

Images in Allergy

Leukotriene-Associated Rash in Aspirin-Exacerbated Respiratory Disease

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Aspirin-exacerbated respiratory disease (AERD) is a syndrome of asthma, nasal polyposis, and reactions to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Reaction symptoms are generally confined to the respiratory tract, but approximately 20% of patients also develop a characteristic pruritic rash.¹ The NSAID-induced rash develops in patients whose reactions involve the most substantial release of cysteinyl leukotrienes (cysLTs) and prostaglandin D₂ (PGD₂). We have found that 14% of the 387 patients with AERD queried at the Brigham and Women's Hospital since 2013 report occurrence of a similar rash even during periods of NSAID avoidance. As with the NSAID-induced rash, our patients describe an erythematous, pruritic, macular eruption, most notable on the distal upper and lower extremities, including palmar and plantar surfaces, that tends to spare the trunk.

Case 1: A 35-year-old woman with AERD diagnosed at age 27 years reported a 2-year history of an intermittent, pruritic rash on her feet, ankles, legs, and chest. The rash would last for 2 to 4 weeks without clear triggers. The rash did not improve with fexofenadine 360 mg twice a day and montelukast 10 mg daily. At age 34 years, she underwent oral aspirin desensitization, during which she experienced a fall in FEV₁ of 17%, as well as a pruritic, macular, blanching rash that mirrored her previous rash. Zileuton ER (1200 mg) was given, with prompt resolution of the rash and the bronchoconstriction within 45 minutes.² Four months later the rash returned, and she was started on zileuton ER 1200 mg twice a day with complete resolution of the rash. Because of a lapse in insurance 3 months later, she stopped zileuton and the rash returned within 1 week (Figure 1). She was able to resume zileuton a week later, with complete resolution of the rash.

Case 2: A 58-year-old woman with AERD diagnosed at age 44 years reported a 13-year history of an intermittent pruritic, macular, blanching rash on her ankles and feet, extensor surfaces of her knees, and around her wrists and elbows. Workup at the

time included evaluation for HIV, hepatitis C virus, syphilis, cytomegalovirus, Lyme disease, parvovirus, and *Rickettsia rickettsii*, which were all negative. This rash lasted 2 to 10 days and would appear every few months without a clear inciting factor. The rash did not improve with fexofenadine 180 mg daily, cetirizine 10 mg daily, montelukast 10 mg daily, and hydroxyzine 50 mg twice a day. In 2014 she initiated omalizumab 300 mg monthly for asthma, which led to moderate improvement in her asthma but no change in the frequency or severity of her rash (Figure 2). In January 2020, she switched to dupilumab 300 mg every-other-week, which provided good control of asthma and complete resolution of the rash within 2 months.

These cases illustrate the presentation of a rash commonly reported by patients with AERD. Anecdotally, we have observed that oral antihistamines are not generally helpful, but many patients, as in Case 1, report that zileuton, a 5-lipoxygenase inhibitor, is an efficacious treatment for the rash. As in case 2, several of our patients with AERD who are treated with dupilumab, an mAb that blocks IL-4R α , report dramatic improvement in their intermittent rash. Zileuton inhibits production of cysLTs and may also indirectly block mast cell activation and release of PGD₂; inhibition of IL-4R α with dupilumab likely also blocks mast cell activation and release of both cysLTs and PGD₂. We suspect that these rashes reflect an effect of either cysLTs or PGD₂ in the skin. Recognition of the rash, and its likely etiology, in patients with AERD will allow for prompt diagnosis and appropriate treatment.

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FIGURE 1. Photograph of erythematous, macular eruption on Case 1's lower leg (left), thigh (center), and neck (right).



FIGURE 2. Photograph of erythematous, macular eruption on Case 2's lower leg (left) and foot (right).