive sleep apnea, morbid obesity, anxiety, hypermenorrhea, and left ovarian cyst
- Surgical History
  - None
- Home Medications: EpiPen (epinephrine injection USP), Zyrtec (cetirizine), Allegra (fexofenadine), Singular (montelukast), Zantac (ranitidine, Hcl), Requip (ropinirole Hcl), and labetalol.
- Pre-op VS
  - BP: 134/79, HR: 89, Resp Rate: 16, O2 sat: 98%, Temp: 36.9 degrees Celsius
- Pertinent labs: all WNL
- Airway evaluation: Mallampati 2, TMD adequate, incisor distance adequate

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Medications

- Drugs:
  - Premedicated
    - **2mg Versed**
    - **25mg Diphenhydramine**
    - **10mg Dexamethasone**
  - Induction
    - **150mg Fentanyl**
    - **14mg Etomidate**
    - **30mg Rocuronium**
  - Maintenance
    - **Sevoflurane 2%**
    - **Dexmedetomidine 0.5mcg/kg/hr**
  - Emergence
    - **Glycopyrrolate 0.6mg**
    - **Neostigmine 4mg**
- Drugs:
  - Intraoperative
    - **Albuterol**
    - **Solumedrol 125mg**
  - Emergency meds on hand
    - **Epinephrine diluted to 10mcg/ml**

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Intraoperative Issues

- Bronchospasm X2
  - #1) After intubation
    - Sats 70%, ↑ PIP, ↑ height & "shark-fin" appearance on capnography waveform, diminished breath sounds, wheezing.
    - Treatment: Positive pressure with fio2 100%, Increased sevoflurane gas, albuterol administered endotracheally (10 puffs), Solumedrol 125mg after spasm resolved
  - Maintenance:
    - Sevoflurane kept at 2.8%
  - Most likely caused from intubation stimulation
    - Possibly Etomidate or Rocuronium.

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Intraoperative Issues

- Bronchospasm #2
  - ↑ PIP, Sats declining, ↑ height on capnography waveform, no audible breath sounds.
  - Treatment:
    - Positive pressure with fio2 100%, Increased sevoflurane gas, albuterol administered endotracheally (10 puffs)
    - Resolved within one minute
  - No explainable cause except for current surgical stimulation

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Emergence & PACU

- Decision to extubate deep
  - Sevoflurane at 2.5%, full reversal per kg given, Dexmedetomidine infusion continued on
  - Spontaneously breathing (Vt & RR adequate)
  - TOF confirmed with strong tetany hold
  - Albuterol administered endotracheally
  - Oral airway placed
  - Suctioned while deep
  - Extubation on 10L oxygen simple mask

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PACU

- Notified of patient with highly irritable airway
- Referral for respiratory therapy, and CPAP therapy on standby
- No bronchospasm or respiratory issues
- Patient discharged home later that day

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Discussion

- Anaphylaxis due to a "massive mast cell mediator release is present in a significant portion of systemic mastocytosis (SM) patients (22–49%) and can be elicited by either known or unknown triggers through diverse mechanisms involving IgE- or non-IgE mediated pathways" (Matito et al., 2015).
- The severity of reactions that occur in the operating room depend on the "cardiovascular homeostasis disturbances, as profound vasodilatation following mast cell degranulation with subsequent histamine release may, at the extreme, result in life-threatening conditions" (Renauld et al., 2011).
- Suggested prophylaxis regimens found throughout the medical literature suggest that anti-histamines and steroids be taken, as well as acquiring a baseline tryptase level and identifying a patient with mast cell activation disease with a med alert bracelet (Klein & Misseldine, 2013).

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Discussion

Mast Cell Degranulation

- **Intraoperative crisis management:**
  - Epinephrine available and ready for use
  - Opposing the effects of mediators that have been released
  - Any reaction, from isolated flushing to anaphylaxis should be investigated in order to identify the mechanism of the reaction and performing an IgE specific assay is recommended to rule out if the reaction was from the disease process or drug/agent-induced IgE-mediated mechanism (Klein & Misseldine).
  - In patients with systemic mastocytosis, bronchospasm is said to usually not occur, although due to where mast cells populate with exposure to the external environment (skin, gastrointestinal, and respiratory tracts), risks are present for severe mast cell degranulation (Renauld et al., 2011).

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Recommendations

- **Preoperative:**
- Preoperative prophylaxis regimes as well as pretreatment for conditions of intraoperative stress (anesthesia and surgery) need to be conducted to prevent possible cardiovascular collapse with adult mastocytosis. Immediate reaction occurring in patients with mastocytosis should be highly investigated for future documentation of the mechanism of the reaction.
- Preparation for cardiovascular collapse is required, especially in a known mastocytosis patient undergoing anesthesia for a surgical case. It is important the practitioner is aware that patients with mastocytosis "experience both immune (IgE-related) and non-immune anaphylaxis, and the overall incidence of anaphylaxis in patients with mastocytosis has been reported to be higher than in the general population" (Klein & Misseldine, 2013).
- The most substantial mediator is histamine. The prophylactic use of H1-receptor and H2-receptor antagonists are given to prevent preformed histamine release.
- Glucocorticoids are used as mast cell stabilizers and have anti-inflammatory properties (Klein & Misseldine, 2013).

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Recommendations

- **Intraoperative:**
  - Maintain avoidance of triggers
    - Medications mentioned earlier
    - Deep anesthetic technique
  - Matito et al., (2014) reviewed 501 mastocytosis patients who underwent anesthetic techniques including general, regional, and local anesthetic techniques, and found that, in adult mastocytosis patients who "underwent anesthetic procedures the frequency of anaphylaxis was 0.6% and mast cell mediator release symptoms was 7% respectively and despite this, anesthetic procedures are considered high risk in mastocytosis since severe reactions (e.g. systemic hypotension/anaphylactic reactions and coagulopathy) resulting in death in individual patients have been recurrently reported" (Matito et al., 2015, p 53).
- **Posteoperative:**
  - Continue treatment with antihistamines, leukotriene antagonists, steroids in postop period.

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Conclusion

- Mast cell degranulation in patients with mastocytosis is unpredictable, and does not occur consistently in any given patient. It is also unclear when drugs that elicit histamine release in normal patients or under study conditions will produce the same response in mastocytosis patients undergoing anesthesia
- There are currently no official guidelines for intraoperative management of mast cell activation disease and no known studies have been found to predict mast cell degranulation in this patient population. Extended research is needed for perioperative antidotes for the anaphylaxis-like incidences in mastocytosis patients.

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Thank You
Are There Any Questions?

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