

Airway inflammation in thunderstorm asthma

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Summary

Background Epidemics of acute asthma associated with thunderstorms occur intermittently worldwide, though airway inflammation during these acute episodes has not been characterized. The aim of this study was to characterize airway inflammation in thunderstorm asthma.

Methods Cases were recruited after presentation to the emergency room with acute asthma immediately following a thunderstorm ($n = 6$). They were compared to two control groups: a group of atopic asthmatics that had presented with acute asthma to the emergency room prior to the thunderstorm ($n = 12$), and a second group of corticosteroid naïve asthmatics who presented to the emergency room in the prior 12 months ($n = 6$). Subjects had spirometry, sputum induction and allergy skin tests acutely and at review 4 weeks later.

Results Thunderstorm (TS) cases were more likely to have a history of hay fever and grass pollen allergy, and less likely to be on inhaled corticosteroids (ICS) prior to presentation. Cases and control groups had a similar degree of moderate to severe acute airway obstruction ($P = 1.0$). TS cases had elevated sputum eosinophils (14.8% of total cell count) compared to controls (1%, 2.6%, $P < 0.01$). TS cases had higher sputum eosinophil cationic protein (ECP; 11 686 ng/mL) compared to controls (1883, 3300, $P = 0.02$) acutely. TS cases had more cells positive for IL-5 (30%) compared to controls (1, 1.5%, $P = 0.02$). When adjusted for ICS use, TS cases had a risk ratio for elevated sputum eosinophils of 2.4 (1.23–4.69).

Conclusion Thunderstorm asthma is characterized by airway inflammation with IL-5-mediated sputum eosinophilia and eosinophil degranulation. These results are consistent with allergen exposure as the cause of the exacerbation, and are consistent with the thunderstorm-induced grass pollen deluge as the cause of epidemic asthma after thunderstorms.

Keywords asthma, eosinophil, IL-5, sputum, thunderstorm

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Introduction

Epidemics of acute asthma in association with thunderstorms have been reported worldwide [1–5]. The environmental changes that have been found to be important are a sudden fall in air temperature and a sudden rise in grass pollen concentration [6]. The subjects who are greatest affected and present to emergency rooms as a consequence appear to be unique when compared to other subjects who present with acute exacerbations of asthma. They are more likely to have a history of hayfever, are much more likely to be allergic to rye grass and are less likely to be taking inhaled corticosteroids at the time of the thunderstorm [5].

The mechanisms of thunderstorm asthma are not well established. Thunderstorm asthma could occur either when bronchoconstriction occurs in response to changes in atmospheric pressure and/or temperature, or alternatively the thunderstorm may cause the sudden release of an allergen. An abrupt increase in airborne rye grass pollen allergen through the release of

respirable, allergenic rye grass starch granules is hypothesized to explain thunderstorm asthma [7]. This may have pathophysiological similarities to experimental allergen challenge. Airway inflammation in asthmatics following allergen challenge is characterized by eosinophilia and an increase in metachromatic cells [8]. In contrast, a number of recent studies of acute asthma have indicated a more heterogenous inflammatory infiltrate with neutrophils and eosinophil degranulation [9–11]. Studying airway inflammation in thunderstorm asthma may help establish the mechanisms of this condition.

The aim of this study was to characterize airway inflammation in subjects with acute exacerbations of thunderstorm asthma and to compare them to a control group of atopic asthmatics.

Methods

Design

A nested case–control design was used, with cases and controls drawn from a cohort study of airway inflammation in acute asthma [12]. Subjects who presented to the emergency room with acute asthma, who were atopic with objectively confirmed

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asthma and who were seen within 4 h of presentation and prior to systemic corticosteroid use were eligible. All cases ($n = 6$) were recruited on 27 October 1998 after presenting to the emergency room at John Hunter Hospital following a spring thunderstorm. Two control groups were used. The first control group (Control group 1, $n = 12$) consisted of subjects who were recruited from atopic asthmatics that presented to the emergency room between June and September 1998 with an acute exacerbation of asthma. The second control group (Control group 2, inhaled corticosteroid naïve, $n = 6$) consisted of atopic asthmatics who were naïve to inhaled corticosteroid and who presented to John Hunter Hospital emergency room with acute asthma over a 12-month period.

All subjects presented spontaneously with an acute exacerbation of asthma and underwent triage, medical assessment and initial bronchodilator treatment. A clinical history was taken defining usual asthma triggers, the presence of other atopic history, medications used for asthma when stable and since symptoms deteriorated, and the time course of the exacerbation. Spirometry was performed (Vitalograph Ltd, Buckingham, UK), and subjects were pre-treated with salbutamol and sputum induced using 0.9% saline. Background asthma severity was assessed using the Aas score, which is based on clinical symptoms, frequency and severity of exacerbations and medication use [13]. Those who produced an adequate sputum specimen were asked to return 4–5 weeks later when they had symptomatically returned to baseline and were no longer on parenteral corticosteroids (visit 2). Subjects again had a clinical history taken, allergy skin prick tests, spirometry, bronchial provocation challenge and sputum induction.

Subjects

Thunderstorm cases ($n = 6$, aged 16–67 years, Table 1) presented to the emergency room following a spring thunderstorm.

All cases had a sudden acute exacerbation of asthma and were asymptomatic prior to the thunderstorm. The controls were recruited from a cohort of subjects who presented to the emergency room with an acute exacerbation of asthma over a 12-month period. Two controls were matched to each case in terms of age and sex, all subjects were non-smokers, atopic and were not on oral corticosteroids at the time of their presentation (Control group 1). A further six controls were recruited with acute asthma who had not used inhaled corticosteroids in the month preceding presentation and fulfilling the above criteria (Control group 2, corticosteroid naïve). Asthma was defined based upon a previous physician diagnosis and ATS criteria of a compatible history, together with either bronchial hyper-responsiveness (BHR; $PD_{20 \text{ saline}} < 15 \text{ mL}$) or an improvement in FEV_1 of $> 15\%$ after salbutamol 200 μg . An acute exacerbation of asthma was defined based on: deterioration in symptoms of wheeze, breathlessness or cough, an increase in use of short-acting β_2 agonist for relief of symptoms, or a deterioration in self-monitored peak expiratory flow (PEF). Subjects were excluded if they had a coexisting physician diagnosis of chronic obstructive pulmonary disease, if they had an infiltrate on chest radiograph suggesting pneumonia, if their FEV_1 was less than 1 L after salbutamol 200 μg , or if they had another contraindication to sputum induction.

Allergy skin prick test

Sensitization to 19 common aero-allergens was determined by an immediate reaction to skin prick testing (weal = 3 mm), carried out using a 1 : 10 weight/volume dilution of *Aspergillus fumigatus*, *Aspergillus mix*, penicillium, *Alternaria tenuis*, *Dermatophagoides pteronyssinus*, *D. farinae*, cockroach, peanut, hazelnut, wild oats, plantain, timothy, bent grass, blue grass, rye grass, cat hair, dog hair, feather mix and horse dander, with

Table 1. Subject characteristics

	Cases	Controls	ICS naïve controls	Analysis
n	6	12	6	NA
Sex, % male	2 (33%)	2 (17%)	1 (20%)	$P = 0.4$
Age, years	32 (28–36)	34 (28–46)	38 (30–46)	$P = 0.6$
Aas severity score	1 (1–1)	4 (4–5)	3 (2–5)	$P = 0.07$
History of allergic rhinitis	6* (100%)	6 (50%)	4 (67%)	$P = 0.03$
Admitted to hospital	4 (67%)	7 (58%)	4 (67%)	$P = 0.6$
FEV_1 , % predicted at visit 1	57.7 (50–65.4)	53.5 (41.5–80.5)	47.9 (42.3–53.4)	$P = 1.0$
FEV_1 , % predicted at visit 2	86.1 (82.9–89.3)	83.6 (61.8–92.3)	88.9 (71.4–94.8)	$P = 0.6$
$PD_{20 \text{ saline}}$, mL	4.65 (3.1–6.2)	2.45 (1.88–3.01)	2.31 (0.7–4)	$P = 0.8$
Proportion using inhaled steroids at presentation	2 (33%)	8 (67%)	0†	$P = 0.3$
Skin reaction to rye grass, mm	19.5* (19–20)	0 (0–4)	0 (0–6)	$P = 0.03$

Analysis of the three groups using the Kruskal–Wallis test. Differences between each group analysed using Wilcoxon rank sum or sign-rank test. ICS-inhaled corticosteroids. n (%) or medians (interquartile ranges). *Thunderstorm asthma significantly greater than both control groups.

†Comparison not made with inhaled corticosteroid naïve controls.

histamine and saline as controls (Bayer Australia Ltd, Pymble, Australia).

Sputum induction

Sputum induction was performed by a medical practitioner in the emergency department after pre-treatment with salbutamol 200 µg delivered via a Volumatic spacer (Allen and Hanbury's, Melbourne, Victoria, Australia). All subjects received supplemental oxygen during sputum induction, and inhaled sterile normal saline (0.9%) from a DeVilbiss 2000 ultrasonic nebulizer (Oregon, Pike, PA, USA) with 23-cm corrugated tubing and a Hans Rudolph 2700, 2-way nonrebreathing valve box (Hans Rudolph Inc, Kansas City, MO, USA) with a rubber mouthpiece. The nebulizer output was 1.8 mL/min and particle size (MMAD) < 5 µm. Saline was nebulized for 30 s, 1 min and then for 2 × 2-min periods. Spirometry was performed before and after salbutamol and then 1 min after each nebulization period. Sputum induction was ceased when an adequate sample was obtained, if FEV₁ fell below 20% of preinduction baseline, or at the subject's request. Salbutamol 200 µg was given following the induction if there had been a fall in FEV₁ of at least 15% from baseline, and repeated at 5-min intervals until the FEV₁ had returned to within 10% of baseline.

At the second visit, sputum was induced using ultrasonically nebulized hypertonic saline (4.5%) as described [14]. Briefly, 4.5% saline was nebulized for a DeVilbiss 2000 ultrasonic nebulizer as above for periods of 30 s, 1 min, 2 min and 4 min. FEV₁ was measured 1 min after each dose and sputum obtained by assisted expectoration.

Sputum analysis

Sputum portions were selected from saliva and processed as described [15]. Sputum was dispersed using 0.1% dithiothreitol (DTT; Sputolysin 10%; Calbiochem Corp., La Jolla, CA, USA) and a total cell count (TCC) of non-squamous cells and viability was performed. Supernatant was stored at -70 °C, and cyto-centrifuge slides prepared from the resuspended cell pellet (Shandon Cytospin, Sewickley, PA, USA). A differential count was obtained from 400 cells counted on May-Grunwald-Giemsa (MGG)-stained cytopreps. Cytokine-positive cells were assessed on periodate-lysine-paraformaldehyde fixed slides, incubated with anti-human IL-5 monoclonal antibodies (Pharmingen, San Diego, CA, USA), and detected by the APAAP technique [14, 15]. Positive and antibody controls were included in each staining run. The concentration of eosinophil cationic protein (ECP) was determined in thawed sputum supernatant by radioimmunoassay (ECP RIA; Kabi Pharmacia Diagnostics AB, Uppsala, Sweden), and IL-8 by enzyme-linked immunosorbent assay (ELISA; IL-8: R&D Systems, Minneapolis, MN, USA). Standard curves were based on dilutions of purified ECP, and recombinant IL-8 and the limits of detection of the fluid phase assays were 2 ng/mL for ECP and 32 pg/mL for IL-8. Albumin was measured by radial immunodiffusion (Immagine Immunocytochemistry Systems, Beckman Coulter Inc., Fullerton, CA, USA).

Statistical analysis

Statistical analysis was carried out using STATA (STATA Corporation, College Station, TX, USA). Most variables were not normally distributed and values have been expressed as

medians and the interquartile range. Differences in proportions between groups were analysed by Fisher's exact test or Chi-square test. Differences between multiple groups were analysed using a Kruskal-Wallis test, differences between two groups were analysed using the Wilcoxon rank-sum test, while differences between the paired samples from visit 1 and visit 2 were analysed using the sign rank test. A multivariate logistic regression analysis was performed to predict factors associated with elevated sputum eosinophils. Significance was accepted when P was < 0.05.

Results

We recruited six subjects who presented to the emergency room on the evening of a spring thunderstorm with a sudden acute exacerbation of asthma. All but one had a previous diagnosis of asthma and all had reported that they had been asymptomatic from their asthma before the storm. Two cases were on regular inhaled corticosteroids, one at low dose, the other admitted to poor compliance (Table 1). None of the subjects reported symptoms of an upper respiratory tract infection in the preceding 4 weeks. All the cases had a history of allergic rhinitis and reported their nasal symptoms had worsened along with the asthma. Thunderstorm asthma cases were allergic to each of the grass allergens tested, with greater reactions to most of the grasses tested by skin prick test compared to the controls (Table 2). Of particular note was the response to rye grass, with a median wheal of 19.5 mm and responses that ranged from 7 to 25 mm (Fig. 1, Table 2).

The control subjects were all residents of the local area at the time of the thunderstorm. While matched for age and sex they tended to have more severe chronic asthma; with a higher Aas score ($P = 0.02$, Table 1), and they were more likely to describe a recent respiratory tract infection ($P < 0.001$). All three groups had a moderate to severe degree of airflow obstruction (Table 1) that had improved at follow-up (Table 1). Bronchial provocation challenge at follow-up demonstrated that the groups had moderate to severe airway hyper-responsiveness. ($P = 0.8$, Table 1). The six controls recruited naïve to inhaled corticosteroids were similar to the two groups above in terms of airflow obstruction and pre-existing asthma severity (Table 1).

Sputum measures of airway inflammation

The thunderstorm asthma cases had an elevated proportion of eosinophils at visit 1 (14.8%, Table 3 and Fig. 2a) that had fallen by visit 2 (3.1%, $P = 0.03$, Table 3). In contrast, in the control groups the proportion of sputum eosinophils was significantly less than in the cases at visit 1 (median 1%, 2.6%, $P < 0.001$, Table 2). There were no significant differences between the groups in the other inflammatory cells. There was evidence of marked eosinophil activation in all groups at visit 1 with elevated sputum ECP. This was highest in the thunderstorm asthma cases (median 11 686 ng/mL) compared to Control groups 1 and 2 (1883, 3330, $P = 0.02$, Table 2). Thunderstorm cases had a greater proportion of cells staining positive for IL-5 at visit 1 (30%, Table 2 and Fig. 2b), than the controls (1.5%, 1% $P = 0.02$, Table 2 and Fig. 2b). Sputum albumin levels were elevated in both groups at visit 1 and had dropped dramatically by the followup visit (Tables 2 and 3).

Table 2. Measures of airway inflammation in sputum at visit 1, medians and interquartile ranges

	Cases	Controls	ICS naïve controls	Analysis
Total cell count × 10 ⁶ /mL	2.12 (0.99–3.24)	4.5 (2.7–9.5)	6.9 (4.7–9.2)	<i>P</i> = 0.3
Viability percentage	70.8 (66.7–75)	51.1 (30.3–86.3)	61.8 (42.3–88.9)	<i>P</i> = 0.4
Neutrophils percentage	21.1 (15.2–27)	47.8 (23.6–77.6)	48.1 (26.9–69.2)	<i>P</i> = 0.2
Eosinophils percentage	14.8* (14.5–15.6)	1 (0.5–6.3)	2.6 (1.5–3.8)	<i>P</i> = 0.01
Lymphocytes percentage	0.9 (0.4–1.1)	1.4 (0.8–2.3)	1.2 (0.8–1.9)	<i>P</i> = 0.4
Macrophages percentage	46 (42–50)	32.1 (19.6–42.4)	25.4 (24–26.8)	<i>P</i> = 0.4
IL-8 ng/mL	60 (55–65)	23.8 (11.6–41)	31.1 (28.3–34)	<i>P</i> = 0.3
ECP ng/mL	11686* (11639–11733)	1883 (1150–3606)	3300 (2993–3606)	<i>P</i> = 0.02
Epithelial cells	0.8 (0.79–0.85)	1.2 (0.8–2.8)	1.1 (0.7–2.8)	<i>P</i> = 0.5
Squamous cells	5.5 (5–6)	10.8 (3.5–19.5)	9.4 (3.1–16.4)	<i>P</i> = 0.6
Albumin mg/L	353.5 (351–356)	1098 (289.9–1539)	989 (243–1432.1)	<i>P</i> = 0.4
IL-5% positive cells	30 (25–30)	1.5 (0–3)	1 (0–2)	<i>P</i> = 0.02

Analysis of the three groups using the Kruskal-Wallis test. Differences between each group analysed using Wilcoxon rank sum or sign-rank test. ICS-inhaled corticosteroids. *Thunderstorm asthma significantly greater than both control groups.

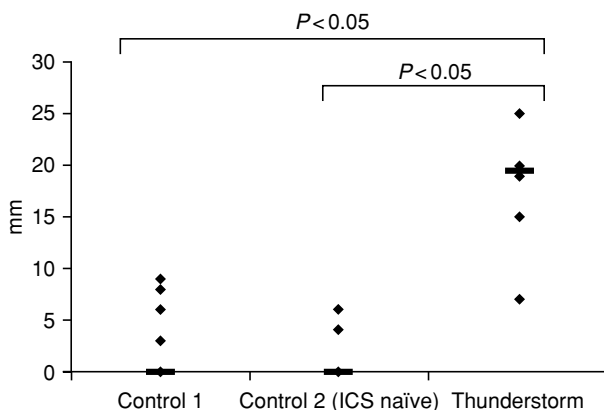


Fig. 1. Immediate skin prick test reaction to rye grass extract. Control 1, subjects matched for age and sex to those subjects who presented with acute thunderstorm asthma. Control 2 (ICS naïve), subjects with acute asthma who had not used inhaled corticosteroids for at least 3 months prior to presentation. Thunderstorm, subjects who presented with acute asthma following a thunderstorm. ♦, Individual data-points. —, Median. Differences between the groups calculated using the Wilcoxon rank-sum test.

A logistic regression model was developed to predict sputum eosinophilia during the acute exacerbation, as defined by sputum eosinophils $> 3.0\%$ [16], with thunderstorm presentation, inhaled corticosteroids use, sex, age and asthma severity (Aas score) as variables (Table 4). Presentation with thunderstorm asthma led to a risk ratio for sputum eosinophilia of 2.4 [95% confidence interval (CI) 1.23–4.69]. Female sex was also an independent predictor 2.0 (1.2–3.4), but age, inhaled corticosteroids use and background asthma severity (Aas score) were not significant contributors.

Discussion

Airway inflammation in subjects who present with an exacerbation of asthma induced by a thunderstorm is characterized by increased sputum eosinophils, sputum ECP and an increase in cells positive for IL-5. This contrasts to controls that present with acute asthma due to another aetiology, who have evidence of less intense eosinophilic inflammation. In keeping with previous studies [5], subjects with thunderstorm asthma had less severe chronic asthma, used fewer inhaled corticosteroids, but were more likely to have a history of allergic rhinitis and had a greater reaction to rye grass on allergy skin testing compared to controls.

These findings are important in defining the mechanisms of thunderstorm-induced asthma. Proposed mechanisms to account for this phenomenon are the sudden atmospheric changes that occur, with the fall in temperature and air pressure along with rainfall and humidity [6], which have been hypothesized to trigger smooth muscle contraction and bronchoconstriction in susceptible asthmatics. However, these reasons alone seem insufficient to explain why there is a tendency for some storms to initiate an asthma epidemic and others not. One explanation for this is that those storms that are responsible also cause the release of an allergen that triggers airway inflammation. This is suggested by the springtime occurrence of thunderstorm asthma and the marked elevation in rye grass pollen counts that have been found during these storms [6, 7]. Rye grass pollen grains have been shown to rupture on contact with rainwater leading to the release of hundreds of starch granules that are of a respirable size ($< 3 \mu\text{m}$) and have been shown to elicit an IgE-mediated acute response in asthmatics with eosinophil degranulation [7]. There are approximately 700 rye grass starch granules per pollen grain, and they contain rye grass allergen Lol p IX [7].

Table 3. Measures of airway inflammation in sputum at visit 2, medians and interquartile ranges

	Cases	Controls	ICS naïve controls	Analysis
Total cell count $\times 10^6/\text{mL}$	1.94 (1.8–2.1)	3.5 (1.8–5.1)	4.5 (2.1–5.4)	$P = 0.6$
Viability percentage	68 (66–69.7)	71.4 (69.4–74.7)	74.4 (69.4–78.6)	$P = 0.6$
Neutrophils percentage	23.5 (20.9–26)	39.9 (26.1–62.9)	38.1 (22.1–59.9)	$P = 0.1$
Eosinophils percentage	3.1 (3–3.1)	1.6 (0.3–2)	1.2 (0.2–1.8)	$P = 0.04$
Lymphocytes percentage	1.1 (0.6–1.2)	0.66 (0.3–2.1)	0.76 (0.2–2.0)	$P = 0.3$
Macrophages percentage	55.6 (38.4–72.7)	53.2 (25–68.7)	54.2 (23–69.9)	$P = 0.3$
IL-8 ng/mL	9.5 (4.2–14.7)	32.3 (7.1–70.3)	30 (6.9–69.3)	$P = 0.07$
ECP ng/mL	923.6 (889.3–958)	1229.6 (161.6–3665)	1025 (156–3601)	$P = 0.3$
Epithelial cells	1.6 (1.64–1.65)	3.6 (1–11.1)	3.1 (1–9.5)	$P = 0.5$
Squamous cells	18.1 (9.3–27)	7.4 (2.3–15.5)	12.6 (2.1–20.5)	$P = 0.6$
Albumin mg/L	21 (18–24)	23 (22–62)	20 (19–56)	$P = 0.6$
IL-5% positive cells	12 (5–19)	0 (0–8)	0 (0–7)	$P = 0.04$

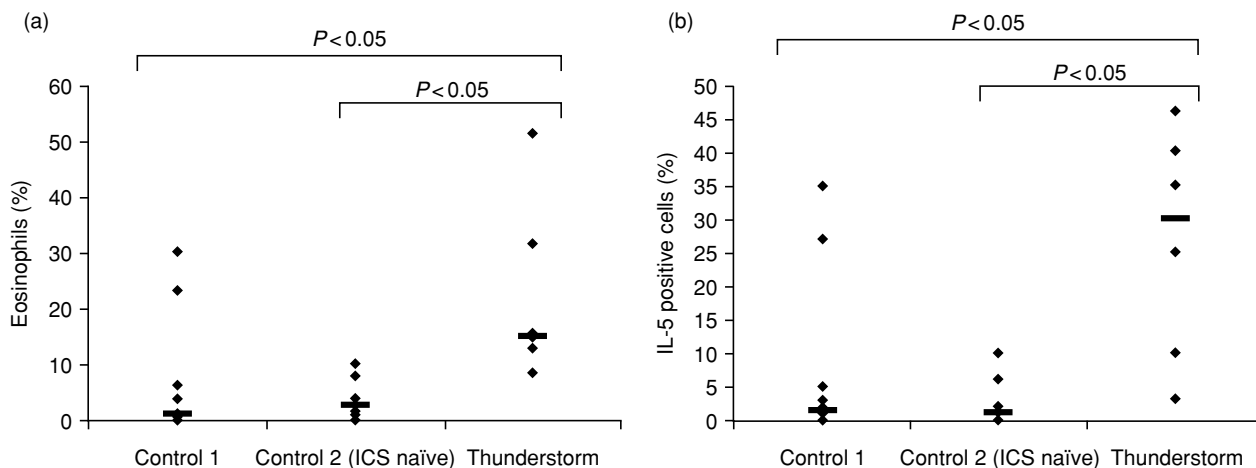


Fig. 2. (a) Sputum eosinophils measured at acute presentation. (b) Sputum cells positive for IL-5 at acute presentation. Control 1, subjects matched for age and sex to those subjects who presented with acute thunderstorm asthma. Control 2 (ICS naïve), subjects with acute asthma who had not used inhaled corticosteroids for at least 3 months prior to presentation. Thunderstorm, subjects who presented with acute asthma following a thunderstorm. ♦, Individual data-points. —, Median. Differences between the groups calculated using the Wilcoxon rank-sum test.

The sudden exposure of high doses of aeroallergens would seem to closely mirror the situation that occurs during experimental allergen challenge. As a model for acute asthma, allergen challenge causes an increase in airway hyper-responsiveness [17] and an increase in eosinophils along with eosinophil degranulation [18]. In addition there is a dramatic increase in IL-5-positive cells [19] and IL-5 is known to play a crucial role in eosinophil recruitment and activation [20], particularly after allergen challenge [21]. Our results support the hypothesis that an acute increase in eosinophilic airway inflammation is important in thunderstorm asthma, with an increase in IL-5 and eosinophil degranulation. This differs from other causes of acute asthma, where airway inflammation in acute asthma is

more heterogeneous with an increase in neutrophils [9, 10] that may be due to associated viral infections. In support of this the subjects who were controls were more likely to report a recent respiratory tract infection and had more severe chronic asthma.

To characterize airway inflammation in thunderstorm asthma we adopted a nested case-control design. The cases were matched with non-smoking atopic asthmatics that had presented at other times with acute asthma and who lived in the same geographical area as the cases when the thunderstorm occurred. A limitation of the study is the small number of cases recruited with thunderstorm asthma. Unfortunately, the occurrences of such epidemics are unpredictable and the recruitment of these cases was fortunate. Despite this, our thunderstorm

Table 4. Logistic regression analysis

Variable	Risk ratio	95% CI
Thunderstorm	2.4	1.23–4.69
ICS	0.53	0.01–41.1
Sex	2	1.2–3.4
Age	0.99	0.88–1.1
Aas	1.4	0.22–8.34

Model to predict sputum eosinophils >3.0%. Log likelihood –5.99.
Prob > chi-squared = 0.97.

cases appear to be representative of the subjects who presented with thunderstorm asthma in a previous large epidemiological survey [5]. In order to reduce selection bias, we recruited both the cases and controls from a cohort of subjects who presented to the emergency room over a 12-month period with acute asthma. All the subjects who were selected as controls would have been eligible to be cases if they had presented on the evening of the thunderstorm, they were non-smokers and atopic and not using prednisone and both groups had a similar severity of acute airflow obstruction. The cases, however, used less inhaled corticosteroids and this may be an important confounder affecting inflammatory indices. To overcome this we recruited a further group of control subjects with acute asthma who had not used inhaled corticosteroids in the month prior to presentation and in addition controlled for inhaled corticosteroid use when analysing the results in a logistic regression model. We still found that presentation with acute asthma after a thunderstorm was an independent predictor of acute sputum eosinophilia. In addition the differences between the thunderstorm cases and controls in terms of eosinophilia were marked and associated with a marked increase in expression of IL-5. Most of the control subjects with acute asthma reported symptoms of an upper respiratory tract infection prior to their exacerbation and it is possible that this may also have influenced sputum cell counts. Other investigators have found an association between viral respiratory tract infection and sputum neutrophilia [22]. If this is the case it further reinforces the point that different triggers for acute asthma may uniquely influence acute airway inflammation. The method of sputum induction varied between the visits, where 0.9% saline was used initially for safety reasons in acute asthma; however, a change in saline concentration has not been shown to influence cell counts [23]. There was a tendency for the inductions to require less time to induce sputum at visit 1 and this has been shown to influence cell counts [24]. However, there were no differences in time between cases and controls at visit 1 though the time to induction tended to be longer at visit 2, the differences in induction time did not exceed 4 min. This would be an inadequate difference to explain the changes in sputum eosinophils alone and the shorter time at visit 1 in fact would tend to reduce sputum eosinophils where in the cases the opposite was seen.

The use of inhaled corticosteroids effectively attenuates the increase in eosinophil progenitors following allergen challenge [25] and it is interesting that subjects with acute thunderstorm asthma were either steroid naïve or on low doses, suggesting steroids may be effective in suppressing acute eosinophilic airway inflammation in this instance. Whether increasing inhaled corticosteroids prior to the thunderstorm would prevent acute asthma remains to be established.

In conclusion, our results demonstrate that acute thunderstorm asthma is characterized by an elevation in sputum eosinophils, eosinophil degranulation and a greater proportion of cells positive for IL-5. This contrasts to the more heterogeneous airway inflammation seen in other causes of acute asthma. These results emphasize that there are important differences in airway inflammation in acute asthma and this will be important in understanding the mechanisms of pathogenesis of acute asthma and in evaluating treatment strategies.

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