

Case Reports

Anaphylactoid reaction to intravenous contrast in patient with systemic mastocytosis

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SUMMARY

Systemic mastocytosis is a rare disorder characterised by tissue infiltration of morphologically abnormal mast cells and has been associated with severe anaphylactoid reactions during general anaesthesia. We report the case of a 43-year-old woman who developed a severe anaphylactoid reaction to iodinated contrast media. Persistently elevated serum tryptase levels led to further evaluation and the eventual diagnosis of systemic mastocytosis. This case highlights the importance of repeated measurements of serum tryptase levels following severe anaphylactoid reactions. The anaesthetist should also be aware of the propensity of these patients to develop severe anaphylactoid reactions during general anaesthesia and use treatment strategies to minimise this risk.

Key Words: mastocytosis, iodinated contrast media, tryptase level

Systemic mastocytosis is a rare disorder characterised by tissue infiltration of morphologically abnormal mast cells^{1,2}. Mast cell activation results in degranulation and release in a myriad of substances including histamine, leukotrienes, prostaglandins and cytokines^{3,4}. Activation of mast cells through the IgE receptor results in an allergic or anaphylactic reaction. Activation of mast cells through a non-IgE mediated mechanism, such as occurs with contrast dye, results in an anaphylactoid reaction. The signs and symptoms of an anaphylactic and an anaphylactoid reaction are similar and usually not clinically distinguishable. Multiple organ involvement and cardiovascular collapse during general anaesthesia in patients with mastocytosis have been previously reported⁵⁻⁷. Patients with mastocytosis tend to have more severe anaphylactic and anaphylactoid reactions to the offending substances because of their increased mast cell burden. We present a case of a patient with undiagnosed systemic mastocytosis

who experienced cardiovascular collapse after the intravenous administration of an iodinated contrast agent.

CASE HISTORY

Permission (for single case) and patient consent were waived by the Mayo Clinic, Rochester, Minnesota, Institutional Review Board. A 43-year-old Caucasian woman underwent elective coiling of an asymptomatic paraclinoid internal carotid artery aneurysm under general anaesthesia. She had a past medical history significant for obesity, asthma treated with inhaled fluticasone/salmeterol and albuterol, and seasonal allergies treated with oral loratadine and intranasal mometasone. She reported numerous allergies including a rash to aspirin and penicillins; urticarial rashes and shortness of breath to oxycodone, morphine, ciprofloxacin and sulfonamides; and anaphylactic reactions to bee stings and latex for which she carried an adrenaline auto-injector kit. Pre-anaesthetic examination was unremarkable with chest auscultation revealing clear lung fields and oxyhaemoglobin saturation of 96% on room air.

Because of a reported history of an allergy to latex, the procedure was performed without latex as per standard protocol. General endotracheal anaesthesia was induced with 100 mg lignocaine, 2 mg midazolam, 50 µg fentanyl, 170 mg propofol and 10 mg vecuronium. Anaesthesia was maintained

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with 1% isoflurane and 50% nitrous oxide in oxygen. A 5 Fr catheter was advanced to the right internal carotid artery through the right femoral artery. At the radiologist's request, 6000 units of heparin were administered intravenously. Next the radiologist injected a test injection of less than 1 ml of an iodinated contrast agent (Omnipaque™ Injection 300 mgI/ml, GE Healthcare AS Oslo, Norway) to confirm correct placement of the catheter.

Immediately after injection, the patient became hypotensive with the blood pressure falling from 102/55 mmHg to 63/32 mmHg and developed bronchospasm as evidenced by an increase in the peak inspiratory pressure from 26 cmH₂O to 47 cmH₂O and a fall in the oxyhaemoglobin saturation by pulse oximetry from 97 to 86%. She was successfully resuscitated with 3 litres of lactated Ringer's solution, 500 ml of 6% hetastarch, 50 mg ephedrine, 600 µg phenylephrine, 550 µg adrenaline, 10 mg dexamethasone and 20 mg diphenhydramine. The entire episode lasted 15 minutes. The procedure was cancelled and the patient transferred to the intensive care unit where she made a full recovery.

Four hours after the episode, the plasma tryptase level was elevated, 67.4 ng/ml (range <11.5 ng/ml). Twenty-four hour urinalysis demonstrated an elevated beta prostaglandin F₂-alpha level, 7566 ng/24h (range <1000 ng/24h). These values were consistent with mast cell activation. She underwent subsequent allergy skin prick and intradermal testing to vecuronium, propofol and fentanyl, but these tests were negative. An allergy test to latex was not performed as she reported a previous latex allergy. One month from the episode, repeat plasma tryptase level remained elevated at 30.4 ng/ml, and 24-hour urinary beta prostaglandin F₂-alpha was slightly elevated, 1042 ng/24h. A dermatologic examination did not reveal urticaria pigmentosa lesions. A bone marrow biopsy demonstrated systemic mast cell disease involving 5 to 10% of a hypercellular bone marrow and a diagnosis of systemic mastocytosis was made.

Six months later, she underwent a subsequent neuro-angiogram of her aneurysm under general anaesthesia without incident. Preoperatively she was treated with 40 mg/day oral prednisone for five days, 50 mg oral prednisone 13 hours, seven hours and one hour prior to the procedure, and 50 mg oral diphenhydramine one hour prior to the procedure. Post-procedurally she was placed on a steroid taper.

DISCUSSION

Anaphylactoid reaction to administration of iodinated contrast media is a well known phenomenon. Such responses are secondary to

activation and degranulation of mast cells, as evidenced by elevated histamine and tryptase levels following severe contrast reactions⁸. Systemic mastocytosis represents a heterogenous group of disorders characterised by abnormal accumulation of mast cells in a variety of tissues including the skin and bone marrow. Because these patients have an abnormally high mast cell load, systemic degranulation of mast cells can produce profound anaphylactoid reactions. Therefore it is recommended that iodinated agents be used with caution in this patient population⁹. Adult patients with systemic mastocytosis frequently, but not universally, have urticaria pigmentosa skin lesions¹⁰. These lesions are discrete multiple brown, violaceous or yellow hyperpigmented macules with truncal distribution, and are the result of proliferation of mast cells in the dermis. The presenting signs and symptoms of patients with systemic mastocytosis who lack these characteristic urticaria pigmentosa lesions can include any combination of pruritus, urticaria, wheezing, tachycardia, hypotension, diarrhoea and/or syncope with or without a stimulus. They can also present with an anaphylactoid reaction (non-IgE mediated) to hymenoptera stings¹¹. Our patient had a presentation of systemic mastocytosis without skin lesions and is the first reported case of the diagnosis of systemic mastocytosis being made in response to an anaphylactoid reaction to iodinated contrast media. There is a remote possibility that this represented an anaphylactoid reaction to intravenous heparin; however, we feel this is unlikely because anaphylactoid reactions to heparin are very rare and the sequence of events strongly suggests the reaction was in response to the contrast media. Unfortunately, a definitive test for heparin sensitivity does not exist. Allergy testing for skin preparation solutions was not performed in this case, but the timecourse of events would make a reaction to either povidone-iodine or chlorhexidine highly unlikely.

The World Health Organization recognised four variants of systemic mastocytosis². Indolent systemic mastocytosis is the most common and the variant that our patient had. Systemic mastocytosis with associated clonal haematological non-mast cell lineage are associated with a coexisting haematologic disorder such as leukaemias and myelodysplastic/proliferative diseases. Aggressive systemic mastocytosis is associated with significant proliferation of mast cells in the liver, spleen, lymph nodes and bones, and patients can manifest with organ dysfunction from overwhelming organ infiltration. Mast cell leukaemia is very rare and carries a poor prognosis¹⁰.

Diagnosis of systemic mastocytosis is based on major and minor criteria adopted by World Health

Organization². Patients must have the major criteria and one minor criterion, or three minor criteria (Table 1). Our patient met both the major criteria of having mast cell infiltrates on a bone marrow biopsy and one minor criterion of a persistent elevated tryptase level.

TABLE 1

World Health Organization criteria for diagnosis of systemic mastocytosis. Patient must fulfill one major and one minor criterion or three minor criteria².

<i>Major</i>
Multifocal, dense infiltrates of mast cells in bone marrow or other extracutaneous organs (>15 mast cell aggregating)
<i>Minor</i>
>25% of mast cells show spindle shape or atypical morphology
Detection of a <i>KIT</i> codon 816 point mutation
Expression of CD2 and/or CD25 by mast cells
Persistent elevation of serum total tryptase >20 ng/ml

This case illustrates the importance in measuring a tryptase level following perioperative anaphylactoid or anaphylactic reactions. After such a reaction, this test should be performed at a post-reaction follow-up several weeks later to rule out mastocytosis. Mast cells contain numerous inflammatory mediators including histamine, prostaglandins, leukotrienes, interleukins and many proteases including tryptase^{12,13}. Overwhelming degranulation of mast cells and release of vasoactive substances can manifest as a severe anaphylactoid or anaphylactic reaction with cardiopulmonary collapse¹⁴. Tryptase can be produced in very small amounts by basophils but not other leukocytes. An elevated tryptase level suggests a mast cell mediated reaction has occurred^{15,16}. Tryptase levels peak approximately one hour after an anaphylactic or anaphylactoid reaction has begun and slowly return to normal baseline levels after 8 to 12 hours. Tryptase levels stay consistently elevated in those with under-lying mast cell disease¹⁷. In our patient the initial tryptase level was elevated. It is recommended in cases where the serum tryptase level is elevated immediately after a severe allergic reaction to measure the level again several weeks later to ensure it returns to normal¹⁸. In our patient the tryptase level remained elevated, which prompted a bone marrow biopsy which allowed for the diagnosis of systemic mastocytosis.

Anaphylactoid reactions in patients with systemic mastocytosis undergoing general anaesthesia have been reported^{5-7,19}. Others have reported

unremarkable administration of general and regional anaesthetics in patients with systemic mastocytosis²⁰⁻²⁶, urticaria pigmentosa²⁷⁻³⁰ and solitary cutaneous mastocytosis²⁹. In order to minimise the chance of mast cell degranulation, different strategies have been reported, including the administration of intravenous histamine blockers^{5,20-29}, corticosteroids^{20,21,23,25,28}, cromolyn sodium²⁵, aspirin or nonsteroidal anti-inflammatory drugs^{22,24,25}. Mild symptoms related to histamine are well controlled by H1- and H2-receptor antagonists and prophylactic administration should be helpful to mitigate symptoms from mast cell degranulation³¹. However, symptoms from degranulation are not entirely secondary to histamine release. In our patient, elevated prostaglandin metabolites were detected in her urine. Corticosteroids have a direct inhibitory effect on mast cells and can minimise degranulation, and therefore are useful in the perioperative period in patients with systemic mastocytosis^{10,32,33}. Cromolyn sodium is most useful in controlling gastrointestinal effects of systemic mastocytosis and administration in the perioperative period is not critical³⁴. Aspirin and related agents interfere with prostaglandin production, but have been associated with idiosyncratic responses of vascular collapse in some patients and should be used with caution^{10,14}. Avoidance of drugs used in anaesthesia that are known to release histamine should be considered^{28,35}. Some authors described preoperative skin testing with planned anaesthetic agents, which identified sensitivities to pancuronium and etomidate^{22,25}. Intraoperatively, the anaesthetist should be prepared for anaphylactic reactions by having adequate intravenous access and immediate access to adrenaline, antihistamines and glucocorticoids.

In conclusion, we describe the first case of systemic mastocytosis which was diagnosed in response to a severe anaphylactoid reaction to iodinated contrast agent. This case highlights the importance of repeated tryptase levels after severe anaphylactoid or anaphylactic reactions. The anaesthetist should be aware of risks of anaesthesia in patients with mastocytosis. Perioperative administration of antihistaminics and corticosteroids, avoidance of histamine-releasing medications and adequate preparation for the treatment of potential anaphylactoid reactions are prudent treatment recommendations for patients with systemic mastocytosis.

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