Case Report: Perioperative immediate hypersensitivity involves not only allergy but also mastocytosis

Présentation de cas: L'hypersensibilité immédiate per-opératoire ne concerne pas seulement l'allergie mais également les mastocytoses

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Abstract

Purpose We report a case of drug-induced immediate hypersensitivity occurring after atracurium injection in a patient with cutaneous mastocytosis.

Clinical features A 69-yr-old woman was scheduled for hysterectomy. She was premedicated with hydroxyzine, and anesthesia was induced with sufentanil, propofol, and atracurium. Within two to three minutes following the injection of atracurium, the patient experienced an episode of generalized erythema and arterial hypotension associated with tachycardia. No bronchospasm was observed. Her cardiovascular signs resolved spontaneously within five minutes, while her cutaneous signs disappeared within 30 min. Anesthesia and surgery remained uneventful. The patient's serum tryptase levels were measured at different time points following the clinical reaction. An in vitro flow cytometry-based basophil activation test was performed with atracurium, and in vivo skin tests to latex and all drugs which were administered just before the clinical reaction were also done. The serum tryptase showed increased concentrations that remained elevated for 24 hr,

48 hr, and even four weeks after the clinical reaction. Atracurium did not induce either CD63 or CD203c upregulation, and the skin tests were negative in response to the medications received (propofol, sufentanil, and atracurium) as well as to latex.

Conclusions Allergic hypersensitivity to atracurium was ruled out. Increased tryptase concentrations following the clinical reaction, persistent increased levels of basal serum tryptase, and negative skin tests suggested the onset of mast cell degranulation in a patient with mastocytosis. Immediate reaction occurring in patients with mastocytosis should be investigated in order to identify the mechanism of the reaction, either histamine release due to the disease itself or due to a concurrent drug/agent-induced IgE-mediated mechanism.

Résumé

Objectif Nous rapportons une réaction d'hypersensibilité immédiate documentée survenue après injection d'atracurium chez une patiente atteinte de mastocytose cutanée.

Éléments cliniques Une hystérectomie était programmée chez une patiente âgée de 69 ans, prémédiquée par hydroxyzine. L'induction anesthésique associait sufentanil, propofol et atracurium. Un érythème généralisé suivi d'une hypotension artérielle associée à une tachycardie est survenu deux à trois minutes après l'injection d'atracurium. Aucun bronchospasme n'a été observé. Les signes cardiovasculaires étaient résolutifs en moins de cinq minutes et les signes cutanés ont disparu en 30 min. La chirurgie et l'anesthésie ont eu lieu sans incidents. La concentration de tryptase sérique a été mesurée à différents moments après la réaction clinique. Un test

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d'activation in vitro des basophiles avec atracurium ainsi que des tests cutanés avec le latex et les médicaments injectés juste avant la réaction clinique ont été réalisés.

Résultats *Les concentrations de tryptase sérique étaient augmentées immédiatement après la réaction clinique ainsi que 24 h, 48 h et quatre semaines après. Aucune expression à la hausse des récepteurs CD63 ou CD203c n'a été observée en présence d'atracurium. Les tests cutanés sont demeurés négatifs aux médicaments (propofol, sufentanil et atracurium) et avec le latex.*

Conclusion *Une hypersensibilité allergique à l'atracurium a été écartée. L'augmentation des concentrations de tryptase immédiatement après la réaction clinique et leur persistance à distance, associée à la négativité des tests cutanés, suggéraient une dégranulation mastocytaire chez une patiente atteinte de mastocytose. Une réaction immédiate chez un patient atteint de mastocytose doit être documentée afin d'identifier le mécanisme de la réaction (histaminolibération non spécifique imputable à la maladie elle-même ou bien anaphylaxie IgE-médiée à un médicament/agent).*

Mastocytosis is a heterogeneous disease characterized by an accumulation of mast cells in one or more organ systems.¹ Albeit mastocytosis does not belong to allergic diseases, this clinical entity is often confused with IgE-mediated immediate hypersensitivity, i.e., IgE-mediated anaphylaxis.² Mastocytosis may be involved in the occurrence of perioperative immediate hypersensitivity through different triggers, including chemical agents and related direct pharmacological effects (i.e., histamine release). Clinical features arise following excessive mast cell mediator release, primarily histamine. We report a case of drug-induced immediate hypersensitivity occurring after induction of anesthesia in a patient with cutaneous mastocytosis. A thorough allergological assessment of the patient was performed in order to identify the pathophysiological mechanism of the reaction. The patient gave written consent for publication of this report.

Case report

A 69-yr-old woman (158 cm, 57 kg) without a history of any drug or latex allergy was scheduled for hysterectomy. She was premedicated with hydroxyzine 50 mg the day of the surgery, and anesthesia was induced with sufentanil (cumulative dose: 15 µg) and propofol 130 mg. Tracheal intubation was facilitated with atracurium 25 mg *iv*, and mechanical ventilation was initiated. Within two to three

minutes following the injection of atracurium, the patient developed generalized erythema and arterial hypotension (from 140/90 to 77/50 mmHg) associated with tachycardia (heart rate from 90 to 120 beats·min⁻¹). No bronchospasm was observed. Her cardiovascular signs normalized within five minutes (108/62 mmHg, heart rate: 70 beats·min⁻¹), while cutaneous signs resolved within 30 min. Anesthesia was maintained with sufentanil and desflurane, and anesthesia and surgery remained uneventful. Postoperatively, multimodal analgesia with morphine and nefopam was administered uneventfully. With the patient's consent, skin tests were performed six weeks later,³⁻⁵ with negative results in response to the medications received (i.e., propofol, sufentanil, and atracurium) as well as to latex. The patient's plasma histamine and serum tryptase levels were measured at different time points following the clinical reaction and showed increased concentrations (Table), which, in the case of tryptase, remained 24 hr, 48 hr, and even four weeks after the clinical reaction. The level of specific IgEs against quaternary ammonium and latex (ImmunoCAP, Phadia SAS, Uppsala, Sweden) remained undetectable. The basophil activation test was analyzed using a FACSCanto II flow cytometer (Becton-Dickinson, Rungis, France). Atracurium did not induce upregulation of CD63 or CD203c expression, ruling out basophil sensitization by specific IgE towards this drug.⁶

Discussion

In the present case, the primary goal of the allergological evaluation was either to confirm or to rule out atracurium-induced IgE-mediated hypersensitivity, since neuromuscular blocking drugs (NMBDs) are the drugs involved most frequently during perioperative anaphylaxis in adults.^{7,8} Atracurium-induced IgE-mediated anaphylaxis was ruled out based on the spontaneous recovery of the patient's moderately intense clinical features and the results of the basophil activation test concordant with the negative skin tests. Conversely, increased histamine and tryptase concentrations, persistent increased levels of basal serum tryptase, and negative skin tests suggested the onset of mast cell degranulation in a patient with mastocytosis.⁸ Apparently, the patient forgot to divulge her condition of cutaneous mastocytosis to her anesthesiologist preoperatively. As a result of a skin biopsy a few years previously, her condition was classified as *urticaria pigmentosa*.

Mastocytosis is a rare condition (with an incidence estimated at one in 150,000 patients),¹ which is seldom known by anesthesiologists. The initial event leading to mastocytosis is believed to be related to activating mutations in the c-kit receptor, the receptor for stem cell factor,

Table Plasma histamine and serum tryptase concentrations measured at different time points following the onset of clinical features

	T0 + 5 min	T0 + 90 min	T0 + 3 hr	T0 + 24 hr	T0 + 48 hr	T0 + 4 weeks
Plasma histamine ($n < 10 \text{ nmol}\cdot\text{L}^{-1}$)	> 100	22.8	NA	NA	NA	NA
Serum tryptase ($n < 10 \text{ }\mu\text{g}\cdot\text{L}^{-1}$)	NA	69	66.6	47	53.1	73.4

T0 = onset of clinical features; NA = not available

thus resulting in increased proliferation of mast cell precursors that migrate in various tissues with subsequent mast cell degranulation leading to the clinical features. The clinical course ranges from “asymptomatic” with normal life expectancy to “highly aggressive” forms.⁹ Mast cell hyperplasia may be restricted to the skin (*cutaneous mastocytosis*), or it may be found in extracutaneous organs (*systemic mastocytosis*). The corresponding clinical features and symptoms depend on the involved organs or tissues, for example, the gastrointestinal tract (nausea, diarrhea, abdominal pain), bone marrow (hematological disease), and the cardiovascular system (hypotension, cardiovascular collapse, cardiac arrest).¹⁰ Cutaneous mastocytosis is observed during childhood and usually disappears at or shortly after puberty, whereas systemic mastocytosis involving one or more organs or tissues is observed primarily in adulthood. The most common clinical cutaneous manifestation in adults with mastocytosis is *urticaria pigmentosa*, which is characterized by multiple persistent small reddish brown hyperpigmented maculopapular exanthemas caused by an increased number of mast cells in the skin, as observed in our patient (Figure).

Figure *Urticaria pigmentosa* is characterized by multiple persistent small reddish brown hyperpigmented maculopapular exanthemas due to an increased number of mast cells in the skin. In this patient, exanthema was located on the abdomen, back, and lower limbs and spared the face, palms, soles, and scalp. The figure shows the lateral aspect of the patient's right thigh

The exanthema may be disseminated over the entire body but spare the face, palms, soles, and scalp.¹¹

Perioperative immediate reactions have been reported to occur in patients either with cutaneous^{12,13} or with systemic mastocytosis.^{14–18} Mast cells are localized predominantly around blood vessels, and they preferentially populate tissues in contact with the external environment, including the skin and the gastrointestinal and respiratory tracts.¹⁹ The severity of clinical expression, however, is related to the cardiovascular homeostasis disturbances, as profound vasodilatation following mast cell degranulation with subsequent histamine release may, at the extreme, result in life-threatening conditions. Cardiovascular symptoms do not correlate with the cutaneous vs systemic description of the disease.¹ Bronchospasm usually does not occur.¹⁴ Accordingly, cutaneous and cardiovascular signs have been reported primarily during perioperative immediate reactions occurring in patients with either cutaneous or systemic mastocytosis.^{12–18} Mast cell degranulation occurs secondary to a variety of non-immune triggers specific for each patient, including psychological, chemical (i.e., histamine-releasing drugs), traumatic (tourniquet), and physical (rubbing, extreme temperatures) agents. Since the value of the preoperative use of H_1 - and H_2 -receptor antagonists has not been established, whenever possible, these triggers should be avoided in accordance with the patient's personal clinical history.

In cases of perioperative immediate reactions, skin tests remain the gold standard to detect the pathomechanism.⁸ Among the different perioperative cases reported,^{12–14,16,17} only two authors performed skin tests, the results of which remained negative to the suspected agents, i.e., anesthetic¹⁷ or antibiotic.¹⁸ Russell *et al.*¹⁷ reported a patient with systemic mastocytosis experiencing cardiac arrest after combined spinal and general anesthesia, and in whom cardiac arrest was attributed to the hemodynamic effects of spinal anesthesia. Lastly, the diagnosis of systemic mastocytosis remains doubtful in the case reported by Goldfinger *et al.*,¹⁸ as both the bone marrow aspirate and the bone biopsy revealed normal cellularity.

There are no published reports attributing perioperative IgE-mediated anaphylaxis in patients with mastocytosis either to an anesthetic or to another agent, such as latex. Many suggestions of contraindications to certain medications are not supported by scientific evidence. Morphine is

usually contraindicated, although this drug has been used uneventfully in patients with mastocytosis.^{12,17,20} In our patient, morphine was administered without adverse effects. Additionally, we find no reason to contraindicate steroid-based NMBDs as well as succinylcholine or cisatracurium, hypnotics, morphinomimetics, and/or local anesthetics, since these drugs have been administered uneventfully in patients with mastocytosis.^{12,14,20-24} In contrast, potent histamine-release NMBDs, such as atracurium and mivacurium, should be avoided. Moreover, as various triggers (i.e., psychological, chemical, traumatic, physical) may be involved, one should keep in mind that anesthetic drugs are not the only factor that may induce mast cell degranulation. Accordingly, of three reported cases of severe perioperative cardiovascular disturbances in adult patients with systemic mastocytosis where hemodynamic disturbances were followed by death, only one case could be attributed to the anesthetic drugs (i.e., atracurium).¹⁵ In the two other reports, flushing and acute hypotension occurred immediately following rectal tumor resection¹² and biopsy of the pancreas,¹⁴ 90 min and 255 min, respectively, after induction of anesthesia. One could therefore suggest that surgery itself might have triggered mediator release, as the mucosa and submucosa of the intestine are infiltrated by mast cells.

In conclusion, mastocytosis is not related to an allergic disease. However, this condition may be involved in the occurrence of perioperative immediate reaction. We suggest 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.

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References

1. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007; 37: 435-53.
2. Dewachter P, Mouton-Faivre C, Hermine O. Mastocytosis is not related to allergic diseases. *Allergy* 2008; 63: 1248.
3. Société Française d'Anesthésie et de Réanimation. Reducing the risk of anaphylaxis during anaesthesia. Abbreviated text. *Ann Fr Anesth Reanim* 2002; 21(Suppl 1): 7s-23s.
4. Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; 51: 655-70.
5. Harper NJ, Dixon T, Dugue P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; 64: 199-211.
6. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; 62: 471-87.
7. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg* 2003; 97: 1381-95.
8. Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anaesthesia: controversies and new insights. *Anesthesiology* 2009; 111: 1141-50.
9. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001; 25: 603-25.
10. Brockow K, Metcalfe DD. Mastocytosis. *Curr Opin Allergy Clin Immunol* 2001; 1: 449-54.
11. Castells MC. Mastocytosis: classification, diagnosis, and clinical presentation. *Allergy Asthma Proc* 2004; 25: 33-6.
12. Hosking MP, Warner MA. Sudden intraoperative hypotension in a patient with asymptomatic urticaria pigmentosa. *Anesth Analg* 1987; 66: 344-6.
13. Tirel O, Chaumont A, Ecoffey C. Arrêt circulatoire au cours d'une anesthésie chez un enfant porteur d'une mastocytose. *Ann Fr Anesth Reanim* 2001; 20: 874-5.
14. Desborough JP, Taylor I, Hattersley A, et al. Massive histamine release in a patient with systemic mastocytosis. *Br J Anaesth* 1990; 65: 833-6.
15. Vaughan ST, Jones GN. Systemic mastocytosis presenting as profound cardiovascular collapse during anaesthesia. *Anaesthesia* 1998; 53: 804-7.
16. Schwab D, Raithel M, Ell C, Hahn EG. Severe shock during upper GI endoscopy in a patient with systemic mastocytosis. *Gastrointest Endosc* 1999; 50: 264-7.
17. Russell WJ, Smith WB. Pseudoanaphylaxis. *Anaesth Intensive Care* 2006; 34: 801-3.
18. Goldfinger MM, Sandadi J. Undiagnosed systemic mastocytosis in a teenager revealed during general anaesthesia. *Paediatr Anaesth* 2010; 20: 290-1.
19. Castells M. Mast cell mediators in allergic inflammation and mastocytosis. *Immunol Allergy Clin North Am* 2006; 26: 465-85.
20. Carter MC, Uzzaman A, Scott LM, Metcalfe DD, Quezada Z. Pediatric mastocytosis: routine anesthetic management for a complex disease. *Anesth Analg* 2008; 107: 422-7.
21. Smith GB, Gusberg RJ, Jordan RH, Kim B. Histamine levels and cardiovascular responses during splenectomy and splenorenal shunt formation in a patient with systemic mastocytosis. *Anaesthesia* 1987; 42: 861-7.
22. Lemo G, Slaats G, Coenen E, Herregods L, Rolly G. Anaesthetic management of systemic mastocytosis. *Br J Anaesth* 1990; 65: 254-7.
23. Borgeat A, Ruetsch YA. Anaesthesia in a patient with malignant systemic mastocytosis using a total intravenous anesthetic technique. *Anesth Analg* 1998; 86: 442-4.
24. Konrad FM, Schroeder TH. Anaesthesia in patients with mastocytosis. *Acta Anaesthesiol Scand* 2009; 53: 270-1.