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## Massive Airway Edema after Azathioprine

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AZATHIOPRINE is an antimetabolite widely used to suppress the immune system in recipients of organ transplants, as well as in patients with primary autoimmune disorders. Over the past 30 yr, it has proved to be an effective agent. However, multiple side effects have been reported, ranging in severity from fever and rash to cardiovascular collapse.<sup>1,2</sup> We report an acute idiosyncratic reaction to azathioprine in a patient undergoing kidney transplantation, characterized by life-threatening upper airway edema and circulatory collapse, both of which were elicited again after rechallenge.

### Case Report

A 57-yr-old woman with end-stage polycystic kidney disease presented for kidney transplantation. Medical history was significant for long-standing hypertension controlled with verapamil and furosemide, atrial fibrillation with ventricular rate controlled to 68-75 beats/min with digoxin, hypothyroidism corrected with thyroxine, diet-controlled diabetes mellitus, and gastroesophageal reflux for which she took omeprazole. Known drug allergies were to penicillin (rash), morphine (pruritus, shortness of breath), and tetanus toxoid (rash, generalized edema). Physical examination revealed a class II airway, clear breath sounds, and an irregular cardiac rhythm with a grade II/VI systolic murmur.

Anesthesia induction (thiopental 250 mg, fentanyl 250  $\mu$ g, rocuronium 70 mg intravenously) and rapid-sequence intubation was uneventful. Anesthesia was maintained with 50% N<sub>2</sub>O/0.4-0.7% isoflurane, and rocuronium for muscle relaxation. Methylprednisolone 500

mg was administered intravenously before skin incision. An oral airway was not inserted.

One hour after skin incision, azathioprine 400 mg was administered intravenously, followed 30 min later by a sudden decrease in blood pressure from 95/38 to 75/35 mmHg, accompanied by bradycardia at 45 beats/min. Hypotension was initially treated with repeated doses of intravenous ephedrine, then dopamine infusion 5  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>. Dopamine increased heart rate to 80 beats/min, but blood pressure decreased to 70/30 mmHg. Epinephrine, in 20- $\mu$ g bolus doses for a total of 80  $\mu$ g intravenously, followed by dopamine 10  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>, stabilized hemodynamics until the end of surgery, 3 h later. There was no electrocardiographic evidence of ischemia. Arterial hemoglobin oxygen saturation was consistently 100% by pulse oximetry. Airway inspiratory pressure was not increased; lung sounds remained clear. We deduced the hypotension to be a drug or latex reaction absent another apparent cause.

At the conclusion of surgery, blood pressure returned to preoperative baseline value, with pulse 95 beats/min. Neuromuscular blockade was reversed, the patient emerged smoothly from anesthesia and was extubated. She responded appropriately to commands, breathing without difficulty for several minutes. Suddenly, she had difficulty with ventilation, not moving air despite obvious effort, and became agitated. Mask ventilation proved futile because of the patient's struggling and, after her loss of consciousness, because of profound airway obstruction. Laryngoscopy, which on initial intubation had revealed a grade I airway, showed massive swelling of both tongue and upper airway, preventing visualization of the airway distal to the epiglottis. A blind attempt at intubation was unsuccessful. Cardiac arrest ensued, treated by chest compression. Airway patency was reestablished by laryngeal mask airway insertion, which allowed easy ventilation, and hemodynamic stability restored rapidly with epinephrine 1 mg intravenously  $\times$  two and atropine 1 mg intravenously. A tracheotomy was performed. Wheezing never occurred.

As the patient was transferred to the intensive care unit, massive edema of the tongue forced it to protrude 2 cm from her mouth despite manual attempts to contain the tongue into her mouth. Within 30 min of arrival, the patient awoke and moved all extremities to command. No inotropic support was required, and the airway edema subsided over the next 12 h. Repeat azathioprine administration on postoperative day 1, per immunosuppression protocol, was followed within minutes by milder hypotension and upper airway edema. After azathioprine was discontinued, episodes of hypotension or airway edema ceased. The patient never exhibited edema other than that restricted to the upper airway. No fever, rash, or urticaria ever appeared. There was no increase in immunoglobulin E, and latex allergy serology workup was negative. Serial electrocardiograms and troponin levels ruled out a perioperative cardiac event. Neurologic sequelae were limited to short-term memory deficits regarding perioperative events and exacerbation of a preexisting upper-extremity tremor. Sub-

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sequent hospital recovery was unremarkable. The renal allograft functioned well throughout her hospitalization.

## Discussion

This case reveals a previously unreported idiosyncratic response to a drug commonly used in the operating room. It also demonstrates the utility of the laryngeal mask airway in treating acute airway obstruction.

Relatively benign side effects of azathioprine include fever, myalgia, diarrhea, nausea, and vomiting. More serious reported effects are pancreatitis,<sup>3</sup> kidney damage,<sup>4</sup> hepatic injury,<sup>1</sup> bone marrow depression, and pneumonitis.<sup>5</sup> Hypotension is the most serious azathioprine hypersensitivity reaction, previously reported in 12 patients worldwide.<sup>1,2,6-12</sup> The magnitude of hypotension can be consistent with shock, usually with adequate preload and sometimes associated with myocardial dysfunction.<sup>1</sup> An interesting feature of the hypotensive response to azathioprine has been its reproducibility in patients, even with a very small rechallenge dose.<sup>2,6-9,11</sup> The repeated hypotension in our patient on the day after her initial reaction is consistent with previous reports. The exact molecular mechanism underlying azathioprine-induced idiosyncratic reactions is still unknown, but in our case did not involve the immunoglobulin-E release of anaphylaxis.

Isolated acute upper airway edema after azathioprine has not previously been reported, even in cases of profoundly induced hypotension (systolic blood pressure 60–65 mmHg in awake patients). This edema formation differed from classic bronchospasm. In the present case, the airway at and distal to the vocal cords was relatively unaffected, as evidenced by the ease of ventilation by tracheotomy and even with the laryngeal mask airway. However, because the vocal cords could not be visualized by laryngoscopy, we cannot exclude the possibility of some vocal cord edema. It is noteworthy that in the 12 reported cases of azathioprine-induced hypotension,<sup>1,2,6-12</sup> edema was either not mentioned or specifically excluded. It is difficult to imagine that airway edema of the magnitude observed in the present case could have been inadvertently discounted. There is one previous report of mild, self-limited upper airway edema after azathioprine that also recurred after a repeat dose, but that differed from our case in that it was associated with bronchospasm and urticaria but not hypotension.<sup>13</sup> The magnitude of the second episode of hypotension and airway edema in our patient after azathioprine may have been blunted by continued steroid therapy begun in the operating room, but the airway

edema was still sufficient to cause patient anxiety despite her tracheotomy.

The place of the laryngeal mask airway in resuscitation of our patient should be underscored. A laryngeal mask airway can be inserted at least as quickly as a cricothyroidotomy can be performed, or the necessary equipment mobilized for jet ventilation through an intratracheal intravenous cannula. The ease of ventilation after placement of the laryngeal mask airway indicates that there was still an adequate laryngeal aperture, which would not have been the case had the larynx itself been obstructed by edema. It is our opinion that the laryngeal mask airway was lifesaving in this case, and it belongs in the American Society of Anesthesiologists difficult airway algorithm as reviewed by Benumof.<sup>14</sup>

Azathioprine is a common drug for immunosuppression in organ transplant patients, with the anesthesiologist administering the first dose intraoperatively. Given our observation of massive airway edema in a patient who had had a hypotensive reaction to azathioprine, we suggest that the upper airway be evaluated for several hours before extubation when encountering a hypotensive episode where azathioprine sensitivity cannot be ruled out. Our patient had several other known drug allergies, none apparently related to azathioprine, to which she had never been exposed. In a patient with multiple known allergies, it may be prudent to use azathioprine with greater caution in view of its profound potential adverse effects.

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## Successful Use of Hypnosis as an Adjunctive Therapy for Weaning from Mechanical Ventilation

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HYPNOTIC techniques have been used in medical practice in different situations, mainly for pain control and anxiety relief<sup>1-6</sup> and to reduce stress symptoms such as tachycardia or shivering.<sup>7</sup> In burn victims, Crasilneck *et al.* showed that hypnosis could stimulate emotional recovery, mobility, and wound healing.<sup>8</sup> Hypnosis could also reduce by one third the incidence of postoperative nausea and vomiting in women undergoing breast surgery.<sup>9</sup>

In the case we report, hypnotic psychotherapy resulted in hastened weaning from mechanical ventilation as well as to reestablishment the day-night sleep cycle.

### Case Report

We report the case of a 46-yr-old man with a history of pulmonary tuberculosis, ischemic heart disease, gout, psoriasis, heavy smoking, and previous alcohol abuse who underwent right pneumonectomy for

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invasive aspergillosis. The postoperative clinical course was complicated by the development of a right bronchopleural fistulae and empyema. Associated comorbidities included left vocal cord paresis, muscle weakness caused by neuromyopathy of the critically ill, recurrence of gout arthritis with polyarthralgia, and eventually psoriasis.

Postoperative weaning from mechanical ventilation was extremely difficult because unresolving bronchopleural fistula caused multiple septic episodes, and repeated surgical procedures were necessary to seal the leak. Definitive closure was obtained 28 days postoperatively, but pleural infection resolved 48 days postoperatively. On the 77th postoperative day, a tracheotomy was performed. Ventilatory mode consisted in a 25-cm H<sub>2</sub>O pressure support with a fraction of inspired oxygen of 0.3. The weaning protocol consisted in progressive reduction, in 2-cm H<sub>2</sub>O steps, of the pressure support. Pressure support ventilation was also intermittently replaced by periods of 2- to 5-cm H<sub>2</sub>O continuous positive airway pressure. The patient was maintained on continuous positive airway pressure as long as the respiratory rate remained < 40 breaths/min while keeping arterial pH above 7.30. The patient regularly received respiratory and physical therapies, passive and around-the-bed mobilization.

At this stage, the patient demonstrated major sleep disturbances with day-night cycle rhythm loss, an extreme anxiety, and apprehension secondary to multiple life-threatening episodes (cardiac arrest, aspiration) that occurred during periods of awareness, and he developed a feeling of vulnerability, with a permanent fear of impending death. Minor episodes of decreasing oxygen saturation during chest therapy, tracheal aspiration, or physical therapy exacerbated his previous fearful experiences. Although chest radiograph was unchanged, gas exchange and lung mechanics were stable over the ventilatory weaning period (mean arterial oxygen partial pressure/fraction of inspired oxygen ratio was  $308 \pm 30$  mmHg, minute ventilation  $7.7 \pm 1$  l/min, and the relationship between arterial carbon dioxide partial pressure and minute ventilation [an index of mechanical ventilation requirement] was  $7.2 \pm 1.35$  mmHg · l<sup>-1</sup> · min<sup>-1</sup>; fig. 1), and concomitant drug administration was unchanged, including low doses of haloperidol, thioridazine, and midazolam since the 43 postoperative day; he was unable to tolerate more than approximately 12 h without mechanical ventilation. Postoperative enteral nutrition was provided early and was well tolerated. Eighty-