

Kounis Syndrome During Anesthesia: Presentation of Indolent Systemic Mastocytosis: A Case Report

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Mastocytosis comprises a heterogeneous group of disorders characterized by mast cell accumulation and proliferation in distinct organs. Kounis syndrome is defined as the concurrence of acute coronary syndromes with mast cell activation in a setting of allergic or hypersensitivity reactions. This is the first reported case of an intraoperative Kounis syndrome as the onset of an indolent systemic mastocytosis probably triggered by succinylated gelatin infusion during general anesthesia. The presentation of this case is intended to contribute to the knowledge of mastocytosis and Kounis syndrome at the time of diagnostic workup during intraoperative anaphylaxis or myocardial ischemia. (A&A Case Reports. 2017;XXX:00–00.)

It was initially believed that myocardial damage during anaphylaxis (an acute, potentially life-threatening hypersensitivity reaction involving the release of mediators from mast cells, basophils, and recruited inflammatory cells¹) was a consequence of a low preload and decreased cardiac output, due to systemic vasodilatation and increased vascular permeability. However, the heart may be the primary site and target of anaphylaxis. Kounis syndrome is defined as the concurrence of acute coronary syndromes with mast cell activation in a setting of allergic or hypersensitivity reactions. Three forms of Kounis syndrome have been described depending on the preexisting coronary condition of the patient. Type I includes coronary artery spasm in normal or nearly normal arteries, at first without increased cardiac enzymes and troponins but that may progress to myocardial infarction. Type II is associated with rupture and/or erosion of a preexisting coronary atheroma plaque, whereas type III includes thrombosis of drug-eluting coronary stents.²

Mastocytosis comprises a heterogeneous group of disorders characterized by mast cell accumulation and proliferation in distinct organs, mainly skin, bone marrow, and gastrointestinal tract.³ The real incidence is unclear, approximately 1 case per 10,000 inhabitants. Indolent systemic mastocytosis is the most frequent form in adulthood. Skin is chronically affected in 80% of these patients, mostly as urticaria pigmentosa. Clinical manifestations are occasionally related to organ infiltration and above all to the acute or chronic release of mast cell mediators. Clinical onset varies, ranging from recurrent anaphylactic episodes (50% of adult patients) to mild sporadic symptoms.

Cardiovascular symptoms such as dizziness, hypotension, or syncope are common, whereas osteoporosis affects up to 20% of patients. Total tryptase concentration is considered a good marker for mast cell burden in basal conditions and mast cell release in acute reactions. Basal tryptase concentration increases during anaphylaxis and returns to baseline level after 24 to 48 hours, whereas if persistently elevated ≥ 20 ng/mL, mastocytosis must be ruled out.⁴

Here, we report for the first time a case of an intraoperative Kounis syndrome as the onset of an indolent systemic mastocytosis probably triggered by succinylated gelatin infusion during general anesthesia. It is intended that the presentation of this case contributes to the knowledge of mastocytosis and Kounis syndrome at the time of diagnostic workup during intraoperative anaphylaxis or myocardial ischemia. Written consent was obtained from the patient prior to publishing this report.

DESCRIPTION OF THE CASE

A 50-year-old man was admitted for revision spinal surgery (adjacent segment disease). He had no previous history of drug allergies and his medical history included smoking, hypertension, hypercholesterolemia, depression, and anxiety symptoms. His surgical history included 4 knee arthroscopies under spinal anesthesia and 1 spinal decompression and fusion surgery (L4-L5) under general anesthesia. Regular medications included: losartan, hydrochlorothiazide, atenolol, atorvastatin, paracetamol, metamizol, trazodone, sertraline, agomelatine, clonazepam, and fentanyl patches.

The following intravenous (IV) premedication drugs were given 30 minutes before surgery: midazolam 2 mg, ranitidine 50 mg, dexamethasone 8 mg, and cefazolin 2 g. General anesthesia was induced intravenously using fentanyl 300 μ g, propofol 200 mg (mixed with lidocaine 20 mg), and rocuronium 50 mg. Following tracheal intubation, the patient was placed in the prone position. Anesthesia was maintained with sevoflurane within a target bispectral index (BIS) of 40 to 60. The surgical field was pretreated with povidone iodine solution, and the skin was incised.

As revision spinal surgery has a high risk of increased bleeding, a 14-G IV line was placed and a succinylated gelatin perfusion was started. Immediately after succinylated gelatin

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administration, the patient developed sudden hypotension and bradycardia (60/30 mm Hg, 40 bpm), and both BIS value and ETCo₂ (mm Hg) decreased to 9, likely related to a severe decrease in cardiac output. Sevoflurane and succinylated gelatin were discontinued. When IV administration of a total of 30 mg ephedrine, 1 mg epinephrine, and a large volume of crystalloid solution were not effective, the wound was packed and the patient was brought back to the supine position.

Skin signs were absent, and airway pressures were normal. Carotid pulse was undetectable, and cardiopulmonary resuscitation⁵ was started and continued for 30 minutes. The underlying cardiac rhythm was almost exclusively ventricular fibrillation, which required electrical defibrillation attempts every 2 minutes. One episode of slow nodal rhythm was treated with atropine 3 mg IV. After the third shock, epinephrine 1 mg IV every 4 minutes and a single dose of amiodarone 300 mg IV were administered.

Given the lack of response to prolonged resuscitation maneuvers, the following IV drugs were administered empirically to treat potential reversible causes: hydrocortisone 500 mg, dexamethasone 40 mg (allergic reaction), sugammadex 400 mg (clinical improvement has been reported after sugammadex administration in cases of rocuronium anaphylaxis⁶), heparin 5000 IU (coronary or pulmonary thrombosis), 1 M sodium bicarbonate 250 mL, and calcium chloride 1 mg (acidosis or hyperkalemia).

After sinus rhythm was restored, a 12-lead electrocardiogram (ECG) showed ST-segment depression in the left-sided leads (I, aVL, II, aVF, and V2 through V6). A consulted cardiologist performed a transthoracic echocardiogram in the operating room, which showed lateral wall motion abnormalities. The patient was immediately taken to the cardiac catheterization laboratory. Midazolam and cisatracurium were administered because the patient showed signs of wakefulness and patient-ventilator dyssynchrony. Coronary angiography showed normal coronary arteries and isolated spasm of the circumflex artery, which responded to intra-arterial infusion of nitroglycerin. A postcatheterization ECG showed sinus rhythm with descending ST-segment depressions in leads V3 through V6. Serial troponin I and creatine phosphokinase concentrations were compatible with myocardial infarction (Table 1). Moderate therapeutic hypothermia at 32°C to 34°C was initiated and maintained for 24 hours. Continuous IV low-dose noradrenaline (0.1 µg/kg/min) was required for the first 2 hours. Chest X-ray showed mild bilateral interstitial pulmonary edema and 2 rib fractures. Serial ECGs showed no new repolarization abnormalities. The patient was then rewarmed and weaned off sedation and analgesics (midazolam and

remifentanyl). The neurological examination after extubation showed no neurological sequelae. Serum tryptase concentration during the episode confirmed the diagnosis of anaphylaxis (Table 1). The patient received corticosteroids and H1/H2 receptor antagonists for the first 72 hours after the event.

The allergy service evaluated the patient with a suspected diagnosis of systemic mastocytosis given the persistence of high tryptase concentrations (Table 1). The β-blocker treatment was discontinued because these drugs may counteract epinephrine, both endogenous (which may precipitate mast cell degranulation) and exogenous (which may interfere with the treatment of anaphylaxis). Sodium cromoglycate, a mast cell stabilizer, was initiated. Intradermal and skin prick tests were performed 1 month after the event. Substances tested were latex, midazolam, ranitidine, cefazolin, fentanyl, propofol, lidocaine, rocuronium, succinylated gelatin, and relevant allergens in β-lactam allergy: PPL (benzylpenicilloyl polylysine or major determinant) and MDM (minor determinant mixture, consisting of penilloate, penicilloate, and penicillin G). Total concentrations of parathormone (38.5 pg/mL; normal range 15–88 pg/mL) and serum 25-OH-D (34 ng/mL; normal range 20–50 ng/mL) were normal. Bone densitometry showed a bone mineral density T score of 14.3 SDs in lumbar vertebrae (this high value is compatible with a previous surgical arthrodesis) and –1.05 SDs at the femoral neck (mild osteopenia), compared with the mean for 30-year-old Spanish men at each site.

A diagnostic workup was completed 3 months later in the Mastocytosis Research Institute in Castilla-La Mancha, Spain. The basophil activation test with gelatin was negative. Findings of a bone marrow biopsy (which showed a KIT D816V mutation restricted to mast cells) and results of a skin biopsy of brownish 0.1- to 0.2-cm maculopapular lesions detected on both flanks were compatible with mastocytosis.

All these findings led to the diagnosis of a type I Kounis syndrome, as the onset of an indolent systemic mastocytosis probably triggered by succinylated gelatin infusion during general anesthesia.

DISCUSSION

General anesthesia is considered a potentially life-threatening procedure for patients with mastocytosis because mast cells are exposed to multiple drugs and additive stimulating agents, therefore producing an earlier and greater degranulation response. The unusually high tryptase concentrations in this case are compatible with a massive mast cell degranulation. The allergological study did not document an IgE-mediated mechanism in our patient, but mast cells can be activated by drugs via other receptors or by nonspecific mechanisms. Thus, hypersensitivity to succinylated gelatin cannot be excluded.⁷ The patient had a history of uneventful general anesthesia with exposure to the same drugs as during the present surgery, with the exception of gelatin infusion. Furthermore, the more severe the anaphylactic reaction, the faster the response to the trigger agent; in this case, there was an immediate reaction after exposure to gelatin.

After any prolonged resuscitation, there is skeletal and myocardial muscle damage that is related to cumulative defibrillation energy, external cardiac massage, and coronary hypoperfusion. Because there is great variability of muscle creatine phosphokinase release after resuscitation, a threshold value of 4 ng/mL for troponin T (sensitivity 88%, specificity

Table 1. Laboratory Findings

Variable (Units)	Time After Anaphylaxis				
	Immediately After Restoration of Sinus Rhythm	2 h	12 h	48 h	6 mo
Tryptase ^a (ng/mL)	1783	410	...	44.5	50
I-Troponin ^b (ng/mL)	0.24	2.47	6.31	1.38	<0.01
Creatine ^c phosphokinase (U/L)	56	233	852	5010	88

^aNormal values: ≤11.4 ng/mL.

^bCutoff value for acute myocardial infarction: 0.3 ng/mL.

^cNormal values: 30–232 U/L.

Table 2. Perioperative Triggers of Mast Cell Degranulation⁴

Mechanical factors	Tourniquets, skin stimuli, surgery
Psychological factors	Stress and anxiety
Pharmacological factors	Rapid intravenous administration of histamine-releasing medications
Temperature changes	Hypothermia, hyperthermia

95%) has been suggested for biochemical diagnosis of myocardial infarction in this context⁸ (troponin T concentration for detecting uncomplicated acute myocardial infarction lies between 0.1 and 0.5 ng/mL). In our patient, troponin I concentration exceeded the normal value more than 20-fold, the ECG had changes compatible with myocardial ischemia, and coronary vasospasm was demonstrated in coronary catheterization. These findings made it unlikely that the elevated troponin concentration was exclusively caused by cardiac arrest and prolonged cardiopulmonary resuscitation.

To our knowledge, there is only 1 previously reported case of Kounis syndrome related to gelatin IV infusion,⁹ and regarding cases of mast cell disorders presenting as Kounis syndrome, there are 12 confirmed^{10–12} and 5 probable cases.^{13,14} This is the first reported case of an intraoperative Kounis syndrome as the onset of an indolent systemic mastocytosis probably triggered by succinylated gelatin infusion during general anesthesia.

Management of Kounis syndrome requires treatment for both acute coronary syndrome and anaphylaxis, although the drugs used to treat the former may aggravate the latter and vice versa. The use of intracoronary nitroglycerin can directly reverse coronary vasospasm, minimizing adverse systemic effects. Administration of glucagons could have been considered in this patient taking β -blockers.⁵

The objectives during anesthesia of a patient with mastocytosis are to reduce the risk of degranulation (see Table 2 for intraoperative mast cell degranulation triggers⁴) and the severity of symptoms in the case it happens. In our patient, exposure to potential triggers after arrest (hypothermia, cisatracurium) did not prompt new coronary events, probably because there were no remaining stored mediators after a massive mast cell degranulation. Prophylaxis with H1/H2 receptor antagonists, benzodiazepines, antileukotrienes, and steroids 1 hour prior to surgery has been suggested, although further research is needed on this issue.¹⁵

Anesthesiologists should be familiar with mastocytosis and Kounis syndrome because they are both life-threatening conditions that may present during intraoperative anaphylaxis or myocardial ischemia, and they have specific management implications. Moreover, it has been suggested that Kounis syndrome is not a rare disease but a rarely diagnosed condition.² ■■

DISCLOSURES

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