

General Anesthesia in a Patient With Urticaria Pigmentosa Referred for Electroconvulsive Therapy

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Abstract: Urticaria pigmentosa is a rare disorder characterized by an abnormal systemic proliferation of mast cells. In this condition, various triggers can induce either cutaneous histamine release, resulting in rash, or generalized histamine release, resulting in symptomatic hypotension, syncope, or in its severest form, an anaphylactoid reaction resistant to most resuscitative measures. Many anesthetic agents and adjuncts are known potential triggers, and patients who require surgery or procedures under anesthesia must be managed carefully. In this review, we describe the safe use of general anesthesia for electroconvulsive therapy in a patient with urticaria pigmentosa and discuss the association between psychiatric disorders and mastocytoses.

Key Words: urticaria pigmentosa, mast cells, histamine release, anaphylactoid reaction, general anesthesia, electroconvulsive therapy, ECT, mastocytoses

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Urticaria pigmentosa (UP), the most common type of mastocytosis, typically presents in childhood as discreet hyperpigmented cutaneous macules that flare and wheal on superficial stimulation (Darier sign).¹ Like all mastocytoses, UP is characterized by an excessive number of mast cells, and patients with this disease are at risk for the development of a non-IgE-mediated immediate hypersensitivity reaction resulting from massive mast cell degranulation.² Despite a similar presentation with IgE-mediated immediate hypersensitivity reactions, UP is not an allergic disorder, but rather a rare (estimated incidence of 1:150,000) clinical condition.³ Both the cutaneous and the systemic forms of UP can be characterized by episodes of flushing, pruritis, urticaria, nausea, vomiting, and diarrhea.⁴ More severe attacks may be life threatening, involving palpitations, tachycardia, hypotension and syncope, or shock leading to cardiac arrest. The course of the disease is chronic, but degranulation episodes can decrease in both severity and frequency with advancing age⁵; despite this, care should be taken to avoid triggering agents even in adult patients. Triggers include all histamine-releasing medications, some medications which do not result in histamine release in unaffected persons, and alcohol, as well as environmental triggers such as loud sounds, emotional stress, heat, cold, and physical exertion. Many medications required for the administration of anesthesia can

stimulate mast cell degranulation and lead to intraoperative hemodynamic instability in these patients, complicating anesthetic management.

Association With Depression

Patients with chronic diseases have an increased prevalence of depression ranging from 10% to 50%, and the mastocytoses are no exception. Although it is unclear if this is a reaction to physical illness or an intrinsic aspect of the disease, the literature supports an increased prevalence of psychiatric disorders, most commonly depression, among patients with disorders of mast cells. The mast cell disorder may or may not be etiologically linked to the mood disorder, but the fact that mast cells are involved in mechanisms related to emotional regulation and that some disease models of depression implicate neuroinflammation, cytokines and immune responses suggest an etiologic link.⁶ The association of depression with urticarial disease was recently highlighted in a study which found that the hazard ratio for patients with urticaria to develop new-onset depression was 1.68 that of controls.⁷ There are 3 other studies which specifically describe depression in mastocytosis, and report rates of depression ranging from 40% to 70%.^{7–9}

In one of the early investigations examining the association between mastocytosis and psychiatric illness, 4 of 10 patients with systemic mastocytosis (most of whom had been diagnosed with urticarial pigmentosa), were found to have depression.⁹ These patients reported that their depression was triggered by the stress of coping with symptoms of mastocytosis, and seemed more of a reaction to the disorder than an endogenous aspect of it. The most prominent symptoms described were diminished attention span, memory impairment, and irritability. More recently, an investigation into a cohort of 288 patients with indolent systemic mastocytosis found that the most common complaint was depression, with symptoms including lack of motivation, susceptibility to stress, anxiety, and irritability.⁷ Cognitive impairment was also common. Phenomenologically, psychomotor retardation and loss of insight are described as rare in mastocytosis-associated depression, suggesting a lower level of mood disorder severity.⁶ In that study, the severity of physical symptoms was not associated with depression severity, suggesting that mood symptoms are an intrinsic part of the disease, rather than a reaction to illness. Interestingly, the depressive syndrome responded to treatment of the primary disease process with masitinib, a tyrosine-kinase inhibitor with effects on mast cells, in 67% of cases.

Pretreatment Evaluation

In addition to any indicated preanesthetic evaluations (basic metabolic panel, electrocardiogram, and other tests as warranted based on patient presentation), additional tests for the patient with UP may be helpful. Baseline tryptase levels taken before anesthesia can be used as an indication of the level of mast cell burden and subsequently compared to tryptase levels obtained after an immediate hypersensitivity reaction, should one occur.¹⁰ Because UP itself is not a risk factor for IgE-mediated hypersensitivity reactions, skin tests are not routinely recommended.¹¹ Patients

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with a history of immediate hypersensitivity reactions in which the causative agent has not been determined should be evaluated by skin test before receiving anesthesia.²

Procedural Management

Treatment of patients with chronic UP includes the prophylactic use of H1 receptor antagonists such as chlorpheniramine and H2 receptor antagonists such as cimetidine [administered throughout the course of electroconvulsive therapy (ECT)] and additional pretreatment prophylaxis with diphenhydramine. Even in the properly prepared patient, avoidance of potential triggering agents is the key. Because psychological stressors have been identified as potential triggers, modifications to the standard institutional ECT protocol may be required. Anxiety reduction may be enhanced by maintaining a quiet and calm atmosphere in the treatment area and immediate surroundings including noise reduction. For a busy ECT practice, this may necessitate treating the patient as the first case of the day and waiting until the treatment has finished before bringing other patients into the suite. If the presence of a family member or members reduces anxiety, they should be allowed to remain in the treatment and recovery areas while ECT is administered. Family members whose presence increases the level of patient anxiety or agitation should be asked to wait outside. Avoidance of mechanical skin trauma and maintaining normothermia may also reduce the risk of a reaction.

Avoidance of anesthetic agents associated with histamine release reduces the risk of a reaction. If these agents cannot be avoided, judicious use and increased vigilance are mandatory. Historically, vecuronium was recommended as the muscle relaxant of choice in patients with UP due to its minimal histamine release.¹² In ECT however, due to the short duration of treatment, succinylcholine is the agent of choice. With a duration of action of only a few minutes after a bolus of approximately 0.9 mcg/kg,¹³ the use of succinylcholine obviates the need to administer more than a single intravenous bolus of anesthetic, avoids the need for prolonged respiratory support, and allows for faster recovery. The use of succinylcholine in this population is usually not recommended due to the significant potential for histamine release, although it has been successfully administered to children with UP and solitary cutaneous astrocytoma without precipitating a reaction.¹⁴ Considerable risk reduction may be achieved by using rocuronium followed by reversal with sugammadex¹⁵; although at this time, sugammadex is not available for use in the United States. Because acute attacks caused by massive release of prostaglandin D2 and histamine from mast cells typically result in refractory hemodynamic instability, treatment with either intravenous or subcutaneous epinephrine should be considered first-line treatment.

General Anesthesia for a Patient With UP

Ms A is a 19-year-old right-handed woman with a history of UP which was diagnosed at 6 weeks of age. She had been treated primarily with antihistamines from age 3 months to 11 years but had not been on any medications for her condition for 8 years at the time of initial consultation. She had been followed up by a dermatologist every 6 months since discontinuing her medications and at her last visit 3 months prior, some cutaneous reactivity was noted but her response to stimulation was less than it had been in the past. Additionally, she had reported no symptoms suggestive of systemic degranulation over the prior year.

Her psychiatric history included episodic depressions since age 13, and anorexia nervosa at age 15. She had undergone several trials of various antidepressants and she had received 2 ketamine infusions and a trial of rTMS without response. She had undergone an endoscopy with propofol and midazolam at age 14 to evaluate

stomach pain, and had her wisdom teeth removed at age 17 with intravenous sedation, but had never received general anesthesia.

After a 2-week evaluation at a specialized inpatient care center, ECT was recommended as the next logical treatment option, but the staff at this center refused to treat her at their facility due to the increased risk of general anesthesia posed by her condition. Instead, she was referred to our institution for treatment.

After thorough evaluation and discussion of the risks and benefits of treatment under anesthesia, she and her family consented to a course of ECT with several modifications designed to reduce the risk of triggering an episode. Medications at the time of treatment included pramipexole, eszopiclone, L-methylfolate, SAM-E, fish oil, vitamin B12, vitamin D, minocycline, and levonorgestrel/ethinyl estradiol and ethinyl estradiol. She had been taking the monoamine oxidase inhibitor tranylcypromine, but given the increased possibility of the need for hemodynamic support involving indirect acting sympathomimetic agents, the tranylcypromine was discontinued 7 days before treatment.

One week before beginning her acute course of ECT, she began a prophylactic regimen of cetirizine (10 mg QD) and ranitidine (150 mg BID), which she continued throughout the course of her treatment. Pretreatment laboratory studies obtained before the first ECT included a venous blood gas (pH of 7.35, sodium 139, potassium 4.0, calcium 1.4, glucose 79, lactate 0.8 and hematocrit of 36—obtained immediately before her first treatment to be used as a baseline to gauge subsequent management should an untoward event occur), pregnancy test (negative), and an electrocardiogram (normal sinus rhythm). At the time of treatment, a 20-gauge IV was inserted into the left antecubital fossa and a balanced salt solution was infused with the IV running wide open.

Immediately pretreatment she received additional prophylaxis with diphenhydramine (50 mg, intravenously). Pretreatment vital signs were as follows: heart rate, 81 beats per minute; blood pressure, 118/54; respiratory rate, 11 breaths per minute; and oxygen saturation of 100% on room air. Anesthesia was induced with 100 mg of propofol and muscle relaxation was achieved with 50 mg of succinylcholine. Once adequate neuromuscular relaxation had been verified by loss of train of 4 nerve stimulation applied to the posterior tibial nerve, an ultrabrief stimulus of 25 millicoulombs (mC) via right unilateral electrodes was applied, resulting in a generalized grand-mal tonic-clonic seizure of 39 seconds duration and an electroencephalographic seizure of 73 seconds. During the treatment, her peak heart rate was 144 beats per minute and maximum blood pressure was 127/81. Posttreatment vital signs were as follows: heart rate, 93 beats per minute; blood pressure, 108/61; respiratory rate, 17 breaths per minute; and oxygen saturation, 100% on 2L O₂ via nasal cannula. She tolerated the treatment well without complications and received 6 subsequent right unilateral ultrabrief pulse treatments at 150 mCr and 4 at 225 mC on a 3-times-a-week schedule. Her Hamilton Rating Scale for Depression score decreased from a score of 20 pretreatment to 11 after the ninth treatment. Her family reported sustained response after her treatment course.

DISCUSSION

Depression is common in cutaneous and systemic mastocytosis and the treatment may involve support groups, psychotherapy, psychotropic medications, or other interventions including ECT in refractory cases. For patients with coexisting diseases that may complicate anesthetic management, ECT may not be considered by some practitioners as a viable option, especially because an acute course represents multiple exposures to potential triggering agents. We describe a case of severe depression in a patient with UP who sustained significant benefit from a course of

ECT after more than a year of unsuccessful antidepressant medication trials.

There is a wide spectrum of disease in UP, ranging from the cutaneous variants, which are often considered mild or moderate forms of the disease, to the systemic mastocytoses, which are the most severe forms of the disease. Despite having the cutaneous form of the disease, our patient's dermatologist considered her to be at moderate risk for developing a systemic response to a triggering agent based on his clinical evaluation. Because sudden intraoperative hypotension related to massive mast cell degranulation has been reported, even in asymptomatic patients with UP,¹⁶ pretreatment with histamine-blocking medications was administered both orally throughout the course of treatment and intravenously immediately before each ECT session. During the treatment, intravenous fluid remained running as a precaution, and epinephrine as well as other resuscitative equipment was immediately available. We chose to use propofol as the anesthetic induction agent for this patient because of her age and because she had received this drug on one prior occasion and did not have a reaction, although there is no reason to suspect that methohexital would have been an unacceptable alternative. Succinylcholine was chosen as the muscle relaxant, although in areas where sugammadex is approved for clinical use, rocuronium would be an appropriate alternative.

In summary, cutaneous mastocytosis is more common than systemic forms, and although many patients remit after childhood, all patients with a history of this condition warrant careful preprocedural and anesthetic management during ECT and other ambulatory surgical procedures. With careful preparation and management, even high risk patients such as this can be offered the potentially life-saving treatment of ECT.

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