

## ANAESTHETIC MANAGEMENT OF SYSTEMIC MASTOCYTOSIS

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### SUMMARY

*Systemic mastocytosis is an uncommon disorder of mast cell proliferation in connective tissues. Mast cell degranulation may occur on exposure to various stimuli and drugs. The release of histamine, heparin and vasoactive substances such as prostaglandin D<sub>2</sub> may cause severe hypotension and other anaphylactoid manifestations. Anaesthetic management should include perioperative stabilization of mast cells and avoidance of the use of histamine-releasing drugs. Intradermal skin testing is useful in predicting the sensitivity to drugs that may be used during anaesthesia. We present a patient with systemic mastocytosis who underwent uneventful cholecystectomy.*

### KEY WORDS

*Allergy: intradermal testing. Complications: mastocytosis.*

Mastocytosis is an uncommon disorder (1-4 in 10000) of mast cell proliferation, which occurs in both cutaneous (urticaria pigmentosa) and, in about 10% of cases, systemic forms. As the mast cell is a connective tissue cell, the systemic disorder may involve all organs except the central nervous system. Mast cell degranulation occurs in response to a variety of non-immune triggers, including physical or psychological stimuli, in addition to exposure to many nutrients and drugs. The release of the preformed granule-associated mediators such as histamine, heparin and many enzymes (chymases, hydrolases, tryptases) and the generation of leucotrienes, prostaglandin (PG) D<sub>2</sub> and platelet-activating factor may produce significant systemic effects [1]. Cardiovascular collapse, bronchospasm and death during anaesthesia in patients with systemic mastocytosis have been documented [2]. A patient with systemic mastocytosis was anaesthetized for cholecystectomy at our institution.

### CASE HISTORY

A 65-year-old, 63-kg female with systemic mastocytosis was admitted to the surgical department of the University Hospital, Ghent for elective cholecystectomy. From the age of 19 yr the patient had experienced recurrent flushes and urticarial weals, pruritus, dizziness and headaches after consumption of alcohol and exposure to heat. A diagnosis of "urticaria pigmentosa" had been confirmed by skin biopsy 15 yr previously. She had suffered a major syncopal episode and dyspnoea during dental treatment. Severe flushing and dyspnoea had occurred after injection of the local anaesthetic during an earlier attempt to aspirate bone marrow. None of the attacks required her admittance to hospital. Her past medical history included haemorrhoidectomy under regional anaesthesia, appendicectomy and lens implantation under general anaesthesia. Each postoperative period was accompanied by abdominal cramps, diarrhoea, flushing and vomiting.

In January 1989 the patient was admitted to the University Hospital, Ghent with complaints of diarrhoea, abdominal pain in the right upper quadrant and hot flushes associated with dyspnoea. Physical examination showed a moderately obese woman in no acute distress. Her skin had a coalescent brownish-red macular appearance on the trunk, upper and lower extremities. Darier's sign (dermographism) was positive, with a weal and flare after scratching the skin. Abdominal examination showed deep tenderness in the right upper quadrant. The liver edge was felt 8 cm below the costal margin.

ECG and chest x-ray examinations were normal, while x-rays of the thoracic and lumbar spine showed osteoporosis. Abdominal x-ray showed

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calcification in the gall bladder and cholelithiasis was confirmed by ultrasonography. Laboratory results, including coagulation studies, thyroid function, plasma concentrations of catecholamine and urinalysis, were normal. Colonoscopy was negative, but the biopsies contained many mast cells. Gastroscopy showed signs of gastritis. A bone marrow biopsy showed an increased number of mast cells (4% of marrow cells) with a spindle shape.

The diagnosis of systemic mastocytosis was confirmed by the history, bone marrow biopsy and response to antihistamine therapy with normalization of defaecation. Terfenadine and famotidine, H<sub>1</sub>- and H<sub>2</sub>-receptor blockers and enteric coated aspirin were commenced. The patient was scheduled to undergo cholecystectomy.

Premedication comprised famotidine 20 mg, terfenadine 60 mg, aspirin 1 g and lorazepam 2.5 mg, orally. Standard monitoring, including invasive measurement of arterial pressure and bladder catheterization was commenced and skin tests of drugs thought necessary for anaesthesia were performed. The drugs tested included: normal saline control, etomidate, vecuronium, atropine, cefuroxime, adrenaline, hydrocortisone, meglumine-amidotrizate (the water-soluble iodinated radiographic contrast medium for use during the cholangiogram) and fentanyl. After the disappearance of the reactive flare, an erythematous weal persisted at the sites of injection of etomidate and hydrocortisone. Propofol was tested, without a reaction. Cefuroxime 1.5 mg was administered i.v. as antibiotic prophylaxis.

Anaesthesia was induced with propofol, vecuronium and fentanyl. After tracheal and gastric intubation, anaesthesia was maintained with isoflurane and nitrous oxide with an  $FI_{O_2}$  of 0.5 and supplemented with fentanyl and vecuronium. Ventilation of the lungs was adjusted to achieve mild hypocapnia ( $PE'_{CO_2}$  4 kPa). Cholecystectomy was carried out through an upper median incision. The gall bladder had a calcified appearance and was found to be filled with multiple small stones. An intraoperative cholangiogram was performed and showed a normal common bile duct, free of stones. The patient withstood the operative procedure well. There were no episodes of flushing, hypotension, bronchospasm or other untoward events during operation.

I.v. administration of H<sub>1</sub>- and H<sub>2</sub>-receptor blocking agents and aspirin was continued in the postoperative period. Postoperative pain relief

was achieved with i.v. piritramide, after prior skin testing. Postoperative recovery was satisfactory, complicated only by an episode of diarrhoea and mental disorientation on the third night after operation. The patient was discharged on the 11th day after operation, with continuation of aspirin, terfenadine and famotidine therapy, and has remained well.

#### DISCUSSION

The most common sites involved in systemic mastocytosis are skin, bone, gastrointestinal tract, liver, spleen and lymph nodes (table I). The anaesthetic management of systemic mastocytosis has previously been associated with a high perioperative complication rate. Parris, Scott and Smith reported cardiovascular collapse or bronchospasm requiring adrenaline infusion in five of 42 patients (12%) [2].

Complete assessment of the degree of systemic involvement of the disease must be made before operation. Laboratory evaluation of mast cell degranulation involves measurements of plasma and urinary concentrations of histamine [3], urinary PG D<sub>2</sub> and its metabolite PG D<sub>2</sub>M [4] and plasma concentrations of tryptase. Urinary concentrations of histamine correlate better with tissue concentrations of histamine than plasma concentrations of histamine and the complexity of the measurement of PG D<sub>2</sub> restricts its wider clinical application. An immunoassay of tryptase as a marker of the release of mast cell granules may be useful as a measure of perioperative activation of mast cells [5].

The preoperative use of H<sub>1</sub>- and H<sub>2</sub>-receptor blocking agents is generally recommended, although others have doubted their value [6]. The effect of histamine on capillary permeability appears to be mediated via H<sub>1</sub>-receptors, but the vasodilator action involves both H<sub>1</sub>- and H<sub>2</sub>-receptors, so that both must be blocked to have any certain prophylactic effect.

The implication of PG D<sub>2</sub> as a mediator of the hypotensive episodes has led to the use of prostaglandin synthetase inhibitors, such as aspirin. Oral administration of disodium cromoglycate 4 × 100 mg has been shown to produce an improvement in cutaneous and gastrointestinal symptoms. As cromoglycate is poorly absorbed by oral administration, inhalation is preferable. The elimination half-life of cromoglycate is about 80 min, so its use as a premedicant drug is limited.

TABLE I. *Manifestations of systemic mastocytosis*

	Signs	Symptoms
Cutaneous	Dermographism	Pruritus
	Flushing	
	Urticarial weals	
	Reddish-brown papulae	
Cardiovascular	Tachycardia	Palpitations
	Hypotension	
	Syncope	
Gastrointestinal	Hepatosplenomegaly	Nausea
	Predilection for Gastric ulcer	Vomiting
	Malabsorption (rare)	Diarrhoea
	Portal hypertension (rare)	Abdominal pain
Bone	Osteoporosis	Bone pain
	Pathological fractures	
Neurological		Headache
Respiratory	Wheezing	Rhinorrhoea
		Dyspnoea
Haematological	Anaemia	Coagulopathies
	Leucopenia	
	Thrombocytopenia (rare)	
	Decreased clotting factors	
	Leukaemia (rare)	

Ketotifen also prevents mast cell degranulation and may prove to be of value in perioperative treatment.

Stress can precipitate a reaction, so sedative premedication is important and benzodiazepines are appropriate. Extremes of temperature should be avoided and pressure on, trauma to or rubbing the skin must be restricted to a minimum. Temperature, ECG and arterial pressure should be monitored continuously and the possibility of sudden haemodynamic instability some time after a drug has been injected must be borne in mind [7]. The drug of choice for correction of hypotension is adrenaline  $5-8 \mu\text{g kg}^{-1}$  i.v., followed by a continuous infusion of  $5-10 \mu\text{g kg}^{-1} \text{min}^{-1}$ . Doses of  $1-3 \text{ mg kg}^{-1}$  i.v. may be used to manage acute exacerbations of systemic mastocytosis as part of the conventional management of anaphylactoid reactions. Although heparin is released by mast cell degranulation, there are no reports of haemorrhagic complications during anaesthesia, probably because of phagocytosis of the endogenously released heparin. There may, however, be other reasons for a haemorrhagic diathesis, such as hepatic fibrosis, malabsorption of vitamin K secondary to intestinal lesions and thrombocytopenia caused by bone marrow suppression.

The choice of anaesthetic technique depends on the type of surgery. Some authors suggest that, in the absence of a coagulopathy, regional anaes-

thesia with an amide-linked local anaesthetic is preferable. However, a severe urticarial reaction has been described following i.v. regional anaesthesia with lignocaine [8]. Parris, Scott and Smith also experienced more complications with regional anaesthesia and commonly, as in our patient, intolerance to lignocaine [2]. As inhalation anaesthetics tend to inhibit the degranulation of mast cells, general anaesthesia using halothane, enflurane or isoflurane may be preferable.

Intradermal skin testing has been advocated, to enable prediction of reactions to drugs. False negative results are possible, and the chance of a false positive result increases with increasing concentration of drug. A standard procedure using  $0.01-0.02 \text{ ml}$  of a dilute solution ( $10^{-4}-10^{-6}$ ) to raise a  $1-2 \text{ mm}$  weal is advocated in the diagnosis of drug-related acute anaphylactoid reactions [9]. As, in the case of systemic mastocytosis, non-specific histamine release occurs and most patients are receiving antihistamines and disodium cromoglycate at the time of preoperative skin testing, we advocate greater concentrations such as  $10^{-2}$  or  $10^{-3}$ . The criteria for a positive reaction should be strictly defined as a weal appearing within 10 min, lasting at least 30 min and at least 10 mm in diameter for an injected volume of 0.1 ml.

Intradermal testing was useful in the selection

of propofol as the induction agent in the present patient, thus confirming the absence of histamine release after induction doses of the emulsion formulation of propofol [10, 11].

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