Eosinophilic airway inflammation in patients with atopic dermatitis

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To the Editor,

Atopic dermatitis (AD) is a chronic inflammatory skin disorder described as the first clinical manifestation of the atopic march leading to allergic asthma (AA) then allergic rhinitis (AR). AD, however, is not limited to childhood onset[1], with some patients developing asthma first[2]. Most AD patients are reported to have airway hyperresponsiveness (AHR)[3,4] airway eosinophilia[5], and concurrent asthma. The Hamilton Integrated Research Ethics Board approved this study. In cohort 1 we evaluated AHR and sputum eosinophils in AD patients (6 mild, 6 moderate-severe) but with no history of asthma, to determine if undiagnosed asthma was present in this population. AD patients were characterized using skin prick test (SPT) Eczema Area and Severity Index (EADI), Asthma Control (ACQ-5) and Leicester Cough (LSQ) questionnaires, spirometry, AHR, and sputum eosinophils, and compared to mild AA (n=14) with no history of AD. Refer to supplement for eligibility and methods. Neither group had used parenteral or oral anti-inflammatory therapy for >1 month. Twenty-one of the 26 patients had a history of AR with 9/21 (43%) reporting AR first in a 'reverse atopic march' sequence. AD had a significantly higher EASI score and methacholine PC_{20}, and lower ACQ-5 score compared to AA (all p<0.01) (Table 1). Despite having no history or clinical diagnosis of asthma, 3/12 (25%) AD demonstrated AHR defined by methacholine PC_{20} <16mg/ml, with data from all AD patients showing negative correlations between methacholine PC_{20} versus blood eosinophils (r = -0.81, p = <0.01), EASI score (r = -0.74, p = <0.01), and a trend versus IgE (r = -0.53, p = 0.07). When AD patients were grouped by AHR present/absent, those with AHR had significantly higher EASI score (p = 0.02) and blood eosinophils (p<0.001) (Table 1). Furthermore, when AD patients were grouped as mild (n=6) or moderate-severe (n=6) by EASI score, those with AHR were all classified as moderate-severe. The difference in AHR was not explained by allergen sensitivity because the number of positive SPT for animal, mould, house dust mite, or pollen was similar between AD subgroups when divided by AHR present/absent, or by AD severity. Nine of 12 (75%) AD patients demonstrated sputum eosinophilia, as defined by [?]3%[6], with levels similar to AA. In AD there was no relationship between sputum eosinophils versus methacholine PC_{20} or EASI score. We measured cough by LCQ to determine if sputum eosinophils in AD could be explained by eosinophilic bronchitis, however we found no relationship between LCQ score versus sputum eosinophils or blood eosinophils, and additionally there was no relationship between LCQ versus methacholine PC_{20} or EASI score. To further interrogate the concept of reverse atopic march, in cohort 2 we obtained biopsies of unaffected skin from the lower back of patients with moderate to severe AD (n=17), AA with no history of AD (n=14) and healthy controls (HC, n=15) to measure histological features common to AD. Internal controls showed lesional skin of AD had greater lymphocytic infiltration, epidermal thickening (both p<0.01) and spongiosis compared to their unaffected skin (p=0.04). (Table 2). In unaffected skin, lymphocytic infiltrate was significantly higher in AD versus AA (p=0.03) and HC (p = <0.01), with no difference between any groups for spongiosis, neutrophilic infiltration, vacuole numbers, or

epidermal thickening. Eosinophils in unaffected skin were too infrequent for analysis. Notably, skin from AA was histologically similar to HC. Taken together, our observations from this small study suggest that allergic disorders can occur independently or in reverse order to that described by the atopic march. Furthermore, a significant proportion of patients with AD have AHR and eosinophilic airway inflammation indicating potential development of airways inflammatory disease including asthma.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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