

COMPANION OR PET ANIMALS

Management of an anaphylactoid crisis due to mast cell degranulation in a dog during general anaesthesia

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SUMMARY

It is widely stated within the veterinary literature that manipulation of a mast cell tumour can lead to an anaphylactoid reaction; however, there is limited information on the frequency or management of such cases in companion animals. A nine-year-old, 38.4 kg, female neutered, labrador (retriever) presented for excision of a cutaneous mast cell tumour located on the left lower eyelid. This report describes a Grade III anaphylactoid crisis (hypotension, bradycardia and bronchospasm) that occurred when the dog was under general anaesthesia following mast cell degranulation. Prompt management following fluid resuscitation, administration of an aerosolised bronchodilator and intravenous atropine, successfully addressed the underlying pathophysiology of anaphylactoid crisis.

BACKGROUND

It is widely accepted that manipulation of canine cutaneous mast cell tumours can result in degranulation and potentially cause anaphylactoid reactions (Gross and others 2005, Dobson and Scase, 2007, Thamm and others 2007, Welle and others 2008, van Nimwegen and others 2012). However, there are no reports in dogs detailing this potentially fatal reaction to date. The only reference is an anecdotal report of mast cell degranulation causing anaphylactoid reaction following cryosurgery (Goldstein and Hess 1976). In fact, reports of canine anaphylactoid or anaphylactic reactions in general are limited within the veterinary literature (Armitage-Chan 2010). The aim of this case report is to describe mast cell degranulation following surgical preparation, leading to an anaphylactoid reaction under general anaesthesia, and to describe successful management of a Grade III anaphylactoid reaction (Table 1) in a dog.

CASE PRESENTATION

A nine-year-old, 38.4 kg, female neutered, labrador (retriever) was referred for the removal of a mast cell tumour. The dog was previously diagnosed with hypothyroidism and was successfully managed with thyroxine by the referring veterinarian. The dog first presented with an incompletely excised, Grade I (Patnaik) mast cell tumour on the left third eyelid, treated with definitive radiation therapy. During the follow-up period, clinical signs developed consistent with *Darier's sign* (erythema, urticarial and angioedema) on the left lower eyelid. Four months postoperatively, a suspected de novo

mast cell tumour was diagnosed on the left lower eyelid. Fine needle aspirates of left and right mandibular lymph nodes were cytologically consistent with metastasis. Surgical removal of the mast cell tumour via globe exenteration and mandibular lymph nodes extirpation was recommended with an intent to follow with a standard chemotherapy protocol for high-risk mast cell tumours. The dog was started on 1.6 mg/kg diphenhydramine (Nytol, GlaxoSmithKline Consumer Healthcare) every 12 hours and 0.5 mg/kg famotidine (TEVA UK Ltd) every 12 hours orally for 15 days until surgical intervention.

Prior to surgery, 8 mg chlorphenamine (Archimedes Pharma UK, Ltd) was administered intramuscularly. Preanaesthetic medication consisted of intramuscular 20 µg/kg acepromazine (Novartis Animal Health UK Ltd) and 0.3 mg/kg methadone (Physeptone, Martindale Pharmaceuticals Ltd). General anaesthesia was induced using intravenous alfaxalone (Alfaxan, Jurox) given to effect (total dose of 1.2 mg/kg). Anaesthesia was maintained on a rebreathing circle system with isoflurane (IsoFlo, Abbott Laboratories Ltd) delivered in 100 per cent oxygen at 2 litres initially. Nitrous oxide was added 20 minutes after induction to the gas mixture at a flow of 60 ml/kg/min with 30 ml/kg/min oxygen. An arterial line was placed into the right metatarsal artery. Intravenous fluid therapy was initiated using compound sodium lactate (Vetivex 11, Dechra) solution at a rate of 5 ml/kg/h. The dog was connected to a multiparameter patient monitor (Kontron Instruments Minimon 7137B, Kontron Instruments, Watford, UK) and a gas analyser (Datex Capnomac II, Instrumentarium Corp., Helsinki, Finland). Vital parameters remained stable, with a heart rate (HR) of 102–108 bpm, respiratory rate (RR) of 10 breaths per minute and haemoglobin oxygen saturation (SpO₂, using a pulse oximeter placed on the tongue) above 98 per cent. Direct blood pressure monitoring was unavailable in the preparation room. During preparation of the surgical site, local degranulation of the tumour (*Darier's sign*) occurred with no change in patient parameters. Eighty minutes after induction of anaesthesia, the dog was moved into the surgical theatre and connected to a multiparameter patient monitor (Datex Ohmeda S/5, Instrumentarium Corp., Helsinki, Finland). The HR, RR and SpO₂ were within previously recorded values. On connection to direct blood pressure monitoring, systolic blood pressure (SBP), was above 100 mm Hg. During placement and securing of surgical drapes, a significant reduction in HR (60 bpm) and acute apnoea



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TABLE 1: Modified classification system of anaphylactoid clinical signs (Ring and others 1977, Brown 2004, Sinkiewicz and others 2008)

Grade	Clinical signs
I	Cutaneous signs, Darier's sign (erythema, urticaria, +/- angioedema)
II	Cutaneous signs, +/- hypotension, +/- tachycardia, +/- respiratory disturbance (difficulty to inflate)
III	Tachycardia/bradycardia, +/- dysrhythmia, +/- profound hypotension, +/- bronchospasm
IV	Cardiac and/or respiratory arrest
V	Death

developed. SBP decreased to 40 mm Hg. Nitrous oxide and isoflurane delivery were discontinued, and oxygen flow was increased to 100 ml/kg/min. SpO₂ decreased to 85 per cent over 5 minutes and manual intermittent positive pressure ventilation (IPPV) was attempted. An increase in resistance during manual positive pressure ventilation ('sighing') was noted and minimal thoracic movement were observed. Reduced pulmonary compliance was suspected resulting in inadequate lung inflation and poor gas exchange.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses to account for the acute hypotension, decreased HR, subjectively decreased lung compliance and decreased SpO₂ to 85 per cent are limited and include anaphylactoid reaction and allergic reactions. Many injectable agents have been associated with reactions of this nature including antibiotics, vaccines, thiopental, acepromazine, meperidine, xylazine-ketamine and iodinated contrast agents (Armitage-Chan 2010). There was no administration of antibiotics before this event and the dog's vital parameters had remained stable for 80 minutes from induction to reaction. Due to the local *Darier's sign* noted during aseptic preparation of the area and the timing of the event, which coincided with the manipulation of the area during placement and securing of surgical drapes, a Grade III anaphylactoid reaction due to mast cell tumour degranulation was considered the most likely diagnosis.

TREATMENT

Fluid administration was increased to the maximum capacity of the fluid pump (26 ml/kg/h) and a 4 ml/kg bolus of 6 per cent hydroxyethyl starch (Voluven, Fresenius Kabi) administered intravenously. As manual IPPV remained ineffective and SpO₂ was 85 per cent, three actuations of aerosolised salbutamol (Ventolin, Allen and Hanburys) (100 mcg actuation; total dose 7.8 mcg/kg) were administered. This was achieved by disconnecting the dog from the breathing system, and administering two actuations of salbutamol directly into a fixed elbow capnograph connector attached to the breathing system, before reconnecting the patient and continuing IPPV to facilitate drug delivery. Subjective improvement of lung compliance was noted and SpO₂ increased to above 92 per cent. Single bolus of atropine (Atropine Sulphate, Hameln Pharmaceuticals Ltd) was administered intravenously (15.6 µg/kg) following this.

Airway resistance, subjectively assessed during manual IPPV, decreased and SpO₂ remained above 98 per cent. The HR increased to 100–115 bpm and SBP increased to 160 mm Hg. An additional dose of chlorphenamine (8 mg) was administered intravenously. The dog's vital parameters returned to baseline within 20 minutes and stabilised.

OUTCOME AND FOLLOW-UP

The decision was made to continue with the surgery as planned. Manual ventilation was ceased and IPPV was maintained using a flow cycled electronic ventilator (Merlin Small Animal Ventilator, Vetronic Services). Due to deep tissue dissection, a constant rate infusion (CRI) of 0.1 mg/kg/h morphine (Morphine Sulphate, Martindale Pharmaceuticals Ltd) was initiated for further analgesia. No further adverse events occurred during surgery. The dog made a full and uneventful recovery in the intensive care unit, and continued on 8 mg chlorphenamine (Piriton, GlaxoSmithKline Consumer Healthcare) q8h and 20 mg famotidine every 12 hours.

As the dog had tolerated well both famotidine and diphenhydramine orally preoperatively, therapy continued postoperatively with famotidine 20 mg every 12 hours orally and diphenhydramine 50 mg orally every 12 hours. The dog was discharged from the hospital three days postoperatively. Histopathology was consistent with a completely excised Grade II (Patnaik) mast cell tumour with mast cell tumour metastasis to the left mandibular lymph node. Histopathologically, the right mandibular lymph node did not show evidence of mast cell metastasis. The owners elected not to pursue adjunctive chemotherapy or routine diagnostics for restaging. Thirteen months postoperatively, there was no evidence of tumour recurrence or clinical signs associated with mast cell tumour metastasis.

DISCUSSION

Mast cell degranulation after manipulation of a tumour is categorised as an anaphylactoid reaction. Anaphylactoid reactions are clinically indistinguishable from anaphylaxis. However, the initiation of the pathway is independent of the IgE antibody (Lagopoulos and Gigi 2011). Using a modified human classification system (Ring and Messmer 1977, Brown 2004, Sinkiewicz and others 2008) (Table 1), this dog experienced a Grade III anaphylactoid reaction with hypotension, bradycardia and bronchospasm.

Anaphylactoid and anaphylactic reported reactions are limited within the veterinary literature, and only a few potential causative agents have been identified (Armitage-Chan 2010). None of the drugs selected for this case have been implicated to cause anaphylactoid reaction to date. Although alfaxalone was historically associated with anaphylactoid reaction due to inclusion of cremophor EL as an emulsifier, the preparation of alfaxalone used contained hydroxypropyl β-cyclodextrin and has not been associated with anaphylactoid events.

In any emergency situation, a systematic approach is recommended. Our response followed the current recommendation for cardiopulmonary cerebral resuscitation, namely ensuring an adequate airway, breathing and circulation (Fletcher and others 2012).

At the start of the anaphylactoid reaction, delivery of the volatile agent and nitrous oxide was promptly stopped while oxygen was delivered at high flows; these actions follow current human recommendations (Dewachter and others 2009, Norred 2012). While isoflurane may contribute to hypotension through its vasodilation effect, it promotes bronchodilation, and is recommended for management of bronchospasm during general anaesthesia (Looseley 2011). Despite the bronchoconstriction in this dog, continued use of isoflurane to promote bronchodilation was unlikely to overcome the detrimental effect on generalised tissue perfusion. In this dog, correcting the systemic hypotension was judged to be more significant, while bronchoconstriction was addressed by alternative measures.

The perceived change in airway resistance was presumed to be due to acute bronchospasm secondary to mast cell degranulation. Injectable administration of β -adrenoreceptor selective agonists (terbutaline, isoproterenol) is preferable over aerosol administration (salbutamol), due to increased accuracy of dosage and more reliable uptake when bronchoconstriction is evident. However, an injectable bronchodilator was not available. In human beings, inhaled β -adrenoreceptor selective agonist is also effective in managing acute bronchospasm (Mertes and Laxenaire 2002, Hepner and Castells 2003, Brown and others 2006, Dewachter and others 2009) and salbutamol was used in this case. In this instance, delivery of salbutamol directly into the capnograph connector was successful, leading to a subjective improvement in lung compliance, and an increase in oxygen saturation from 85 per cent to 92 per cent within 5 minutes. However, administering salbutamol directly into the endotracheal tube may be a more appropriate method. The decision to administer three actuations of salbutamol was made due to the dog rapidly deteriorating and the perceived inaccuracy of the dosing method.

Direct blood pressure monitoring revealed hypotension (mean arterial blood pressure <60 mm Hg), likely to be the result of vasodilation and increased vascular permeability leading to a fluid shift from intravascular to the extravascular space (Brown and others 2006, Dewachter and others 2009, Armitage-Chan 2010, Norred 2012, Shmuel and Cortes 2013). Positive chronotropy is most commonly seen in response to hypotension. However, in severe anaphylactoid reactions, negative chronotropy can occur (Dewachter and others 2009, Armitage-Chan 2010). This is known as the Bezold–Jarisch cardiac reflex, which is thought to increase ventricular filling time and improve cardiac output when severe hypovolaemia and hypotension affect preload (Mark 1983, Dewachter and others 2009). It is important that the pathophysiology of this reflex be recognised and addressed systematically. In these cases optimising oxygen delivery and management of hypovolaemia and vasodilation are the first priorities to maintain stroke volume. If positive chronotropes and inotropes are administered first, poor cardiac output can result due to reduced preload and decreased ventricular filling, thus increasing oxygen demand of the myocardium in the face of hypoxia.

In this dog, management consisted of correcting SpO₂ using manual ventilation with a bronchodilator, concurrent with volume resuscitation using crystalloids and colloids. Atropine was subsequently administered to increase the HR and further decrease bronchospasm. Adrenaline (epinephrine) is frequently recommended as first line treatment when faced with anaphylactoid reaction in the human and veterinary literature (Mertes and Laxenaire 2002, Brown and others 2006, Dewachter and others 2009, Armitage-Chan 2010, Norred 2012). Adrenaline has multiple beneficial effects including vasoconstriction, a positive inotropic effect and bronchodilation. It is also thought to offset the effect of histamine release. However, conflicting evidence of the use of adrenaline in cardiovascular shock, including established anaphylactic reactions, has been published. In vivo studies have found that adrenaline has little or no effect on fully developed cardiovascular shock, and can have a detrimental effect on the cardiovascular system (Mink and others 1998, Bautista and others 2002, Shmuel and Cortes 2013). Had the anaphylactoid reaction been less severe in this dog, the use of adrenaline may have been more appropriate.

The use of the unlicensed preparation of methadone for pre-medication was justified as the licenced preparation was not available at the hospital. Intraoperative use of morphine CRI

during surgery was initiated for analgesia. Morphine has been implicated to cause dose and rate dependant histamine release in dogs (Armitage-Chan 2010, Guedes and others 2006). Despite this, the decision was made to start a low dose of morphine CRI without a loading dose. No adverse effects were noted after the initiation of CRI (tachycardia, hypotension), and variables remained stable throughout surgery, and the decision was made to continue administration into the postoperative period. In retrospect, an alternative full μ -agonist not associated with histamine release, such as fentanyl, may have been a more appropriate choice.

The decision to continue with surgery was justified in this dog as prompt and successful management of her anaphylactoid reaction occurred and there remained a risk of another degranulation event at the rescheduled surgery. Canine mast cell tumours are frequently diagnosed, and surgical removal is the treatment of choice for most tumours without widespread metastasis. Mast cell degranulation, although infrequent, can potentially be fatal, and this risk should be communicated to the client. The human literature favours the use of adrenaline in anaphylactoid and anaphylactic reactions, and the veterinary literature also supports its use as a first line treatment. However, this case was effectively managed with fluid resuscitation, an aerosolized bronchodilator and atropine in order to both improve oxygen delivery and manage hypotension and bradycardia. This proved to be an effectual response to a severe anaphylactoid reaction due to mast cell degranulation in a dog under general anaesthesia.

Contributors HH: performed the anaesthesia reported under the guidance of the senior supervisor JCD who has been a significant contributor in writing this case report. DY was the senior soft tissue surgeon of the case and was directly involved with the incident reported and has been a significant contributor to this case report. JL is head of the oncology department and referred this case to the surgical department. JL also assisted me with assessment of the dog prior and post the reaction, as well as being a significant contributor to this case report.

Competing interests None.

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