

Grand Rounds Review

Management of Mastocytosis in Pregnancy: A Review

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In this article, the authors present a case of pregnancy complicated by the need for management of indolent systemic mastocytosis. The diagnosis of mastocytosis is reviewed, as well as subtypes of mastocytosis and management options particularly in pregnancy. A table of pregnancy/lactation categories for common medications used in mastocytosis is presented. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Tryptase; Mastocytosis; C-kit; Antihistamines; Interferon alfa 2b; Pregnancy; Anaphylaxis*

CASE

A 35-year-old female, gravida 1 para 0, with indolent systemic mastocytosis with D816V KIT mutation was seen in clinic. Her diagnosis had previously been confirmed by bone marrow biopsy, which demonstrated 80% to 90% marrow cellularity, which was composed of 50% to 60% mast cells on core biopsy. Mast cells were diffusely immunoreactive for CD117 (c-kit), mast cell tryptase, coexpression of CD25, but negative for CD2. Her baseline serum tryptase level was markedly elevated and ranged from 100 ng/mL to 180 ng/mL.

The patient first began having symptoms of mastocytosis at the age of 19 years with episodes of flushing, hypotension, and palpitations approximately 5 to 6 times per year and was ultimately diagnosed with systemic indolent mastocytosis at the age of 22 years (initial values of tryptase unknown from previous evaluations). She did not have skin involvement. She had a history of reactions to nonsteroidal anti-inflammatory drugs, computed tomography intravenous contrast agents, opioids, and aspirin with resultant hypotension and hives, consistent with mast cell degranulation. Her disease had been difficult to control with frequent emergency department visits and hospitalizations

for episodes of acute decompensation with diffuse flushing, pruritus, hypotension, palpitations, abdominal pain, and nausea/vomiting/diarrhea, consistent with anaphylaxis.

The patient was placed on and failed multiple therapeutic options including antihistamine monotherapy, aspirin desensitization, cromolyn, ketotifen, and hydroxyurea. It was not until she was initiated on interferon alfa-2b that she improved. Interferon alfa-2b was started at a subcutaneous dose of 600,000 units, 3 times a week (final effective dose, 1.2-2.4 million units 3 times/wk), in September 2010. After initiation on interferon, she reported reduction in mastocytosis symptoms including gastrointestinal symptoms, tachycardia, and flushing with corresponding reduction in emergency department visits and tryptase levels (last tryptase level before interferon start was 131 ng/mL, first tryptase level checked after start of interferon was 51 ng/mL). She continued to fluctuate in tryptase levels but often in the 100 ng/mL range and did not have much higher levels as in the past (up to >200 ng/mL measured during an anaphylactic episode). She similarly noted a reduction in the frequency of home oral glucocorticoid courses needed to manage her symptoms.

Because of her desire to become pregnant, in order to minimize the potential risks to the fetus during pregnancy, she was taken off interferon; however, this resulted in multiple symptomatic recurrences of her mastocytosis that required oral and intravenous courses of corticosteroids. Her symptoms included increased flushing, tachycardia, nausea, diarrhea, and abdominal discomfort. Two of these episodes required inpatient admission and one of which required epinephrine usage. During the inpatient admission that followed her home use of a self-injected epinephrine, the decision was made to resume her interferon alfa-2b at a dose of 600,000 units, 3 times a week, and titrated up to 2.4 million units, 3 times a week, which finally resulted in better symptom control at the beginning of her pregnancy.

A preconception consultation with the maternal-fetal medicine team was obtained and given the lack of definitive adverse fetal effects in the current medical literature and her improved disease control, she was continued on interferon. She then became pregnant. At the time of her pregnancy, she was stable on a regimen of antihistamines, leukotriene antagonists, prednisone as needed, and interferon alfa-2b. She never required epinephrine during her pregnancy course.

Her pregnancy was managed by a multidisciplinary team, including high-risk obstetrics, anesthesia, and allergy. A plan for her delivery was made, including labor and postpartum pain control with epidural/combined spinal-epidural without opioid medication to avoid mast cell activation and premedication with intravenous methylprednisolone 40 mg.

During her pregnancy, she had fluctuating symptoms of her mastocytosis. In her first trimester, she felt improved with symptoms well controlled on antihistamines and interferon

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TABLE I. Medications taken

Pregnancy	Labor and delivery	Postpartum
Hydroxyzine 50 mg bid	Propofol 350 mg	Hydroxyzine 50 mg bid
Montelukast 10 mg qd	Fentanyl 200 µg	Montelukast 10 mg qd
Ranitidine 150 mg bid	Hydrocortisone 100 mg	Ranitidine 150 mg bid
Cetirizine 10 mg bid	Succinylcholine 100 mg	Cetirizine 10 mg bid
Interferon alfa 2b 1.2-2.4 million units 3×/wk	Ondansetron 4 mg	Interferon alfa 2b 2.4 million units 3×/wk
Diphenhydramine 25-50 mg prn	Cefazolin 2 g	Diphenhydramine 25-50 mg IV prn
Prednisone 50 mg qd prn	Bupivacaine 0.1% 3-12 mL/h	Bupivacaine 0.1% 3-12 mL/h
	Dexamethasone 8 mg	POD 0: Methylprednisolone 120 mg IV
	Famotidine 40 mg IV	POD 1: Methylprednisolone 40 mg IV
		POD 2: Methylprednisolone 40 mg IV
		POD 3: Prednisone 40 mg

bid, Twice a day; *IV*, intravenous; *POD*, postoperative day; *prn*, as needed; *qd*, every day.

alfa-2b at 1.2 million units 3 times a week. In her second trimester, she began having increased flushing, nausea/vomiting, hypotension, and dizziness, which required an emergency department visit and observation, and several short courses of prednisone tapers to an average of 120 mg of prednisone/mo. Her interferon was increased to 2.4 million units 2 times a week with better control. Her pregnancy was complicated by an episode of flushing, pruritus, palpitations, and decreased fetal movement at the end of her 37th week of pregnancy, for which she presented to the hospital. Upon presentation, the fetus was found to be bradycardic and required emergent cesarean delivery. She underwent general anesthesia with propofol, fentanyl, and succinylcholine without complication (for full list of perioperative medications, see Table I). She did have an epidural placed and was started on bupivacaine 0.1% for postoperative pain control. She gave birth to a healthy male infant.

INTRODUCTION

Mastocytosis is a rare disorder that is characterized by increased mast cell proliferation and accumulation in organs. It is broadly separated into 2 subgroups: cutaneous and systemic mastocytosis. Cutaneous mastocytosis results from increased dermal accumulation of mast cells with involvement limited to the skin.¹ It presents with skin lesions usually during infancy and may also be associated with urticaria, pruritus, flushing, and dermatographism. Systemic mastocytosis involves extracutaneous organs and may or may not have skin manifestations. It commonly involves the bone marrow, liver, lymph nodes, and gastrointestinal tract.¹ Symptoms can be a result of mast cell mediator release (such as hypotension, abdominal pain, syncope, vascular collapse, and flushing) or a result of mast cell organ infiltration (cytopenias, portal hypertension, malabsorption).¹⁻³

In systemic mastocytosis, mast cell mediator release can be provoked by any number of stimuli including stress (physical and emotional), infections, and medications (alcohol, nonsteroidal anti-inflammatory drugs, opioids, radiopaque agents), among many others.⁴ Studies investigating a correlation between mast cell burden (tryptase levels) and risk of anaphylaxis have yielded conflicting results.^{5,6} Pregnancy, a time of great physiological change, and also labor provide numerous stressors that can trigger worsening of mastocytosis symptoms. Mastocytosis, in turn, can potentially complicate obstetric and prenatal care.

Systemic mastocytosis is classified into several categories by the World Health Organization including indolent, smoldering, aggressive, associated clonal hematological non—mast-cell lineage disease, and mast cell leukemia.^{1,7-9} Indolent systemic mastocytosis, the most common form of systemic mastocytosis, is distinguished by a stable or slowly progressing course and the absence of end-organ dysfunction (cytopenias, malabsorption, etc). Smoldering systemic mastocytosis is characterized by high mast cell burden (usually >30% marrow involvement and a tryptase level of >200 ng/mL) but absence of other hematologic disease or aggressive features. Aggressive systemic mastocytosis is notable for end-organ dysfunction secondary to mast cell infiltration including liver dysfunction with ascites, pathologic fractures, bone marrow failure, malabsorption, and weight loss. Systemic mastocytosis with associated clonal hematological non—mast-cell lineage disease is most commonly associated with myelodysplastic or myeloproliferative disorders and rarely lymphoproliferative diseases. Mast cell leukemia occurs when immature mast cells are present in more than 10% of the peripheral blood or more than 20% of bone marrow smears.

Patients with cutaneous and indolent systemic mastocytosis are managed using a combination of anti—mast cell mediator medications usually including H1 and H2 antihistamines, anti-leukotriene agents, and oral cromolyn. Cyto-reductive therapy in mastocytosis is considered in those with advanced disease and those with recurrent life-threatening mast cell activation symptoms despite first-line management strategies. Current cyto-reductive treatment options for mastocytosis include alfa interferon, cladribine, and imatinib.^{10,11} Imatinib can be effective in a handful of cases who do not carry the D816V KIT mutation.⁹ Investigational tyrosine kinase inhibitors including midostaurin have shown promise in early clinical trials.^{12,13} Among these options, alfa interferon has recently fallen out of favor because of its slow onset of action and poor tolerability. However, given the potential harmful effects of kinase inhibitors on germ cells and cladribine on the fetus (both pregnancy category D), alfa interferon may still be the safest option in pregnancy in those who require cyto-reductive therapy.

MASTOCYTOSIS IN PREGNANCY

There is limited information on the impact of mastocytosis on pregnancy, and vice versa. Mast cells, which have both estrogen and progesterone receptors, are found in the placenta and

myometrium.^{14,15} Their mediators, in particular histamine, are involved in numerous aspects of pregnancy, from implantation of the blastocyst to development of the placenta to affecting myometrial contractions.¹⁴⁻¹⁶ The role of histamine in labor, particularly that elevated histamine levels may result in uterine contractions, raises concerns about the increased risk of preterm labor in mastocytosis.^{14,15,17} One study found that the rate of spontaneous miscarriage in Poland appeared to be slightly higher than the rate in the general population in a cohort with mastocytosis (25%-30% vs 8%-20%).^{17,18} However, whether mastocytosis results in significantly increased rates of adverse maternal or fetal outcomes from that of the normal population is unclear. Matito et al¹⁹ and Worobec et al²⁰ reported that mastocytosis did not significantly change pregnancy or fetal outcomes. Indeed, although the complications of mastocytosis in pregnancy are not well described in the literature, a review of 45 cases of pregnancy in mastocytosis by Matito et al¹⁹ revealed that 3 out of 45 births were preterm (6.6%), which is comparable to the European rate (~5%) and developed nation rate (~8%) of preterm birth.²¹ The few other smaller case series and case reports in the literature suggest similar findings, with no significant complications in labor or delivery.^{14,19,20}

Treatment of mastocytosis in pregnancy is directed toward alleviating symptoms while weighing the risks of medications to the fetus. Conservative management typically involves avoidance of triggers, prophylactic antihistamine therapy, and corticosteroids and additional antihistamines as well as epinephrine as needed.^{14,19} Often, medication doses are reduced for fetal protection. This raises the difficult question of how best to balance maternal symptom management against minimization of fetal harm, and whether medication effect or mast cell release might have the greater negative impact on fetal health. There are minimal recommendations in the literature regarding medication use in the management of mastocytosis in pregnancy. The general accepted treatment method, however, favors titration of medications to symptomatic control with the thought that mast cell mediator release has the greater potential for fetal harm than a potential medication effect, while trying to avoid pregnancy category C and higher medications. Most sources agree that H1 and H2 antihistamines are safe in pregnancy.^{14,19} Interestingly, although approximately 22% to 33% of patients in studies experienced a worsening of their mastocytosis-related symptoms during pregnancy,^{14,19,20} approximately 33% experienced an improvement.¹⁹

In our case, the patient had previously failed antihistamine, steroid, and mast cell stabilizers with resultant need for hospitalization. She was stabilized on interferon alpha-2b and did not tolerate discontinuation in the preconception period. There are no previous case reports of systemic mastocytosis being managed with interferon alpha-2b in pregnancy, and minimal overall data of interferon alpha-2b use in pregnancy.

ANTIMEDIATOR THERAPY IN PREGNANCY

Antihistamines

A key aspect of mastocytosis management is symptom control, with antihistamines as the cornerstone of pharmacologic treatments.^{1,2,11} Antihistamines are used to treat the wide spectrum of mastocytosis symptoms, although there is some preference for H1 antihistamines in the treatment of flushing, pruritus, and urticaria, whereas H2 antihistamines are used for

gastrointestinal-related symptoms.^{1,11} There is significant use of antihistamines, even in the general population, during pregnancy with 10% to 15% reporting use.¹¹ The literature suggests that antihistamine use is generally safe. Antihistamines carry a pregnancy risk category of B or C (see Table II).

First-generation H1 antihistamines are notable for their ability to cross the blood-brain barrier and are frequently more sedating than the second-generation H1 antihistamines,²² which is why second-generation H1 blockers are generally preferred. H1 antihistamines have not been associated with significant birth defects.²³ There are a few case reports and case series that report associations such as between diphenhydramine (category class B with no reported teratogenic effects in animals) and cleft palate, although this has not been confirmed in the current literature.^{22,23} Other such associations include doxylamine and neural tube defects, oral clefts, and hypoplastic left heart, among others but all of which were not demonstrated on subsequent epidemiologic studies.²³ Hydroxyzine, which does not have a Food and Drug Administration pregnancy risk category designation, has similarly not shown increased risk of birth defects.¹⁷ Of note, the use of most first-generation H1 antihistamines is not recommended while breast-feeding.

Second-generation H1 antihistamines are likewise without significant associations with significant birth defects.²² Loratadine has been linked to hypospadias in the past, although multiple recent studies did not demonstrate an association between them.^{22,23} Newer H1 blockers such as fexofenadine lack significant data in pregnancy, thus earning a pregnancy category C designation. For this reason, many physicians consider loratadine and cetirizine, both pregnancy category class B, to be the preferred H1 antihistamines in pregnancy.²⁴

H2 antihistamines such as ranitidine and famotidine are pregnancy risk category B medications and have not been shown to increase the risk of birth defects.²²

Glucocorticoids

Oral glucocorticoids are often used in the management of mastocytosis, particularly for prevention of anaphylaxis, refractory abdominal pain, malabsorption, and widespread cutaneous disease.^{1,11} The ability of glucocorticoids to cross into the placenta raises concerns about safety of use in pregnancy, although the current literature suggests that systemic glucocorticoid use is largely safe.²⁵⁻²⁹ The placental enzyme 11B-hydroxysteroid dehydrogenase is able to reduce the percentage of active drug to around 10% through conversion of cortisol/corticosterone to the inactive 11-keto form.^{26,27} Of note, fluorinated glucocorticoids such as betamethasone and dexamethasone are less readily metabolized by the placenta and should be used sparingly.²⁶ Risks associated with glucocorticoid use include an approximately 3-fold risk of oral clefts during the first trimester and somewhat controversially, a reported association with reduced fetal size.²⁴⁻²⁹ Dexamethasone in animal studies has been shown to have 300 times the "cleft palate activity" than hydrocortisone.³⁰ Rare reports of neonatal cataract and fetal adrenal suppression have been associated with high-dose corticosteroid use in pregnancy.^{26,27} Prolonged use of oral glucocorticoids increases the risk of gestational diabetes, maternal hypertension, and, in a few reports, premature rupture of membranes and preeclampsia.²⁶⁻²⁹ Stress dose steroids during delivery are recommended in patients on long-term glucocorticoid therapy. The use of moderate doses of glucocorticoids while

TABLE II. Mastocytosis treatments and pregnancy risk

Group	Medication	Risk category	Pregnancy implications	Lactation
First-generation H1 antihistamines	Brompheniramine	C	Increased risk of birth defects	Use with caution
	Chlorpheniramine	C	No increased risk of birth defects	Excreted in breast milk, use with caution
	Dimenhydrinate	B	Crosses placenta, no increased risk of fetal abnormalities	Excreted in breast milk, use with caution
	Diphenhydramine	B	Crosses placenta, unclear historical association with cleft palate	Excreted in breast milk, breast-feeding contraindicated
	Doxylamine	C	Historical association with neural tube defects, oral clefts, hypoplastic left heart	Breast-feeding contraindicated
	Hydroxyzine	Not assigned	Crosses placenta, no increased risk of birth defects but not recommended in early pregnancy	Breast-feeding not recommended
	Meclizine	B	No increased risk of birth defects	Unknown if excreted into breast milk
Second-generation H1 antihistamines	Cetirizine	B	No increased risk of birth defects	Excreted in breast milk
	Levocetirizine	B	No increased risk of birth defects	Unknown if excreted into breast milk, not recommended
	Loratadine	B	No increased risk of birth defects, prior historical association with hypospadias	Small amounts excreted into breast milk
	Fexofenadine	C	Limited information available	Excreted in breast milk
	Desloratadine	C	Adverse events in animal studies	Excreted in breast milk
H2 Antihistamines	Cimetidine	B	Crosses placenta, no increased risk of birth defects	Excreted in breast milk, breast-feeding not recommended
	Famotidine	B	Crosses placenta, no increased risk of birth defects	Excreted in breast milk, use with caution
	Ranitidine	B	Crosses placenta, no increased risk of birth defects	Excreted in breast milk, use with caution
Mast cell stabilizer	Cromolyn	B	Safe in pregnancy	No data on excretion into breast milk, use with caution
	Ketotifen	C	Adverse events in animal studies	Breast-feeding not recommended
Anti-IgE antibody	Omalizumab	B	No increased risk of birth defects	Likely excreted in breast milk, not recommended
Glucocorticoids	Hydrocortisone	C	Increased risk of oral clefts with use in first trimester	Excreted in breast milk, wait 4 h after dose
	Prednisone	C/D	Increased risk of oral clefts with use in first trimester	Excreted in breast milk
	Betamethasone	C	Increased risk of oral clefts with use in first trimester, nonfluorinated corticosteroid preferred	Excreted in breast milk, wait 4 h after dose
	Dexamethasone	C	Increased risk of oral clefts with use in first trimester, nonfluorinated corticosteroid preferred	Excreted in breast milk, wait 4 h after dose
Leukotriene receptor antagonist	Montelukast	B	No increased risk of birth defects	Unknown if excreted into breast milk, use with caution
Cytoreductive therapies	Cladribine	D	Teratogenic effects and fetal mortality observed	Not recommended
	Imatinib	D	Pregnancy not recommended (in mother or father) within 2 wk of last imatinib dose	Not recommended
	Interferon alpha 2b	C	No clear association, contraindicated in combination therapy with ribavirin	Excreted in breast milk

breast-feeding has been found to be safe with only trace amounts of steroid excreted into human breast milk.²⁶

Omalizumab

Omalizumab is a recombinant anti-IgE mAb used in the treatment of moderate-to-severe asthma and chronic urticaria.^{15,31} It has shown potential use in the treatment of mastocytosis-related symptoms, particularly in those with recurrent anaphylaxis.¹¹ It is classified as a pregnancy category B medication and has not shown maternal toxicity, teratogenicity, or adverse fetal effects.^{28,31} Animal reproduction studies with omalizumab have not shown evidence of fetal harm despite doses up to approximately 10 times the maximum recommended human dose.³² The only adverse events seen were decreased blood platelet levels at suprapharmacologic doses.³¹ The Xolair Pregnancy Registry (EXPECT) so far has demonstrated that the rates of major congenital defects, risk of preterm birth, or small for gestational age infants is similar to the rates seen in the general asthma population.³¹ The use of omalizumab in breast-feeding mothers should be approached with caution given the limited data available. It is not yet known whether omalizumab is excreted in breast milk, although it is a reasonable assumption because IgG is excreted into breast milk.

Cromolyn sodium

Cromolyn, a mast cell stabilizer, is a frequently used medication in mastocytosis for the reduction of gastrointestinal symptoms, such as abdominal pain and diarrhea, pruritus, and flushing.^{1-3,33} It has been designated a pregnancy category B medication and has not demonstrated any increased risk of major congenital malformation.²⁹

Leukotriene receptor antagonists

Leukotriene receptor antagonists, such as montelukast, are used in mastocytosis for flushing, musculoskeletal pain, and bronchoconstriction.¹¹ It is classified as a pregnancy category B medication and studies have not demonstrated teratogenicity or increased rates of preterm labor.^{24,28,29} No teratogenicity was noted in animal studies with montelukast at doses 100 to 110 times the maximum recommended human dose, although montelukast was found to cross the placenta.³⁴ Rare structural limb defects were reported, although a relationship with montelukast was not established.^{34,35} Two prospective studies using leukotriene receptor antagonists did not show an increase in the rate of major malformation with leukotriene receptor antagonist use. Both studies did report statistically significant decrease in mean birth weight, which was attributed to maternal asthma severity.^{35,36}

Ketotifen

Ketotifen, a medication with mast cell stabilizing and antihistamine properties, has been shown to be useful in mastocytosis symptoms such as abdominal pain, flushing, pruritus, and anaphylaxis.^{5,11} It is a pregnancy category C medication, with animal studies demonstrating adverse events.³⁷

Epinephrine

Anaphylaxis is a life-threatening emergency that can have a catastrophic effect on both the mother and the fetus. It is the result of massive mast cell activation and degranulation.^{38,39} Mastocytosis, characterized by a pathologic accumulation of

mast cells in different tissues, is associated with increased risk of IgE and non-IgE-mediated anaphylaxis.

The principles of management of anaphylaxis in pregnancy are similar to anaphylaxis in the general population. The inciting trigger should, if possible, be removed and 0.3 mg of intramuscular epinephrine injected and repeated as needed. Isotonic saline bolus for hypotension should be rapidly administered with a goal of maternal systolic blood pressure of 90 mm Hg to maintain adequate placental perfusion. Supplemental oxygen should be provided and instruments for endotracheal intubation available should the patient's airway become compromised. In the pregnant patient, of note, the patient should be placed on her left side to prevent the gravid uterus from reducing venous return from the inferior vena cava.³⁸ In addition, the patient should not sit or stand abruptly due to the risk of empty ventricle syndrome and potential for resultant cardiac arrest.³⁸ Any evidence of fetal distress should be managed with aggressive maternal treatment of hypotension and/or hypoxemia. The decision for emergent cesarean should be weighed against the risks of maternal and neonatal morbidity/mortality, particularly in pregnancies less than 32 weeks gestation. The utility of other medications commonly used in the management of mastocytosis, such as antihistamine or glucocorticoids, in immediate management of anaphylaxis is less clear. They should be administered as long as they do not delay life-saving therapies such as epinephrine.

A concern about the use of epinephrine in pregnancy is the potential reduction in uterine blood flow and its effect on the fetus.^{38,40} However, this concern is diminished in comparison to the more definitive risk of hypoperfusion and uterine contractions associated with anaphylaxis. Ephedrine, which is believed to spare uterine blood perfusion, was previously recommended for hypotension in pregnancy.^{37,38} However, recent literature suggests that intravenous phenylephrine is more effective at maintaining maternal blood pressure than ephedrine, and closely titrated epinephrine remains the vasopressor of choice for anaphylaxis.³⁸ Indeed, animal studies of epinephrine in pregnancy seem to suggest a relative sparing of uterine blood flow when used in low vascular resistance conditions such as anaphylaxis.⁴⁰

CYTOREDUCTIVE THERAPIES IN PREGNANCY

Interferon alpha 2B

Interferon alpha has an unclear mechanism of action but has demonstrated reduction in mast cell mediator release, mast cell infiltration, and symptomatic improvement in mastocytosis.^{1,3,11} It is a class C medication in pregnancy. Previous use in the literature has been limited to management of acute hepatitis C, essential thrombocytopenia, and malignancy. In these small case series, interferon alpha 2b use was not clearly associated with maternal or fetal complications or malformations.^{41,42} An increased incidence of intrauterine growth restriction was seen in infants exposed to interferon alpha 2b relative to the general population, but causality could not be established because of the limited data available.⁴¹ In our patient, in the absence of clear adverse fetal effects when weighed against the risk of frequent symptomatic worsening of mastocytosis and after significant discussion with the patient and high-risk obstetrics, interferon alpha 2b was continued at a decreased dose of 1.2 million units 3 times a week, from 2.4 million units 3 times a week before conception. This was increased in her second trimester when she

became more symptomatic to preconception dosing. She did not experience significant obstetric complications during her pregnancy until her 37th week with fetal bradycardia, which prompted an emergency c-section.

Although more research is needed on the use of interferon in pregnancy, in severe cases of systemic mastocytosis refractory to conservative therapy, interferon alpha 2b can be considered. Our patient tolerated this therapy without significant side effects and was able to deliver a healthy infant.

Tyrosine kinase inhibitors

Imatinib mesylate is the only tyrosine kinase inhibitor that is currently Food and Drug Administration—approved for use in systemic mastocytosis. Its use is limited to patients without locus 816 KIT mutation, as the conformational change from the point mutation reduces drug binding.^{1,11} More than 90% of patients with systemic mastocytosis carry the D816V KIT mutation, and hence do not benefit from this drug.^{1,11} A 33% response rate, with reduction of mast cell burden, has been shown in the small portion of patients with systemic mastocytosis without the D816V KIT mutation.^{3,11} Patients on imatinib, and partners of patients on imatinib, are advised not to become pregnant while on the medication. Although there are case reports of successful pregnancies without complications, the current literature suggests increased risk of spontaneous abortion, skeletal abnormalities, and other congenital abnormalities such as, but not limited to, pyloric stenosis and hypospadias.⁴³⁻⁴⁷

Cladribine

2-Chlorodeoxyadenosine or cladribine is a nucleoside analog that has shown transient improvement in mastocytosis.^{1,3,11} It is a pregnancy category D medication, with animal studies demonstrating teratogenic effects and fetal mortality. It is not recommended that patients become pregnant while on this medication.⁴⁸

CONCLUSIONS

The case we report highlights the complexity of managing a patient with mastocytosis during pregnancy. Such patients require careful and early interdisciplinary team management to minimize risk to the patient during preconception, pregnancy, and peripartum time periods. This patient population is diverse and each patient should be approached as an individual while managing mastocytosis during pregnancy.

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