

Pulmonary eosinophils express HLA-DR in chronic eosinophilic pneumonia

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Background: Chronic eosinophilic pneumonia is a rare idiopathic disorder. What role the eosinophil plays in the pathogenesis of this disease is unknown. The recent finding that mature eosinophils can express the class II major histocompatibility complex molecule HLA-DR suggests an immunologic role, perhaps through antigen presentation. The purpose of this research was to determine whether lung-derived eosinophils exhibit *in vivo* expression of HLA-DR.

Methods: Eosinophils were obtained simultaneously from bronchoalveolar lavage and peripheral blood from a 59-year-old woman with asthma and chronic eosinophilic pneumonia. Eosinophil-enriched aliquots of peripheral blood were cocultured with human lung fibroblasts (with or without additional granulocyte-macrophage colony-stimulating factor). The percentage of cells expressing HLA-DR was quantitated by flow cytometric analysis.

Results: Eosinophils derived from bronchoalveolar lavage displayed *in vivo* expression of HLA-DR (86%) in contrast to those from peripheral blood (7%), suggesting compartmentalization of eosinophil activation within the lung. Peripheral blood eosinophils retained the capacity for HLA-DR expression when cocultured with lung fibroblasts (83%) with augmentation by granulocyte-macrophage colony-stimulating factor (93%).

Conclusion: These data demonstrate that lung eosinophil HLA-DR expression occurs *in vivo*; it may contribute to the pathogenesis of inflammatory lung injury. (*J ALLERGY CLIN IMMUNOL* 1993;92:442-9.)

Key words: Pulmonary eosinophilia, eosinophils, HLA-DR antigen, bronchoalveolar lavage fluid, asthma

The eosinophil is a bone-marrow-derived granulocyte, which resides largely within tissues that have an interface with the environment.¹ Tissue and blood eosinophilia are known to occur in parasitic infections in which this cell has a well-defined role in parasite killing.¹ Eosinophilia is also present in inflammatory and allergic conditions in which the eosinophil's role is not well-

Abbreviations used

BAL:	Bronchoalveolar lavage
CEP:	Chronic eosinophilic pneumonia
GM-CSF:	Granulocyte-macrophage colony-stimulating factor
MHC:	Major histocompatibility complex
PBEs:	Peripheral blood eosinophils

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defined but in which it may be harmful. Clinical evidence suggesting that the eosinophil may damage lung tissue comes from studies of idiopathic pulmonary fibrosis showing that the presence of bronchoalveolar lavage (BAL) eosinophilia correlates with more severe and less treatment-responsive disease.^{2, 3} Patients with asthma have been shown to have increased bronchial mucosal eosinophils, compared with both normal and nonasthmatic atopic control subjects.⁴ Additionally, disease severity in asthma has been shown to correlate with levels of eosinophils in blood and in BAL fluid.⁵

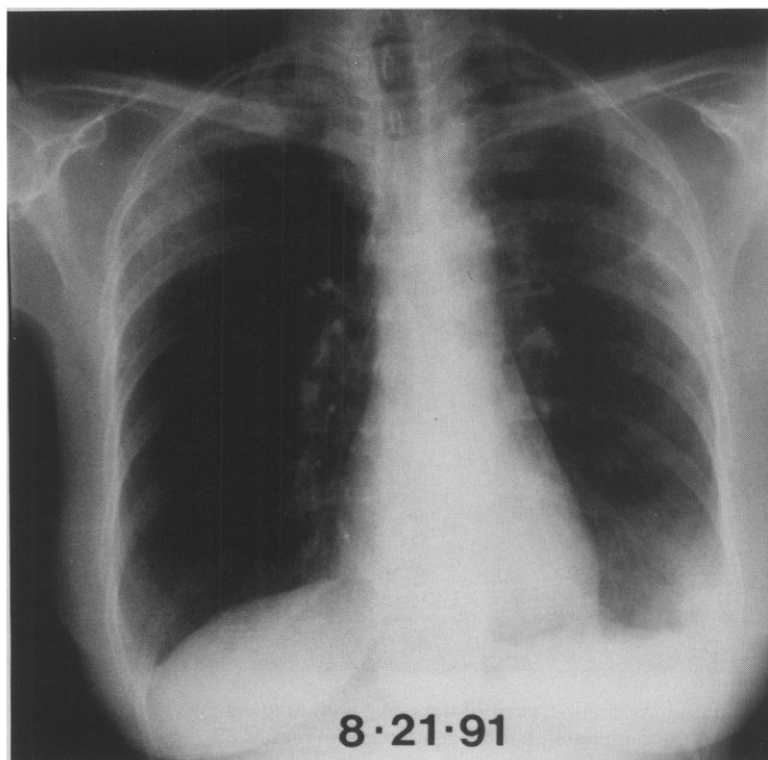


FIG. 1. Frontal chest radiograph shows peripheral, nonsegmental airspace consolidation with an upper lung predominance.

The concept of eosinophil-mediated lung injury is also supported by a growing body of *in vitro* evidence.⁶ Eosinophils are capable of direct cytotoxicity to lung parenchymal cells, and they possess collagenase activity, which promotes destruction of the lung matrix.^{7, 8} Several groups of investigators have also demonstrated that eosinophils can cause pulmonary vascular injury.^{9, 10} In these experimental studies toxic oxygen products were thought to have played a significant role in the eosinophil-mediated lung injury. Eosinophils may also promote lung fibrosis by direct stimulation of fibroblasts.¹¹

Eosinophils may also function as immune effector cells through antigen presentation. In 1989 Lucey et al.¹² reported that mature human eosinophils can, if appropriately stimulated *in vitro*, express the major histocompatibility complex (MHC) class II surface antigen HLA-DR. The function of HLA-DR is to bind processed segments of exogenous protein for presentation to CD4-bearing lymphocytes. Hansel et al.¹³ have demonstrated that eosinophils stimulated to express HLA-DR *in vitro* present antigen to autologous lymphocytes in an MHC-restricted fashion.

This same group has also shown that eosinophil HLA-DR expression occurs *in vivo* in patients with asthma.¹⁴ We describe the case of a middle-aged asthmatic woman with chronic eosinophilic pneumonia with *in vivo* eosinophil HLA-DR expression compartmentalized to BAL but not peripheral blood eosinophils.

CASE REPORT

A 59-year-old woman with chronic asthma was referred to our clinic for evaluation of cough, peripheral blood eosinophilia, and pulmonary infiltrates. She enjoyed excellent health until the age of 53 when she began to experience cough, wheezing, and dyspnea on exertion. She was diagnosed with asthma and was initially refractory to β_2 agonists, requiring long-term oral administration of prednisone during the period of 1986 to 1988. Since that time her symptoms have been well controlled with a regimen of inhaled albuterol, cromolyn, and triamcinolone acetonide. Three weeks before her referral, she had a nonproductive cough, subjective fevers, and malaise. She did not have dyspnea or wheezing. She denied taking tryptophan-containing substances. Her medical history was remarkable for chronic sinusitis and aspirin-induced wheezing.

On physical examination she appeared chronically ill

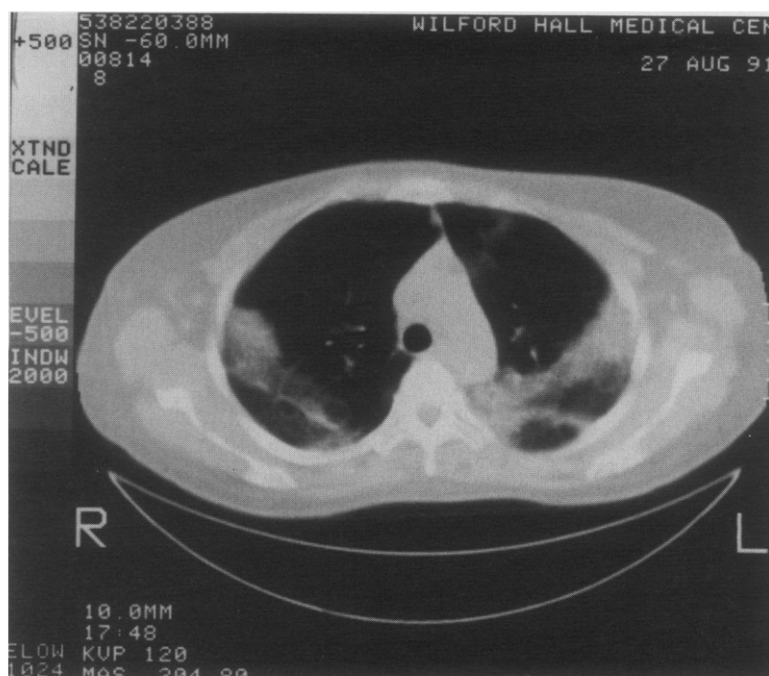


FIG. 2. A computed tomographic scan of the chest with lung windows at the level of the aortic arch demonstrates the peripheral, band-like airspace infiltrates.

and was afebrile. The only abnormality was the presence of increased bronchial breath sounds at the left lung base. She had no wheezing or rales and no digital clubbing.

Laboratory examination revealed a white blood cell count of 22,300 cells/mm³ with a differential cell count of 43% segmented neutrophils, 6% band forms, 5% lymphocytes, 2% monocytes, and 44% eosinophils (absolute eosinophil count of 9800/mm³). Pulmonary function testing revealed forced vital capacity of 2.10 (74% of predicted), forced expiratory volume in 1 second of 1.70 (82% of predicted), forced expiratory volume in 1 second/forced vital capacity of 0.81, total lung capacity of 3.99 (89% of predicted), and residual volume of 1.93 (118% of predicted). Arterial blood gas (room air) showed pH 7.44, Pco₂ of 38 torr, and Po₂ of 76 torr. Serologic test results for coccidioidomycosis were negative for both IgG and IgM.

Radiographic examinations (Figs. 1 and 2) showed peripheral infiltrates characteristic of chronic eosinophilic pneumonia.^{15, 16}

Fiberoptic bronchoscopy was performed to rule out infection. A right upper-lobe BAL was performed with 4 aliquots (50 ml each) of normal saline solution. The fluid was hazy with a red blood cell count of 200/mm³ and a white blood cell count of 5700/mm³; differential count was 7% lymphocytes, 2% macrophages, and 91% eosinophils (Fig. 3). Cultures and stains were negative for mycobacterial or fungal organisms. Transbronchial biopsy specimens (Fig. 4) demonstrated an intraalveolar and interstitial infiltrate of eosinophils and

macrophages; bronchiolitis obliterans is demonstrated by fibroblast tufts. These features are consistent with the diagnosis of chronic eosinophilic pneumonia.¹⁷⁻²⁰

Because of her mild pulmonary function impairment, the patient was discharged with no additional therapy pending culture results; she did continue her admission medications including inhaled triamcinolone acetonide. She was seen in follow-up at 4 weeks and reported significant lessening of her cough and malaise. Her eosinophil count fell to 1500/mm³, and her chest radiograph showed nearly complete resolution. By 12 weeks she was free of symptoms, her spirometry results were normal, her total eosinophil count was 140/mm³, her chest radiograph (Fig. 5) was normal, and her cultures had remained negative for fungal or mycobacterial organisms.

METHODS

Separation of peripheral blood eosinophils

After informed consent was obtained, peripheral blood was drawn and eosinophils were purified as described by Yazdanbakhsh et al.²¹ Briefly, whole blood was suspended in 6% dextran/2% sodium citrate, and the buffy coat was collected. A granulocyte suspension was collected by centrifugation over Ficoll-Paque (Pharmacia, Uppsala, Sweden). The eosinophil content of this suspension was enriched to greater than 90% by centrifugation over a discontinuous Percoll density gradient (Pharmacia). The use of blood by human volunteers was approved by the Institutional Review Board.

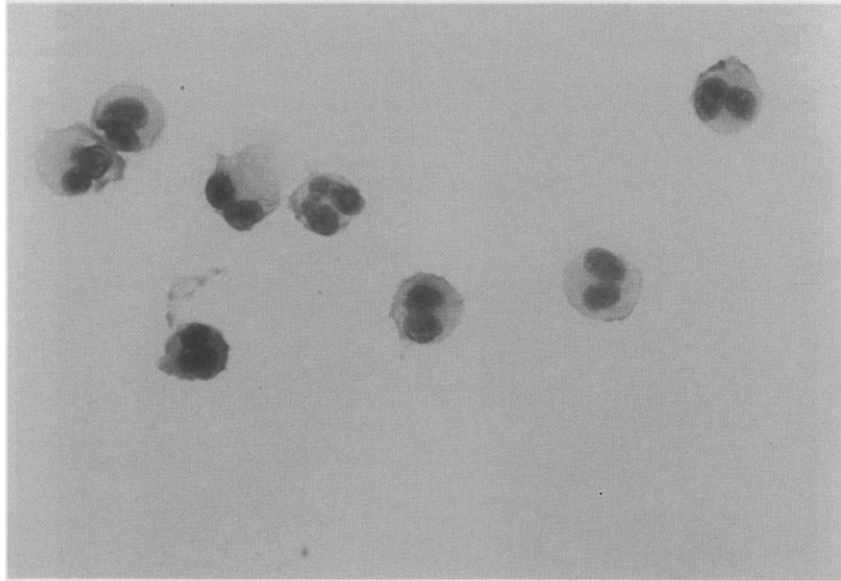


FIG. 3. BAL specimen demonstrating numerous eosinophils. Note the cytoplasmic vacuoles and relative paucity of cytoplasmic granules. (Wright-Giemsa stain; original magnification $\times 1000$.)

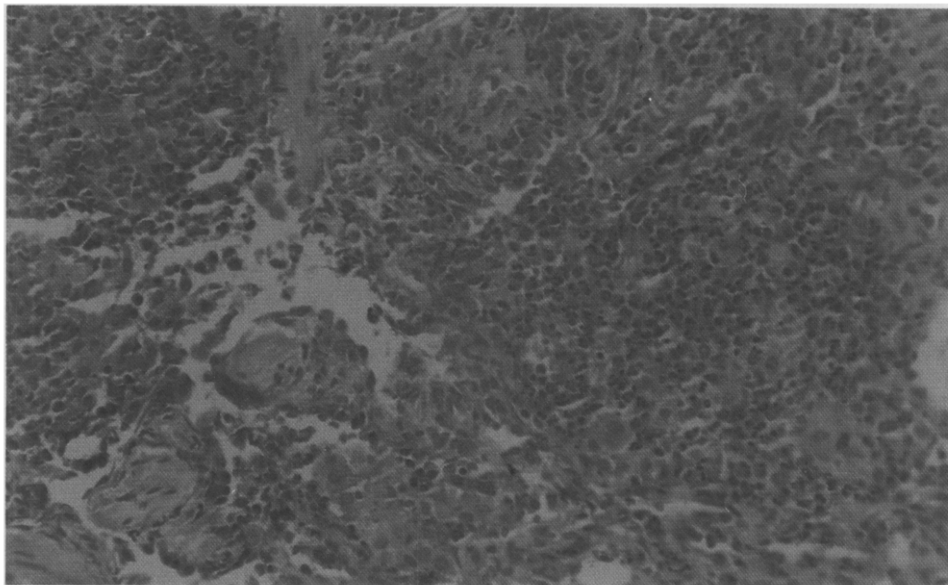


FIG. 4. Transbronchial biopsy specimen showing an intra-alveolar and interstitial infiltrate of eosinophils and macrophages; bronchiolitis obliterans is demonstrated by the fibroblast tufts. (Hematoxylin and eosin stain; $\times 200$.)

Staining for flow cytometric analysis

The eosinophil suspensions from BAL, peripheral blood, and eosinophil-fibroblast coculture were stained with monoclonal antibodies directed against HLA-DR, CD14, CD45, CD2, CD5 (HLA-DR FITC, Leu M-3 PE, HLe-1 FITC, Leu-1 FITC, Leu-16 PE; Becton Dickinson Immunocytometry Systems; San Jose, Calif.), CD4, CD3, and CD19 (T4-RD1, T3 FITC, B4 FITC

Cytostat; Coulter Immunology; Hialeah, Fla.). Eosinophil viability was assessed by staining with propidium iodide and exceeded 95% for all specimens. Aliquots (100 μ l) of eosinophil suspension were incubated at room temperature for 30 minutes with the manufacturer's recommended volume (20 μ l for Becton Dickinson and 10 μ l for Coulter) of monoclonal antibody and with appropriate isotype control. Suspensions were washed



FIG. 5. Frontal chest radiograph at 3 months of follow-up, demonstrating resolution of all infiltrates.

twice with phosphate-buffered saline (FTA hemagglutination buffer; 0.923%, pH 7.2 to 7.7; Becton Dickinson and Co., Cockeysville, Md.). After the second wash, the cells were resuspended in 250 μ l of phosphate-buffered saline. Surface marker analysis was performed on a Coulter EPICS Profile II (Counter EPICS, Coulter Immunology, Hialeah, Fla.). Fluorescence limits were set such that only 2% of control-stained cells fell within the positive domain. Results of surface antigen expression are presented as the percentage of cells exhibiting greater fluorescence than isotype control. Quality control and instrumentation for flow cytometric analysis were as previously described.²²

Eosinophil-fibroblast coculture

Eosinophils were suspended in culture medium (RPMI 1640 with 10% heat-inactivated fetal bovine serum). Aliquots containing 2×10^6 eosinophils were seeded onto confluent monolayers of human lung fibroblasts in 6-well plates. Parallel wells contained 50 pmol/L recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) (Genzyme, Cambridge, Mass.). Fibroblast cell lines were obtained by tissue explant from grossly normal areas of lung from patients undergoing pneumonectomy for lung cancer. On days 5 and 7 eosinophils were removed from the

fibroblast monolayer, and surface marker expression was assessed by flow cytometric analysis as described above.

RESULTS

The presence of contaminating cells in the BAL fluid and PBE suspensions was low as measured by staining with a panel of antibodies directed against lymphocytes (CD3, CD19), monocytes (CD14, CD33), and neutrophils (CD16). The BAL fluid had 5.7% of cells staining with CD19, and the PBEs had 6.2% staining with CD16; staining with other monoclonal antibodies was less than 4%. The results of flow cytometric analysis are summarized in Table I. HLA-DR expression was present on 86% of BAL eosinophils. In contrast, only 7% of PBEs had *in vivo* HLA-DR expression. The PBEs retained the capacity for HLA-DR expression as demonstrated by the increase noted after coculture with lung fibroblasts. Addition of GM-CSF to the medium augmented this effect by 12%. Surface expression of CD4 was negative on both PBEs and BAL eosinophils. Expression of this marker was not

TABLE 1. Eosinophil surface marker expression

	BAL eosinophils	Peripheral blood eosinophils		
		Day 0	Coculture (maximum)	Coculture + GM-CSF (maximum)
HLA-DR (% of cells)	86	7	83	93
CD4 (% of cells)	1	2	2	62

induced by cocubation with lung fibroblasts alone (2%), but it was markedly increased with the addition of exogenous GM-CSF (62%).

DISCUSSION

We have described a patient with asthma who presented with constitutional symptoms, peripheral blood eosinophilia, and pulmonary infiltrates without an identifiable precipitant. This syndrome, which has been well-described in patients with asthma, is that of chronic eosinophilic pneumonia (CEP).²³ Lung histopathologic studies demonstrated an eosinophilic alveolitis with fibrosis and fibroblast plugs within the airways, findings that further establish this diagnosis.¹⁷⁻²⁰ No change was made in the patient's baseline asthma therapy, and she experienced a complete clinical, physiologic, and radiologic resolution within 12 weeks.

The etiology, pathogenesis, and natural history of this unusual condition are poorly understood. There is a long list of drugs and underlying conditions that have been associated with CEP, but no unifying pathogenic mechanism has been proposed.²⁴ Bartter et al.²⁵ note the similarities in the radiologic and pathologic findings and the response to treatment between CEP and bronchiolitis obliterans organizing pneumonia and propose that bronchiolitis obliterans organizing pneumonia may be a later stage in the course of CEP. According to this theory, eosinophils, which predominate early in the disease, are replaced by fibroblasts and eventually collagen. Asthma is a more common disorder that demonstrates eosinophilic inflammation, abnormal subepithelial fibroblast proliferation, and collagen deposition.²⁶ Our finding of BAL eosinophils with altered structure and with *in vivo* HLA-DR expression in a patient with asthma provides further support for an immune effector role of the eosinophil in the pathogenesis of asthma.

The BAL eosinophils (Fig. 1) demonstrate cytoplasmic vacuolization and possibly decreased numbers of secondary granules. These ultrastruc-

tural alterations have been described in eosinophils from a number of human disease states and are thought to result from release of granule contents.²⁷ Eosinophil granules contain cytotoxic compounds including major basic protein, eosinophil-derived neurotoxin, eosinophil cationic protein, and eosinophil peroxidase.²⁷ Given the relative paucity of other leukocytes in the patient's BAL fluid and transbronchial biopsy specimens, we postulate that the eosinophils were at least partly responsible for the lung damage seen.

The significance of *in vivo* expression of HLA-DR by the BAL eosinophils is less clear. The HLA-DR glycoprotein is a cell surface antigen of the class II MHC. MHC class II antigens are present on antigen-presenting cells where their established function is to bind processed peptide antigens for presentation to the T-cell receptor-CD4 complex on lymphocytes. Class II MHC can mediate presentation of a specific conventional antigen, to which 0.01% of helper T cells will bind, or of superantigens, to which 20% of T cells can bind via the V β region of the T-cell receptor.²⁸ Data suggesting that human eosinophils expressing class II MHC molecules can present superantigens to T cells have been recently reported.²⁹ To our knowledge *in vivo* eosinophil HLA-DR expression has only been described twice before in adults. Lucey et al.¹² described low-level *in vivo* HLA-DR expression on the PBEs of a normal, healthy, nonatopic female volunteer. Hansel et al.¹⁴ found low levels of surface HLA-DR on sputum eosinophils in subjects with asthma.

Inducible surface HLA-DR expression by mature human eosinophils was first reported in 1989.¹² PBEs cultured with murine 3T3 fibroblasts in the presence of GM-CSF were induced to express significant levels of HLA-DR. It has been reported that human eosinophils produce messenger RNA for GM-CSF, suggesting that this stimulation can occur in an autocrine fashion.³⁰ Hansel et al.¹⁴ have extended this model with their demonstration of antigen presentation by

eosinophils. In their experiment eosinophils, which had been stimulated to express HLA-DR by *in vitro* cytokine exposure, stimulated autologous lymphocyte proliferation. Interestingly, this was blocked by anti-HLA-DR, implying that the effect was MHC-dependent. This finding provides a mechanism by which eosinophils could promote an immune response within tissues in which they had been stimulated to express HLA-DR. These results also suggest that HLA-DR is an activation marker for eosinophils, because expression of this antigen corresponded with the functional activity of antigen presentation.

In our patient, eosinophil HLA-DR expression was localized to the lung and not seen on the PBEs. This may mean that the factor responsible for their activation was localized in the lung (e.g., an inhaled antigen). Recruitment may have been based on expression of adhesion molecules, for which we did not assay. The presence of functional adhesion molecules on activated eosinophils was suggested by Hansel et al.¹³ in experiments that showed increased adhesion to lymphocytes in relation to induction of ICAM-1 expression. Another explanation would be that there is something intrinsic to the interaction between the lung fibroblast and an appropriately prestimulated eosinophil. This is implied by the inducible expression of HLA-DR by coculture with lung fibroblasts.

Other investigators have described localized activation of eosinophils in disease. Nishikawa et al.³¹ report on four patients with eosinophilic pneumonia in whom surface CD69 was measured on BAL eosinophils and PBEs. *In vivo* this antigen was seen on BAL eosinophils, but not on PBEs. When the PBEs were activated *in vitro* by exposure to phorbol myristate acetate, interleukin-3, GM-CSF, or interleukin-5, *de novo* CD 69 expression was noted, suggesting that it too is an eosinophil activation marker. Although the function of CD 69 on eosinophils is not known, it appears to be regulated by the same factors that control expression of HLA-DR.^{13, 31} Our results, taken together with these findings, support the theory that in eosinophilic pneumonia the eosinophil is functionally activated and may actively contribute to the disease.

Eosinophilic alveolitis is associated with a worse prognosis in idiopathic pulmonary fibrosis.^{2, 3} It is not known which factors are mediators of eosinophil-associated fibrosis. Soluble eosinophil-derived mediators, which may play a role in promoting fibrosis, include platelet activating factor, transforming growth factor- α , and interleu-

kin-1.³² In addition, the identification of surface CD4 on a subset of human lung fibroblasts suggests that direct intercellular signaling between HLA-DR-bearing eosinophils and fibroblasts may occur.³³ Studies to address this potential interaction are in progress.

In 1989 eosinophils were first reported to be capable of expressing low levels of CD4, particularly after coculture with 3T3 murine fibroblasts and recombinant human GM-CSF, and to be able to bind the human immunodeficiency virus envelope protein gp 120 via CD4.³⁴ Rand et al.³⁵ also showed that ligands binding to CD4 on eosinophils could cause migration of these cells, analogous to other CD4⁺ leukocytes. In our patient, demonstration of HLA-DR, but not CD4, on lung eosinophils suggests that *in vivo* expression of these two proteins is under differential control. The *in vitro* eosinophil culture models to date have not demonstrated this phenomenon in so far as expression of HLA-DR and CD4 both increase when eosinophils are cultured with fibroblasts and recombinant human GM-CSF.^{12, 34}

To our knowledge there has been one prior report that eosinophils from the site of an active disease process exhibited *in vivo* expression of HLA-DR. Our finding provides independent confirmation of the report by Hansel et al.¹⁴ that tissue eosinophil HLA-DR expression occurs at the site of human disease. Confirmation of this phenomenon also complements recent work by Hansel et al.¹³ which demonstrates that HLA-DR⁺ eosinophils can present antigen to CD4⁺ lymphocytes. The eosinophil-lymphocyte interaction merits more investigation because of its potential importance in the pathogenesis of several important pulmonary diseases. Most notable of these is asthma. Recent studies of the inflammatory airway lesion in asthma emphasize the presence of both eosinophils and activated lymphocytes.⁴⁻⁵ A better understanding of the interaction between these cells may contribute to improved therapy of diseases such as asthma and idiopathic pulmonary fibrosis.

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