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The relationship between bronchial immunopathology and hyperresponsiveness in asthma

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The relationship between bronchial immunopathology and hyperresponsiveness in asthma. L.W. Poulter, C. Power, C. Burke.
ABSTRACT: Physiological and immunopathological parameters were investigated in 15 patients with diagnosed asthma, and 6 non-asthmatics presenting with other chest symptoms. The 15 symptom-free asthmatics expressed bronchohyperresponsiveness with a mean provocative dose producing a 20% fall in forced expiratory volume in one second ($PD_{20}FEV_1$) of 1 mg histamine. None of the non-asthmatics responded to 16 mg histamine. Twenty four hours later bronchoscopy was performed and endobronchial biopsies were obtained. Histological staining of frozen biopsy sections revealed a mononuclear cell infiltrate in all 15 asthmatics, while only 1 of the 6 non-asthmatics showed mild inflammation. Monoclonal antibodies were used to identify subsets of lymphocytes, activation markers, macrophages, and HLA-DR expression within the peribronchial infiltrates. In all samples, activated T-cells and macrophages were identified and HLA-DR expression was found to be raised, but the CD4: CD8 ratio was highly variable. No clear relationship was found between cellular distribution and measured lung function parameters. A highly significant correlation was found between the level of HLA-DR expression on the infiltrating cells (quantified microdensitometrically) and bronchial hyperresponsiveness. These results show for the first time that a chronic T-cell-mediated immune response is present in the bronchial tissue of asymptomatic asthmatics, and that the HLA-DR expression promoted correlates with the hyperresponsive status. These data promote the hypothesis that a T-cell-mediated response contributes to a predisposition to bronchial hyperresponsiveness in asthmatics.
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Although it is well-established that environmental antigens such as pollens and products of mites *etc.* can promote bronchospasm, the emergence of bronchial hyperrresponsiveness in only a restricted proportion of the population makes it clear that exposure to these substances is not in itself sufficient to cause this disease. Furthermore, it is well-documented that stress and changes in temperature can also precipitate bronchospasm. Indeed, any patient with variable airway obstruction and bronchial hyperreactivity is diagnosed as asthmatic irrespective of aetiology [1]. Other clinical features such as a cough without initial evidence of airway obstruction [2], progression in minority of patients to progressive airway obstruction [3] and the efficacy of immunosuppressive drugs such as corticosteroids and methothrexate [4, 5] cannot be explained if the asthmatic state results exclusively from an anaphylactic hypersensitivity response. One is led to conclude that some underlying pathology present in these individuals must predispose them to express bronchial hyperresponsiveness.

The pathology of asthma has been extensively investigated since Curshmann [6] first showed the presence of respiratory epithelial cells in the sputum of asthmatic patients in 1883. Subsequent studies of sputum [7, 8], bronchoalveolar lavage [9, 10], bronchial biopsy specimens [11, 12] and autopsy material [8] have confirmed that generalized airway inflammation is an integral part of the asthmatic syndrome.

However, the nature of this inflammatory process and, in particular, its relationship to the altered physiology in asthmatics, is poorly understood. Recently, evidence has emerged that a heightened T-cell responsiveness may be present in asthmatic individuals [13, 14]. Several histological and electronmicroscopic studies of peribronchial biopsies have revealed that damage to the bronchial epithelium in asthmatics is associated with infiltration of the lamina propria by lymphocytes and macrophages [15–17]. These studies were performed at a time when patients were asymptomatic. Recently, studies have indicated a relationship between lymphocyte infiltration, epithelial damage and bronchial

responsiveness. Such observations point to a possible link between chronic inflammation in the bronchial wall and a predisposition to bronchial hyperresponsiveness. Studies into ozone-induced bronchospasm in animals have further emphasized the possible importance of airway inflammation to the hyperresponsive state [18, 19].

In the light of these observations the present study was designed to identify and characterize the inflammatory reaction in the peribronchial tissues of asymptomatic asthmatics using monoclonal antibody probes to dissect the populations of immunocompetent cells involved. Furthermore, this immunopathological approach was combined with a study of lung function in the biopsied subjects to determine whether any relationship existed between the inflammatory reaction in the bronchioles and the aberrant physiological responsiveness of this asthmatic population.

Materials and methods

Patients lung function

Fifteen patients with diagnosed asthma, (American Thoracic Society) (ATS) criteria, were recruited. Six patients not satisfying ATS criteria for asthma and not exhibiting bronchial hyperresponsiveness, but investigated for persistent cough and/or haemoptysis were recruited as a control population. All gave informed consent and the study was approved by the Ethics Committee of the James Connelly Memorial Hospital. Details of all subjects are presented in table 1. Although a variability in smoking status existed in these groups, no evidence was found that this reflected in the results obtained (see discussion). All therapy, with the exception of β_2-agonists, was withdrawn 48 h prior to investigation, to avoid any acute effect on immunological parameters. All subjects were asymptomatic when studied.

On day 1, baseline spirometry was performed, using a computerized Gould 2400 system. The best of three technically acceptable forced expiratory manoeuvres was recorded. A standardized bronchial provocation protocol [20] was performed one hour after baseline studies were completed. Following inhalation of nebulized saline control solution, nebulized buffered histamine phosphate was inhaled for 3 min *via* a face mask, using a nebulizer driven by oxygen at 7 $l\cdot min^{-1}$. Spirometry was recorded at 30 s and 90 s and subsequently every 90 s after each dose until either forced expiratory volume in one second (FEV_1) fell by 20% or, if FEV_1 value failed to fall, the next strength of histamine was given. The initial dose of histamine was 0.03 mg and this was doubled at successive stages until a dose of 16 mg was given. In this way, the provocative dose of histamine to reduce FEV_1 by 20% ($PD_{20}FEV_1$) was calculated.

Table 1. – Subjects studied

Subjects	Age	Sex	Symptoms months	Cigarettes pack yrs	Current treatment
Asthmatics					
1	27	F	D/W(3)	-	IS/β_2
2	15	F	W(6)	-	IS/β_2
3	29	M	W (6)	10 (ex)	IS/β_2
4	29	M	D/W(3)	5	-
5	26	M	D/W(180)	-	IS/β_2
6	21	M	D/W(108)	2	β_2
7	39	M	D/W(36)	-	β_2
8	21	M	D/W(206)	-	IS/β_2
9	23	M	D/W(218)	-	β_2
10	26	F	D/W(276)	-	IS/β_2Ti
11	44	M	D/W(480)	-	IS/β_2/Th/OS
12	41	M	D/W(180)	21 (ex)	IS/β_2/Th
13	63	M	D/W(36)	-	IS/β_2/IP
14	20	F	D/W(6)	-	-
15	33	M	D/W/C (24)	10 (ex)	-
Non-asthmatics					
1	45	M	C (60)	-	-
2	17	M	C/haem (A)	4	-
3	56	M	C(3)	-	-
4	16	F	W/C/haem(12)	-	
5	23	F	C(12)	-	-
6	24	M	RTI(A)	-	-

D: dyspnoea; W: wheeze; C: cough; haem: haemoptysis; RTI: respiratory tract infection; IS: inhaled steroids; β_2: β_2 agonists; Ti: tilade; Th: theophyllines; OS: oral steroids; IP: ipratropium; A: acute case.

Twenty four hours later baseline spirometry was again recorded and four puffs (400 mg) of salbutomol was given *via* a metered dose inhaler. Spirometry was then repeated after 5 min and every 15 min for one hour. Bronchodilator response was recorded as the maximum increment in FEV_1 over baseline values.

Bronchoscopy

Five hours after measuring bronchodilator response, fibreoptic bronchoscopy was performed. Premedication was with 50 mg pethidine, 25 mg Phenergan and 0.6 mg atropine. The bronchoscope was introduced nasally. Airway anaesthesia was achieved with 0.5% lignocaine. Endobronchial biopsies were obtained under direct vision using cup forceps to sample areas on sub-carina of subsegmental airways in the right lower lobe. These were placed on small cork discs, covered in OCT medium, (a freezing support medium, BDH Poole Dorset), and snap frozen in isopentane cooled in a bath of liquid nitrogen. Frozen biopsies were stores below -70°C for 1 wk to 1 month until used.

Immunohistology

Six micron cryostat sections were cut from the biopsies, air-dried for 60 min and fixed in a 1:1 mixture of chloroform/acetone for 5 min. Sections of all samples were stained with toluidine blue to identify mast cells and haematoxylin and eosin to demonstrate histology. Specific cell types within the tissue were identified using indirect immunoperoxidase methods. Monoclonal antibodies used were "T mix" (a cocktail of monoclonal antibodies (MoAbs) against CD2, 5, 8 identifying all T-cells), "B mix" (a cocktail of MoAbs against CD19, 20 identifying all B-cells); UCHL1 (CD45RO antigen within common leucocyte antigen complex expressed on memory T-cells [21]); CD7 MoAb (at concentration detecting T-blasts [22]); RFD7 (77Kd antigen in mature macrophages of normal tissues [23]); RFD1 (epitope on HLA-DR molecule with restricted expression to interdigitating cells and some B-cells in normal tissues [23]). All test reactions were accompanied by negative controls omitting primary layer reagents, (to identify endogenous peroxidase), and positive controls where MoAbs were used on sections of human palatine tonsil. In some studies, sequential sections were used to gain a subjective assessment of proportions of cells. All immunoperoxidase preparations were counterstained with haematoxylin.

CD4 and CD8 MoAbs, (OKT4, ortho Pharmaceuticals and RFT8, Royal Free Hospital Medical School), were combined in "double" immunofluorescence methods [24] in which the second layer applied to the section contained a mixture of goat anti-mouse immunoglobulin G (IgG) conjugated to FITC and goat anti-mouse IgM conjugated to TRITC.

Immunoperoxidase reactions were examined using Kohler illumination and immunofluorescent preparations were examined using a Zeiss fluorescence microscope with epi-illumination and appropriate barrier filters for FITC and TRITC. Expression of HLA-DR molecules was detected using MoAb RFDR1 (anti HLA-DR framework epitope) conjugated to the enzyme glucose oxidase. This conjugate allows the use of tetrozolium based developing solutions and facilitates quantification by microdensitometry [25] (see below).

Quantification

The presence and distribution of T-cells, B-cells and macrophage subsets was assessed over the whole section. In not less than 5 high power fields of the lamina propria the number of positive cells was counted and related to the total number of mononuclear cells present identified by the haematoxylin counterstain. The percentage of positive cells was recorded. By comparing sequential sections stained for T mix (total T-cells), and then either CD45RO or CD7 the percentage of T-cells also expressing these antigens was assessed. Duplicate immunoperoxidase preparations were examined in all cases. Proportions of CD4+ and CD8+ cells were quantified by counting positive cells fluorescing with barrier filters for FITC or TRITC. Counts were made of all positive cells within each section studied. (As the size of sections was inevitably very small (1–3 mm^2) these counts were of up to 50 cells within each sample.)

HLA-DR expression was measured microdensitometrically using a Vickers M85 integrating microdensitometer set at 565 nm with a spot size of 1, slit width of 20, and aperture size A6. Threshhold was zeroed off the section and 10 readings of relative density of the formazan reaction product representing antigen expression, were then obtained across areas of lamina propria. Results were expressed as relative density per unit area. Reproducibility both between samples, between operators, and after repeat tests of the same sample have been fully established for this method [25].

Statistics

Where appropriate significance was determined using Student's t-test for non-paired data. Correlation coefficient was calculated where appropriate using the Pearson method. All immunopathological studies were performed on coded samples without prior knowledge of the clinical status of the sample donors or the results of the lung function tests.

Results

Spirometry

Spirometric tests on the asthmatic and non-asthmatic patients showed no significant difference in forced vital capacity (FVC) (table 2). The asthmatic group did show

Table 2. – Lung function data on subjects studied

	FVC % pred	FEV_1 % pred	ΔFEV_1	FEV_1/FVC	FEF_{25-75} % pred	$PC_{20}FEV_1$ mg histamine
Asthmatics						
Mean	95	82	22	71	74	1
SD	12	28	18	14	20	1
n=15						
Non-asthmatics						
Mean	97	108	9	79	121	>16 mg
SD	10	13		6	18	
n=6						
Probability	NS	<0.01	<0.05	NS	<0.01	<0.0001

SD: standard deviation; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; FEF_{25-75}: forced mid-expiratory flow; $PC_{20}FEV_1$: provocative concentration producing 20% fall in FEV_1.

a significant reduction in FEV_1, FEV_1/FVC and forced mid-expiratory flow FEF_{25-75}. The increase in FEV_1 after salbutamol was also significantly greater in the asthmatic group, although no difference between the two groups of patients was noted after salbutamol with respect to FEF_{25-75}. A highly significant difference in $PD_{20}FEV_1$ between the two groups was, however, recorded, with a mean histamine challenge dose of 1 mg causing a 20% reduction in FEV_1 in the asthmatics while in the non-asthmatic group no response was recorded to a 16 mg histamine challenge.

Histology

On 5 of 6 biopsies of the non-asthmatic group no evidence of inflammation was seen. In one case (no 6), inflammatory reactions were seen, characterized by small numbers of lymphocytes and macrophages infiltrating the lamina propria.

In all biopsies (15 of 15) of asthmatic patients a mononuclear cell infiltration was observed in the lamina propria. Both lymphocytes and macrophage-like cells could be seen, but no giant cells or epithelioid cells were present. The extent of the inflammatory reaction varied from specimen to specimen, appearing relatively mild in some cases with the inflammatory cells being restricted to a perivascular or diffuse distribution in the lamina propria. In some asthmatic specimens, however, extensive accumulations of mononuclear cells were seen with lymphocytes present within the epithelium and clustered along the basal layer of the epithelium.

The appearance of the epithelium in the asthmatic samples ranged from intact to severely damaged with apparent loss in some cases. In the control cases the epithelium was intact. Small numbers of mast cells (identified by metachromasia using short toluidine blue stain), were seen in the majority of samples, but no more than 2–3 of these cells were seen in any specimen. Eosinophils were also observed in small numbers in the asthmatic samples but were not detected in controls. It should be emphasized, however, that using these small frozen tissues there is a possibility of artefactual damage to these granulocytes. This study was aimed at investigating the antigens expressed by lymphocyte and macrophage subsets. The histological observations are reported as they appeared but must be viewed with the knowledge that some elements, particularly the mast cells and eosinophils, may be affected by the use of fresh frozen material.

Table 3. – Presence of infiltrating immunocompetent cells in bronchial biopsies

	Lymphocytes		Macrophage-like cells		
	T-cells	B-cells	RFD1+	RFD7+	UCHM1+
Asthmatics	15/15*	3/15	11/15	15/15	8/15
Non-asthmatics	1/6	0/6	1/6	1/6	1/6

*: Specimens where cells are present/total specimens studied.

Presence of lymphocyte and macrophage subsets

Using indirect immunoperoxidase methods, T-lymphocytes were identified in the inflammatory infiltrates of all asthmatic samples examined (table 3) while only two of the non-asthmatic samples contained T-cells. In contrast, B-lymphocytes were only identified in 3 of 15 asthmatic samples and none of the control group. As regards phenotypically distinct macrophage-like cells, all asthmatic tissue contained RFD7+ cells, 13 of 15 samples contained RFD1+ cells, but monocytes (CD14+) were only identified in 6 of 15 samples. Of the control tissues, only the two cases with mild inflammatory reactions present contained macrophage-like cells identified with these probes.

Table 4. – Immunopathology of asthmatic biopsies

Case	CD4:CD8 ratio	% T-cells UCHL1+	% T-cells CD7+	D1	D7	M1	DR**
1	0.76	40	25	+*	++	+	1.94
2	0.83	60	NT	±	+	-	2.3
3	0.91	75	40	+	++	+	2.2
4	1	60	<10	+	++	+	1.49
5	1.5	60	40	++	++	-	2.39
6	1.5	75	30	+	++	+	2.62
7	0.91	80	20	+	++	+	1.55
8	0.4	NT	<10	±	+	-	3.06
9	5.25	30	<10	-	+	±	2.08
10	7	NT	<10	±	+	±	2.88
11	9	NT	-ve	-	++	-	1.98
12	0.48	80	25	-	++	-	1.22
13	10	30	25	+	++	-	1.59
14	0.37	60	25	+	++	+	1.82
15	1	NT	25	-	+	-	1.49

*: subjective assessments, cells positive (within section): -: none; ±: <5; +: 5–10; ++: >10; **: relative absorption/unit area (see methods). NT: not tested.

Immunopathological profile

The fifteen asthmatic samples were investigated with further MoAb probes to reveal the relative disposition of the lymphocyte and macrophage subpopulations present. Indirect double immunofluorescence methods were used to quantify the proportions of CD4+ and CD8+ T-cells. The ratios are recorded in table 4. In 10 of 15 samples either equal proportions of these subsets or a predominance of CD8+ cells was recorded. In five samples, however, CD4+ outnumbered CD8+ and in four of these cases this predominance was significant, being up to 10:1 CD4:CD8.

Immunoperoxidase methods were used on sequential sections (see methods), to assess the proportions of T-lymphocytes expressing CD45RO and CD7 antigen. A wide variability in the proportion of T-cells expressing CD45RO, was recorded, and only limited numbers of T-cells expressed CD7 (table 4). In two patients no CD7+ cells could be detected, and in four others less than 10% of T-cells appeared CD7+. Of the other samples, the number of CD7+ lymphocytes identified appeared to reflect 25–40% of total T-cells, (table 4).

The distribution of subsets of macrophage-like cells was assessed from immunoperoxidase stained samples using MoAbs RFD7, RFD1 and UCHM1 (CD14). RFD7+ cells were present in all specimens and constituted the major population of macrophages present (table 4). Eleven specimens contained RFD1+ cells, although in three of these less than 5 positive cells could be found throughout the entire section. Very small numbers of CD14+ cells were detected in eight of the fifteen specimens studied.

The expression of HLA-DR within the inflammed lamina propria was quantified microdensitometrically following the use of glucose oxidase conjugated MoAb RFDR1. Readings of relative absorption per unit area showed a wide range between asthmatic specimens from 1.22–3.06 units, (table 4). Of the six control samples the recorded relative absorption for HLA-DR expression ranged from <0.1–1.5, 5 of 6 of these specimens giving readings below the range of all the asthmatics (fig. 1).

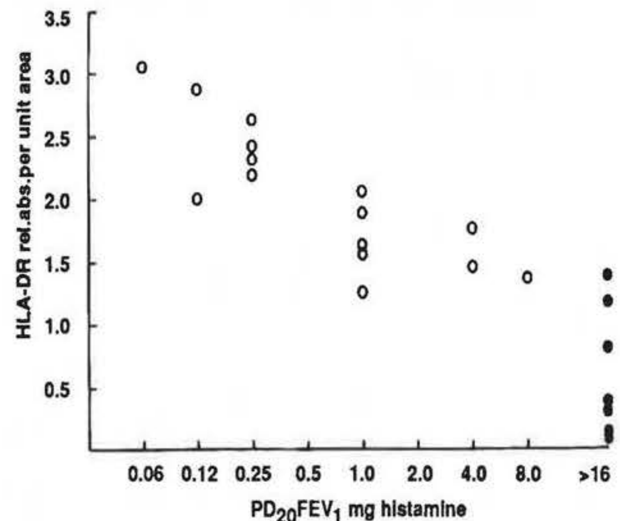

Fig. 1. – HLA-DR expression by cells of the bronchial infiltrate in asymptomatic asthmatics quantified using microdensitometry is plotted against bronchial hyperresponsiveness quantified by $PC_{20}FEV_1$ in 15 asthmatics (open circles) and 6 controls (closed circles). Correlation coefficient 0.84 ($p<0.001$). $PD_{20}FEV_1$: provocative dose producing a 20% fall in forced expiratory volume in one second.

Relationship between bronchial hyperreactivity and immunopathology

Within the limits of the immunopathological investigation undertaken, no correlation was found between the degree of bronchial hyperresponsiveness in the asthmatic patients and the CD4+:CD8+ ratio, the proportions of T-cells expressing CD45RO or CD7, or

the distribution of the macrophage subsets. When bronchial hyperresponsiveness was plotted against the level of HLA-DR expression, however, a close relationship was seen, (fig. 1), which gave a correlation coefficient of 0.84, ($p<0.001$). No significant correlation could be found with any other lung function test parameter.

Discussion

This study confirms the work of others [11, 12, 15, 16] in identifying the presence of an inflammatory reaction in the bronchial tissue of asymptomatic asthmatic patients. It goes further in demonstrating that the immunopathological features of this reaction are characteristic of a chronic cell-mediated immune response. A direct correlation between raised levels of HLA-DR antigen expressed by the inflammatory cells and the degree of bronchial hyperresponsiveness in the patients was observed. This offers, for the first time, a possible link between this inflammatory reaction and a predisposition to bronchospasm.

The presence of lymphocytes and macrophages and the lack of polymorphonuclear cells in the bronchial wall reported here and shown by others [15–17] strongly suggest that this inflammatory response is not simply a residue of immediate type hypersensitivity, but more an underlying chronic inflammatory reaction. The absence of mast cells or eosinophils in any numbers, also noted by other workers [15], would support this suggestion, although it is accepted that the frozen sections used here may result in the loss of integrity of these cells. The fact that this inflammatory response is associated with damage to the epithelium is elegantly documented [15–17] and could explain the overt hyperresponsiveness of these individuals.

The major presence of T-lymphocytes but not B-cells, the consistent presence of macrophages including a subset with the phenotype of antigen presenting cells, (RFD1+), and the raised expression of HLA-DR are all features consistent with a T-cell mediated immune response that have been observed in other inflammatory diseases such as arthritis [26], inflammatory bowel disease [27], psoriasis [28] and sarcoidosis [29]. The presence of significant numbers of T-cells expressing CD45RO antigen (thought to include the memory cell population) [21], and the relatively low frequency of monocytes might suggest that the turnover of the reaction is low and it thus represents a chronic rather than acute phenomenon. There is, however, a high degree of variability from sample to sample in terms of the CD4 and CD8 ratio, the expression of CD45RO and the expression of CD7 antigen. This variability remains unexplained and prevents this inflammatory response being neatly aligned immunopathologically with any of the inflammatory diseases mentioned above.

Of course, the aetiology of this "subclinical" inflammation in these asthmatics is unknown, and such variability could be taken to indicate that the cause of this reaction might itself be different from patient to patient. It is clear from the details presented that the patient groups studied are themselves heterogeneous in terms of duration of disease, smoking status, age and therapy. These factors may well contribute to this variability. It is important to note, however, that despite this variability a common feature in all cases is the raised expression of HLA-DR molecules on the inflammatory cells. Most significantly, this is the only recorded immunological feature of the inflammatory reaction that correlates with the level of bronchohyperresponsiveness recorded in these subjects. As well as offering cogent evidence of a link between the bronchial inflammation and the bronchial hyperresponsiveness, it may also give a clue to the mechanisms involved.

It is known that active cell-mediated responses cause the local release of cytokines including the release of IF from T-cells. This soluble mediator has been shown to increase the expression of HLA-DR on a variety of cells including macrophages and epithelial cells [30], and such a mechanism has been shown to occur in chronic inflammatory lung disease [31]. The level of HLA-DR expression in bronchial lamina propria of the asthmatics may thus be a reflection of the aggression of the inflammatory response. Recent studies have shown, however, that raised HLA-DR expression is associated with a down regulation of T-cell reactivity [32, 33]. In the asthmatic airway raised HLA-DR may thus represent an attempt to control the inflammatory reaction.

Neither of these possibilities detract from the studies of others that have probed the "immediate" type inflammatory reaction directly associated with bronchospasm. Indeed the mononuclear cell predominance observed in our studies would confirm the acute nature of the eosinophil/mast cell response identified with antigenic provocation [11, 34]. It has been shown that T-cells can release factors chemotactic for granulocytes [35] and thus the observations made here could be seen as identifying the "fertile ground" on which anaphylactic responses might be promoted. If an existing chronic inflammatory reaction does predispose asthmatic individuals to bronchial hyperresponsiveness this would also explain how non-organic stimuli such as stress or changes in temperature or humidity might also promote bronchospasm. Such suggestions lead to the formulation of an hypothesis that the emergence of a chronic cell mediated immune response within the bronchial wall creates airway inflammation which predisposes the individual to bronchial hyperresponsiveness.

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Relations entre l'immuno-pathologie bronchique et l'hyperréactivité dans l'asthme. L.W. Poulter, C. Power, C. Burke.

RÉSUMÉ: Les paramètres physiologiques et immunopathologiques ont été investigués chez 15 sujets atteints d'asthme et chez 6 non-asthmatiques accusant d'autres symptômes thoraciques. Tous ont subi des épreuves fonctionnelles pulmonaires, y compris une provocation à l'histamine à doses croissantes. Chez les 15 asthmatiques en période intercritique, l'hyperréactivité bronchique s'est traduite par une PD_{20}VEMS moyenne de 1 mg d'histamine. Aucun des non-asthmatiques n'a réagi à 16 mg d'histamine. Une bronchoscopie avec biopsies endobronchiques a été pratiquée 24 h. plus tard. La coloration histologique des coupes congelées de biopsies a montré un infiltrat mononucléaire chez tous les 15 asthmatiques, et une légère inflammation chez 1/6 des non-asthmatiques. Les anticorps monoclonaux ont été utilisés pour identifier les sous-groupes de lymphocytes, les marqueurs d'activation, les macrophages, ainsi que l'expression HLA-DR dans les infiltrats péri-bronchiques. Dans tous les échantillons, l'on a identifié des cellules T et des macrophages activés, ainsi qu'un acrroissement de l'expression

HLA-DR, mais le rapport CD_4/CD_8 s'avéra très variable. Les observations immuno-pathologiques ont été comparées aux données fonctionnelles. L'on n'a pas trouvé de relation évidente entre la distribution cellulaire et les paramètres fontionnels. Une corrélation hautement significative a été mise en évidence entre le niveau d'expression HLA-DR sur les cellules infiltratives (quantification micro-densitométrique) et l'hyperréactivité bronchique. Les résultats montrent pour la première fois qu'une réaction immune chronique médiée par les cellules T est présente dans le tissu bronchique d'asthmatiques asymptomatiques, et que l'expression HLA-DR provoquée est en corrélation avec l'état d'hyperréactivité bronchique. Ces données sont en faveur de l'hypothèse selon laquelle une réponse médiée par les cellules T contribue à une prédisposition à l'hyperréactivité bronchique chez les asthmatiques.
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