

Detection of IL-5 and IL-1 receptor antagonist in bronchoalveolar lavage fluid in acute eosinophilic pneumonia

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Background: *Acute eosinophilic pneumonia is an idiopathic cause of respiratory failure, characterized by very high numbers of alveolar eosinophils without significant blood eosinophilia.*

Objective: *The purpose of this study was to determine which cytokines are associated with acute eosinophilic pneumonia.*

Methods: *Soluble IL-1 type II receptor and the cytokines IL-1 β , IL-1ra, IL-3, IL-5, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor- α were measured in serum and in bronchoalveolar lavage fluid from two patients with acute eosinophilic pneumonia during both acute and convalescent phases.*

Results: *Compared with patients with adult respiratory distress syndrome, the patients with acute eosinophilic pneumonia had high bronchoalveolar lavage fluid levels of IL-5, IL-1ra, and soluble type II IL-1 receptor but not IL-1 β , tumor necrosis factor- α , IL-3, or granulocyte-macrophage colony-stimulating factor. Bronchoalveolar lavage fluid levels of IL-5 and IL-1ra fell after resolution of symptoms. In the serum of patients with acute eosinophilic pneumonia, IL-5 was not detectable, and IL-1ra was initially high but fell after corticosteroid treatment.*

Conclusion: *Acute eosinophilic pneumonia is characterized by locally high levels of IL-5, IL-1ra, and soluble type II IL-1 receptor in the alveolar space. (J Allergy Clin Immunol 1996;97:1366-74.)*

Key words: *IL-5, IL-1ra, IL-3, GM-CSF, IL-1 β , TNF- α , bronchoalveolar lavage, acute eosinophilic pneumonia, eosinophil*

Idiopathic acute eosinophilic pneumonia is a recently identified syndrome characterized by respiratory failure and a high percentage of bronchoalveolar lavage (BAL) eosinophils. The diagnostic criteria for this syndrome include recent onset (less than 5 days) of pulmonary symptoms,

Abbreviations used

ARDS:	Adult respiratory distress syndrome
BAL:	Bronchoalveolar lavage
GM-CSF:	Granulocyte-macrophage colony-stimulating factor
IL-1ra:	Interleukin-1 receptor antagonist
TNF:	Tumor necrosis factor

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respiratory failure ($PO_2 < 60$ while breathing room air), diffuse pulmonary infiltrates on chest x-ray film, a high percentage of BAL eosinophils (generally greater than 25%), the absence of any identifiable infectious cause of the symptoms, and a prompt, complete response to corticosteroids.¹ Acute eosinophilic pneumonia differs from chronic eosinophilic pneumonia in that patients have only

a small or no increase in blood eosinophil numbers, despite the extremely high percentages of lung eosinophils, and patients do not relapse after receiving a brief course of corticosteroids. The cause or causes of acute eosinophilic pneumonia remain uncertain, and the mechanism of the massive eosinophil influx into the lungs is unknown.

There have been several recent developments in the understanding of eosinophil regulation. The eosinophil originates from undifferentiated myelocytic cells in the bone marrow. Production appears to be largely under the control of lymphocytes² and can be enhanced by a number of cytokines including granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, and IL-5.^{3,4} The most specific of these is the T-helper lymphocyte product, IL-5. Serum levels of this cytokine have been found to precede increases in blood eosinophil numbers in patients with eosinophilia in diseases other than acute eosinophilic pneumonia.^{5,6} Interleukin-1 β is a monocyte and alveolar macrophage product, which has recently been shown to be an important coregulator of eosinophil accumulation and transmigration in vitro.⁷

In order to better understand the mechanism of pulmonary eosinophil recruitment in acute eosinophilic pneumonia, we developed ELISAs to measure IL-5, GM-CSF, and IL-3. Levels of these cytokines were then measured in the serum and BAL fluid of two patients with acute eosinophilic pneumonia and compared with levels in the BAL fluid of patients with the adult respiratory distress syndrome (ARDS). To determine whether IL-1 β could be involved in the pathogenesis of acute eosinophilic pneumonia, BAL fluid was also analyzed for the presence of IL-1 β , IL-1 receptor antagonist (IL-1ra), and soluble IL-1 type II receptor.

METHODS

Subjects

A diagnosis of acute eosinophilic pneumonia was established in two patients on the basis of previously described criteria.¹ In each patient, BAL fluid remaining after microbiologic stains and cultures were performed was frozen at -70°C pending development of cytokine assays. Each patient returned for a second bronchoscopy with BAL after completing a course of corticosteroids.

Patient 1 was a previously healthy 17-year-old boy with no history of atopy or allergies, who was first seen in the emergency department with a 2-day history of dyspnea, fever, pleuritic chest pain, and myalgias. He was a nonsmoker who was taking no prescribed or over-the-counter medications, and he denied drug use. The chest roentgenogram revealed diffuse interstitial infiltrates.

Hypoxemic respiratory failure necessitated endotracheal intubation and mechanical ventilation. The peripheral blood eosinophil count was 0, and BAL fluid demonstrated 32% eosinophils. Results of stains and cultures of the BAL fluid for bacteria, *Legionella* spp., fungi, mycobacteria, and viruses were negative; results of stool examination for ova and parasites were also negative. Administration of methylprednisolone (125 mg intravenously every 6 hours) resulted in a rapid clearance of interstitial infiltrates, resolution of hypoxemia, and defervescence. The patient was able to be extubated 3 days after initiation of treatment with steroids and was discharged with a tapering dose of prednisone 9 days after initiation of treatment with steroids. He returned for follow-up evaluation and BAL 6 weeks after discharge, at which time he was free of symptoms, was no longer receiving steroids, and had a normal chest roentgenogram. He has since remained free of symptoms without further steroid treatment.

Patient 2 was a 47-year-old woman with a history of depression who was first seen in the emergency department with a 2-day history of dyspnea, fever, pleuritic chest pain, and myalgias. She was a smoker who was being treated for depression with desipramine on a long-term basis. She had no history of atopy or allergies and denied use of over-the-counter or illegal drugs. The chest roentgenogram demonstrated diffuse alveolar infiltrates, Kerley's B lines, and small pleural effusions. The Po_2 was 35 mm Hg while breathing room air. The peripheral blood eosinophil count was 1056 and BAL fluid demonstrated 45% eosinophils. Results of stains and cultures of the BAL fluid for bacteria, *Legionella* spp., fungi, mycobacteria, and viruses were negative; results of stool examination for ova and parasites were also negative. Because of a history of potting house plants with an organic potting mixture, fungal infection was considered, and an open lung biopsy was performed, which also failed to demonstrate any bacterial, fungal, viral, or mycobacterial pathogens. Administration of intravenous methylprednisolone (125 mg every 6 hours) resulted in defervescence, rapid resolution of roentgenographic changes, and resolution of hypoxemia, allowing extubation with removal from mechanical ventilation. She was discharged from the hospital on day 8 with a tapering course of prednisone. When she returned for repeat BAL, she was no longer receiving steroids, was free of symptoms, and had a normal chest roentgenogram.

ARDS was diagnosed in seven patients on the basis of criteria proposed by Murray et al.⁸ All patients underwent BAL for clinical indications, and all BAL fluid samples contained an increased percentage of neutrophils and less than 1% BAL eosinophils. BAL fluid supernatants remaining after clinical testing were stored at -70°C .

Six healthy male and female volunteers were recruited for measurement of the type II IL-1 receptor. None of these subjects had a history of lung disease, and none

were taking any medications at the time of bronchoscopy. All normal subjects had greater than 90% alveolar macrophages and less than 1% eosinophils in the BAL fluid.

In all cases BAL was performed as previously described by using five 20 ml aliquots of saline solution.¹ Human subject involvement in this study was approved by the institutional review board; normal volunteers and patients with acute eosinophilic pneumonia in remission gave written consent.

Cytokine measurement

All cytokines were measured by ELISA. The IL-1 β ELISA has been previously described⁹ and uses a mouse anti-human IL-1 β monoclonal antibody (B1, provided by Dr. Ann Berger, Upjohn, Kalamazoo, Mich.), rabbit polyclonal anti-human IL-1 β antisera (prepared by repeated subcutaneous injection of carrier-free recombinant IL-1 β into 3-month-old rabbits), and a horseradish peroxidase-conjugated goat anti-rabbit antibody (BioRad Laboratories, Hercules, Calif.). This assay is specific for IL-1 β and is sensitive to 15 pg/ml.

The tumor necrosis factor- α (TNF- α) ELISA has been previously described¹⁰ and uses a mouse monoclonal anti-human TNF- α antibody (Boehringer Mannheim, Indianapolis, Ind.) and polyclonal anti-human TNF- α antisera (prepared by repeated subcutaneous injection of recombinant TNF- α [Knoll Pharmaceuticals, Whippany, N.J.] into 3-month-old rabbits). This ELISA is sensitive to 47 pg/ml and is specific for TNF- α .

The IL-1ra ELISA has also been previously described.¹¹ This ELISA uses polyclonal rabbit anti-human IL-1ra antisera for the capture antibody (prepared by repeated subcutaneous injection of rabbits with recombinant human IL-1ra; rIL-1ra was provided by Dr. Daniel Tracey, Upjohn Laboratories, Kalamazoo, Mich.) and polyclonal goat anti-human IL-1ra antisera for the sandwich antibody (R&D Systems, Minneapolis, Minn.). This ELISA is specific for IL-1ra and does not cross-react with other members of the IL-1 family of proteins. It is sensitive to 30 pg/ml.

The GM-CSF ELISA was prepared by using a monoclonal mouse anti-human GM-CSF antibody (5 μ g/ml; Genzyme, Cambridge, Mass.) as the capture antibody, polyclonal goat anti-human GM-CSF antisera (10 μ g/ml, R&D Systems) as the sandwich antibody, and horseradish peroxidase-conjugated rabbit anti-goat antisera (1:40,000, BioRad) as the developing antibody. It is sensitive to 47 pg/ml and is specific for GM-CSF without cross-reactivity to recombinant IL-3, IL-5, TNF- α , or IL-1 β .

For the IL-5 ELISA, polyclonal goat anti-human IL-5 antisera (10 μ g/ml, R&D systems) was used as the capture antibody, polyclonal rabbit anti-human IL-5 antisera (10 μ g/ml, Genzyme) was used as the sandwich antibody, and horseradish peroxidase-conjugated goat anti-rabbit antisera (1:5000; Sigma Chemical Co., St.

Louis, Mo.) was used as the developing antibody. This ELISA is sensitive to 180 pg/ml and is specific for IL-5 without cross-reactivity to recombinant IL-3, GM-CSF, TNF- α , or IL-1 β .

The IL-3 ELISA was prepared by using polyclonal rabbit anti-human IL-3 antisera (5 μ g/ml, Genzyme) as the capture antibody, goat anti-human IL-3 antisera (5 μ g/ml, R&D Systems) as the sandwich antibody, and horseradish peroxidase-conjugated rabbit anti-goat antisera (1:5000, BioRad) as the developing antibody. This ELISA is sensitive to 180 pg/ml and is specific for IL-3 without cross-reactivity to recombinant IL-5, GM-CSF, TNF- α , or IL-1 β .

The capture antibody for the soluble type II IL-1 receptor ELISA was a rat anti-human monoclonal antibody (M22; Immunex, Seattle, Wash.) plated at 250 ng/ml. The sandwich antisera was prepared by repeated subcutaneous injection of rabbits with recombinant human IL-1 type II receptor (a gift of Steven Dower and Michael Widmer, Immunex) and was used at a dilution of 1:6000 in the ELISA. The developing antibody was horseradish peroxidase-conjugated goat anti-rabbit antisera (BioRad). This ELISA is sensitive to 50 pg/ml and specific for the type II IL-1 receptor without cross-reactivity to IL-1 α , IL-1 β , IL-1ra, proIL-1 β , or TNF- α .

Statistical analysis

Results are expressed as means $\pm$ SEM.

RESULTS

BAL eosinophil percentages and peripheral blood eosinophil counts

All patients with ARDS had fewer than 1% BAL eosinophils. The percentage of BAL eosinophils was elevated in both patients with acute eosinophilic pneumonia at the time of initial clinical evaluation (32% and 45%, respectively). In contrast, at the time of admission to the hospital, blood eosinophils were undetectable in the first patient and increased (1056/mm³) in the second patient (Fig. 1). In both patients, the blood eosinophil count was elevated above 300/mm³ at some point before diagnosis, and in both patients the eosinophil count fell rapidly after initiation of treatment with corticosteroids. Patient 2 demonstrated an increase in the blood eosinophil count on hospital day 7, 1 day after her treatment was changed from intravenous methylprednisolone every 6 hours to oral prednisone every 24 hours. The BAL fluid also contained increased percentages of neutrophils in both patients (18% and 30%, respectively) and an increased percentage of lymphocytes in patient 1 (28%). When reevaluated after completion of a course of corticosteroids, both patients with acute eosinophilic pneumonia had

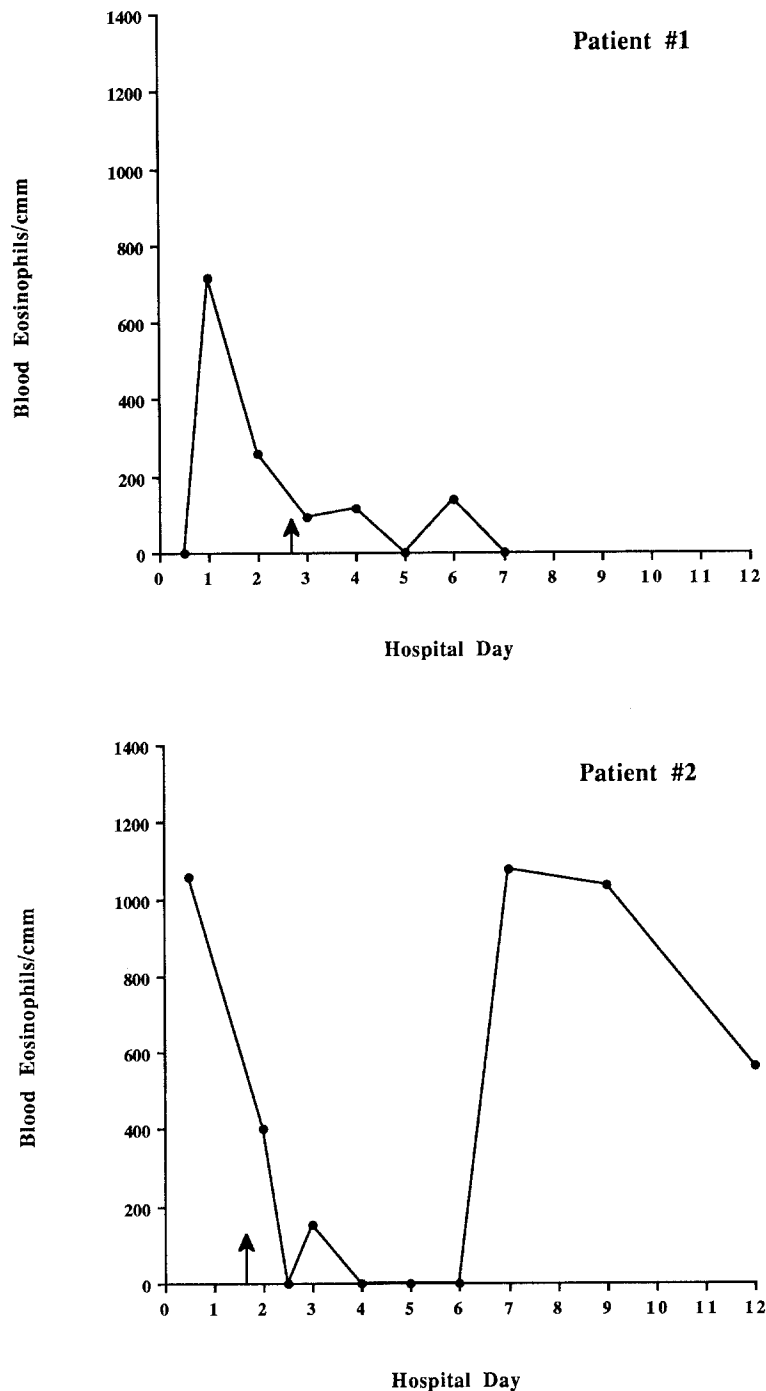


FIG. 1. Time course of blood eosinophil counts in two patients with acute eosinophilic pneumonia. Arrows indicate the initiation of treatment with intravenous methylprednisolone.

normal BAL cell differentials with less than 1% BAL eosinophils.

BAL cytokine levels

High levels of IL-5 were found in the unconcentrated BAL fluid from the two patients with acute eosinophilic pneumonia at the time of admission

to the hospital (1950 pg/ml and 846 pg/ml, respectively, Table I). In contrast, no IL-5 was detectable in the BAL fluid from these patients after resolution of all symptoms and completion of a course of corticosteroids. IL-5 was detectable in two of seven patients with ARDS (180 and 264 pg/ml, respectively).

TABLE I. Cytokine levels in serum and BAL fluid from two patients with acute eosinophilic pneumonia and seven patients with ARDS

	Patient 1			Patient 2			Patients with ARDS
	Acute serum	Acute BAL	Remission BAL	Acute serum	Acute BAL	Remission BAL	BAL
IL-1ra	1,142	25,660	68	771	31,754	95	465 ± 202
IL-5	ND	1950	ND	ND	846	ND	47 ± 10
IL-1β	ND	ND	ND	ND	ND	ND	ND
IL-1R II	NT	NT	182	NT	9,200	5,500	NT
IL-3	550	1,529	77	ND	649	1,189	850 ± 458
GM-CSF	ND	ND	ND	ND	847	191	56 ± 56
TNF-α	44	ND	ND	ND	ND	ND	326 ± 283

All values are expressed as picograms per milliliter of unconcentrated BAL fluid.

ND, Not detectable at the level of the sensitivity of the assay; NT, not tested.

IL-3 was also detectable in the unconcentrated BAL fluid of both patients with acute eosinophilic pneumonia at the time of admission. After completion of a course of corticosteroids, levels of IL-3 subsequently fell in one patient and rose in the other. IL-3 was detectable in four of seven patients with ARDS (mean, 850 ± 458 pg/ml).

GM-CSF was detectable in the BAL fluid of patient 1 but not patient 2 at the time of admission but was undetectable in the BAL fluid of either patient when in remission. GM-CSF was detectable in one of seven patients with ARDS (390 pg/ml).

TNF-α and IL-1β were not detected in BAL fluid of either patient with acute eosinophilic pneumonia.

A surprising finding was marked elevation of the antiinflammatory cytokine, IL-1ra, in the BAL fluid of the patients with acute eosinophilic pneumonia (25,560 pg/ml and 31,754 pg/ml). After resolution of symptoms and completion of a course of corticosteroids, the BAL fluid IL-1ra levels fell to 95 and 68 pg/ml, respectively. IL-1ra was detectable in six of seven patients with ARDS (mean, 465 ± 202 pg/ml).

Soluble IL-1 type II receptor levels were high in the BAL fluid of patient 1 at the time of admission and after resolution of symptoms. There was insufficient BAL fluid available from patient 2 to perform the soluble IL-1 type II receptor ELISA in the acute phase of the disease, but BAL fluid from this patient did show detectable levels after resolution of symptoms. Soluble type II IL-1 receptor was not detectable in BAL of six normal volunteers and was not tested in the BAL fluid of patients with ARDS.

Serum cytokine levels

At the time of admission to the hospital, GM-CSF and IL-5 were undetectable in the serum of either patient with acute eosinophilic pneumonia. IL-3 was undetectable in the serum of patient 2. In the serum of patient 1, IL-3 was detectable (550 pg/ml), although in concentrations lower than in the BAL fluid obtained simultaneously from this patient (1529 pg/ml).

In contrast, the IL-1ra level was high in the serum of both patients initially and fell after the initiation of treatment with methylprednisolone (Fig. 2). Patient 2 had a slight rise in the serum IL-1ra level on hospital day 8, which occurred after her treatment was changed from intravenous methylprednisolone every 6 hours to oral prednisone every 24 hours on hospital day 6. This rise in the serum IL-1ra level correlated with a simultaneous rise in the blood eosinophil count in this patient. Soluble type II receptor levels were not tested in serum of patients with acute eosinophilic pneumonia.

DISCUSSION

Acute eosinophilic pneumonia has gained increasing recognition as an uncommon but important cause of reversible respiratory failure. It clinically resembles ARDS, except that the predominant cell in BAL fluid is the neutrophil in ARDS and the predominant cell is the eosinophil in acute eosinophilic pneumonia.¹² Additionally, acute eosinophilic pneumonia responds quickly to corticosteroids, unlike ARDS. In acute eosinophilic pneumonia, the common causes of pulmonary eosinophilia (such as parasites, fungi, malig-

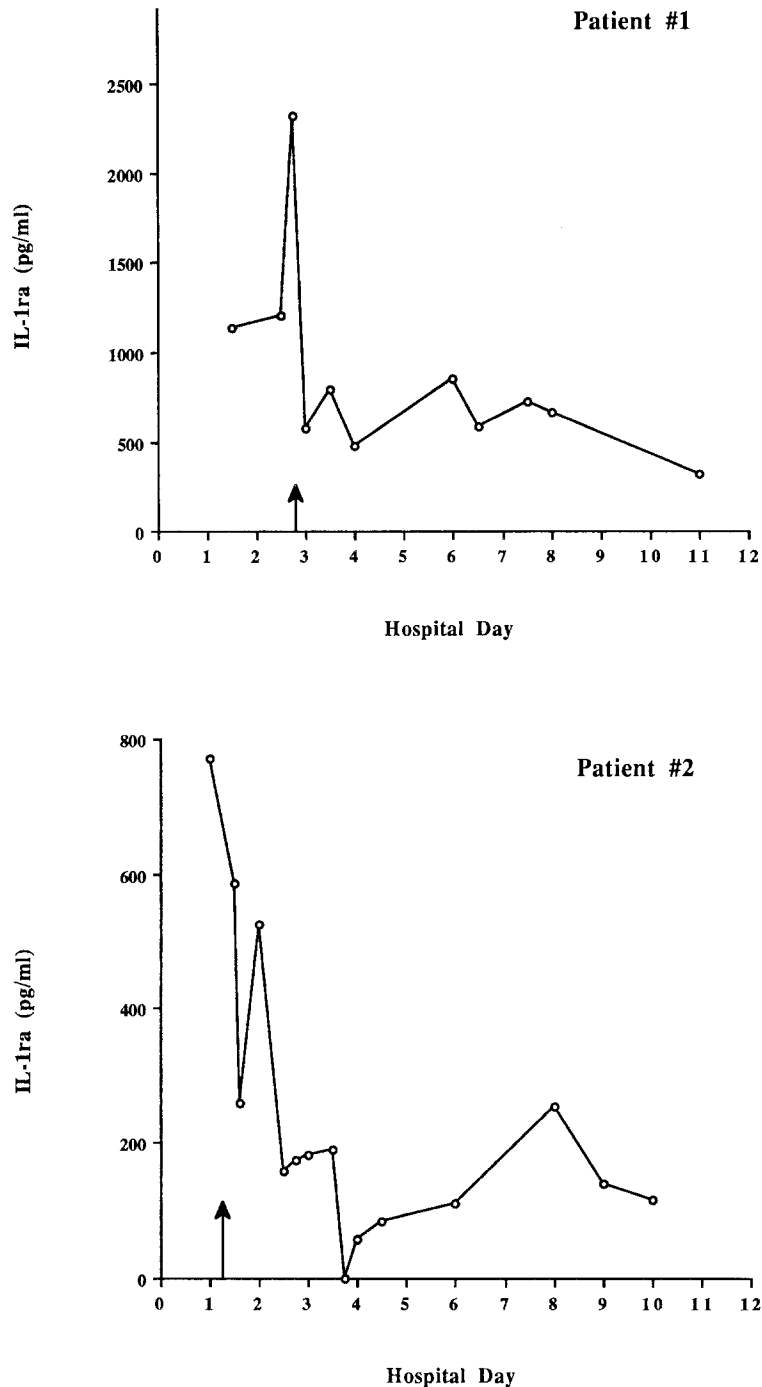


FIG. 2. Time course of serum IL-1ra levels in two patients with acute eosinophilic pneumonia. IL-1ra was measured by sandwich ELISA. Arrows indicate the initiation of treatment with intravenous methylprednisolone.

nancy, and drugs) are absent. Furthermore, acute eosinophilic pneumonia can be clinically distinguished from other eosinophilic lung diseases such as simple pulmonary eosinophilia (Löfller's syndrome), chronic eosinophilic pneumonia, the idiopathic hypereosinophilic syndrome, allergic

bronchopulmonary aspergillosis, bronchocentric granulomatosis, and Churg-Strauss syndrome.¹³ The cause or causes and pathophysiologic events of acute eosinophilic pneumonia are unknown.

IL-5 is likely a mediator in the pathogenesis of acute eosinophilic pneumonia. Receptors for this

cytokine are uniquely expressed by eosinophils but not lymphocytes, neutrophils, or monocytes.^{14, 15} It is a potent chemotaxin for eosinophils.¹⁶ Furthermore, it can cause release of eosinophil granules¹⁷ and can prolong eosinophil survival by inhibiting apoptosis.¹⁸ Elevated serum levels of IL-5, as high as 4500 pg/ml, have been noted in patients with blood eosinophilia^{5, 6, 19} and have been found to precede increases in blood eosinophil numbers in patients with the syndrome of episodic angioedema and eosinophilia.⁵ IL-5 has been reported to be either undetectable²⁰ or present in quantities less than 0.5 U/ml^{21, 22} in the BAL fluid of normal volunteers. Recombinant IL-5, administered nasally to normal volunteers, is a potent inducer of nasal eosinophil infiltration.²³ IL-5 can be identified in the BAL fluid of atopic volunteers after segmental lung challenge with ragweed antigen and correlates with eosinophil infiltration.^{24, 25} BAL IL-5 levels have been shown to correlate with BAL eosinophil percentages in patients with a variety of eosinophilic lung diseases.²¹ IL-5 levels were reported to be increased to a mean of 6 U/ml in concentrated BAL fluid of patients with chronic eosinophilic pneumonia²¹ and increased to levels as high as 512 pg/ml in BAL fluid of patients with the idiopathic hypereosinophilic syndrome.²⁰ However, there are no previous reports of IL-5 levels in acute eosinophilic pneumonia.

The importance of IL-5 as a regulator of pulmonary eosinophilia has been verified by experiments in which an anti-IL-5 monoclonal antibody prevented infiltration of eosinophils into the lungs of mice stimulated with transnasal *Ascaris suum* extract,²⁶ guinea pigs stimulated with aeroallergens,²⁷⁻³⁰ mice stimulated with inhaled *Aspergillus fumigatus* antigens,³¹ and mice stimulated with *Schistosoma mansoni*.³²

IL-5 appears to be produced mainly by T-helper lymphocytes. T-helper cells have recently been demonstrated to fall into two subclasses in human beings: T_{H1} and T_{H2} cells.³³ Both of these subclasses produce IL-3 and GM-CSF. However, only T_{H2} cells secrete IL-5. These subpopulations may be relevant to the pathogenesis of eosinophilic lung diseases. For example, patients with asthma and allergic bronchopulmonary aspergillosis tend to demonstrate evidence of selective T_{H2} activation, and patients with sarcoidosis demonstrate evidence of selective T_{H1} activation. Patients with other eosinophilic lung diseases, including chronic eosinophilic pneumonia, show evidence of a combination of T_{H1} and T_{H2} activation.^{21, 34} There is no previous published information regarding the T-

cell cytokines involved in the pathogenesis of acute eosinophilic pneumonia.

Both patients tested had very high levels of IL-5 in unconcentrated BAL fluid (846 and 1950 pg/ml, respectively) and undetectable IL-5 in the serum at the time of admission to the hospital. The BAL fluid normally contains approximately 1% alveolar epithelial lining fluid, and the alveolar epithelial lining fluid protein concentration is approximately 10% of the usual plasma protein concentration.³⁵ According to these estimates of the epithelial lining fluid to BAL ratio, the actual epithelial lining fluid IL-5 level in acute eosinophilic pneumonia may be as much as 100 times the level measured in unconcentrated BAL fluid. The high BAL IL-5 concentrations with undetectable serum IL-5 suggest that IL-5 is locally produced in the lungs in acute eosinophilic pneumonia, which is consistent with the observation of selective accumulation of eosinophils in the BAL fluid but not in the blood. These observations illustrate the poor ability of lung cytokines to spill over into the circulation.

The roles of IL-1ra and soluble type II IL-1 receptor in eosinophilic lung disease are unknown. Soluble type II IL-1 receptor can be shed from inflammatory cells and can bind free IL-1, thus blocking proinflammatory effects of IL-1.³⁶ IL-1ra is a pure receptor antagonist that blocks binding of IL-1 to its receptors and thus inhibits the effect of IL-1. This cytokine is largely produced by alveolar macrophages,³⁷ is not present in BAL fluid from normal volunteers,³⁸ and is not known to be elevated in other eosinophilic lung diseases. However, it is known that IL-1 can induce eosinophil accumulation in skin and that this eosinophil influx can be blocked by IL-1ra,⁷ suggesting that IL-1ra and soluble type II IL-1 receptor may be produced in response to abnormal levels of IL-1. The fall in serum IL-1ra levels after the administration of methylprednisolone is consistent with previous observations that IL-1ra production is inhibited by corticosteroids.³⁹ The rise in the serum IL-1ra level in patient 2, noted on hospital day 8, correlated with a rise in the blood eosinophil count in this patient and followed a reduction in the dose of corticosteroids and a change from intravenous to oral administration.

The absence of detectable IL-1 β or TNF- α in the BAL fluid of the patients with acute eosinophilic pneumonia may indicate that these cytokines were not present or may indicate that IL-1 and TNF inhibitors in the BAL fluid, such as soluble IL-1 type II receptors and soluble TNF receptors,

bound free IL-1 β and TNF- α and thus interfered with the ELISA measurements. Because the alveolar macrophage is the main source of IL-1 β and TNF- α in the lungs, it is also possible that macrophages are not stimulated in acute eosinophilic pneumonia and that the cytokines measurable in the BAL fluid originate from other lung cells, such as lymphocytes or even eosinophils. The production of IL-1 β and IL-1ra is known to be differentially regulated in mononuclear phagocytes,³⁸ and it is thus alternatively possible that acute eosinophilic pneumonia is associated with a strong IL-1ra-specific stimulus.

The importance of the persistently elevated soluble type II IL-1 receptor in the BAL fluid of the patients with acute eosinophilic pneumonia is unclear. Possible explanations are that corticosteroids perpetuated the release of soluble type II receptors; that abnormal levels of soluble type II receptor resolve more slowly than the eosinophilia and clinical symptoms attendant to acute eosinophilic pneumonia; and that these patients have baseline immune dysfunction (including abnormal release of soluble type II receptor), which predisposed them to the development of acute eosinophilic pneumonia.

Although these results suggest that IL-5 and members of the IL-1 family of cytokines may be involved in the pathogenesis of acute eosinophilic pneumonia, we cannot exclude the co-involvement of other eosinophil activators and chemotaxins such as leukotriene B₄,⁴⁰ platelet activating factor,⁴¹ IL-4,⁴² IL-8,⁴³ bradykinin,⁴⁴ RANTES,⁴⁵ or lymphocyte chemotactic factor.⁴⁶

In summary, BAL IL-5 levels are elevated in acute eosinophilic pneumonia and may be involved in the pathogenesis of this uncommon syndrome. The results suggest that production of this cytokine is localized to the lungs, although the specific cell type responsible for IL-5 production is uncertain. The importance of the very high levels of BAL IL-1ra and soluble type II IL-1 receptor in acute eosinophilic pneumonia and other eosinophilic lung diseases has yet to be defined but warrants further investigation.

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