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Letter to the Editor

Celecoxib induced respiratory symptoms without urinary LTE 4 increase in a patient with AERD

Dear Editor,

Aspirin-exacerbated respiratory disease (AERD) is a non-allergic pathological condition that presents with prominent airway symptoms including asthma attack and nasal discharge induced by non-steroidal anti-inflammatory drugs (NSAIDs). Because NSAIDs inhibit cyclooxygenase (COX) activity, one of the main pathologies of AERD is thought to be the overexpression of cysteinyl leukotrienes (CysLTs). A previous study reported that selective COX-2 inhibitors, such as celecoxib, can be safely used in AERD patients.^{1,2} However, cases with AERD presenting with respiratory symptoms induced by selective COX-2 inhibitors have rarely been reported.^{3,4} Baldassarre *et al.*, reported a rare case of AERD that developed celecoxib-induced asthma attack (decreased forced expiratory volume in 1 s (FEV1)) with increased urinary leukotriene E4 (LTE4) concentration.⁴ Here, we describe a case of AERD who showed a significant decrease in FEV1 and exacerbation of nasal symptoms after celecoxib oral provocation without an increase in urinary LTE4 concentration. This case suggests the importance of another mechanism of NSAID-induced exacerbation other than increased CysLTs in AERD.

A 42-year-old man who was an ex-smoker (20 pack-years) was referred to our hospital to undergo an aspirin challenge test. He experienced severe bronchospasm due to the oral administration of sodium loxoprofen three months before the visit to our hospital. He had no history of pediatric asthma, sinusitis, nor nasal polyps. His peripheral blood leukocyte count was 8000/ μ L (eosinophil ratio, 2%) and the serum total IgE concentration was 75 IU/mL. His serum specific IgE measured using MAST 36 (Hitachi Chemical Diagnostics Systems, Tokyo, Japan) was positive for Dermatophagoides mite antigen (7.68 U/mL, class 2), cat epithelium antigen (5.72 U/mL, class 2), and house dust (2.57 U/mL, class 1). The aspirin oral challenge test suggested a diagnosis of AERD with the development of nasal discharge, nasal obstruction, dyspnea, and FEV1 decline at the level of 60 mg aspirin. Urinary LTE4 concentration increased from 106.9 pg/mg creatinine at baseline to 519.8 pg/mg creatinine after 60 mg aspirin administration where the patient experienced bronchospasm and the symptoms described above (Fig. 1). Treatment with fluticasone 500 μ g/salmeterol 50 μ g twice a day and montelukast 10 mg per day was initiated. The patient underwent a celecoxib oral challenge test to elucidate whether selective COX-2 inhibitors could be used safely. The protocol of the celecoxib challenge test was based on the aspirin oral challenge

test (Table 1).⁵ In brief, the case was diagnosed as positive if the FEV1 (measured every 30 min) declined (FEV1 $\geq$ 20% of baseline) or related respiratory symptoms (nasal discharge, nasal obstruction, cough, or dyspnea) developed. Anti-asthma medication was discontinued 24 h prior to the challenge test. Figure 1 shows the test result. The placebo induced no changes in respiratory function or symptoms, but after the oral administration of celecoxib 25 mg, the patient developed mild nasal obstruction, which worsened after oral provocation with celecoxib 50 mg. In addition, the decrease in FEV1 was $>$ 20% indicating the oral celecoxib challenge test was positive and we discontinued the challenge test. Intriguingly, when the celecoxib challenge test was stopped, the urine LTE4 level (50.5 pg/mL-creatinine) had not increased compared with the level before celecoxib challenge (63.5 pg/mL-creatinine) (Fig. 1).

Urinary LTE4, a stable metabolic product of CysLTs is increased 2–30-fold during oral provocation of AERD patients with aspirin.⁶ Because COX1 is constitutively expressed in most tissues, inhibition of COX1 by NSAIDs might decrease anti-inflammatory prostanoide PGE2 levels and increase proinflammatory CysLTs in the airways.⁶ Selective COX2 inhibitors that specifically inhibit inflammation-induced COX, showed no cross reactivity with COX1 inhibitors and might be a safe alternative for reducing pain in AERD patients. However, along with our present case, previous studies reported selective COX2 inhibitors induced exacerbation in AERD patients.^{3,4} Few reports have addressed a change in urine LTE4 concentrations in AERD cases with selective COX2 inhibitor-induced asthma attack. Baldassarre *et al.*, suggested the high sensitivity of CysLT production might explain why their reported case developed an asthma attack and had increased urinary LTE4 concentrations after celecoxib oral challenge.⁴ In our case, however, urinary LTE4 did not increase after celecoxib provocation despite a significant FEV1 decline and nasal symptoms, suggesting mechanisms other than the overproduction of CysLTs might be involved. Cahill *et al.*, reported high dose aspirin therapy for AERD patients induced aspirin tolerability despite increasing type 2 inflammatory markers including urine LTE4 concentrations.⁷ This report suggests that bronchoconstriction induced by COX inhibitors does not always correspond to the overproduction of CysLTs.

Previous studies indicated that 5-LO activity and CysLTs production were enhanced in AERD patients compared with aspirin tolerant asthma patients, even under stable conditions.⁸ However, our patient showed very low levels of urine LTE4 at baseline before the COX inhibitor provocation. Relatively low activity of 5-LO may reflect no increase in CysLTs by the selective blockade of COX2.

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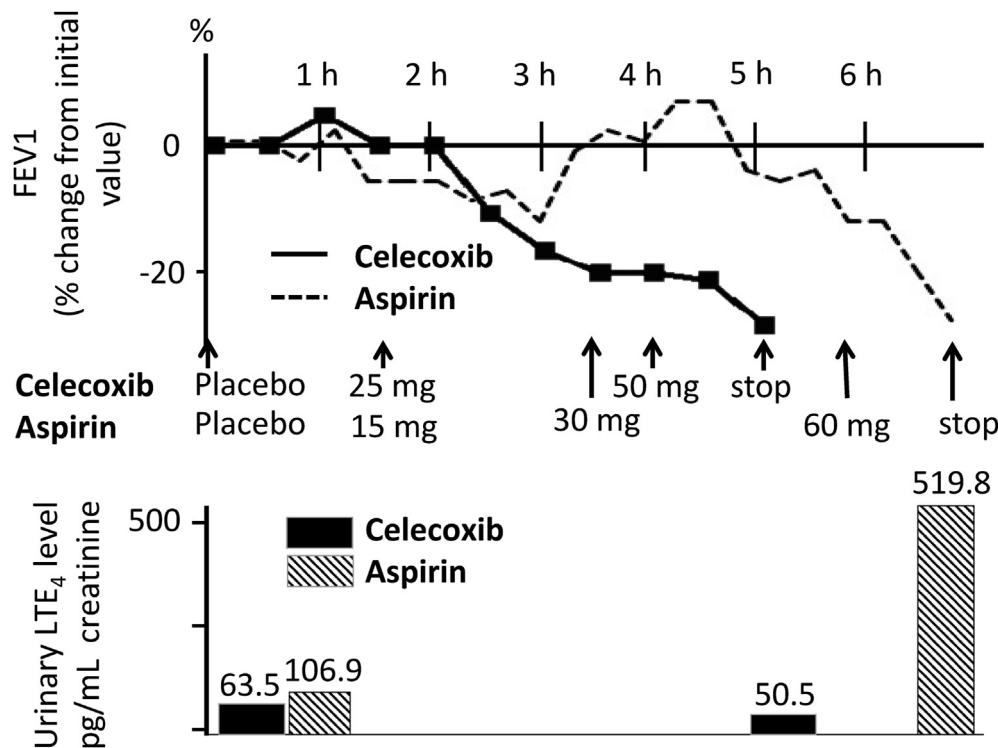


Fig. 1. Changes in FEV1 and urinary leukotriene E4 levels during celecoxib and aspirin oral challenge test. FEV1 declined more than 20% compared with the initial value after 50 mg celecoxib (continuous line) or 60 mg aspirin (dotted line) along with obvious nasal discharge and obstruction. Urinary leukotriene E4 did not increase after celecoxib provocation (black column), although it increased more than 5-fold after aspirin administration (hatched column).

Table 1
Protocol of oral celecoxib challenge test.

Time (h)	Celecoxib dose (mg)
0.0 (start)	Placebo
1.5	25
4.0	50
6.5	100

Pulmonary function test was performed every 30 min and newly developed symptoms were observed for 2.5 h. If the following conditions were observed, we determined the challenge test was positive: (1) FEV1 declined more than 20% from the initial value, (2) FEV1 declined more than 15% along with non-bronchial symptoms including nasal symptoms, flushing, or conjunctival hyperemia, and (3) progressing oxygen desaturation or overt symptoms (cough, nasal symptoms, digestive organ symptoms, dermal symptoms, or chest tightness).

Baldassarre *et al.*, speculated another possible mechanism whereby a low dose of celecoxib might stimulate mast cells directly.⁴ The airway symptoms at the time of induction by NSAIDs were largely related to the activation of mast cells.⁹ A recent study reported that during non-classical activation (not via FcεRI activation), mast cells require constitutive COX1 activity for CysLTs, PGD₂, or thromboxaneA₂.¹⁰ Selective COX2 inhibitors might enhance COX1-mediated proinflammatory mediator and bronchoconstrictor production from mast cells. Unfortunately, we could not measure the concentration of PGD₂ or its metabolites in the blood or urine of our patient because the volumes of samples left were too small.

The reliability of our measurement of urine LTE₄ should be discussed. The measurement of LTE₄ in our sample was performed in the most experienced institute in Japan (the National Hospital Organization Sagamihara National Hospital). Indeed, we detected a significantly high increase in urine LTE₄ concentration after

provocation with aspirin. This suggests there was no measurement failure regarding our urine sample.

Although the precise mechanism involved is unknown, selective COX2 inhibitors rarely induce airway hypersensitivity in AERD patients. Our case suggests a mechanism other than the overproduction of cysLTs might be involved in anaphylaxis in AERD patients caused by COX inhibitors.

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Conflict of interest

The authors have no conflict of interest to declare.

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