Eosinophils and Mast Cells in Aspirin-Exacerbated Respiratory Disease

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KEYWORDS

• Eosinophil • Mast cell • Leukotriene • Cyclooxygenase • Prostaglandin
• Aspirin-exacerbated respiratory disease • Arachidonic acid

KEY POINTS

- Aspirin-exacerbated respiratory disease (AERD) is a disease of overproduction and hyperresponsiveness to lipid mediators.
- Mast cells and eosinophils are key drivers of AERD pathogenesis through production of proinflammatory mediators following aspirin stimulation.
- Because of their involvement, therapies that target mast cells and eosinophils may be useful in providing clinical benefit in AERD.

INTRODUCTION

In 1968, the term Samter triad was coined and was defined by the presence of nasal polyps, aspirin sensitivity, and asthma[1]; however this disease is now referred to as aspirin-exacerbated respiratory disease (AERD) because asthma is not always present despite reactions to aspirin. AERD comprises as many as 7% of adult-onset asthmatics and up to 12% to 14% of adult asthmatics with severe asthma.[2,3] This disorder is characterized by the unique intolerance to aspirin and other nonselective cyclooxygenase (COX) inhibitors.[4–6] Other characteristics include hypereosinophilia, both in the circulation and in the tissue; a tendency to develop de novo in adulthood[5,7,8]; and often an absence of identifiable atopy.[5,7] Sinusitis is present in this disorder,

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the degree of which is often severe, and this is associated with complete or near-complete opacification of the sinus cavity.[8] Although not a requirement, when asthma is present it often progresses in severity and is associated with aggressive airway remodeling.[9]

During aspirin reactions, many mediators are released, including cysteinyl leukotrienes (CysLTs), tryptase, eosinophil cationic protein (ECP), and prostaglandin D_2 (PGD_2), suggesting both mast cell and eosinophil activation.[10–12] Recently, aspirin was shown to directly activate both of these cell types ex vivo potentiating mediator release.[13] A predominant physiologic feature of AERD is the robust overproduction and overresponsiveness to CysLTs (inflammatory),[11,14] while at the same time there is underproduction and underresponsiveness to the antiinflammatory lipid mediator PGE_2.[15–17] These CysLTs have important proinflammatory and profibrotic effects that contribute to the asthma severity and to the extensive hyperplastic sinusitis and nasal polyposis.[8,18,19] In addition, conversely, the downregulation of PGE_2 pathways reduces the constraints that would normally act to attenuate these proinflammatory pathways.[20] This article focuses on the role that eosinophils and mast cells play in contributing to these cardinal features of AERD.

EOSINOPHIL AND MAST CELL NUMBERS IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Chronic sinusitis (CRS) is now recognized as a collection of disorders that result from inflammation of the sinuses and in many cases can be separated into different types based on the cellular infiltrate. One distinguishing feature in the nasal polyps that often form in association with chronic sinusitis is the presence or absence of eosinophils and among eosinophilic polyps a distinction can be made between AERD, allergic fungal sinusitis (AFS), and chronic hyperplastic eosinophilic sinusitis (CHES).[21,22] Within the eosinophilic polyps, AERD has more than twice the number of eosinophils in the polyp tissue than AFS or CHES, implicating them as important cells in the disease process.[22] Examination of bronchial biopsies from patients with AERD also revealed highly increased eosinophil numbers compared with aspirin-tolerant asthmatics and nonasthmatics.[23] These eosinophils were in an activated state, as shown by the presence of secretory ECP.[23]

The authors have reported lower numbers of mast cells in nasal polyps from eosinophilic sinus disease compared with healthy tissue by both toluidine blue and chloroacetate (chymase) staining, and there was no difference between aspirin-tolerant and AERD groups.[22] This finding contrasts with a previous report that found no difference in mast cell numbers in nasal polyps from AERD groups compared with allergic or nonallergic individuals via tryptase staining.[24] The differences in the results of these studies may reflect the use of different markers of mast cells (chymase vs tryptase) or the stratification of the groups, the study by Park and colleagues[24] not taking into account eosinophilic infiltration into the polyp tissue. Regardless, there do not seem to be more mast cells in nasal polyps in patients with AERD. However, this result may be erroneous, given the high expression of mast cell–derived mediators, and perhaps reflects the inability to stain for activated, granule-depleted mast cells (so-called phantom mast cells). Similarly, when the lungs have been examined, as with nasal polyposis (NP), smaller numbers of mast cells have been found in patients with AERD compared with nonasthmatic controls using immunohistochemistry to stain for tryptase-positive cells.[23] Another study examining the bronchial mucosa found increased numbers of tryptase-positive mast cells only in subjects