



Letter

Severe life-threatening asthma precipitated by a topical nonsteroidal anti-inflammatory drug

Aspirin-exacerbated respiratory disease (AERD) is a condition that occurs in a subset of patient with asthma who are susceptible to asthma exacerbation within 4 hours after exposure to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). This condition is associated with chronic rhinosinusitis with nasal polyps.¹ AERD is thought to arise from disruption of the eicosanoid pathway in the upper and lower airways, with increased constitutive production of proinflammatory cysteinyl leukotrienes, that is aggravated by exposure to cyclooxygenase (COX) inhibitors. The prevalence of AERD is approximately 7% in patients with asthma but 14% in patients with severe asthma.²

Most AERD cases described in the literature are related to oral ingestion, although there is a documented case in which the trigger was ketorolac eyedrops.³ In this report, we describe a patient who was diagnosed with AERD after applying an over-the-counter topical NSAID on her skin.

A 43-year-old nonsmoking woman presented to the emergency department with 2 days of breathlessness that had markedly worsened during the past hour. During the past week, she had been experiencing fever and cough. She had been having nasal discharge and congestion for the past year. She did not have anosmia or a history of asthma. She had a history of angioedema on exposure to diclofenac.

On examination, she was in respiratory distress. Bilateral wheeze and bibasal inspiratory crackles were heard on chest auscultation. Arterial blood gas analysis revealed acute hypercapnic respiratory failure. The result of chest radiography and electrocardiography were normal.

The patient was treated for severe bronchospasm with intravenous corticosteroids and consecutive administrations of nebulized salbutamol. The emergency department attending physician was on the verge of performing endotracheal intubation, but fortunately her condition stabilized and she did not require emergency intubation or mechanical ventilatory support.

In the ward, further history revealed that she had applied a few millilitres of a locally manufactured, over-the-counter medicated oil on her chest 2 hours before her presentation. This oil contained 15% methylsalicylate and 16% menthol. One millilitre is equivalent to approximately 200 mg of aspirin. Her serum eosinophil count was elevated at 460/ μ L. Spirometry revealed severe airflow obstruction with a forced expiratory volume in 1 second (FEV₁) to forced vital capacity ratio of 59% and a FEV₁ that was 49% of predicted. There was a significant bronchodilator response to salbutamol, with an increase in FEV₁ of 27% and 230 mL. The patient

also developed wheeze, tearing, and rhinorrhea 45 minutes after an open bottle of the medicated oil was unintentionally placed at her bedside. This reaction ceased after the oil was discarded. She was diagnosed with AERD. Otolaryngology examination revealed turbinate mucosal hypertrophy with copious mucus but no evidence of nasal polyps.

The patient was prescribed high-dose combination inhaled corticosteroids and long-acting β agonists, a leukotriene receptor antagonist, and intranasal corticosteroids and discharged when well. Morning spot urinary leukotriene E₄ (LTE₄) measurement performed at follow-up when the patient was stable revealed an elevated level of 916 pg/mg of creatinine and a steady-state IgE level of 979 IU/mL (reference range, <100 IU/mL). Subsequent prebronchodilator and postbronchodilator FEV₁ measurements were 68% and 78% predicted, respectively.

The patient's clinical history was suggestive of a clear temporal relationship between exposure to the oil and worsening of her asthma symptoms. Her symptoms were consistent with the natural history of AERD described by Szczeklik et al¹ in which persistent rhinitis is the initial symptom followed by the development of asthma within 2 years and the development of nasal polyps 5 years after the onset of rhinitis.

Several learning points can be gleaned. First, AERD is often underrecognized in clinical practice despite significant evidence implicating NSAIDs as a trigger for serious exacerbations. Picado et al⁴ retrospectively reviewed the records of 92 patients who received mechanical ventilatory support for life-threatening asthma and found that 7 had previous exposure to NSAIDs. There should be a high suspicion of AERD in patients with recurrent, severe asthma, including severe life-threatening exacerbations.

Second, occult exposures can trigger exacerbations of AERD, including oral and nonoral routes, such as topical or inhalational routes. In the study by Picado et al,⁴ one case was due to an antacid (AlkaSeltzer) containing aspirin, whereas another was due to an aspirin-containing capsule prepared by an herbalist. Many patients with asthma may not volunteer information about complementary therapies, which may contain aspirin or salicylates, unless asked.

Controversy exists regarding the safety of salicylates in AERD. Nonacetyl salicylates are much weaker inhibitors of COX compared with acetyl salicylates (aspirin) and may instead exert their anti-inflammatory effects via nuclear factor κ B (NF- κ B)-dependent pathways,⁵ leading to the common view that nonacetyl salicylates do not cross-react in AERD. However, studies have found that salicylate inhibits COX *in vivo*⁶ in an NF- κ B-independent manner by competing with arachidonic acid for binding to an active site on COX.⁷ There have also been case reports of nonacetyl salicylates precipitating reactions in AERD.⁸ A preliminary trial has also demonstrated that a low-salicylate diet may improve symptoms in AERD.⁹ Taken

Disclosures: Authors have nothing to disclose.

<https://doi.org/10.1016/j.anaai.2017.12.024>

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together, these data indicate that salicylate is able to trigger exacerbations in at least a subset of patients with AERD.

Third, confirmation of AERD in a patient who has poorly controlled asthma is difficult. The gold standard for diagnosis is oral or nasal challenge testing, which involves administering incremental doses of oral aspirin or intranasal ketorolac and monitoring for decline in FEV₁ or appearance of respiratory symptoms. However, in patients with poorly controlled asthma or respiratory failure triggered by aspirin or NSAID exposure, the risk of challenge testing outweighs empirical avoidance of these substances. In this setting, urinary LTE₄ level may have utility as a biomarker for supporting the diagnosis of AERD. Bochenek et al¹⁰ found that an elevated urinary LTE₄ level of 800 pg/mg of creatinine has a sensitivity of 49% and specificity of 81% for discriminating AERD from aspirin-tolerant asthma. Our patient's urinary LTE₄ level was greatly elevated at 916 pg/mg of creatinine. This, together with her elevated IgE level and serum eosinophil count, points toward eosinophilic inflammation with involvement of the cysteinyl leukotriene pathway that is seen in AERD.

In conclusion, this case seeks to report, for the first time to our knowledge, a case of severe, life-threatening asthma precipitated by topical application of NSAIDs on skin. It highlights the challenges of identifying and diagnosing AERD in clinical practice.

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