

Systemic Mastocytosis Complicating Pregnancy

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BACKGROUND: Systemic mastocytosis is a rare medical disorder in which an increased number of mast cells can precipitate immediate hypersensitivity reactions, leading to hypotension, shock, and death. It is characterized by persistent elevated serum tryptase levels. The few published reports on pregnancy complicated by systemic mastocytosis indicate favorable maternal and fetal outcomes in gravidas known to have systemic mastocytosis.

CASE: A pregnant woman treated with terbutaline at 31 weeks of gestation developed severe hypotension which resulted in fetal demise; this was initially diagnosed to be an anaphylactic reaction. The finding of persistently high maternal tryptase levels led to the diagnosis of systemic mastocytosis. In her subsequent pregnancy she was treated with an H1 blocker. Hypotension during her cesarean delivery was managed with steroid and epinephrine therapy.

CONCLUSION: Exacerbations of systemic mastocytosis during pregnancy can lead to significant maternal and fetal complications. Treatment with H1 blockers, and when indicated, steroids and epinephrine, can reduce these complications.

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Mastocytosis is a rare condition of unknown etiology, in which mast cells exceed their normal number. Mast cells are normally involved in the inflammatory cascade and have a major role in type I or immediate hypersensitivity reactions (allergic reactions). Circulating immunoglobulin (Ig) E molecules specific for a particular allergen bind to IgE receptors located on the surface of mast cells. Bound IgE molecules cross-link on encountering an allergen re-

sulting in mast cell activation, initiating an allergic or anaphylactic response.

Histamine, heparin, and tryptase are the most recognized preformed mediators that are released. Newly formed mediators at the time of the reaction include prostaglandins, leukotrienes, chemokines and cytokines. Together these chemical compounds produce a response that increases vascular permeability while also promoting tissue damage, leukocyte chemotaxis, and cardiovascular, gastrointestinal, and bronchial smooth muscle contraction. This cascade of events is often started and limited to the specific site of allergen contact, such as the lungs or the skin. However, if this reaction progresses, it can affect a patient on a systemic level, leading to anaphylaxis. Severe anaphylaxis can result in hypotension, shock, and death.

Mastocytosis is subdivided into two categories based on pathology and clinical manifestations: cutaneous and systemic. Cutaneous mastocytosis is a condition in which accumulations of mast cells are present in the dermal tissue. It is diagnosed with gross skin findings, histopathology, and symptoms including pruritus, urticaria, blisters, or cutaneous irritation and hemorrhage. Complications associated with cutaneous mastocytosis are episodic and primarily dermatologic. Laboratory findings in patients with cutaneous mastocytosis are usually normal, including complete blood count, tryptase levels, and urinary histamine. Markers of inflammation can be increased depending on the extent of cutaneous involvement.¹

Systemic mastocytosis is the abundance of mastocytes in extradermal tissues, with or without cutaneous involvement. Two types of symptom groups can occur in systemic mastocytosis, either from mast cell mediator release or from tissue infiltration and organ function compromise. Mediator release can lead to the general symptoms associated with anaphylaxis: hypotension, facial flushing, urticaria, pruritus, and syncope.² The organ most commonly infiltrated in systemic mastocytosis is the bone marrow. Bone marrow involvement can also lead to depression of all hematopoietic lines, resulting in anemia or thrombocytopenia. Although bone marrow involvement is most common, symptoms associated with gastrointestinal and neuropsychiatric involvement suggest that clinical symptoms can be widespread and variable.³ A diagnostic tool in the laboratory is bone marrow examination to determine the percent of bone marrow infiltration with mast cells. Also noteworthy in systemic mastocytosis is an elevated tryptase level and an elevated urinary histamine.⁴

There is limited information on systemic mastocytosis complicating pregnancy, and reports are lim-

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ited to gravidas known to have this condition before pregnancy occurred. We present a case of systemic mastocytosis in which both fetal and maternal complications occurred.

CASE

A 32-year-old white woman, gravida 7 para 2, presented to our clinic in early pregnancy. Her obstetric history was remarkable for four spontaneous early pregnancy losses, all of which occurred between 6 and 7 weeks of gestation. Six years before this pregnancy, she had undergone a vacuum-assisted vaginal delivery at 37 weeks of gestation, without obstetric complications.

Four years before this pregnancy, the patient presented to her local hospital at 31 weeks of gestation with regular contractions and abdominal pain. She was treated with subcutaneous terbutaline and shortly thereafter developed severe hypotension. The clinical diagnosis was an anaphylactic reaction. An emergency cesarean delivery was performed for fetal bradycardia, which resulted in fetal demise. A terbutaline allergy was suspected. Postoperative evaluation included a tryptase level that was markedly elevated at 231 ng/mL (normal <11.5 ng/mL). A follow-up tryptase level obtained 3 weeks later was still significantly elevated at 49.7 ng/mL. Further evaluation included elevated levels of 24-hr urine 11-beta prostaglandin F₂ alpha 6,837 ng/24 h (normal <1,000 ng/24 h) and N-methylhistamine 628 micrograms/g creatinine (nl 39–200 micrograms/g creatinine). Because of suspicion of systemic mastocytosis, a bone marrow biopsy was recommended, but the patient refused this procedure.

During the current pregnancy, the patient was seen in consultation with the allergy and immunology service. Initial laboratory values showed a normal complete blood count and a normal calcitonin; her tryptase level was elevated at 50.7 ng/mL. A 24-hour urine showed 5-HIAA to be within normal limits, but there was a markedly elevated 11-beta prostaglandin F₂ alpha at 8,373 ng/24 h, and her N-methylhistamine level was elevated at 473 micrograms/g creatinine. The serum c-Kit ASP 816VAL gene mutation analysis was positive. A clinical diagnosis of systemic mastocytosis was made; the patient again refused a confirmatory bone marrow biopsy.

Because of the concern for a flare of mastocytosis, she was treated with an H1 blocker throughout the pregnancy, cetirizine 10 mg, once daily. She was counseled on the signs and symptoms of mastocytosis and their management. The anesthesiology team met with the patient 1 month before her delivery date and formulated an anesthetic plan. The initial plan was for a repeat cesarean delivery under spinal anesthesia at term, in as low-stress environment as possible.

At 35 weeks, the patient developed a flu-like illness, was hospitalized, and because of continuing contractions, was delivered at 36 weeks of gestation. One hour before her cesarean delivery, she was administered 30 cc of oral

sodium citrate and 2 g of intravenous cefazolin. Four milligrams of intravenous dexamethasone and 12.5 mg intravenous diphenhydramine were administered for prophylaxis of mast cell release. A spinal anesthetic was performed with 1.6 cc 0.75% heavy bupivacaine with 0.1 mg epinephrine and 20 micrograms fentanyl. A phenylephrine infusion was initiated at 0.5 micrograms/kg/min and titrated throughout the low transverse cesarean delivery. Vital signs remained stable from the time of the spinal anesthetic until birth with systolic blood pressure between 110 and 130 mm Hg and heart rate between 60 and 100 beats per minute.

Ten minutes after the birth of a vigorous neonate, the patient began to complain of throat tightness and difficulty breathing. Her systolic blood pressure dropped to 80 mm Hg and her heart rate remained stable around 80 beats per minute. Her hemoglobin oxygen saturation dropped to 92% and oxygen was administered by close fitting face mask at 10 L/min. Epinephrine 0.05 micrograms, diphenhydramine 12.5 mg, and dexamethasone 4 mg were administered intravenously and an arterial line was placed. Intravenous epinephrine 0.05 micrograms was given three more times over the next 5 minutes, for a total dose of 0.2 micrograms epinephrine. Her systolic blood pressure responded to the interventions and remained greater than 110 mm Hg throughout the remainder of the case. The patient was transferred to the intensive care unit for postoperative observation where she recovered uneventfully.

COMMENTS

Mast cells cannot be identified in peripheral blood, but can be found in tissues adjacent to blood vessels, and under epithelial surfaces. Tryptase is a neutral protease, which, along with histamine, is a preformed component in mast cells. An elevated tryptase level helps confirm a mast cell mediated reaction and is therefore high in anaphylactoid reactions. Tryptase levels peak 1 hour into an allergic reaction and return to normal over 4 to 8 hours. Levels should be obtained in patients with an atypical severe allergic reaction. If the level is elevated, it should be repeated greater than 24 hours later to see if it normalized. A persistently elevated tryptase raises the suspicion for an underlying mast cell disorder such as systemic mastocytosis. A tryptase level is thought to be the best test to screen for mastocytosis. In patients with systemic mastocytosis, tryptase levels are chronically elevated, and further elevated during a mastocytosis flare. An underlying mast cell disorder should be suspected in patients with a history of recurrent anaphylactic-type episodes, especially in those without a clear cause. As seen in our case, however, this history may not be present.

In systemic mastocytosis, abnormally high levels of mastocytes can precipitate an environment in which a patient is extremely susceptible to uncon-



trolled IgE mediated release. Triggers for the release of mast cell mediators in systemic mastocytosis can be variable. These triggers include physical (physical and emotional stress, extreme temperatures), chemical (alcohol, radiocontrast material) and biologic (infections, animal venoms) agents.⁵ This phenomenon has recently been seen in hymenoptera venom allergy. The wide variety of triggers for mediator release makes systemic mastocytosis a volatile, erratic, and dangerous disease that can complicate the health of any patient, especially those with prior chronic health conditions or stress of any kind, including pregnancy. Because of the wide variety of triggers for release, patients with mastocytosis may not be able to adequately avoid a trigger that produces this life-threatening reaction. The exact mechanism by which these triggers cause mediator release from mast cells has not been elucidated.

Researchers have targeted several molecular factors for their possible link to the development of mastocytosis. C-kit, or CD117, is a mast cell marker and receptor whose gene, KIT, has been implicated in c-kit over expression.⁶ An activating mutation in KIT leads to over expression of c-kit on the cell surface of mastocytes that can cause signaling abnormalities, cell cycle dysregulation, and overgrowth of mast cells.⁷ The ligand for the c-kit receptor, stem cell factor, is also thought to be a source of cellular dysregulation that can lead to a state of mastocytosis.

Pregnancy is known to cause many physiologic changes, including significant increases in circulating blood volume and cardiac output. Despite a higher circulating blood volume, blood pressure decreases. Systemic blood pressure can decrease by 10 mm Hg, and diastolic can decrease even more, by up to 15 mm Hg. This decrease in blood pressure in a pregnancy complicated by systemic mastocytosis can exacerbate hypotension, posing danger to both the mother and the child.

Furthermore, pregnancy-induced changes in the immune system could be potentially harmful in pregnant women with systemic mastocytosis. In pregnancy, the innate immune system is favored over the adaptive immune system to prevent immune detection of the developing fetus. With the depression of the adaptive immune system and the enhancement of the innate immune system, the number and concentration of mast cells in circulation has the potential to increase, making any triggered release potentially even more significant.

Stress is also a well-known trigger for mediator release in systemic mastocytosis. Pregnancy complications can be associated with increased levels of

maternal stress, and labor is clearly a time of increased maternal pain and stress. These events can become triggers for mast cell release in a pregnant woman with systemic mastocytosis.

Several cases of systemic mastocytosis in pregnancy have been previously documented. In these cases, the diagnosis of systemic mastocytosis was known before pregnancy. Worobec et al reported a retrospective series of eight women with mastocytosis who were studied via a questionnaire.⁸ Five of these women had cutaneous mastocytosis and three had systemic mastocytosis, with bone marrow and skin involvement. In those with systemic mastocytosis the presenting symptoms before pregnancy were fatigue, nausea, pruritus, musculoskeletal pain and gastrointestinal symptoms; two of the three were treated with steroids during the pregnancy. There were no obstetric complications attributable to systemic mastocytosis, and no neonates had symptoms of mastocytosis. No serious or life-threatening maternal complications occurred.

In another report a woman with previously diagnosed systemic mastocytosis used a labor coach and a controlled calm environment for her delivery method. No complications ensued in the pregnancy or delivery.⁹ Several other cases with cutaneous mastocytosis have also been published with no obstetrical complications but only a mild worsening of dermatologic symptoms including pruritus and flushing.^{10,11}

Anesthetic management of patients with systemic mastocytosis focuses on preventing an anaphylactoid reaction and being prepared to treat mast cell degranulation should it occur. Perioperative mast cell degranulation can occur as a result of emotional or physical stress, exposing the patient to an allergen to which they have been sensitized or as a result of administering a drug that stimulates the release of histamine. Therefore, prevention includes maintenance of a reassuring intraoperative environment, maintenance of normothermia, avoiding any exposures that resulted in prior reactions for the patient, and avoidance of drugs known to release histamine such as morphine. Some experts recommend pretreatment with glucocorticoids, H1 and H2-histamine receptor antagonists, or Cromolyn sodium. However, it must be noted that studies have not shown efficacy of such treatment in recurrent anaphylaxis.¹²

Perioperative mast cell degranulation can also occur spontaneously, and therefore even with the most thorough prevention plan, preparation to treat a reaction is essential. Ready access to epinephrine, adequate intravenous access, and the availability of additional anesthesia personnel to assist in resuscitation is essential. In this case, preparation of all providers for possible adverse



events, prophylaxis with dexamethasone and diphenhydramine, and early treatment with diluted epinephrine resulted in a favorable outcome.

The case we presently report demonstrates that systemic mastocytosis may be a cause of obstetric complications. We think that the fetal demise which occurred at 31 weeks of gestation was caused by an exacerbation of systemic mastocytosis which resulted in severe hypotension and a critical decrease in uterine blood flow. Even with optimal pretreatment and preparation for emergency in a patient with known systemic mastocytosis, hypotension can occur, as was seen in our patient during her most recent pregnancy. Our patient has the c-kit mutation; the mechanism by which this mutation occurs is not known. There is no evidence to date that the ASP 816 VAL (D816V) mutation is passed from generation to generation.

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Bilateral Internal Carotid Artery Dissection in the Postpartum Period

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BACKGROUND: Bilateral internal carotid artery dissection is a rare event associated with pregnancy, especially in a patient without any predisposing risk factors.

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CASE: A 34-year-old woman presented with postpartum unilateral weakness, headaches, and blurry vision 14 days after vaginal delivery. Radiologic imaging revealed bilateral cervical internal carotid artery dissections and cerebral infarctions. She was treated with anticoagulation and showed radiographic and clinical improvement.

CONCLUSION: The pathophysiology of cervical artery dissection appears multifactorial, with evidence suggesting environmental and genetic contributions. Intimal injury related to the Valsalva maneuver during labor as well as hemodynamic and hormonal changes related to pregnancy are presumed causes of peripartum spontaneous carotid artery dissection. Antithrombotic therapy for at least 3 to 6 months after dissection and follow-up neuroimaging are suggested.

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The incidence of spontaneous bilateral internal carotid artery dissection is an extremely rare event, especially in association with pregnancy. Although it is presumed that physiologic changes associated with the peri- and postpartum period are the cause of this vascular injury, there have been reports of genetic

