Aneurysm Repair in a Patient With Systemic Mastocytosis

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WHILE INTRAOPERATIVE anaphylaxis usually is attributed to IgE hypersensitivity reactions, other causes such as mastocytosis may be responsible. Mastocytosis is a rare hematologic disorder characterized by mast cell proliferation in 1 or more organs.[1] It carries profound perioperative implications as various stimuli and medications can result in anaphylaxis.[1] However, anaphylaxis from mastocytosis is different from IgE-mediated hypersensitivity anaphylaxis, in that the precipitating agent directly activates mast cells without IgE mediation.[2] The authors report the successful perioperative management of a patient with undiagnosed systemic mastocytosis complicated by undiagnosed drug-induced IgE hypersensitivity.

CASE PRESENTATION

A 53-year-old male with a past medical history significant for obesity, hyperlipidemia, mitral valve prolapse, bicuspid aortic valve, and ascending aortic aneurysm (maximal diameter 4.9 cm) presented for elective valve-sparing root and ascending repair of a dilated ascending aorta. His current medications included simvastatin, atenolol, and aspirin. He denied history of allergies to medications or problems with previous anesthetics. In addition, he denied history suggestive of clinical symptoms for mastocytosis such as skin lesions (urticaria pigmentosa), flushing, abdominal pain, nausea, diarrhea, syncope or previous anaphylaxis episodes. Surgery was performed in a latex-free environment per routine hospital practice.

Anesthesia was induced with midazolam, fentanyl, lidocaine, propofol, and vecuronium. Per the authors' institutional cardiac surgery protocol, prophylactic antibiotic coverage with vancomycin at 16.5 mg/min was started via a peripheral intravenous catheter after endotracheal intubation. Shortly after intubation, invasive radial arterial access and internal jugular central venous access were obtained. During central venous cannulation, the patient became severely hemodynamically unstable with systolic blood pressure approximately 50 mmHg and heart rate initially 50 to 60 per minute. The vancomycin infusion was stopped, and the patient had refractory hypotension despite multiple boluses of phenylephrine (1,400 μg), ephedrine (10 mg), vasopressin (14 units), calcium chloride (2 gm), epinephrine (325 μg), and fluid resuscitation (4 liters). Systolic blood pressure remained below 60 mmHg for approximately 30 minutes. Significant tachycardia (sinus tachycardia at 140 per min) with persistent hypotension resulted after epinephrine therapy. Pulmonary artery catheter placement was aborted given hemodynamic instability. Emergent transesophageal echocardiogram revealed an intact aorta without disruption of the aneurysm, no cardiac tamponade, normal right ventricular function, grossly normal valvular function, no left ventricular outflow tract obstruction, and a hyperdynamic empty left ventricle. Bilateral breath sounds were auscultated, chest x-ray excluded pneumothorax, and airway pressures had not changed. Urticaria and a diffuse erythematous rash were noted on the thorax. As an allergic reaction was entertained, hydrocortisone, 100 mg IV, diphenhydramine, 50 mg intravenous (IV), and ranitidine, 50 mg IV, were administered along with methylene blue, 100 mg IV. Shortly thereafter vital signs normalized. Given the severe hemodynamic instability in the setting of diffuse erythematous rash, the diagnosis of anaphylaxis was entertained. Surgery was cancelled given the protracted hemodynamic instability and vasopressor requirement. The patient was extubated successfully a few hours later. Anaphylaxis was further presumed given markedly elevated tryptase (154 ng/mL, normal <11 ng/mL). Postoperative skin testing revealed hypersensitivity to cisatracurium, vecuronium, midazolam, and vancomycin. No reaction to propofol, succinylcholine, lidocaine, and fentanyl was elicited. Allergy consult recommended strict avoidance of trigger medications and consideration of pretreatment with diphenhydramine, ranitidine, and an antileukotriene agent prior to the next anesthetic.

Surgery was rescheduled, and the patient was treated with hydrocortisone, 100 mg IV, famotidine, 20 mg IV, and diphenhydramine, 50 mg IV, in the preoperative waiting room. Dexmedetomidine was utilized for sedation for preoperative arterial catheter placement. Anesthesia was induced with propofol, fentanyl, lidocaine and succinylcholine, all agents that skin testing suggested were safe. Given the positive vancomycin skin test, prophylactic antibiotic coverage with linezolid 600 mg IV over 60 minutes was infused after no initial test dose reaction. Shortly after intubation, internal jugular central venous access was obtained. During central venous cannulation, similar to the previous anesthetic, the patient became severely hemodynamically unstable with a systolic blood pressure of approximately 50 mmHg and heart rate of 120 per minute. The linezolid infusion was stopped, and the patient had refractory hypotension with a systolic blood pressure below 65 mmHg for approximately 15 minutes despite multiple boluses of phenylephrine (400 μg), ephedrine (15 mg), vasopressin (5 units), calcium chloride (500 mg), epinephrine (50 μg) and fluid resuscitation (2 liters). The patient was started on norepinephrine (0.06 μg/kg/min) and vasopressin (2 units/h) infusions with gradual improvement in hemodynamics. Emergent transesophageal echocardiogram revealed an intact aorta without disruption of the aneurysm, no cardiac tamponade, normal biventricular function, and grossly normal valvular function. Bilateral breath sounds were auscultated, chest x-ray excluded pneumothorax, and airway pressures were

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unchanged. Chest wall and upper extremity piloerection and erythema were appreciated. Surgery again was cancelled given the hemodynamic instability and the vasopressor requirement. The patient was successfully weaned off all vasopressors and extubated a few hours later. Repeat mast cell degranulation was suspected given markedly elevated tryptase (56.2 ng/mL, normal <11 ng/mL). Postoperative skin testing revealed no reaction to dexmedetomidine, sufentanil, and linezolid. Given the recurrent episodes of anaphylaxis, elevated tryptase from mast cell degranulation, and negative skin tests to the intraoperative medications, a non-IgE-mediated diagnosis for anaphylaxis was suspected. Newly developed hyperpigmented lesions seen about 6 weeks after surgery on the patient's chest suspicious for urticaria pigmentosa led to a bone marrow biopsy, which was diagnostic of systemic mastocytosis.

The patient was rescheduled with recommendations to receive prednisone, 50 mg per os (PO) 24 hours, 12 hours and 2 hours prior to surgery. In addition, the patient received montelukast, 10 mg PO, diphenhydramine, 50 mg PO, and ranitidine, 150 mg, 12 hours and 1 hour prior to surgery. Dexmedetomidine was utilized for preoperative radial arterial access and internal jugular central venous access with placement of a pulmonary artery catheter. Anesthesia was induced with propofol, fentanyl, lidocaine, and succinylcholine. General anesthesia was maintained with inhaled isoflurane, and dexmedetomidine and fentanyl infusions. Given the history of sensitivity to both aminosteroid and benzylisoquinoline non-depolarizing muscle relaxants, intraoperative non-depolarizing neuromuscular blockade was avoided. Linezolid, 600 mg IV over 60 minutes, and cefuroxime, 1.5 gm, were utilized for prophylactic antibiotic coverage. Three units of autologous blood were removed from the patient prior to cardiopulmonary bypass at the surgeon's discretion to help minimize post-bypass transfusion requirement. The prebypass period proceeded with stable hemodynamics (systolic blood pressure greater than 100 mmHg and heart rate approximately 50 per min) requiring a low-dose phenylephrine infusion at 30 μg/min and intermittent boluses of phenylephrine (totaling 300 μg). Airway pressures remained unchanged throughout. Cardiopulmonary bypass was conducted in usual fashion with systemic cooling to 32 degrees Celsius. Phenylephrine infusion at 20 μg/min was utilized to maintain adequate perfusion pressures (mean arterial pressure greater than 65 mmHg). The ascending aortic aneurysm was replaced with a 32-mm dacron graft. Given minimal calcifications and good aortic valve leaflet apposition, no intervention was made to the bicuspid aortic valve. Cardiopulmonary bypass and aortic cross-clamp times were 101 and 73 minutes, respectively. Protamine was administered to reverse systemic heparinization. Given the patient's history of vasectomy, diphenhydramine, 50 mg IV, hydrocortisone, 100 mg IV, and famotidine, 20 mg IV, were administered prior to protamine administration per usual hospital policy. The patient remained hemodynamically stable (systolic blood pressure greater than 100 mmHg) in the postbypass period requiring intermittent boluses of phenylephrine (totaling 600 μg) with no vasoactive infusions. He was extubated approximately 12 hours later. Postoperative management included continuing montelukast, 10 mg PO daily, ranitidine, 150 mg PO daily, prednisone taper over 5 days, and cetirizine, 10 mg PO daily. Analgesia was provided with intravenous fentanyl and oral acetaminophen. The patient was discharged home on postoperative day 4.

DISCUSSION

Mastocytosis is a rare heterogenous disease characterized by clonal proliferation of mast cells in the cutaneous and extracutaneous sites and usually is associated with the 816D>V mutation in the C-KIT gene.[1] It has an estimated worldwide incidence of 1:150,000.[2,3] Symptoms of mastocytosis are related to the increased mast cell burden with the subsequent release of a multitude of mast cell mediators, including histamine and prostagladin D2.[1,4] Cutaneous mastocytosis, mast cell hyperplasia restricted to the skin, usually is observed in children, and usually resolves shortly after puberty.[3,5] The most common cutaneous manifestation is urticaria pigmentosa, which consists of fixed, reddish-brown maculopapular lesions that urticate in response to physical irritation (Darier's sign).[5] In contrast, adults who present with cutaneous mastocytosis will have evidence of systemic involvement and persistent disease.[5] Adult-onset disease most commonly presents as systemic mastocytosis, abnormal clonal proliferation of mast cells in extracutaneous organs.[6] Symptoms of systemic mastocytosis occur from mast cell infiltration into affected organs compounded by mast cell mediator release.[4] The symptoms of systemic mastocytosis are variable. However, episodes of life-threatening anaphylaxis are a recognized feature.[7] The most common subtype of disease in adults, indolent systemic mastocytosis, is characterized by disease lacking end-organ dysfunction, which can delay the diagnosis of systemic mastocytosis, as in the authors' case.[5,6] Patients suffering from systemic mastocytosis are at risk for provoked and unprovoked anaphylaxis secondary to mast cell degranulation.[2] The cumulative incidence of anaphylaxis in adult patients with mastocytosis is as high as 49%.[7]

Routine preoperative skin testing is not always advocated.[1] However, perioperative hypersensitivity may present as IgE-mediated anaphylaxis but never may be diagnosed if not investigated.[8] Of the anaphylactic reactions described in the literature in the perioperative setting, skin testing only was performed in three patients, all of which were negative to the suspected anesthetic(s) or antibiotic.[2,9,10] However, given that the cause of intraoperative anaphylaxis rarely is known, and could be IgE-or non-IgE-mediated anaphylaxis, it would be prudent to perform skin testing in the preoperative setting to ascertain safe medications. A history of immediate hypersensitivity associated with increased tryptase concentration and a positive skin test to a suspected agent confirm the diagnosis of IgE-mediated allergic hypersensitivity.[8] However, history of immediate hypersensitivity that may or may not be associated with increased tryptase concentration and a negative skin test to a suspected agent suggests non-IgE-mediated immediate hypersensitivity, which may represent immediate mastocytosis hypersensitivity reaction.[8] Serum tryptase levels are a reflection of mast cell activation; however, since tryptase levels increase in both non–IgE-mediated mastocytosis reactions and IgE-mediated anaphylaxis, it is not specific for either disease.[1] In the authors' patient, the surgery first was canceled for suspected