

Anosmia and an uncommon nonsteroidal anti-inflammatory drug reaction in a 38-year-old man

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ABSTRACT

Anosmia with asthma and nasal polyposis raises suspicion for aspirin-exacerbated respiratory disease (AERD). Guidelines for desensitization of patients with AERD to prevent recurrent nasal polyposis and improve upper and lower respiratory symptoms are well established. We present a patient with an uncommon reaction to acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs who required deviation from the standard ASA desensitization approach.

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CASE PRESENTATION

Chief Complaint

Anosmia.

History of Present Illness

A 38-year-old man with anosmia and allergic rhinitis presented to an allergy clinic with a 2-year history of asthma. Nasal polypectomy 1 year earlier provided initial improvement in anosmia; however, anosmia and polyps recurred within 3 months. His medications included loratadine at 10 mg daily, montelukast at 10 mg daily, fluticasone/salmeterol at 250/50 q.h.s., olopatadine at 65 μ g b.i.d., mometasone furoate at 50 μ g b.i.d., albuterol 2 puffs q4 hours, p.r.n., and amlodipine at 10 mg daily.

Medical history included hypertension and hypercholesterolemia. He was a lifetime nonsmoker. Family history was positive for allergic rhinitis and asthma.

Physical Examination

He was a comfortable-appearing man, afebrile with age-appropriate vital signs. Sclera was mildly injected without any discharge. Nasal mucosa was boggy with evidence of nasal polyps bilaterally. Neck was supple without lymphadenopathy or thyromegaly. Cardiac

exam revealed a regular rate with no murmurs. Lungs were clear to auscultation bilaterally. The remainder of the physical examination was unremarkable.

Diagnostic Findings

Initial laboratories revealed normal electrolytes, renal function, liver function, serum tryptase and complete blood count with an elevated absolute eosinophil count on the differential (Table 1). Initial spirometry revealed minimal obstructive airways disease with a reduced forced expiratory volume at 1 second (FEV₁)/forced vital capacity ratio and reduced forced expiratory flow at 25–75% (Table 2). Bronchodilator therapy was administered followed by repeat spirometric testing, revealing a significantly increased FEV₁ (Table 3).

QUESTION 1

What is the differential diagnosis of bilateral nasal polyps?

- a. Cystic fibrosis
- b. Allergic rhinitis
- c. Fungal sinusitis
- d. Chronic rhinosinusitis
- e. Aspirin-exacerbated respiratory disease (AERD)
- f. Churg-Strauss syndrome
- g. Nonallergic rhinitis with eosinophilia syndrome

QUESTION 2

What additional investigations might be helpful?

- a. Sweat chloride testing
- b. Fasting blood glucose test
- c. Cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA)
- d. Sinus CT
- e. Allergy skin testing

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Table 1 Initial CBC with differential

Cell Type	Value	Reference Range	Units
WBC	6.1	3.3–11.5	K/mol
HGB	15.8	12.7–17.8	g/dL
HCT	46.0	39.0–50.0	%
Platelet count	215	150–450	K/mol
Absolute neutrophil count	3.1	1.5–6.6	K/mol
Absolute lymphocyte count	1.8	1.5–3.5	K/mol
Absolute monocyte count	0.5	0.1–0.9	K/mol
Absolute eosinophil count	0.7	0.0–0.6	K/mol
Absolute basophil count	0.0	0.0–0.1	K/mol

CBC = complete blood count; WBC = white blood cell count; HGB = hemoglobin; HCT = hematocrit.

Table 2 Initial spirometry

Lung Mechanics		Actual	Predicted	% Predicted
FVC	L	6.68	5.89	113
FEV ₁	L	4.71	4.62	98
FEF _{25–75}	L/s	2.98	4.46	67
FEV ₁ /FVC	L	69%	81%	86

FEV₁ = forced expiratory volume in 1 s; FEF_{25–75} = forced expiratory flow at 25–75%; FVC = forced vital capacity.

Table 3 Postbronchodilator spirometry

Lung Mechanics		Actual	% Predicted	% Change
FVC	liters	7.01	119	5
FEV ₁	liters	5.28	112	14
FEF _{25–75}	l/second	4.39	98	48
FEV ₁ /FVC	Liters	75%	93	9

FEV₁ = forced expiratory volume in 1 s; FEF_{25–75} = forced expiratory flow at 25–75%; FVC = forced vital capacity.

- f. Spirometry post-acetylsalicylic acid (ASA) challenge

Discussion of the Differential Diagnosis

The patient had no fever, headache/facial pain, or thick nasal discharge and his sinus CT scan confirmed nasal polyps but no sinus disease. He was not diabetic or immune compromised, making fungal sinusitis unlikely. Cystic fibrosis was unlikely because he had no history of pneumonia or recurrent respiratory infections and no family history of cystic fibrosis. He did not have a long-standing history of asthma or vasculitis, making Churg-Strauss syndrome unlikely. Poorly controlled allergic rhinitis, AERD, and nonallergic rhinitis with eosinophilia syndrome remained in the differential.^{1,2}

Additional History

On three occasions, the patient reported upper respiratory symptoms, asthma exacerbation, and lip swelling hours after consumption of aspirin-containing products. All three events resolved spontaneously within 5 hours.

CLINICAL COURSE

Given his asthma, nasal polyps, and ASA history, aspirin desensitization according to standard practice paper approach for AERD³ was initiated 3 weeks after repeat nasal polypectomy. All of his home medications were continued for the ASA desensitization.

On challenge day 1, he received and tolerated 20 mg of ASA. Three hours later, he received and tolerated 40 mg of ASA, remaining asymptomatic for 3 hours.

On challenge day 2, he received 81 mg of ASA. Three hours post-ASA administration, he experienced a 15% decrease in FEV₁, urticaria on his chest and upper extremities, throat itching, and chest tightness. He required two albuterol treatments, 10 mg of montelukast and 25 mg of diphenhydramine, after which spirometry, urticaria, and pruritus improved.

QUESTION 3

What is the differential diagnosis now?

- ASA/nonsteroid anti-inflammatory drug (NSAID)-induced asthma and rhinitis in an asthmatic patient (AERD/triad asthma)
- ASA/NSAID-induced urticaria/angioedema in a patient with chronic urticaria
- ASA/NSAID-induced urticaria/angioedema in an otherwise normal patient
- “Blended” reaction, choice a + choice b and/or choice c
- Single NSAID-induced urticaria/angioedema in an otherwise normal subject

Given his 15% decrease in FEV₁ and urticarial reaction with exposure to ASA, he met the definition of a “blended” reaction (choice d). AERD with single NSAID-induced urticaria/angioedema (choices a + e) remained in the differential.

CLINICAL COURSE CONTINUED

On challenge day 3, 3 hours after receiving 81 mg of ASA, he developed urticaria on his legs, hands, and feet. Spirometry remained stable. He received 25 mg of diphenhydramine and 10 mg of cetirizine and symptoms subsequently improved.

On challenge day 4, to rule out single NSAID-induced urticaria/angioedema, the patient received 50 mg of ibuprofen. Three hours after administration of

Table 4 Mechanisms responsible for aspirin/NSAID allergy syndromes

COX-1 Inhibition	IgE-Like
Cross-reactive	Single agent
Time course >30 min	Time course <60 min
First dose	Requires previous doses
COX-1 = cyclooxygenase 1.	

ibuprofen, he developed urticaria on his trunk and legs. He denied any respiratory symptoms and spirometry remained unchanged, thus displaying respiratory component tolerance, but continued cutaneous symptoms.

DISCUSSION

Eight types of pseudoallergic and allergic reactions to ASA and other NSAIDs have been identified.⁴ AERD is characterized by inflammation of the respiratory tract with progressive nasal polyposis and asthma in response to ASA/NSAID-containing products, whereas the “blended” type ASA sensitivity reaction is characterized by AERD in combination with ASA/NSAID-induced urticaria/angioedema, in this case in a patient without chronic urticaria. There are no sensitive and specific *in vitro* tests to identify AERD patients. ASA oral challenges⁵ (and in some cases intranasal aspirin-lysine or NSAID challenges)^{6–8} have therefore been developed to differentiate patients with AERD from patients with similar presentations. During ASA challenges, AERD patients experience respiratory reactions ranging from naso-ocular symptoms to bronchospasm or any combination.^{9,10}

The mechanisms responsible for the various allergic and pseudoallergic ASA/NSAID sensitivity reactions include cyclooxygenase (COX) 1 inhibition and “IgE-like” reactions (Table 4). In reactions secondary to COX-1 inhibition, cross-reactions are present, whereas in IgE-like reactions, patients characteristically react to a single NSAID or ASA alone. In addition, reactions mediated by COX-1 inhibition take at least 30 minutes to occur, whereas IgE-like reactions often occur within minutes of the ingestion. Reactions mediated by COX-1 inhibition can occur on first exposure, whereas IgE-like reactions usually require previous exposures.^{4,11} Although pure AERD can be attributed to COX-1 inhibition, the mechanism responsible for blended reactions is poorly described.

Although the pathogenesis of AERD is still unclear, abnormalities in arachidonic acid metabolism have been implicated.^{9,12,13} COX-1 and COX-2 inhibition is common to ASA and all classic NSAIDs.¹⁴

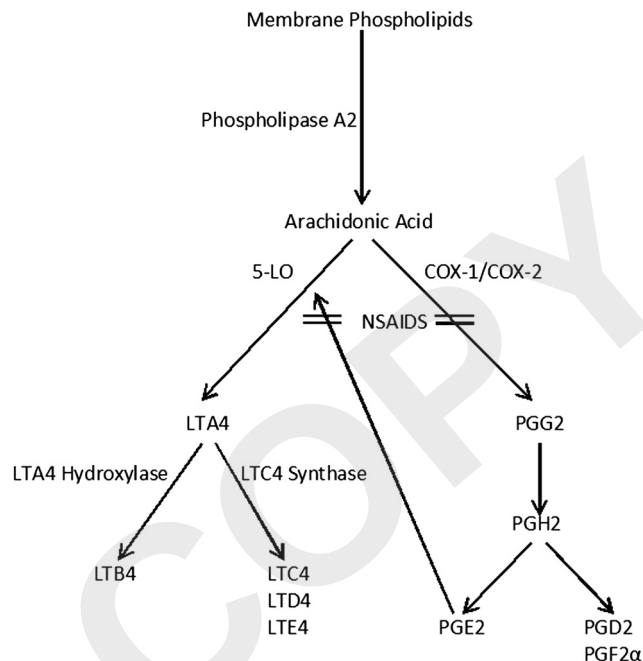


Figure 1. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase (COX) pathway and subsequently divert arachidonic acid metabolites to the lipoxygenase (LO) pathway. NSAIDs also decrease levels of prostaglandin E₂ (PGE₂) allowing unfettered 5-LO activation. Leukotriene C₄ (LTC₄) synthase overexpression in aspirin-exacerbated respiratory disease (AERD) patients further increases the number of cysteinyl leukotrienes resulting in a proinflammatory response.

This mechanism is responsible for aspirin’s anti-platelet effects. As a secondary effect, arachidonic acid is shunted toward the 5-lipoxygenase (5-LO) pathway increasing the production of cysteinyl leukotriene (CysLT) mediators.¹² In addition, ASA/NSAIDs suppress prostaglandin E₂ (PGE₂) and PGD₂ production.^{12,15} PGE₂ normally inhibits 5-LO and, therefore, loss of PGE₂ leads to increased synthesis of leukotrienes (Fig. 1).¹⁶ Leukotrienes induce powerful and prolonged bronchospasm, vasodilation, mucous secretion, and recruitment of additional eosinophils in bronchial smooth muscles.¹⁷ These mediators are partly responsible for the smooth muscle constriction that leads to typical asthma symptoms of wheezing, cough, and dyspnea in sensitive individuals.¹⁸ In addition to causing respiratory symptoms, CysLTs cause vasopermeability that could augment urticaria.¹⁴ Although COX-1 inhibitors cause AERD symptoms in sensitive individuals, COX-2 inhibitors are a safe alternative in patients with AERD.^{12,19}

The cytokine IL-4 also plays an important pathogenic role in AERD. Increased IL-4 leads to overproduction of CysLTs by up-regulating leukotriene C₄ synthase and the CysLT receptors (CysLT1 and -2). IL-4 also leads to decreased secretion of PGE₂, which in turn, causes increased secretion of CysLTs. ASA is

known to directly inhibit T-cell IL-4 expression and thus may be another mechanism providing therapeutic benefit in the treatment of AERD.²⁰

PGE₂ and PGD₂ also have protective effects on mast cells. Loss of these PGs leads to destabilization of cutaneous mast cells and ultimate discharge of histamine and tryptase into the skin and soft tissues. This destabilization of mast cells is the likely mechanism responsible for the cutaneous component of the blended type reaction.⁴

In the late 1990s, leukotriene modifier drugs (LTMDs) were introduced in the United States. There are currently two mechanisms by which LTMDs act: antagonism of the CysLT receptor (montelukast and zafirlukast) or inhibition of the 5-LO enzyme (zileuton).²¹ Several studies have shown that for patients with pure AERD reactions, treatment with LTMDs provides some protection from significant aspirin-induced bronchospasm during oral aspirin challenge.^{9,21,22} The effectiveness of LTMDs for the treatment of urticarial reactions is less well known.¹⁷

CLINICAL COURSE CONTINUED

Given that our patient continued to have urticaria, despite respiratory tolerance, the decision was made to add zileuton CR at 1200 mg b.i.d. to the medication regimen.

On day 5, he received 50 mg and then 100 mg of ibuprofen without any reactions. On day 6, he received 200 mg of ibuprofen and had no cutaneous or respiratory symptoms. After 6 hours of monitoring, he was discharged on ibuprofen at 200 mg b.i.d. and was instructed to keep zileuton CR at 1200 mg b.i.d. in his medication regimen.

In follow-up at 1, 3, and 6 months, he had no polyp regrowth, respiratory or cutaneous symptoms. Transaminases and spirometry remained normal. At 6-month follow-up, he requested stopping zileuton. Two days after discontinuing zileuton, urticaria, but not respiratory symptoms, recurred. Zileuton was subsequently restarted, which led to resolution of the cutaneous symptoms. At 1-year follow-up, he reported that he was doing "great." He denied any respiratory or cutaneous symptoms and there was no regrowth of polyps.

Final Diagnosis

Blended-type ASA/NSAID sensitivity reaction with induction of tolerance dependent on zileuton.

SUMMARY AND CONCLUSIONS

Controversy exists regarding classification of the blended ASA reaction and therefore desensitization

for these patients arguably poses an even greater challenge for clinicians. Our patient experienced a 15% decrease in FEV₁ and an urticarial reaction during challenge/desensitization, meeting the definition of a blended reaction. He experienced both cutaneous and respiratory symptoms 2–3 hours after exposure to both aspirin and ibuprofen, suggesting that COX inhibition is the shared mechanism for both the cutaneous and the respiratory components of the blended ASA sensitivity reaction. Cutaneous tolerance was achieved and maintained only after introducing zileuton. Cutaneous tolerance but not respiratory tolerance was lost when zileuton was discontinued. For patients with blended reactions to ASA/NSAIDs, augmentation with the 5-LO inhibitor zileuton may be necessary for successful cutaneous induction of tolerance to occur.

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