Multiple Abnormal Cutaneous Findings in a Patient With Hypomelanosis of Ito Undergoing General Anesthesia

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Hypomelanosis of Ito (HI), a neurocutaneous syndrome, is characterized by skin depigmentation and skeletal, muscular, central nervous system, cardiac, and renal manifestations. A wide variety of cutaneous manifestations besides depigmentation have been reported. Herein we describe a 23-year-old woman with HI whose extracutaneous symptoms included severe mental and motor impairment, convulsions, and deformity of the orofacial region. She also had severe obesity, asthma, multiple allergies, and skin hypersensitivity. Although no extracutaneous manifestations were problematic during perioperative management of dental procedures under general anesthesia, erythema developed at 3 time points: during induction, during emergence, and in recovery. We speculated that mechanical stimuli to the skin and administration of multiple drugs likely caused histamine release, leading to the 3 episodes of erythema. Because patients with HI often have hypersensitivity reactions in the skin, both cutaneous and extracutaneous manifestations should be considered in the anesthetic management of patients with HI.

Key Words: Hypomelanosis of Ito; Cutaneous manifestations; Erythema; Mechanical stimulus; Drug hypersensitivity reactions.

Hypomelanosis of Ito (HI) is a rare condition that has both cutaneous and extracutaneous manifestations. The characteristic cutaneous manifestation is hypopigmentation that forms whorled, linear, or irregularly shaped patterns along the lines of Blaschko, where the cells constructing the skin differentiate and from which they migrate during the embryonic period. HI is considered to be a mosaic chromosomal disorder in which genetic mutations occur spontaneously. Differential migration of the resultant, genetically different cell lines with chimerism or mosaicism can impact not only the skin but also the systemic organs, such as the brain, to which they migrate.[1] Patients with HI generally develop various combinations of extracutaneous manifestations, primarily neurological (ie, cognitive and motor) impairment, cramps and seizures, congenital cardiac abnormalities, and renal anomalies.[2–5] Moreover, several reports have detailed cutaneous manifestations and abnormal histopathological findings relating to allergy, hypersensitivity, and vulnerability of the skin.[6–8]

We herein describe a patient with HI who developed cutaneous erythema 3 times during general anesthesia. These episodes occurred (1) after administration of rocuronium during mask ventilation, (2) after administration of sugammadex, and (3) first noted in the recovery room on her right hand near where the sphygmomanometer cuff had been placed.

CASE PRESENTATION

The patient was a 23-year-old woman (height, 156 cm; weight, 90 kg; body mass index, 36.9 kg/m^2). She had

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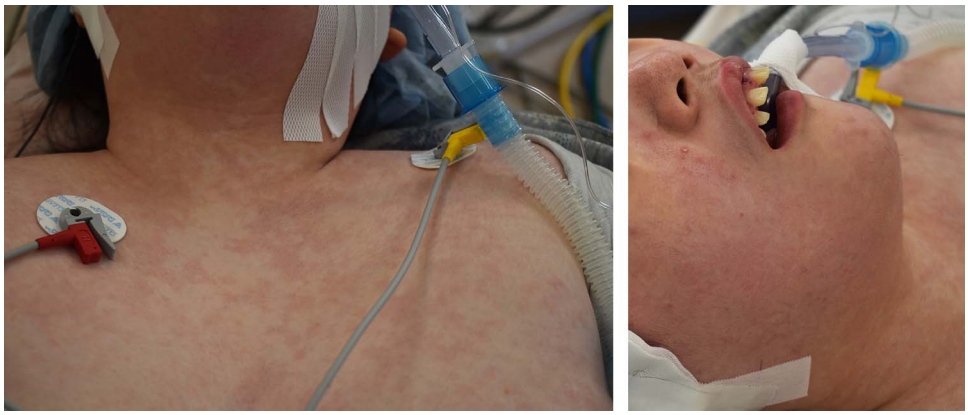
Figure 1. First Episode of Erythema During Induction



After intubation, the patient developed generalized erythema extending from her face to the thoracoabdominal region.

significant developmental delay involving her cognitive and motor function and had been diagnosed with HI at 1 year of age. She was unable to speak or walk on her own. Convulsive seizures had developed following multiple febrile seizures in childhood; therefore, carbamazepine (1000 mg, twice daily) had been prescribed which largely prevented any major epileptic seizures. However, she still had occasional brief tonic seizures. Her pediatrician told us that the patient had a history of allergy to antiepileptics but that diazepam could safely be used for perioperative seizure management if needed. When the patient developed mild epileptic seizures at home in the form of twitching limbs, her mother often administered a benzodiazepine (10 mg) suppository to the patient.

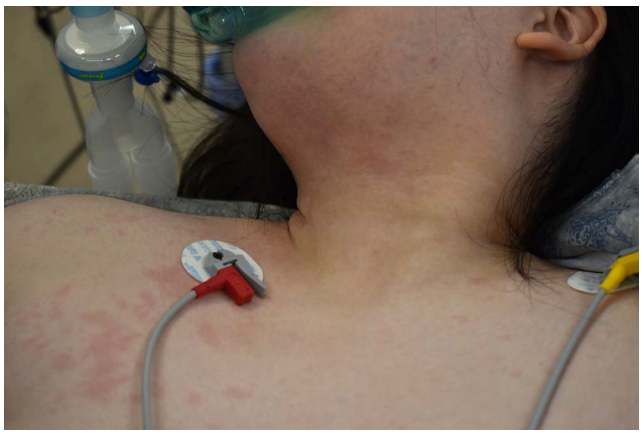
In addition, the patient had atopic dermatitis and multiple allergies, including milk, nuts, pollen, dogs, and cats. She also had bronchial asthma which was well controlled. She had been prescribed levocetirizine (10 mg, twice a day) for allergies, pranlukast (450 mg, twice a day) for asthma, and zolpidem (10 mg) and lemborexant (5 mg) before sleep for insomnia. Moreover, her mother told us that certain stimuli readily caused skin erythema and that the patient had hypersensitivity to skin contact.

The patient was scheduled for maxillary third molar extractions due to caries under general anesthesia. Her routine preoperative blood tests and electrocardiographic findings were normal. A posteroanterior chest radiograph was unremarkable except for revealing slight scoliosis. She had abnormal maxillofacial morphology, including a small mandible, labially inclined maxillary incisors, prognathism, and a narrow maxillary dental arch. Her Mallampati score was class III, despite her being able to fully open her mouth. The only preoperative instructions given to the patient was to take nothing orally except for her regular medications.

We administered oral midazolam (10 mg) in the hospital ward approximately 30 minutes before transferring her to operating room. Upon her arrival, standard anesthesia monitors were applied, and the patient was placed into a ramped position because of anticipated intubation difficulties. General anesthesia was gradually induced via facemask with sevoflurane (5%), oxygen (2 L/min), and nitrous oxide (4 L/min) with no difficulties with ventilation. Following induction, intravenous (IV) access was secured, and a remifentanil infusion (0.3 μg/kg/min), propofol (90 mg), and rocuronium (40 mg; 0.6 mg/kg based on the patient's ideal weight) were administered. Using a video laryngoscope (McGRATH, Covidien Japan) for indirect visualization, an oral endotracheal tube (ETT) with an inner diameter of 7.5 mm (RAE, Parker Medical) was advanced through the vocal cords to secure the airway without difficulty. Erythema appeared on the patient's face extending down to thoracoabdominal region approximately 1 minute after administration of the rocuronium (Figure 1); however, there were no abnormalities in airway pressure or volume, capnography waveform, or vital signs (blood pressure, 132/86 mm Hg; heart rate, 102 beats/min; oxygen saturation [pulse oximeter], 100%), and no evidence of bronchial narrowing or lung murmurs. Thus, there was no evidence of anaphylaxis and or acute asthma. Approximately 5 minutes after IV administration of chlorpheniramine (10 mg) and betamethasone (4 mg), the erythema began to decrease in severity.

A protective skin covering (SECURA; Smith & Nephew) was applied overtop the tape used to secure the ETT because she had a history of developing rashes when tape was applied to her skin. Intragastric suction, which we routinely perform in patients who have received premedication, was performed. This patient also had a known tendency to aspirate which reinforced the need to perform intragastric suction prophylactically. Additionally, IV ampicillin (1 g) was administered before the start of surgery.

Figure 2. Second Episode of Erythema After Administration of Sugammadex



The second episode of erythema, which involved the patient's neck and chest, developed after administration of sugammadex with the erythema being more pronounced on the right side of the chest. This photograph was taken approximately 15 minutes after the erythema appeared and after extubation.

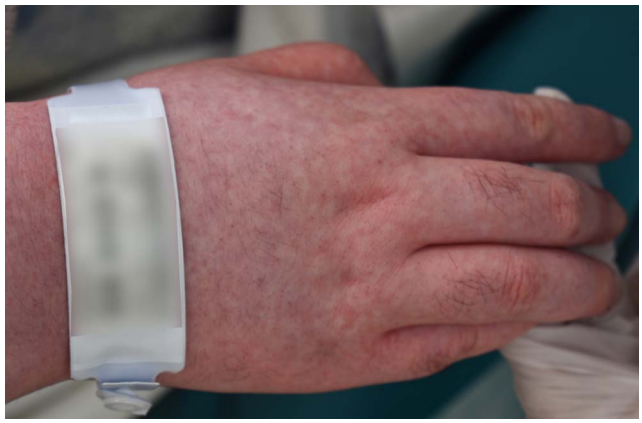
General anesthesia was maintained with desflurane (5%), oxygen (1.5 L/min), air (2 L/min), and a remifentanil infusion (0.05–0.1 μg/kg/min). During maintenance of anesthesia, IV atropine (0.5 mg) and phenylephrine (0.1 mg) were administered for bradycardia and hypotension, respectively. Considering the possibility of aspiration on extubation, we administered IV famotidine (20 mg) in advance. The local anesthesia via infiltration with 1.8 mL of 2% lidocaine (36 mg) with 1/80,000 epinephrine (22.5 μg) was performed. For postoperative analgesia, IV acetaminophen (1000 mg) was administered at the end of the operative procedure.

The dental extractions took 1 hour and 32 minutes. Prior to extubation, neuromuscular blockade was reversed with sugammadex (150 mg). The erythema on the patient's face and chest recurred and was more pronounced on the right side of the chest (Figure 2). At this time, 100% oxygen was administered, and mechanical ventilation continued. No abnormalities in the patient's ventilation parameters or vital signs were observed similar to when the erythema appeared initially. Even though the erythema on this second occasion was less pronounced, we continued to closely observe the patient. The erythema began to decrease after approximately 5 minutes.

The patient was extubated deeply, but she emerged from anesthesia with no respiratory difficulties or evidence of airway narrowing or seizure.

During recovery and before returning to the ward, her mother was reunited with her and pointed out reticular erythema on her right hand which was not usually present (Figure 3). The erythema appeared to denote vascular congestion and was only present on the right hand, suggesting that it was attributable to mechanical stimulation from the sphygmomanometer cuff that had been used for continuous noninvasive monitoring of the blood pressure every 5 minutes during anesthesia. We ceased monitoring her blood pressure measurements at the end of the case, and the localized erythema resolved in approximately 1 hour. The patient's recovery was uneventful, and she was discharged home the same day with no complications.

Figure 3. Third Episode of Erythema First Noted in Recovery



Reticular erythema, attributed to the noninvasive blood pressure cuff compression, was noted on the patient's right hand during recovery and before returning to the ward.

DISCUSSION

HI was first described by a Japanese doctor, Minoru Ito, in 1952.[9] The reported incidence of HI is 1:7540 births and the prevalence is 1:82,000 individuals in the general population.[10] In general, there is no specific treatment for the hypopigmented skin areas.

The term erythema denotes subcutaneous vasodilation that is visible as redness in areas of thin skin. It is caused by release of histamine from mast cells and basophils, together with phospholipid mediators such as prostaglandins and leukotrienes, which results in vasodilation.[11] The causes for histamine release by degranulation from mast cells are roughly classified as allergic hypersensitivity, including IgE- and non-IgE-mediated, and non-allergic hypersesitivity.[12] In this case, given that a histamine H1 antagonist was administered, release of histamine was presumably responsible for the erythema. However, we did not measure serum concentrations of histamine and tryptase at the time the erythema developed or the steady state of serum histamine as a control level, and we were not able to conduct skin prick or intracutaneous reaction tests after discharge. Thus, we could not make a definitive diagnosis but feel confident this did not represent an allergic/immune reaction.

Possible non-allergic causes of erythema include mechanical stimulation of the skin, temperature changes, autonomic

nervous system dysfunction, mental and psychological factors such as anxiety and panic disorders, and various drugs.[13] Given that the first episode of erythema occurred during induction and mask ventilation, contact with the facemask was a possible causative factor. Certainly, it was highly likely that mechanical compression from the blood pressure cuff was responsible for the third episode of erythema. Temperature changes were an unlikely cause because there were no remarkable changes in either body or operating room temperatures. Vasodilation in the orofacial region can result from parasympathetic stimulation and sympathetic inhibition.[14] We postulated that the parasympathetic dominance that would have resulted from the administration of propofol and sevoflurane during induction would have contributed to more ready dilation of peripheral blood vessels, and therefore erythema.

Furthermore, it is well known that mast cells respond to physical stimuli such as mechanical stimuli. TRPV2 receptors expressed on mast cells are activated by mechanical stress, causing degranulation.[15] One of the adhesion G protein-coupled receptors, the ADGRE2 receptor on mast cells responds to vibration-induced stimulation. Furthermore, mutated ADGRE2 has been shown to reduce the threshold for activation and promote degranulation in human mast cells.[16] However, whether these receptors are abnormal in patients with HI remains unclear.

Mast cell degranulation is mediated via pathways through various surface receptors such as IgE, the above-mentioned receptors, toll-like receptors, protease-activated receptors, and Mas-related G-protein-coupled receptor member X2.[17] Therefore, mast cells respond to numerous exogenous (many drugs and chemical compounds) and endogenous (cytokines, chemokines, anaphylatoxins, immunoglobulin G, and neuropeptides) stimuli. However, it may be difficult to differentiate between allergic and nonallergic hypersensitivities clinically.

If the erythema was due to drug hypersensitivity reactions, there are several possible candidates. Given that it was administered immediately before the first cutaneous symptom, rocuronium is one possibility. It has been reported that muscle relaxants (38%) and antibiotics (31%) are frequently responsible for allergic reactions.[18] The reported incidence of immediate allergic hypersensitivity reactions to rocuronium during anesthesia varies between countries, ranging from 1:10,000 to 20,000 patients.[19] However, rocuronium has little histamine-releasing effect via either non-specific[20] or non-IgE pathways.[21] Rocuronium has been shown to bind to a mast cell-specific receptor called Mas-related G-protein-coupled receptor X2. This causes mast cell activation and release of histamine via a non-allergic hypersensitivity reaction.[22]

Remifentanil and propofol were administered, and the trachea was stimulated during intubation. Although there is consensus that remifentanil does not cause histamine release,[23,24] remifentanil allergy accounted for <0.08% of 2516 patients with suspected intraoperative hypersensitivity in 1 study.[25] Propofol, which was administered before rocuronium, is another possible candidate. In vitro experiments have shown that it has the potential to release histamine from mast cells in human skin.[26] Propofol use in patients with a history of various allergies, including bronchial asthma, atopic dermatitis, and contact dermatitis, reportedly results in increased plasma histamine concentrations more than 50% greater than the control value in 15% of patients immediately after its injection and in 35% after intubation.[27] However, in contrast to our findings, the researchers did not observe erythema or flushing of the skin at either time point. It has been suggested that administration of propofol and the mechanical stimulation associated with intubation may cause histamine release in allergic patients. Additionally, the redness of the skin was particularly pronounced in our patient with HI because of the hypopigmentation of her skin.

The sugammadex or the rocuronium-sugammadex inclusion complex was a likely possible trigger for histamine release in the second episode of erythema because it occurred immediately after administration of sugammadex and there was virtually no mechanical irritation of the skin. A study in which sugammadex (4 mg/kg) was administered intravenously to normal participants showed that the incidence of drug hypersensitivity reactions other than anaphylaxis was 0.7%. Furthermore, no relevant histamine release was observed in basophil histamine tests.[28] The mechanism of sugammadex-related allergy has not been fully elucidated, sensitization to γ-cyclodextrin is a possible cause.[29] Moreover, the rocuronium-sugammadex inclusion complex that forms in vivo could serve as an allergen. Both the tertiary ammonium in the complex and quaternary ammonium groups that cause allergic reactions to rocuronium are potential sites for IgE binding. The physical and chemical properties of rocuronium and the carrier cyclodextrin can be altered during formation of inclusion complexes.[30] It is therefore difficult, and sometimes impossible, to predict whether a drug that is already known to cause allergic reactions will prove more or less allergenic when presented as an inclusion or some other complex.

In 1 case study, skin tests were positive for the complex despite being negative for both rocuronium and sugammadex individually.[31] Additionally ampicillin, which we administered prior to sugammadex, contains beta-lactam, which can cause both allergic and nonallergic hypersensitivity reactions, resulting in a relatively high frequency of drug hypersensitivity.[32] Porebski et al[17] hypothesized that the cumulative effect of this combination of co-factors is strong enough to achieve a sufficient level of mast cell activation to cause degranulation. In particular, several co-factors may have accumulated during general anesthesia, resulting in the second episode of erythema. In addition, the fact that the second episode was milder than the first suggests that the antihistamine and steroid that had been administered provided some degree of protection against further substantial histamine release. If we had

known that rocuronium and sugammadex might trigger mast cell degranulation, we could have avoided rocuronium by spraying lidocaine into the larynx and pharynx before intubation and avoided sugammadex by using a muscle relaxant monitor verify return of appropriate neuromuscular function (ie, no need for reversal) prior to awakening the patient.

Several reports have addressed the relationship between HI and allergy, hypersensitivity, and vulnerability of the skin. A 3-month-old male infant with HI who had very delicate skin frequently developed superficial infections and infectious eczema all over his body, which was exacerbated and progressed to skin necrosis.[5] This condition was described as infected asthmatic eczema. His skin was also susceptible to itching, likely as evidenced by him constantly rubbing his right foot against the mattress when a dynamic splint had been applied to it. Whether he was allergic to the bandage used was unclear because that possibility was not subjected to allergy testing.

In another report, a patient developed streptococcal exanthema only in hypopigmented skin.[6] In another case series, 4 of 5 patients with HI who underwent sweat testing were found to be anhidrotic in the depigmented areas of skin.[33] Some groups have reported that increased numbers of Langerhans cells are associated with immune responses,[7] as is an apparent increase in the number of nerve endings at the dermoepidermal edge.[8] These findings suggest that unusual allergic or inflammatory reactions may occur in the skin. Histological features of peripheral nerve endings may be associated with hypersensitivity to mechanical stimuli. Because we did not perform a skin biopsy, we do not know whether there were histopathologic abnormalities present in our patient. However, patients with HI may manifest other abnormalities in the skin besides hypopigmentation.

CONCLUSION

Our patient with HI had 3 episodes of erythema during general anesthesia. We were unable to definitively identify the triggering factors; however, these episodes may have involved histamine release in response to mechanical stimuli or drug hypersensitivity. Although we could not elucidate the relationship between HI and the noted erythema, it is worth considering the possibility of unexpected abnormal skin findings in patients with HI and asthma, multiple allergies, and hypersensitivity to skin contact.

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