Blood eosinophil counts and arterial oxygen tension in acute asthma

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Abstract

***Objective*—To investigate whether during acute asthma episodes a decrease in blood eosinophil count could correlate with the severity of the disease.**

***Design*—Prospective study on paediatric asthmatic patients admitted for acute asthma exacerbation between January 1992 and August 1993. All patients were regularly followed up in an outpatient clinic and had had a complete clinical evaluation <1 month before admission.**

***Setting*—Pulmonary division of the G Gaslini paediatric research institute, Genoa, Italy.**

***Subjects*—21 asthmatic patients, 59 (SEM 9) months of age, admitted for acute asthma exacerbation. On the basis of clinical evaluation and the results of blood and microbiological tests performed during acute asthma exacerbations, patients were divided into two subgroups: infected (n=13) and non-infected (n=8).**

***Results*—All but one of the patients showed a marked decrease in blood eosinophil count during the acute asthma episode, in comparison with recent count (<1 month before admission) obtained in clinically stable conditions: 662 (116) *v* 210 (54) eosinophils/mm^3, p<0·0003. The decrease in the eosinophil count was more pronounced in the infected patients than in the non-infected patients, but the difference was not statistically significant (p>0·05). Similarly, transcutaneous arterial oxygen pressure (PaO_2) values measured during acute asthma exacerbations tended to be lower in infected patients, without, however, reaching statistical significance: 8·6 (0·7) *v* 10·1 (0·9) kPa, p>0·05). The correlation between the decrease in blood eosinophil count and PaO_2 during the acute asthma exacerbations was significant in all the patients (r^2=0·235, p=0·022) and in the non-infected patients (r^2=0·653, p=0·015), but not in infected patients. In this latter subgroup, a significant negative correlation was found between blood neutrophil counts during acute asthma exacerbations and PaO_2 (r^2=349, p=0·026).**

***Conclusions*—During acute asthma exacerbations in atopic patients without clinical evidence of infection, the decrease in blood eosinophil count correlates significantly with the decrease in PaO_2, further supporting the role of eosinophils in allergic asthma.**

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Keywords: acute asthma, blood eosinophils, arterial hypoxia.

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Although the basic immunological defect in asthma is still unknown, continuing investigations are yielding insights into the pathogenic components of this disorder.[1–3] Bronchoalveolar lavage, bronchial biopsy, and in vitro studies have provided convincing evidence that mast cells, T lymphocytes, and eosinophils are important components of the inflammatory reaction in allergic as well as in non-allergic (intrinsic) asthma.[4–6] In this context, cytokines released by T cells (with the Th_2 phenotype) and by mast cells, which include interleukin (IL)-3, IL-4, IL-5, IL-10, and granulocyte macrophage colony stimulating factor (GM-CSF),[7 8] not only modulate the production of allergen specific IgE in the airways,[9] but also regulate the maturation, recruitment, and activation of eosinophils.[3 10] Experimental exposure of atopic subjects with asthma to allergen inhalation results not only in degranulation of mast cells, but also in increased numbers of activated T lymphocytes and in recruitment of eosinophils.[11 12] Similarly, in exercise induced asthma, degranulation of mast cells is associated in some patients with migration of eosinophils in the airways.[5] The role played by eosinophils in the pathogenesis of asthma has been debated for years. While these cells have been considered 'beneficial components' of the host reaction, able to suppress mediators of inflammation in immediate-type hypersensitivity reactions,[13] there is increasing evidence that they have the potential to injure host tissue through the release of toxic oxygen radicals and cytotoxic proteins.[3 10 14 15] In this context, the presence of eosinophils in the bronchial mucosa and in the airways has been found to be statistically correlated with damage to the airway epithelium, including loss of epithelial junction,[16] and to bronchial hyperreactivity at baseline[16] or after allergen challenge.[17] Current concepts recognise that airway eosinophilia is the result of the efflux of circulating peripheral blood eosinophils, responding to chemoattractants that drive the cells toward the bronchial structures.[10 14] These chemotactic stimuli have marked effects even on eosinophil activation, converting normal eosinophils into hypodense or degranulated eosinophils, and releasing mediators and cytotoxic products.[10 11] Consistent with this hypothesis is the demonstration that, after allergen inhalation challenge, the increased eosinophilia observed in bronchial biopsies and in bronchoalveolar lavage[11 12] is associated with the decrease of the numbers of circulating eosinophils.[18] We therefore hypothesised that in 'naturally occurring' acute asthma episodes, a similar recruitment of eosinophils from blood

could also be demonstrated and that the decrease in circulating eosinophil numbers could correlate with the impairment of respiratory function.

Methods

PATIENT POPULATION

All the asthmatic patients admitted between January 1992 and August 1993 to the paediatric pneumology division of the Gaslini Institute because of acute bronchospasm severe enough to require hospital admission were retrospectively evaluated. The study inclusion criteria were: (1) a diagnosis of bronchial asthma, according to the definition of the American Thoracic Society[19]; (2) the availability of former clinical records, including a venous white blood cell (WBC) total and differential count, performed within one month of the hospital admission while the patient was in a stable clinical condition; (3) no systemic or inhaled corticosteroids for at least 45 days before admission; (4) the availability of total and differential venous WBC counts and of transcutaneous arterial oxygen pressure (Pa_{O_2}) measurements, performed on hospital admission and before any systemic steroid treatment.

PATIENT EVALUATION

At hospital admission the diagnosis of an acute asthma exacerbation was based on the clinical signs of acute airway obstruction: dyspnoea with wheezing and prolonged expiration, tachypnoea with the use of accessory muscles of respiration, and tachycardia. Examination of the lungs showed wheezing and rhonchi and/or unequal breath sounds in all patients; latent wheeze was inducible in younger patients by the manual compression of the chest during expiration. On admission, routine blood tests and microbiological examinations on blood, serum, and nasopharyngeal secretions were performed in all patients by the central clinical laboratory of our institute. Eosinophil counts were performed with a Technicon H6000 (Technicon Instrument Corporation), a system that automatically counts and differentiates between leucocytes by an alkaline peroxidase method. Approximately 12 000 leucocytes were counted on each occasion. The coefficient of variation for the eosinophil counts was 7·5%. The total peripheral blood eosinophil counts at the hospital admission and the total peripheral blood eosinophil counts previously determined in the same patients under clinically stable conditions were used to estimate the blood eosinophil count decrease during acute asthma episode, so that the patients acted as their own controls.[20] On the basis of the clinical evaluation and the results of blood and microbiological tests performed during acute asthma exacerbations, patients were divided into two subgroups: infected subjects and non-infected subjects. As an objective index of the severity of the asthma, non-invasive assessment of blood gases was carried out at the bedside by transcutaneous oximetry (Tina D280, Radiometer) with a cutaneous probe at 42°C. The Pa_{O_2} data were recorded for at least 1 h and the mean value was chosen. Patients were also classified as atopic or non-atopic according to the total and allergen specific serum IgE levels and skin reactivity to the most common environmental allergens in our area.[21]

DATA ANALYSIS AND STATISTICAL EVALUATION

Data are expressed as arithmetic mean (SEM). Statistical analysis of the eosinophil counts was performed using the t test. The relation between decrease in blood eosinophil count or neutrophil counts and Pa_{O_2} values recorded by transcutaneous oximetry during acute asthma episode was assessed by the correlation test (r^2). Values less than 0·05 for p were considered to be significant.

Results

PATIENT GROUP CHARACTERISTICS

Twenty one patients (11 males, 10 females, 59

Clinical and laboratory details of the patients studied

Patients	Age (years)	IgE mediated allergy	Chest x ray	Signs of inflammation	Pa_{O_2} (kPa)	Eosinophils			Neutrophils	
						Acute asthma	Stable period	Difference	Acute asthma	Stable period
1 RC	6	HDM, pollen	Hyper/Atel	+	7·33	0	250	−250	7200	4000
2 MA	2	No	Hyper/PLM	+	5·33	10	1750	−1740	16 500	3780
2 MA	2	No	Hyper/Atel	+	8·00	40	980	−940	8550	16 840
3 MG	2	HDM	Not done	−	6·67	20	540	−520	1440	2420
4 AC	12	HDM, pollen	Hyper/PLM	+	7·33	20	270	−250	7940	3490
5 CN	10	HDM	Not done	−	12·26	10	320	−310	5410	2510
6 DJS	1	No	Hyper/Atel	+	6·00	700	2490	−1790	6820	2550
7 DS	2	No	Hyper	+	12·53	20	540	−520	7630	4940
8 DAM	5	HDM	Hyper	−	12·80	170	240	−70	2800	2870
9 SA	3	No	Hyper	+	12·00	330	760	−430	4650	4390
10 BA	11	HDM, pollen	Not done	−	12·66	670	710	−40	5000	5670
11 CI	4	HDM	Hyper/BPN	+	8·00	50	290	−240	13 310	3070
12 RS	6	No	Hyper	+	12·00	120	310	−190	2160	8400
13 TV	10	HDM	Hyper/PLM	−	10·00	230	400	−170	12 550	3430
14 ML	2	HDM	Hyper	+	12·53	760	810	−50	2860	3120
15 FM	5	HDM, pollen	Hyper/Atel	+	9·33	10	640	−630	3230	2310
16 SI	2	No	Hyper/Atel	+	7·73	70	310	−240	17 790	4770
17 CM	5	HDM, pollen	Hyper	+	7·33	330	170	160	4650	2650
18 BD	5	HDM	Hyper	−	10·40	320	660	−340	5350	4900
19 FA	2	HDM	Hyper	−	6·00	115	640	−525	6170	2410
20 MF	7	HDM, pollen	Hyper/Atel	+	5·60	30	420	−390	11 420	2540
21 ZM	8	HDM	Hyper	−	10·40	610	1080	−470	3480	3450

HDM=house dust mite; Atel=atelectasis; Hyper=hyperinflation; PLM=prominence of lung markings; BPN=bronchopneumonia.

(SEM 9) months of age), all regularly followed by our outpatient clinic, fulfilled the inclusion criteria. One patient was evaluated during two subsequent asthma episodes. Sixteen patients (76%) were classified as sensitised to environmental antigens. Thirteen patients (62%) had clinical or laboratory signs of infection (infected patient group); eight patients (38%) had no signs of infection (non-infected group). All the patients without infection were sensitised to environmental allergens (table).

EOSINOPHIL COUNT DECREASE DURING ACUTE ASTHMA EPISODES

All patients but one showed a marked decrease in total blood eosinophil count during the acute asthma episodes, as compared with the previous counts under stable clinical conditions: 210 (54) *v* 662 (116) eosinophils/mm^3 respectively, $p<0{\cdot}0003$. The blood eosinophil count decrease was more pronounced in the 13 patients with clinical or laboratory signs of infection (713 (176) eosinophils/mm^3 in stable conditions *v* 177 (69) during the acute asthma episode; $p<0{\cdot}003$) than in the eight patients without signs of infection (573 (94) eosinophils/mm^3 in stable condition *v* 268 (89) during the acute asthma episode; $p<0{\cdot}01$). However, no statistically significant differences were observed between the infected and the non-infected groups in: (a) total blood eosinophil count previously determined in a stable period; (b) total eosinophil count measured during the acute asthma episode; and (c) the blood eosinophil count decrease ($p>0{\cdot}05$, each comparison) (fig 1).

Pa_{O_2} VALUES DURING ACUTE ASTHMA EPISODES

The non-invasive measurement of blood gases at the bedside by transcutaneous oximetry showed that the mean Pa_{O_2} value during the acute asthma episodes was 9·2 (0·6) kPa when evaluating all the patients together. Pa_{O_2} values tended to be lower in the infected group than in the non-infected group, at 8·6 (0·7) kPa and 10·1 (0·9) kPa, respectively) but the differences were not significant ($p=0{\cdot}296$) (fig 2). The arterial hypoxaemia was indeed related to the acute asthma episode, since all patients returned to normal Pa_{O_2} values (>12·8 kPa) within two weeks after recovery.

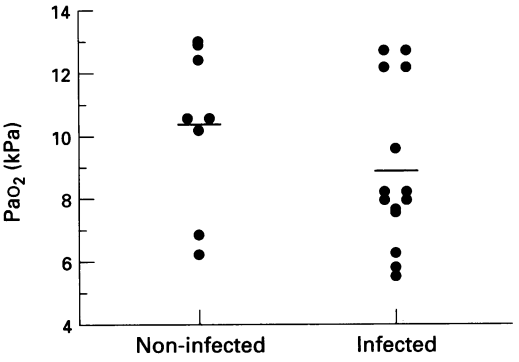

Figure 2 Pa_{O_2} values in infected and non-infected patient groups during asthma attack. Horizontal lines represent the mean values.

CORRELATION BETWEEN Pa_{O_2} VALUES AND BLOOD EOSINOPHIL COUNTS

Evaluating all the patients together or separately (infected and non-infected subgroups), no correlation was found between Pa_{O_2} values and either the eosinophil counts during the acute asthma episodes or the eosinophil counts during the previous clinically stable period (both $p>0{\cdot}05$, each comparison) (not shown). In contrast, a statistically significant correlation was found between Pa_{O_2} values and the decrease in blood eosinophil count during the acute asthma episode in all patients ($r^2=0{\cdot}235$; $p=0{\cdot}022$) (fig 3A), and in the non-infected group ($r^2=0{\cdot}653$; $p=0{\cdot}015$) (fig 3B). In contrast, no significant correlation was found between Pa_{O_2} values and the decrease in blood eosinophil count during the acute asthma episode in the infected group ($r^2=0{\cdot}183$; $p=0{\cdot}127$) (fig 3C). Interestingly, in the infected group a statistically significant inverse correlation was found between the Pa_{O_2} values and the total blood neutrophil numbers during the acute asthma episode ($r^2=0{\cdot}350$, $p=0{\cdot}026$) (fig 4).

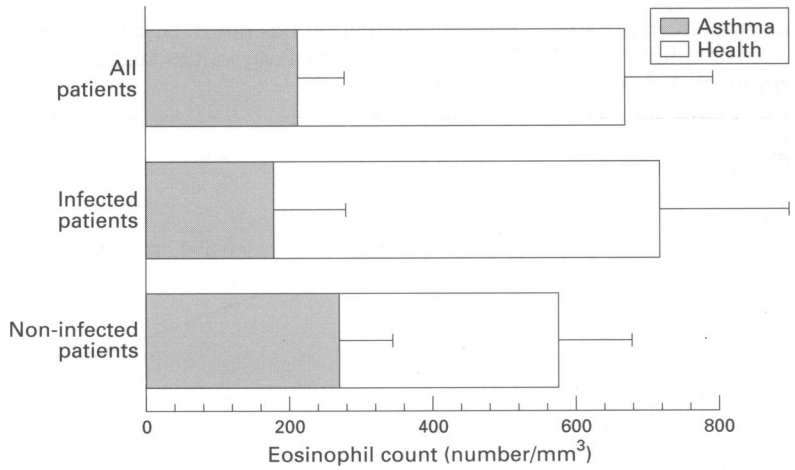

Figure 1 Decrease in blood eosinophil count in asthma attack in different patient groups. Area on the right represents peripheral blood counts in stable conditions, area on the left shows eosinophil count during asthma attack.

Discussion

In this study we have shown that in the vast majority of asthmatic children a naturally occurring acute exacerbation is associated with decrease in the blood eosinophil count, presumably because of pulmonary sequestration of eosinophils. We have also shown that the decrease in numbers of circulating eosinophils is strongly correlated with arterial hypoxaemia, recorded by transcutaneous oximetry. The correlation between decreased blood eosinophil counts and Pa_{O_2} values was greater in atopic patients without clinical or laboratory signs of infection. In contrast, in patients with positive signs of infection, Pa_{O_2} values correlated with blood neutrophilia measured during acute asthma exacerbations, rather than with the decrease in blood eosinophil count. Previous studies have suggested that eosinophils may be potent inducers of tissue

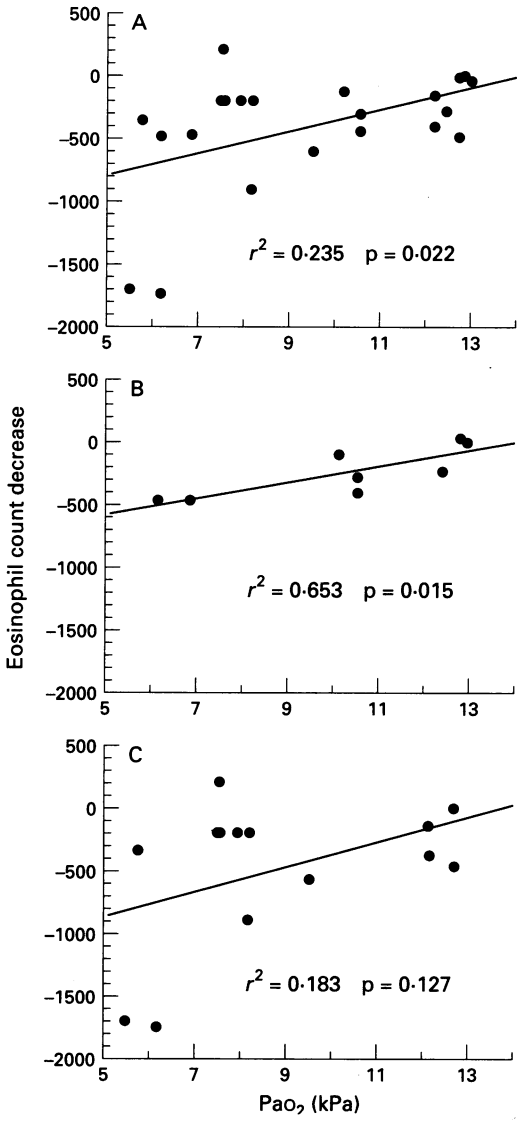

Figure 3 (A) Correlation between eosinophil count decrease and PaO_2 values during asthma attacks in all the patients. (B) Correlation between eosinophil count decrease and PaO_2 values during asthma attacks in the non-infected patient group. (C) Correlation between eosinophil count decrease and PaO_2 values during asthma attacks in the infected patient group.

inflammation and damage in asthmatic lungs.[13 14] The mechanisms by which eosinophils are recruited into the lung structures in bronchial asthma are multiple and of different origins.[2 3 10] To accumulate in the airways, peripheral blood eosinophils must respond to chemotactic stimuli that drive the cells within the bronchial and alveolar structures. Cytokines and mediators produced by endothelial, bronchial epithelial, and immunoeffector cells act as chemoattractants for eosinophils.[10 12] In addition, most of these products also have marked effects on cell activation, converting normal eosinophils into hypodense (or degranulated) eosinophils, which release granule associated proteins, proinflammatory substances, and cytotoxic molecules.[10–14] The best characterised mechanisms for eosinophil recruitment are chemotactic factors released after IgE dependent mast cell activation,[7 8] and after allergen inhalation challenge increase numbers of degranulated mast cells in the bronchial mucosa have been described,[4] associated with increased proportions of eosinophils in bronchial lavage[12] and bronchial tissues.[4 11] Similarly, after specific allergen inhalation challenge in atopic patients with asthma a decrease in circulating eosinophil numbers has been reported, correlated with the magnitude of the late asthmatic response and with changes in bronchial responsiveness to histamine.[18] However, eosinophil infiltration of the bronchial mucosa and degranulated mast cells are also features common to non-allergic, intrinsic asthma,[5 6] and, as well as mast cell derived mediators, it has been shown that even T cell derived cytokines can play a major role in eosinophil biology.[22 23] In this context, in the airways of both allergic and non-allergic asthmatic patients an intense mononuclear cell infiltration is present, including high proportions of activated T lymphocytes.[6 24] T cell derived cytokines having effects on eosinophils include IL-3, IL-5, and GM-CSF.[24–26] IL-3, IL-5, and GM-CSF may prolong the survival of eosinophils in culture, may convert 'normal' into 'hypodense' eosinophils and activate the 'resting' cells to release mediators or cytotoxic products,[25 27] and upregulate the expression of adhesion molecules.[28] IL-5 induces eosinophilia in vivo,[29 30] and in the guinea pig model of allergic asthma the pretreatment of the animal with anti-IL-5 antibody has been shown to be effective in decreasing the eosinophil efflux from the blood to the lungs. In addition, IL-3, IL-5, and GM-CSF may also upregulate the expression of adhesion molecules involved in migration of cells such as Mac-1 (CD11b/CD18 or CR3) on eosinophils,[31] and ICAM-1 on vascular endothelial and airway epithelial cells.[32] In addition, eosinophils migrate in response to factors that are also chemotactic for neutrophils and include C5a, LTB_4, hydroxyeicosaenoic acids (HETEs), PAF-acether, and formyl-methionine-leucine-phenylalanine (f-MLP).[2 3] In the present study we showed a fall in circulating eosinophil numbers during acute asthma episodes both in atopic patients without clinical or laboratory signs of infection and in patients with positive inflammatory signs. Although the fate of eosinophils lost from the circulation has not been determined, the correlation with PaO_2 values suggests that

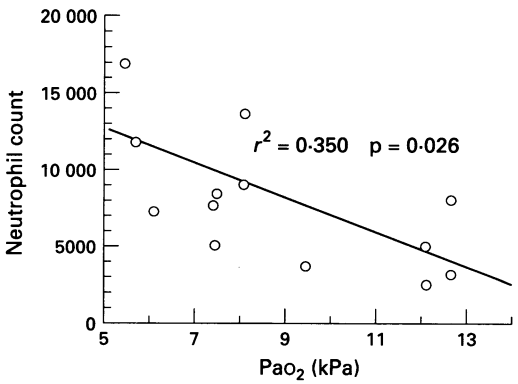

Figure 4 Correlation between neutrophil counts and PaO_2 values during asthma attacks in the infected patient group.

they may have been recruited to the lung, following the release of chemotactic factors by cells present in the airways. This hypothesis is in keeping with studies showing a fall in blood eosinophil counts[19] and bronchoalveolar lavage eosinophilia[5 6 33] after allergen inhalation challenge. The causes of hypoxaemia in asthma are multiple, including bronchospasm, mucosal oedema, inflammatory changes of the airways, increased mucus secretion, and endoluminal mucus plug formation; the resulting decrease in alveolar Pa_{O_2} triggers vasoconstriction reflexes that often are responsible for ventilation/perfusion mismatching. In addition, because of the small diameter of the airways and the absence of collateral ventilation, atelectasis is frequent in young children during acute bronchospastic episodes.[34] The eosinophils can play an important role in several of the mechanisms involved in the pathogenesis of bronchial asthma, through the release of powerful mediators with spasmogenic, proinflammatory, and prosecretory effects.[14 35–38] The involvement of eosinophils in inducing morphological and functional changes in the airways in acute asthma is confirmed by the demonstration – provided by the present study – of a significant link between a fall in circulating eosinophil numbers and arterial hypoxaemia, particularly in atopic patients without clinical laboratory signs of infection. Interestingly, in patients with positive inflammatory signs, we found that Pa_{O_2} values correlated with blood neutrophilia rather than with blood eosinophil count decrease, suggesting that in different clinical settings other mechanisms, mediators, and cells might be involved in the functional damage to the respiratory system.

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