

Systemic mastocytosis presenting as intraoperative anaphylaxis with atypical features: a report of two cases

D. E. BRIDGMAN*, R. C. CLARKE†, P. H. M. SADLEIR‡, J. J. STEDMON§, P. R. PLATT§

Department of Anaesthesia, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

SUMMARY

Two cases of perioperative cardiovascular collapse are presented that were associated with markedly elevated mast cell tryptase levels shortly after the event, leading to the assumption that an immunoglobulin E-mediated, drug-induced anaphylaxis had occurred. However, the clinical picture in both cases was atypical and subsequent skin testing failed to identify a triggering drug. Further blood tests, some weeks later, revealed persistently elevated baseline levels of mast cell tryptase. In both cases bone marrow biopsy and genetic testing confirmed the diagnosis of mastocytosis. We present evidence and speculate that mast cell degranulation was triggered by tourniquet release in the first case and by exposure to peanuts in the second. An atypical presentation of anaphylaxis should alert the anaesthetist to the possibility of previously undiagnosed mastocytosis.

Key Words: anaphylaxis, mastocytosis, mast cell tryptase, intradermal testing

Skin testing is the principal modality used in the standard diagnostic work up of perioperative anaphylaxis¹. Two cases of anaphylaxis are described that were associated with dramatic symptoms, unusual features and markedly elevated levels of mast cell tryptase (MCT), but no drug trigger was identified on skin testing. In both cases a subsequent elevated baseline MCT raised the suspicion of mastocytosis that was later confirmed with a bone marrow biopsy and genetic testing. These cases highlight the importance of baseline MCT in the investigation of anaphylaxis to screen for mastocytosis². Children and adults known to have mastocytosis may be uneventfully anaesthetised with appropriate attention to detail³. There are reports of major complications arising if the condition has been previously diagnosed but not disclosed to the attending medical staff prior to surgery^{4,5} or if the condition is undiagnosed^{6,7}. Reference is made to an increase in the understanding and recent reclassification of mast cell disorders⁸. Consent for publication was obtained from both patients.

CASE HISTORY 1

A 58-year-old female presented for an elective left total knee replacement in a satellite hospital closely aligned to a nearby tertiary hospital. Her past medical history included type 2 diabetes mellitus, mild asthma and hypertension. Her previous surgical history included a right total knee replacement and a cholecystectomy, both five years previously and uneventful. Of note, she had suffered one previous episode of upper airway oedema, associated with airway obstruction, after taking ibuprofen. It is possible she was being medicated with an angiotensin-converting-enzyme inhibitor at this time. However, she denied any other symptoms of allergic reactions in her past.

Anaesthesia was induced with midazolam, fentanyl and propofol and she remained spontaneously breathing via a laryngeal mask airway. Sevoflurane was used to maintain anaesthesia. During the procedure she received cephazolin, paracetamol, parecoxib, dexamethasone and tropisetron. In addition, 30 ml ropivacaine 0.375% was administered as a femoral nerve block under real-time ultrasound scanning, and a urinary catheter was inserted prior to the commencement of surgery.

The procedure was uneventful until the end of the operation, after she received 45 µg intravenous clonidine, when the patient's blood pressure began to decrease. This drop in blood pressure was treated with 1 mg metaraminol and 6 mg ephedrine to which she initially responded. However, after the arterial

* MB, BS, Anaesthetic Senior Registrar
† FANZCA, Consultant Anaesthetist, Anaesthetic Allergy Referral Centre of Western Australia

‡ FANZCA, Consultant Anaesthetist, Department of Anaesthesia, Fremantle Hospital, Fremantle

§ FANZCA, Consultant Anaesthetist, Anaesthetic Allergy Referral Centre of Western Australia

Address for correspondence: Dr P. Platt, Department of Anaesthesia, Sir Charles Gairdner Hospital, Hospital Ave, Nedlands, WA 6009. Email: peter.platt@uwa.edu.au

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tourniquet was released, she became profoundly hypotensive, (systolic blood pressure 60 mmHg) and required further boluses of metaraminol in order to maintain a systolic blood pressure >90 mmHg. Other observations of heart rate, oxygen saturations and end-tidal carbon dioxide partial pressure remained within normal limits during this period. The patient was transferred to the post-anaesthesia care unit and remained dependent on metaraminol, receiving a total of 20 mg in 1 mg boluses over the next few minutes. During her time in the recovery room her hypotension proved unresponsive to these measures and fluid resuscitation, and she subsequently required a total of 1 mg adrenaline in 100 µg increments. In addition, a noradrenaline infusion was started in order to maintain a systolic blood pressure above 100 mmHg. At this time an electrocardiogram was performed which showed widespread ischaemia with possible ST elevation in the praecordial leads. The patient did not develop any bronchospasm, urticaria or chest pain during this time and oxygen saturations remained at 100%.

Due to her unstable condition and lack of local intensive care support, the patient was transferred to the nearby tertiary hospital emergency department where she was reviewed by a cardiology registrar. A transthoracic echocardiogram was performed which showed both hyperdynamic ventricles and acute severe pulmonary hypertension with an estimated pulmonary artery pressure >70 mmHg. Anaphylaxis had earlier been considered as part of a differential diagnosis and blood was taken one hour after the initial hypotension for MCT levels. However, as the clinical picture was not classical of anaphylaxis, a pulmonary embolus was considered to be more likely. As a result, a computed tomography-pulmonary angiogram was performed which proved to be negative. Over the next six hours her blood pressure improved and she was weaned from her inotropic support. MCT results became available during this time which showed a level >200 ng/ml (normal <14 ng/ml), indicative of massive mast cell degranulation, and anaphylaxis as a diagnosis became more likely. Her electrocardiogram also improved and there was no rise in troponin levels over the next 24 hours. A repeat echocardiogram, 24 hours later, showed a significantly improved picture with an estimated pulmonary artery pressure of 37 mmHg. The patient was discharged and underwent a myocardial perfusion scan as an outpatient which failed to show any abnormalities and, in addition, subsequent pulmonary function testing was essentially normal.

Her baseline MCT, performed approximately one month after the episode, was 31.2 ng/ml and remained stable with a second level of 31.2 ng/ml six weeks after the incident when she attended the West Australian Anaesthetic Allergy Referral Centre. At this time, the patient underwent skin testing in order to attempt to identify the cause of her apparent anaphylactic reaction. The intradermal testing included all the drugs administered during her anaesthetic: midazolam, fentanyl, propofol, ropivacaine, clonidine, parecoxib, dexamethasone, ondansetron, cephazolin and chlorhexidine. None of these drugs caused any reaction at the skin test sites and she had a normal response to the histamine positive control.

Due to the consistently high baseline MCT and inability to identify a trigger for the suspected anaphylaxis, the diagnosis of mastocytosis was considered. The patient was referred to a haematologist for further follow-up and investigation, and subsequently underwent a bone marrow biopsy. This demonstrated abnormal small clumps of mast cells and DNA testing confirmed the presence of a D816V mutation associated with systemic mastocytosis.

CASE HISTORY 2

A 50-year-old man underwent a semi-urgent laparoscopic cholecystectomy at a tertiary teaching hospital with abdominal symptoms consistent with acute cholecystitis. He had a history of 35-pack-years of smoking and several surgeries without incident.

The patient was allergic to peanuts, having had several anaphylactic episodes in the past requiring emergency department attendance. In 2006, he was due to be assessed at the anaphylaxis clinic of the same hospital but did not attend. In early 2009, a colonoscopy was arranged at a regional hospital as part of the investigation of intermittent diarrhoea and abdominal pain. Again, he did not attend. He described an apparent worsening of his peanut allergy with age to the point where, at the time of our review, he would feel unwell if he smelled peanuts. He would have a systemic reaction if he ingested as little as a 'grain of sand-sized' portion of peanut. Walnuts caused nausea and urticaria.

On the day of surgery, induction of anaesthesia with fentanyl, midazolam, propofol and rocuronium was uneventful. Anaesthesia was maintained with sevoflurane, and cephazolin, morphine, parecoxib, paracetamol and tropisetron were administered intraoperatively. The case was completed and the patient successfully extubated following reversal of rocuronium with neostigmine and glycopyrrolate. He was transferred to the post-anaesthesia care unit

90 minutes after induction of anaesthesia. At the time of arrival he was agitated and was found to be hypotensive (systolic blood pressure 69 mmHg). A total of 500 ml hydroxyethyl starch solution 6%, metaraminol and midazolam 2 mg were administered; however, his condition rapidly deteriorated with worsening hypotension and a falling conscious state. At this time he was also noted to have a widespread red rash and anaphylaxis was deemed the most likely diagnosis. He was reintubated after administration of propofol 100 mg and suxamethonium 100 mg, following which adrenaline was required intravenously in small increments to a total of 400 µg with a small improvement in blood pressure. This was short lived and he subsequently developed ventricular tachycardia that rapidly progressed to ventricular fibrillation. One 200 J defibrillation was administered, cardiopulmonary resuscitation commenced and 1mg adrenaline was given. After two minutes the rhythm remained ventricular fibrillation and a second defibrillation was administered, changing the rhythm to a sinus tachycardia with a detectable pulse. His condition subsequently improved and an adrenaline infusion was commenced. After a period of stability, he was transferred to the intensive care unit. He was extubated the following day and had no further complications in hospital.

Four blood samples for MCT were taken after the event, all of which were elevated. The first, taken at one hour after the onset of the reaction, was >200 ng/ml. The second and third, taken at 24 hours and 72 hours after the onset of the reaction, were 21.8 and 34.9 ng/ml, respectively. The final assay was performed at the time of skin testing one month later and was 50.6 ng/ml.

Intradermal skin testing to all the drugs to which he was exposed was performed. This included propofol, fentanyl, midazolam, rocuronium, parecoxib, tropisetron, paracetamol, glycopyrrolate, neostigmine, cephazolin, suxamethonium and morphine. He was also tested to chlorhexidine, the contrast medium given during the cholangiogram, and the hydroxyethyl starch solution that was administered in the post-anaesthesia care unit. All were negative.

Following the review of the circumstances surrounding the event, it appeared that on the day a Thai meal containing large amounts of peanuts had been provided for the anaesthetists. At least one of the treating anaesthetists had consumed this meal during a scheduled lunch break and his return to theatre coincided with the onset of the reaction.

Given the persistently elevated mast cell tryptase

levels, this patient was also referred to a haematologist. Systemic mastocytosis was confirmed after clumps of abnormal mast cells were seen on the bone marrow biopsy. Genetic testing demonstrated he had both a JAK-2 and D816V mutation.

DISCUSSION

Serum tryptase measurement

There are a number of mast cell tryptase variants detectable in blood. The ImmunoCAP tryptase (Phadia Ab, Uppsala, Sweden) is an immunoassay that detects all variants and thus is a measure of total tryptase. Under normal circumstances α -tryptase is continuously released into the circulation in amounts proportional to the mast cell population; it is thus a surrogate marker of the mast cell burden that is elevated in many of the mast cell diseases. During an acute episode of mast cell activation, such as anaphylaxis, a large quantity of β -tryptase is released, accounting for the rise in total tryptase. MCT has a half-life of approximately 2.5 hours falling back to normal baseline levels in 12–24 hours. It is becoming more widely recognised that it is important to check a baseline MCT after an acute episode has resolved to rule out an underlying mast cell disorder. Similar diagnostic work up after systemic reactions to hymenoptera stings identified 44 of 379 subjects who had elevated baseline MCT and, after further investigation, 21 were diagnosed as having systemic mastocytosis⁹. This high rate of mastocytosis has not been reported in the perioperative anaphylaxis setting, but if baseline MCT is not performed routinely, it is possible that cases could be undiagnosed. Serum tryptase levels remain the recommended blood test to employ in the diagnostic work up for suspected systemic mastocytosis. Almost all patients with systemic mastocytosis have total tryptase levels exceeding 20 ng/ml, reflecting the increased population of cells¹⁰.

Mast cell disorders

There is a diverse range of clinical disorders characterised by the accumulation of mast cells in one or multiple organs or tissues. The classification and diagnosis of these conditions is beyond the scope of this report, other than a broad outline.

Cutaneous mastocytosis most commonly occurs in children; the accumulation of mast cells is confined to the skin, manifesting as urticaria pigmentosa. It is normally a relatively benign and self-limiting disease, which has a good prognosis and the condition resolves by puberty if diagnosed before the age of ten.

Urticaria pigmentosa starting after ten years of age often persists throughout adulthood.

Systemic mastocytosis always involves the bone marrow and is the predominant form of mastocytosis in adults. There are a number of recognised patterns of the disease from benign to aggressive. Indolent systemic mastocytosis is associated with few symptoms and no evidence of extracutaneous organ dysfunction, whereas aggressive systemic mastocytosis is associated with organ dysfunction and a spectrum of signs and symptoms. Systemic mastocytosis may be associated with proliferation of another haematological cell line and mast cell leukaemia may occur. Mast cell development, accumulation and survival is dependant on the interaction of a mast cell growth factor, called KIT ligand or stem cell factor with KIT, a receptor tyrosine kinase on the mast cell surface. Mutations within the c-KIT oncogene may obviate the reliance on stem cell factor and allow for a gain of function that can lead to proliferation of the mast cell. Some mutations have been recently identified and are helpful in diagnosis and classification of these disorders. This classification has been extended with the recognition that there is a subgroup of patients who do not have an increased population of mast cells, thus normal baseline MCT levels, but they are excessively sensitive to degranulation, thus the designation of 'Monoclonal Mast Cell Activation Syndrome'¹¹. Patients with all these conditions are at increased risk of developing hypotensive episodes resembling anaphylaxis, most commonly triggered by hymenoptera stings, foods, drugs or exercise.

Common signs and symptoms of the more aggressive systemic variety include pruritus, flushing, palpitations, erythematous wheals, gastritis, diarrhoea and abdominal pain¹². The major diagnostic criterion for the diagnosis of mastocytosis is a bone biopsy showing multifocal mast cell clusters of atypical morphology. However, these characteristic bone marrow lesions are not always present¹³. Aberrant expression of cell surface markers CD25 and CD2, as well as the genetic mutations previously mentioned, are also important criteria for the diagnosis and classification of the mast cell disorder¹⁴.

Triggers for mast cell activation in mastocytosis

Ischaemia and reperfusion

An elevated MCT, immediately following an intra-operative incident with characteristics of anaphylaxis, is diagnostic of mast cell degranulation but does not differentiate between immune and non-immune activation¹⁵. In patients with systemic mastocytosis, mast cells may degranulate in response to allergen

exposure, as in allergic disease, although mast cells can degranulate for a variety of different reasons (such as mechanical trauma, high temperature, toxins, venoms and immune mechanisms) that are independent of immunoglobulin E activation¹⁶. In addition, triggers for the initiation of the inflammatory cascade may be tissue injury and hypoxia, and mast cells may be the target for a number of mediators such as complement anaphylotoxins and cytokines¹⁷. We hypothesise that tissue hypoxia during the period of ischaemia, while the tourniquet was inflated, led to mast cell degranulation in the first patient's abnormal population of mast cells. After tourniquet release, massive quantities of mast cell mediators were released into the circulation resulting in the profound cardiovascular collapse.

In support of this hypothesis, research has shown that mast cells play a pivotal role in the inflammatory response of ischaemic reperfusion injury, resulting in an increase in mast cell numbers after a period of ischaemia¹⁸. In addition, it has been proven that ischaemia induces the release of mast cell-derived inflammatory compounds, thus increasing the mast cell tryptase level¹⁹. Ischaemia followed by reperfusion also leads to nonspecific degranulation of mast cells and release of toxic mediators^{20,21}, and the number of degranulated mast cells increases within hours of reperfusion²². In a review article by Bot et al²³, the authors speculate that the triggers of mast cell activation included ischaemia, neuropeptides and stress; all of which could help to explain the degranulation of mast cells that occurred with our patient during surgery.

There is very little literature available regarding the direct effect of anaesthesia and surgery on MCT levels in normal individuals, although it has been shown that there is no increase in MCT levels during coronary bypass surgery using extracorporeal circulation²⁴. A recent study by Garvey et al²⁵ investigated the effect of orthopaedic surgery on MCT levels. This study showed a statistically significant decrease in MCT levels with surgery, conjectured as being due to a dilutional effect of intravenous fluid administration. However, this study investigated the effects of orthopaedic surgery in general and, not specifically, the effect of the arterial tourniquet. The case report previously cited by Vaughan describes anaphylaxis during an orthopaedic case involving a tourniquet. Although there were symptoms prior to discontinuation of surgery, it appears profound cardiovascular collapse occurred after the release of the tourniquet².

In our case, it is also possible that degranulation of a small number of mast cells induced by the

ischaemia of the arterial tourniquet initiated a much greater, amplified response. He et al showed that the release of tryptase from activated mast cells acted as an amplification signal for further secretion by neighbouring mast cells²⁶. It is also possible that the clonidine administered prior to tourniquet release may have exacerbated the hypotension by inhibiting noradrenaline release²⁷.

Allergen exposure

In the second case presented here, there had been no suspicion of mastocytosis prior to the admission for elective surgery. With hindsight, it is possible that this patient's abdominal symptoms, for which he was scheduled to have a colonoscopy, may have been related to his mast cell disorder. His extreme sensitivity to peanuts was noted preoperatively but would not have been considered relevant to the management of his surgery. The onset of the allergic reaction was atypical since most anaphylactic reactions in the operating theatre occur at, or shortly after, induction of anaesthesia associated with the administration of intravenous drugs such as muscle relaxants or prophylactic antibiotics. Reactions apparent during the latter part of a surgical procedure are most commonly caused by colloids, chlorhexidine, patent blue dye or latex, and the temporal relationship may not be so obvious. In this case the patient was either not exposed or skin tested negative to these agents. With such a dramatic presentation and clinical picture associated with the markedly elevated MCT, it is unusual not to elicit a cause and thus the suspicion of mastocytosis was raised. This was subsequently confirmed and thus raised the possibility that the mast cell degranulation was triggered by peanut exposure, although it is recognised that other stimuli such as hypoxia, pain or other unrecognised triggers might have been responsible.

These two reports highlight the importance of baseline MCT in the diagnostic work up of patients having anaphylaxis in the perioperative setting. The association of an atypical presentation, a severe reaction and a negative skin test should alert the investigator to the possibility of systemic mastocytosis. We recommend that tourniquets should not be used in patients known to have systemic mastocytosis. Anaphylaxis is normally triggered in the atopic patient by insect stings, food and drugs. These same agents are responsible for triggering anaphylaxis in the patient with systemic mastocytosis. Although there is only a suspicion that mast cell degranulation was triggered by exposure to peanuts in the second case, it would seem prudent to protect patients with food-induced anaphylaxis from possible

exposure during their hospital stay.

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