Mastocytosis in Pregnancy

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SUMMARY

Objective: Mastocytosis is a rare disorder characterized by abnormal accumulation of mast cells in various organs. Clinical complaints include pruritus, cutaneous flushing, dyspepsia, and episodes of anaphylaxis, and are usually the result of local and systemic mast cell mediator release. The triggers include a variety of factors including drugs, exercise, stress, anxiety, and temperature extremes.

Case Report: A 26-year-old primigravida at 40 weeks' gestation with urticaria pigmentosa presented to our hospital. She was diagnosed with cutaneous mastocytosis based on pathologic examination of her skin biopsy. There were no complications during pregnancy, except for cutaneous manifestations with pruritus and premature uterine contractions at 27 weeks' gestation. After admission, antihistamine agents were administered during labor to treat the above symptoms, and antibiotic agents were given for prophylaxis of chorioamnionitis. Labor pain was successfully managed with warm showers, frequent position changes and massage, and therefore, epidural analgesia was not carried out. After 6 hours of labor, the patient gave birth to a healthy female infant via normal spontaneous vaginal delivery with right mediolateral episiotomy. Neither local anesthetic agents nor antibiotic agents caused any reaction. The postpartum period was uneventful.

Conclusion: Pregnant women with mastocytosis should be treated symptomatically and should avoid factors that may exacerbate symptoms of disease. Clinicians should be aware of preterm labor during pregnancy. As a preventive measure, resuscitation equipment should be available during the labor, delivery and postpartum period to treat unanticipated hypotension and shock. [*Taiwan J Obstet Gynecol* 2010;49(2):192–196]

Key Words: mastocytosis, pregnancy, premature labor

Introduction

Mastocytosis is characterized by an abnormal increase of mast cells in the skin, lymph nodes, liver, spleen, and bone marrow. Cutaneous mastocytosis is the most common form of mastocytosis, which presents as mast cell hyperplasia limited to the skin [1,2]. Types of cutaneous mastocytosis include urticaria pigmentosa, mastocytoma, diffuse and erythrodermic cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans (Table 1). Urticaria pigmentosa is the most common form and is characterized by oval or round red-brown macules, papules, or plaques ranging in number from a few to thousands. Symptoms of cutaneous mastocytosis include pruritus, flushing, urticaria, and dermatographism. Most patients have only skin involvement; however, involvement may be systemic as well. Extracutaneous involvement should be carefully considered in adult patients with cutaneous mastocytosis. Symptoms of systemic mastocytosis include cutaneous symptoms in association with syncope, gastric distress, nausea and vomiting, diarrhea, bone pain, neuropsychiatric symptoms, and anaphylaxis.

The prevalence of mastocytosis in the general population is unknown. There are approximately 200,000 patients with mastocytosis in the US. The incidence of urticaria pigmentosa has been reported to be between 1 in 1,000 and 1 in 8,000 of the population at a

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Table 1. Types of cutaneous mastocytosis

Mastocytoma	Single or multiple macules, plaques or nodules
Urticaria pigmentosa	Multiple macules, papules, and plaques
Diffuse and erythrodermic forms including bullous mastocytosis	–
Telangiectasia macularis eruptiva perstans	–

dermatology clinic [3]. As many as 10% of patients with urticaria pigmentosa will have systemic manifestations with mast cell degranulation [4].

Mastocytosis is perceived as a medical management dilemma because of its potential for unpredictably heightened mast cell activity in response to various physiologic states including pregnancy. We report a case of mastocytosis in a pregnant woman who achieved a successful pregnancy and delivery with a healthy female baby.

Case Report

A 26-year-old, gravida 1, para 0, patient was seen at 27 weeks' gestation with premature uterine contractions and cutaneous manifestations of urticaria pigmentosa with pruritus on the trunk and thighs. Her medical history revealed that the pruritus and flushing occurred on her body when she was situated in a hot environment, became tired and ate chocolate. These symptoms worsened at the time of psychologic stress. She was diagnosed with cutaneous mastocytosis based on pathologic examination of her skin biopsy 2 years previously. At the same time, bone marrow biopsy was performed and reported to be normocellular. Although regular medication with antihistamines was recommended at the time of the diagnosis by the dermatologists, the patient had never taken her drugs regularly. She had experienced an allergic reaction once, with throat swelling and dizziness. Although she did not require hospitalization, she took 2 days to recover. The agent responsible for the allergic reaction remained unknown, since no drugs were taken. The patient had had gastric symptoms such as heartburn for 10 years. Endoscopic biopsy revealed antral gastritis.

On admission, no cervical dilatation was observed, and uterine contractions were confirmed by external tocodynamometry. She was initially recommended bed rest and was hydrated with 1,000 mL of Ringer's lactate solution. Maternal corticosteroids were given (two doses of intramuscular betamethasone 12 mg, 24 hours apart) for fetal lung maturation. After sedation and hydration, magnesium tocolysis was started because of the persistent contractions. The patient was referred to the dermatology department, and intravenous (IV) pheniramine maleate (50 mg per 2 mL) was administered. After cutaneous manifestations were relieved and uterine contractions stopped, she was discharged from the hospital with the recommendation of regular checkups and oral pheniramine maleate (2 × 25 mg/day) as well as multivitamin supplements containing vitamin D, calcium and magnesium. She was also advised to avoid factors that may exacerbate symptoms of the disease.

The patient returned to our hospital at 40 weeks of gestation with premature rupture of the membranes and cutaneous manifestations of urticaria pigmentosa and pruritus. The amniotic membrane had ruptured for 5 hours. On digital examination, the patient had a 1-cm cervical dilation and 50% cervical effacement with a pregnancy in cephalic presentation. Fetal heart rate tracings were reactive, but uterine contractions were minimal. Labor was stimulated by oxytocin. An antihistamine agent (pheniramine maleate, 50 mg per 2 mL, IV) and corticosteroid agent (dexamethasone, 8 mg per 2 mL, IV) to treat the symptoms, and an antibiotic agent (cefazolin, 2 × 500 mg, IV) for prophylaxis of chorioamnionitis were administered. There were no complications during labor. Labor pain was successfully managed with warm showers, frequent position changes, and massage. Since the patient did not require additional analgesia, epidural analgesia was not carried out. After 6 hours of labor, she gave birth to a healthy female infant via normal spontaneous vaginal delivery with right mediolateral episiotomy. A local anesthetic agent (prilocaine hydrochloride, 200 mg per 10 mL) was administered for episiotomy. Neither local anesthetic agent nor antibiotic agent caused any reaction. The postpartum period was uneventful. The patient and her baby were discharged from hospital 2 days after the delivery.

As a preventive measure, resuscitation equipment was available during the labor, delivery, and postpartum period. During pregnancy, the patient showed only cutaneous manifestations of urticaria pigmentosa and pruritus on the trunk and thighs, but there was no other exacerbation of the disease.

Discussion

The presence of too many mast cells, or mastocytosis, can occur in two forms: cutaneous and systemic.

Systemic mastocytosis comprises multiple distinct entities in which mast cells infiltrate the skin and/or other organs. The diagnosis of systemic mastocytosis is made when an increased number of abnormal mast cells is found during an examination of bone marrow. Plasma and urinary levels of histamine and its metabolites can assist the diagnosis, but do not correlate with severity of the disease. The diagnosis of systemic mastocytosis is based on the presence of one major criterion and one minor criterion or three minor criteria. The major criteria include the presence of multifocal infiltrates of more than 15 mast cells in the bone marrow and/or other extracutaneous organs.The four minor criteria include the presence of elevated serum alpha-tryptase levels > 20 ng/mL, the expression of CD2 and CD25 surface markers in c-kit-positive mast cells from bone marrow or other organs, the presence of c-kit mutations on bone marrow and/or other tissues mast cells, and the presence of > 25% abnormal spindle-shaped mast cells in bone marrow and/or tissues [5]. Common minor symptoms of systemic mastocytosis and histamine release include weakness, fatigue, urticaria, pruritus, flushing, abdominal cramps, vomiting, diarrhea, mental confusion, and febrile episodes. Uncommon major symptoms include grand mal seizures, anaphylaxis, and cardiovascular collapse. It is surprising to note that wheezing rarely accompanies these attacks [6–9].

Cutaneous mastocytosis is the most common form of mastocytosis, predominantly affecting children, and presents as mast cell hyperplasia limited to the skin. In contrast to systemic mastocytosis, there are no well-defined pathologic criteria for diagnosis of cutaneous mastocytosis. This diagnosis is generally established by an experienced physician after observation of typical lesions of urticaria pigmentosa or mastocytoma. Skin biopsies show increased numbers of mast cells (generally more than 20 mast cells per high-power field) in the absence of other inflammatory cells, particularly in the upper dermis around blood vessels. The most common cutaneous lesions in patients with mastocytosis are red-brown macules, papules, and plaques of urticaria pigmentosa. The lesions of urticaria pigmentosa tend to be the highest density on the trunk, although they may affect all skin areas, including the mucous membranes. The palms, soles, face, and scalp are often free of lesions. Flushing has been reported to occur in 17–36% of patients with urticaria pigmentosa, although some studies have failed to define the extent of systemic manifestations [10]. Our patient's symptoms were pruritus and flushing; bone marrow biopsy was reported to be normocellular, and skin biopsy revealed cutaneous mastocytosis. Thus, the patient had only cutaneous disease limited to the skin.

The symptoms of mastocytosis may be activated by drugs (opioids, morphine, salicylic acid, codeine, alcohol, reserpine, amphotericin B, polymyxin B, pancuronium, D-tubocurarine, and estrogen), exercise, hot and cold weather, infections, moldy cheese, parasitosis, snake, and bee venom. Our patient stated that her pruritus and flushing were activated by hot weather and physical exercise.

Despite our current understanding of mastocytosis, there is little information on how pregnancy might affect clinical features or tolerance of medications, and outcomes of pregnant patients with mastocytosis. Mast cells have estrogen and progesterone receptors and thus are present in the myometrium and placenta, are increased in number in the myometrium with pregnancy, and appear to affect the second stage of labor [11–14]. Elevated levels of histamine have been reported to increase pregnant myometrial contractions *in vitro*, which may be associated with an increase in preterm labor *in vivo* [15]. Mastocytosis is perceived as a medical management dilemma because of its potential for unpredictably heightened mast cell activity in response to various physiologic states including pregnancy. In addition, during labor and delivery, the stress of labor and the medications given have the potential for activating the disease. Therefore, there are many potential complications of mastocytosis in pregnancy. There are only a few studies of mastocytosis in pregnancy reported in the literature. Worobec et al [9] described nine patients with systemic mastocytosis, who delivered 11 infants with good outcomes, and found that a subset of women with mastocytosis had exacerbated mastocytosis during and after pregnancy, but labor and delivery progressed normally. Infants were born generally healthy and were without mastocytosis. Bruns and Hartmann [16] evaluated 12 pregnant women with mastocytosis and reported that, during pregnancy, four patients experienced deterioration of mastocytosis symptoms, seven patients described no change, and one patient had improved. The most frequent symptoms that became worse during pregnancy were an increase of cutaneous lesions, pruritus, dyspepsia, hypotension, and fatigue. In all 12 patients, there were no significant complications during labor and delivery. In the present case, during pregnancy, cutaneous manifestations of urticaria pigmentosa on the trunk and thighs occurred, but there was no other exacerbation of the disease. Labor and the postpartum period were also uneventful. Villeneuve et al [17] reported the anesthetic management of labor pain and cesarean section in a patient with urticaria pigmentosa at risk for systemic mastocytosis. They found that allergy testing prior to pregnancy is important for the management of labor

Table 2. Cases presenting with mastocytosis in pregnancy that have been published in the English literature

Author	No. of cases	Clinical characteristics	Complications in pregnancy	Delivery (wk)
Present case	One	Urticaria pigmentosa	Pruritus, skin lesions, preterm labor at 27 weeks	40
Villeneuve et al [17]	One	Urticaria pigmentosa	No	36
Kehoe et al [19]	One	Systemic mastocytosis	Preterm labor at 24 weeks	39
Bruns and Hartmann [16]	12	NA	Four cases deteriorated, seven cases did not change, and one case improved. No significant complications during labor and delivery	NA
Worobec et al [9]	Nine women, 11 pregnancies	Five cutaneous mastocytosis four systemic mastocytosis	Pruritus, skin lesions, abdominal cramps, dyspepsia	Eight women carried fetuses to term, 11 live infants
García Collada et al [20]	One	NA	NA	NA
Gupta et al [18]	One	Urticaria pigmentosa	No	Full term
Donahue et al [15]	One	Telangiectasia macularis eruptiva perstans	Preterm labor at 24 weeks	36
Notter et al [21]	One	Urticaria pigmentosa	NA	NA

NA = not available.

pain and anesthesia for cesarean section. Gupta et al [18] also described the anesthetic management during labor of a patient with urticaria pigmentosa. Kehoe et al [19] reported a patient with indolent systemic mastocytosis using a doula for labor coaching. They concluded that predelivery planning can help prepare staff and patients for complications and that doulas can assist with labor preparation and delivery using nonmedical approaches to relief of pain and delivery. Their patient also experienced preterm labor at 24 weeks' gestation. Donahue et al [15] described a woman with telangiectasia macularis eruptiva migrans, a rare form of cutaneous mastocytosis, and suggested that elevated histamine excretion in a biopsy showing cutaneous mastocytosis may be associated with preterm labor. The present case also had preterm labor at 27 weeks' gestation and was treated with magnesium tocolysis. García Collada et al [20] and Notter et al [21] also reported pregnant cases with mastocytosis. Table 2 shows cases presenting with mastocytosis in pregnancy that have been published in the English literature.

There is no cure for mastocytosis, and treatment is aimed at relieving the symptoms. The treatment of mastocytosis requires recognition of specific disease patterns of involvement, with consequent institution of appropriate therapy based on the disease pattern manifested in a patient. Antihistamine agents are used to decrease pruritus and to treat gastric symptoms [7]. Conservative intrapartum management can consist of prophylactic H1 and H2 antihistamine therapy, IV epinephrine (1:10,000 dilution) and corticosteroids if required for women with severe disease [9]. Good pain control may contribute to a decrease in overall anxiety and help reduce the risk of exacerbation of the disease. When mast cell degranulation or anaphylaxis is suspected, corticosteroids, antihistamine drugs and epinephrine should be used to prevent further mast cell degranulation and cardiovascular collapse. Cesarean section is reserved for obstetric indications. When surgery and general anesthesia are necessary, premedication with H1 and H2 antihistamine agents and with benzodiazepine to reduce anxiety levels are recommended [8].

Finally, women with mastocytosis are fertile, and pregnancy and delivery have been successful by blocking mast cell-mediated symptoms. However, clinicians should be aware of preterm labor during pregnancy. Symptomatic treatment aimed at reducing the effect of mediators is effective with antihistamines and mast cell stabilizing agents such as cromolyn sodium. To reduce mast cell burden, interferon alpha, steroids and purine analogs have been used with varying results. Future directions for treatment include tyrosine kinase inhibitors and bone marrow transplants [22]. Pregnant women with mastocytosis should be treated symptomatically, and they should avoid factors that may exacerbate symptoms of the disease. As a preventive measure,

resuscitation equipment should be available during labor, delivery and the postpartum period to treat unanticipated hypotension and shock.

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