Anesthetic Management of an Infant with a Solitary Mastocytoma

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Solitary mastocytoma is one of the variants of mastocytosis, which is a relatively rare disorder characterized by abnormal aggregates of mast cells in the dermis and in various organs of the body[1]. The process of mastocytosis may be confined to the skin (cutaneous mastocytosis) or may involve multiple organs (systemic mastocytosis)[2]. Abnormal aggregations of mast cells release vasoactive mediators such as histamine, heparin and prostaglandin D_2 (PGD_2) and produce a lifethreatening state, because of acute and profound hypotension[2]. One of the most interesting aspects to an anesthetist is the effect of drugs administered perioperatively on mast cell degranulation and chemical mediator released. Although mastocytoma is usually seen only in infants[3], there are few reports on anesthetic management for children with mastocytoma. We present a case of an infant patient with a solitary mastocytoma who required surgical therapy, and was administered ketotifen, a mast cell stabilizer, as a preoperative treatment.

Report of a Case

A three-month-old infant, 7.5 kg, was admitted to our hospital to undergo elective surgery for resection of a pigmented macular with errosion. At his birth, his family observed this brownish round macular, 2 cm in diameter, on the right upper part of his back. It was considered to be due to severe changes in body temperature or rub of the lesion, as taking a bath sometimes caused generalized flushing. Because only an episode of dyspnea and circumoral pallor following generalized flushing occurred, his family took him another clinic. Rubbing of the lesion, with the blunt end of a pen, led to the development of a marked palpable wheal (Darier's sign) followed by flushing and cyanosis. Immediately he had treatment with inhalation of oxygen, then cyanosis disappeared.

Physical examination performed at our hospital revealed that he had no hepatosplenomegaly or lymphadenopathy. Auscultation recognized expiratory wheezing which suggested the presence of stenosis of some part of the airway. We could also confirm positive Darier's sign. When intact skin around the eruption was rubbed, urticaria appeared 3 min after rub associated with reddness around it, followed by extensive flushing from face to upper trunk. Hematological examination including numbers of eosinophil and quantity of IgE indicated normal findings. Bleeding and coagulation time were within normal ranges. A chest roentogenogram showed stenosis of the upper portion of the trachea, considered to be a causative factor of expiratory wheezing. Ultrasound imaging of the abdomen revealed the abscence of a tumor. He was

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Table 1. Whole blood histamine concentrations during anesthesia

Samples	1. Bronchoscopy	2. Intubation	3. Rubbing of the lesion	4. Skin incision (start of operation)	5. After removal of the tumor
Values ($ng \cdot ml^{-1}$)	127	67	39	24	23

A blood sample was taken into a syringe containing EDTA from vein and analyzed for whole blood histamine concentrations by a fluorometric method at the time mentioned below. Normal ranges are 15–80 $ng \cdot ml^{-1}$.

diagnosed as a solitary mastocytoma and scheduled for excision of the tumor. Ketotifen 0.08 $mg \cdot kg^{-1}$ was ingested orally for eight days as a preoperative treatment. From the start of intake of ketotifen until the operation, no flush was observed.

Eight days after admission, bronchoscopy and excision of the tumor were performed under general anesthesia. He was not premedicated. The operating room was warmed in advance to avoid severe changes in his body temperature. Anesthesia was induced with halothane, nitrous oxide (N_2O) in oxygen via mask followed by administration of atropine sulfate 0.07 mg intravenously. Anesthesia was maintained with 1–2% of halothane, 40% of N_2O in oxygen. Muscle relaxation was obtained by intermittent injection of 1 $mg \cdot kg^{-1}$ of succinylcholine. Administration of atropine or succinylcholine did not cause flush or marked changes in blood pressure and heart rate. To observe the state of upper airway, bronchoscopy was performed before intubation, revealing tracheomalacia. After bronchoscopy, the trachea was intubated with a spiral tube of 3.0 mm internal diameter. Table 1 summarizes whole blood histamine concentrations during anesthesia. Erythematous eruption appeared at the time of bronchoscopy consistent with the slightly increased whole blood histamine concentration. Values of other samples measured were within normal ranges. Any operative manipulation did not cause urticaria or flushing. During surgical excision of the tumor, anesthesia was uneventful not involving severe changes in blood pressure and heart rate. Dexamethasone (2 mg) was injected at the end of the operation to prevent edema of the upper airway owing to the use of bronchoscopy. In postoperative course there was no episode of flushing, cyanosis or hypotension including shock. Histological examination indicated abnormal proliferation of mast cells from corium to subcutaneous fatty tissue.

Discussion

Mastocytosis is an uncommon disease, divided into five types according to the state and range of infiltration of mast cells as follows; (1) solitary mastocytoma, (2) urticaria pigmentosa, (3) diffuse cutaneous mastocytoma, (4) systemic mastocytosis and (5) telangiectasia macularis[2,3]. The reported incidence of mastocytosis in a general patient population ranges from 1 in 8000 to 1 in 1000 patients[4–6]. The onset of the initial disease may be helpful in differentiating patients with isolated cutaneous disorders from those with extra cutaneous involvement[2]. Mastocytoma is usually seen only in infants[3]. Although thus far, about 80 cases of solitary mastocytoma have been reported in Japan, no reports on solitary mastocytoma associated with tracheomalacia have been published. It is likely that cyanotic attack following flush in the present case resulted mainly from an increase in the extent of tracheal stenosis in the concurrent presence of trachaomalacia, by various kinds of chemical mediators released from mast cells.

It is well established that abnormal aggregations of mast cells release chemical

vasoactive mediators such as histamine, heparin and PGD_2 and produce acute and profound hypotension. Recently it has been reported that mast cells release new chemical mediators such as leukotrienes C_4, D_4 and E_4, platelet activating factor (PAF), and some kinds of protease, which may make the pathological state or symptoms much more complicated[2,3]. In particular PAF may also contribute to the hypotension observed in patients with systemic mastocytosis[3]. Stimuli that may release chemical mediators from mast cell granules include mechanical irritation of the skin lesion, psychological stress, extreme temperature changes, alcohol ingestion, and a variety of histamine-releasing medications, such as opiates, salicylates, atropine, muscle relaxants and polymycin B[1]. Precipitating factors of release, however, are unclear in most instances. In the present case the most possible causative factors that produced the attack seemed to be mechanical irritation of the lesion or temperature changes.

Treatment of mastocytosis has been directed either at stabilizing the mast cell membrane or blocking the effects of histamine[8]. Preoperative symptomatic therapy provides variable results and includes H_1 or H_2 receptor antagonists and corticosteroids[1]. Although inhibitors of prostaglandin formation such as aspirin or nonsteroidal anti-inflammatory drugs have been used[7,8], aspirin is considered to be contraindicated by some investigators, on the basis of an alleged ability of this drug to initiate mast cell degranulation[9]. James et al. believe that the indications for and benefits of the use of H_1 or H_2 and prostaglandin blockers as prophylaxis have not been demonstrated and they may not be indicated[10]. It is obvious that excision of the lesion is the sole treatment for solitary mastocytoma associated with systemic symptoms to control the progress of the disease, although most of infants with mastocytomas do not require treatment because of spontaneous resolution of the disease[1,2]. There has been many reports on anesthetic management for mastocytosis in adults recommending no specific anesthetic techniques[1,11], but few reports in children. James and co-workers recently reviewed 42 cases of cutaneous mastocytosis in children over the past 25 years and demonstrated the data suggesting that patients with urticaria pigmentosa or solitary cutaneous mastocytoma were not at increased risk of life-threatening complications under general anesthesia[10]. They concluded that a conservative approach (monitoring closely, keeping the full range of therapeutic and resuscitative drugs readily available and avoiding known histamine-releasing drugs) might prove to be the optimal management for patients with isolated cutaneous mastocytosis undergoing general anesthesia[10]. Even in minor operative procedures, profound cardiovascular collapse has been reported[7,11]. The primary anesthetic considerations, therefore, are the prevention of vasoactive mediator release and the prompt treatment of hypotension, should it occur[1]. Hosking et al. reported an adult case where the use of epinephrine had been lifesaving[12]. Some investigators have claimed that drugs to avoid are atropine, morphine, codein, D-tubocurarine, metocurine, gallamine, pancuronium, thiopentone and salicylates[1,9]. However, atropine was administered at induction time in the present case without any complication. On the other hand, succinylcholine administered in our case, and glycopyralate are considered safe[1,9], but little experience is reported. Inhalational anesthetic agents are considered to be acceptable for administration to patients with mastocytoma. Great care should be exercised that an operating room is kept at a stable temperature in the case where histamine may be released by fluctuations in temperature.

Ketotifen and disodium cromoglycate (DSCG), new inhibitors of mast cell degranulation, have been shown recently to reduce the daily symptom of patients with urticaria pigmentosa and diffuse cutaneous mastocytosis[13–15]. The advantage of the former over the latter are its good ab-

sorption from the gastrointestinal tract, the resulting short lag period before a reduction of symptoms, the high effectiveness and the low cost[2,13]. Ketotifen also has been reported, unlike DSCG, to function as an H_1 receptor antagonist[16] and a calcium channel blocker[17] and to inhibit slow reacting substance of anaphylaxis (SRS-A) release from leukocytes and elevate cAMP levels in different cell types[16,18]. Czarnetzki recommends ketotifen therapy as an effective means for the control of the pruritus and whealing[13].

Kettlehut et al. reported that plasma histamine concentrations in nine children with mastocytosis were remarkably high at rest[19]. As shown in table 1, whole blood histamine concentrations were estimated during anesthesia in the present case where ketotifen had been administered as a preoperative therapy. Rubbing of the lesion during anesthesia did not increase the histamine level, whereas in awake states it caused general flushing. Stimulation produced by bronchoscopy, which was considered to be potent, failed to increase markedly whole blood histamine concentration and no stimulation produced by anesthesia or operation led to critical condition including profound hypotension and severe bronchospasm. The preinduction level could not be measured, but was expected to be lower than that immediately after bronchoscopy. A question arises as to whether or not ketotifen, 0.08 $mg \cdot day^{-1}$ for eight days, has ability to reduce histamine release from mast cells. The possibility exists, however, that this dose of ketotifen was effective in preventing the increase in histamine concentration because in vivo data studied by Magnussen[20] could demonstrate that 2 mg of ketotifen administered 4 hr prior to inhalation challenge with histamine blunted bronchospasm in asthmatic patients. In vitro data from report by Wilhelms[21,22] have demonstrated that ketotifen, 5×10^{-8} $mol \cdot \ell^{-1}$, inhibited the spasms induced by pro-allergic mediators such as histamine, SRS-A and leukotrienes C_4 and 1×10^{-4} $mol \cdot \ell^{-1}$ suppressed release of these mediators leukocytes and rat alveolar macrophages. Furthermore Truneh and co-workers reported that micromolar order of ketotifen could inhibit histamine secretion from rat mast cells[23].

In conclusion, we reported a case of an infant with a solitary mastocytoma and discussed anesthetic management for the disease. Our case demonstrates the possibility that preoperative treatment with ketotifen attenuated the marked increase in whole blood histamine concentrations during anesthesia. Further studies are required to confirm the effects of preoperative ketotifen on histamine release induced by various kinds of stimulation during anesthesia and anesthetic management for mastocytoma.

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