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10-Year Follow-Up of Frequently Relapsed Chronic Eosinophilic Pneumonia Starting at 15 Years Old; Attempts to Treat with Inhaled Corticosteroid (A Case Report)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 15
Final Diagnosis: Eosinophilic pneumonia
Symptoms: Fever up • chest pain • general fatigue • dry cough
Medication: Budesonide • Fulticasone
Clinical Procedure: Inhaled steroids • systemic steroid
Specialty: Immunology

Objective: Rare co-existance of disease or pathology

Background: Eosinophilic pneumonia is recognized both as an eosinophil-associated disease and as bronchial asthma. In eosinophilic pneumonia, the site of eosinophilic infiltration is mainly the alveolus and the peripheral airway; the disability of pulmonary function is restrictive, as opposed to from bronchial asthma, which has a relatively central side bronchus region and obstructive function. Differences in inflammatory region and the activation degree of T-cell and eosinophil parameters were predicted.

Case Report: To determine the extent of inflammation and the region showing the inflammation in eosinophilic pneumonia, parameters like HLADRCD4/CD4 (%), CD25CD4/CD4 (%), ECP, soluble IL2R, and IL5 were examined in BALF and in peripheral blood during the active phase and remission phase. The percentage of HLADRCD4/CD4, IL-5, and the percentage of CD25CD4/CD4 were extremely high during the acute phase in BALF as compared to that in peripheral blood during the active and the remission phase. To avoid the adverse effects of systemic administration of steroids, we tried 5 different kinds of steroid through inhalation. We used %FVC by spirometry as a parameter to determine the recurrence of the disease. However, the inhaled steroids could not control the remission for long. This is the first report in which frequent recurrence of the disease was seen despite treatments and in which %FVC was used to determine the disease condition.

Conclusions: The principle site of inflammation in eosinophilic pneumonia is the peripheral bronchus and the alveolar area. Percent FVC can be a useful parameter for assessment of recurrence of the disease. In the present case, the disease could not be kept under control despite treatment with 5 different steroids through the inhalation route.

MeSH Keywords: Eosinophil Cationic Protein • HLA-DR Antigens • Interleukin-2 Receptor alpha Subunit • Interleukin-5

Abbreviations: **FVC** – forced vital capacity; **FEV1.0** – forced expiratory volume; **ICS** – inhaled corticosteroid

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/915402

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Background

A 15-year old female patient presented with a case of with eosinophilic pneumonia. Development of chronic eosinophilic pneumonia (Figure 1) in childhood is a rare phenomenon. We tried to analyze the immunological mechanism involved in the development of eosinophilic pneumonia. Eosinophilic pneumonia is recognized both as an eosinophil-associated disease as well as bronchial asthma. It is obvious that in eosinophilic pneumonia the site of eosinophilic infiltration is mainly the alveolus and the peripheral airway; the disability of pulmonary function is restrictive, as opposed to that of bronchial asthma, which has a relatively central side bronchus region and obstructive function. However, the antigen of eosinophilic pneumonia is still unknown, unlike bronchial asthma. Eosinophil- and T-lymphocyte-activated parameters such as ECP, CD4HLADR/CD4 (%), CD4CD25/CD4 (%), and IL-5 are the immunological factors usually discussednot only in the context of bronchial asthma [1] but also in eosinophilic pneumonia [2,3].

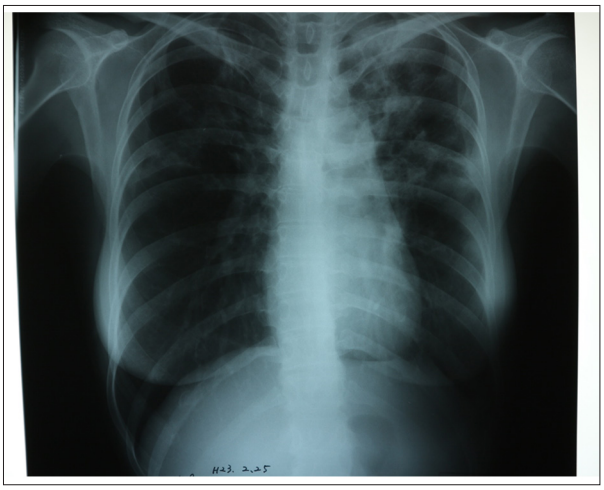

Figure 1. Roentgen photograph. Roentgen photograph shows a borderless, cloudy, wandering shadow-like appearance of the peripheral lung area. Pulmonary function of eosinophilic pneumonia showed a restrictive pattern, indicating that the drug in its aerosol form cannot reach the peripheral lung area. This may be the reason for the ineffectiveness of the inhaled steroids.

Case Report

Chronic eosinophilic pneumonia during childhood is very rare [4]. In December 1997, a 15-year-old girl with chronic refractory pneumonia was referred to Habikino Hospital for evaluation of respiratory distress, dry cough, high temperature, chest pain, pulmonary infiltration, and peripheral eosinophilia. In our hospital, she was diagnosed as having chronic eosinophilic pneumonia for the first time by eosinophilia both in bronchial alveolar lavage fluid (BALF) and in peripheral blood, and eosinophils mainly infiltrated the alveolus region, as shown by fiberscope biopsy. A report of laboratory investigations done on the patient is summarized in Table 1.

Clinical symptoms of eosinophilic pneumonia including increased body temperature, chest pain and dry cough were observed when the patient was admitted to the hospital. Laboratory investigations showed an increase in blood sedimentation rate (BSR). Serological testing (Table 1) results for sedimentation antibody of hypersensitivity pneumonia were all negative. Forced vital capacity (FVC) was found to be decreased and showed a restrictive pattern (%FVC; 39%) in spirometry.

Radiographic examinations (Figure 1) of recurrence showed a peripheral infiltration wandering shadow, which is characteristic of chronic eosinophilic pneumonia on plain chest

Table 1. Data on admission. On admission, clinical symptoms of eosinophilic pneumonia like rise in temperature, chest pain, and dry cough appeared. An increase in BSR was observed during laboratory investigations and a restrictive pattern with decrease in %FVC was observed during spirometry.

Blood cell	Inflammatory data	Immunoglobulin
WBC 13000/mm^3	ESR 110 mm (1h)	IgG 2573 mg/dl
Neu 52%	150 mm (2h)	IgA 231 mg/dl
Ly 9%	CRP 2.9 mg/dl	IgM 277 mg/dl
Mo 6%		IgE 143 IU/ml
Eo 33%		
Ba 0%	**Arterial blood gas**	**Pulmonary function**
RBC 417×10^4/mm^3	pH 7.444	FVC 1.09 l
Hb 9.3 g/dl	PaCO2 34.5 mmHg	%FVC 39.0%
Plat 50.6×10^4/mm^3	PaO2 81.7 mmHg	DLCO 6.9 ml/min/mmHg

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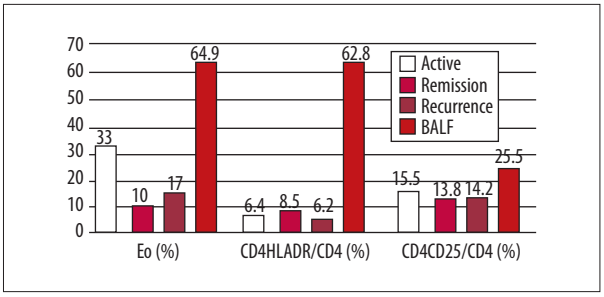

Figure 2. Eosinophil (%), CD4HLADR/CD4 (%), and CD4CD25/CD4 (%). Figure shows the changes of eosinophil (%), CD4HLADR/CD4 (%), and CD4CD25/CD4 (%) on remission, recurrence, and active phase. During all these phases, the level of each of these factors was higher in BALF than in peripheral blood. This phenomenon indicates that higher levels inflammation existed in BALF than in peripheral blood.

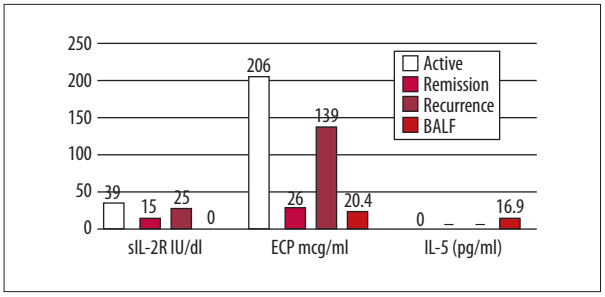

Figure 3. sIL2R, ECP, and IL5. Although the level of IL5 was higher than the other factors, the levels of sIL2R and ECP were not higher in BALF than that in the peripheral blood. These results seem strange and we have no explanation for this phenomenon.

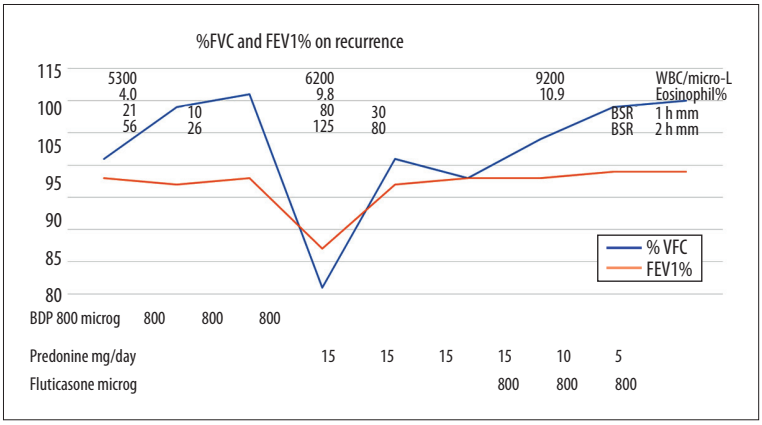

Figure 4. %FVC and FEV1 on recurrence. An extreme decrease in %FVC was seen when the disease recurred. We thought that non-invasive spirometry test could be a parameter for recurrence. FEV1 also responded, so the patient might have had tendency to bronchial asthma.

radiograph and a computed tomography scan of the chest. The culture tests of BALF and sputum showed that they were negative. Trans-bronchial biopsy demonstrated intra-alveolar infiltration of eosinophils and interstitial infiltration of both eosinophils and lymphocytes. These features were consistent with the diagnosis of chronic eosinophilic pneumonia.

Figures 2 and 3 represent the parameters examined in activated T-cells and eosinophils.

Mononuclear cells from venous blood and BALF were double-stained using IgG monoclonal antibodies and analyzed by flow cytometry (FACScan, Becton-Dickinson, CA, USA). Concentrations of soluble interleukin 2 receptor in serum and BALF were measured by enzyme-linked immunoabsorbent assay (ELISA) using a commercially available kit (Cytoscreen, CA, USA). Concentrations of IL-5 in the serum and BALF were also measured by an ELISA current phase (Human IL-5 immunoassay, R and D Systems, MN, USA). Concentrations of ECP in serum and BALF were measured by Pharmacia CAP system ECP fluorescent immunoassay (FEIA, Pharmacia Diagnostics AB, Sweden).

Changes in %FVC and forced expiratory volume/1 second (FEV1.0%) in the recurrence of the disease are shown in Table 2 and Figure 4.

Changed data of %FVC and FEV1.0% on recurrence are shown in Table 2 and Figure 4.

Percent FVC and FEV1.0% [4] was measured using a portable spirometer (Microspiro HI-601, NIHON-KPHDEN COPOLATION, Tokyo Japan). Data of %FVC changed slightly over time. The percent FVC measurement obtained using non-invasive methods like spirometry was taken as an indicator of her condition. On admission with eosinophilic pneumonia, her %FVC was extremely low (39%), and we thought that non-invasive spirometry testing could be used as a parameter for recurrence. There was an initial remission followed by a decrease in %FVC to values below 100%, indicating the disease recurrence. FEV1 also responded, so the patient might have had a slight tendency to bronchial asthma.

Table 3 shows 12 recurrences of eosinophilic pneumonia.

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Table 2. Laboratory data on recurrence to remission. A slight change in %FVC was observed over time. Determination of %FVC was performed using non-invasive spirometry and the %FCV value was used as an indicator of her condition.

Date (YYMMDD)	991029	991126	991216	000107	000112	000117	000128	000204	000218
WBC/micro-L	5300			6200				9200	
Eosinophil%	4.0			9.8				10.9	
1 h mm	21	10		80	30				
2 h mm	56	26		125	80				
FVC	3.10	3.36	3.40	2.48	3.06	3.00	3.34	3.34	3.38
%FVC%	101	109	111	81.0	101	98	109	109	110
FEV1 L	3.02	3.06	3.34	2.48	3.02	2.96	3.32	3.26	3.36
FEV1%	98.7	97.6	98.2	86.9	97.4	98.7	99.4	97.6	99.4
V50 L/Min	5.25	5.58	5.01	4.75	5.17	4.73	5.89	4.72	5.34
V25 L/Min	3.81	2,77	2.73	2.95	2.59	2.53	3.26	2.69	2.83
PEF L/Min	6.09	7.24	7.86	6.35	6.92	6.78	7.44	7.57	7.87
BDP 800 microg	800	800	800						
Predonine mg/day				15	15	15	15	10	5
Fluticasone							800	800	800

FVC – forced vital capacity; FEV1 – forced expiratory volume/1 second; PEF – peak expiratory flow L/min.

Table 3. Eosinophilic pneumonia recurred 12 times despite various steroid inhalation therapies. To control the disease condition and to avoid adverse effects associated with systemic administration of steroids, we tried 5 different dosages of steroids through the inhalation route. The controller became single use of steroid inhalation therapy, but after several months, the eosinophilic pneumonia symptoms re-appeared.

Date (recurrence)	Diagnosis by	Before drug	Added or changed drug
000117 (YYMMDD)	%FVC: 98%	Fultide Discus 800 µg, Pred 5mg	Pred 10 mg
000304	%FVC: 105, Eo: 14.7%	Fultide Discus 800 µg	Pred 10 mg
031215	%FVC: 98%, BSR: 55 mm/1 h	Fultide Discus 800 µg	Pred 10 mg, Pulmicort T; 400 µg
040331	%FVC: 96%	Pulmicort T 400 µg	Pred 10 mg
040810	%FVC: 98%, BSR 56: mm/1 h	Pulmicort T 400 µg	Pred 10 mg
050223	%FVC: 97%	Fultide discus 40 0µg	Pred 10mg. Qvar 400 µg
050621	%FVC: 92%, BSR 91: mm/1 h	Qvar 200 µg	Pred 10mg, Qvar 400 µg
050824 no recurrence		Qvar 400 µg	Fultide air 200 µg
060510	%FVC: 91%	Fultide air 200 µg	Pred 20 mg
070621	%FVC: 100%	Fultide air 200 µg	Fultide Discus 600 µg
090518	BSR: 25 mm/1 h, Eo: 20%	Fultide discus 600 µg	Pred 20 mg
100412	%FVC: 96%	Fultide discus 600 µg	Pred 20 mg, Palmicort S 1000 µg
110225	Chest-xp	Pulmicort S 1000 µg	Transfer to hospital

BSR – blood sedimentation rate; Pulmicort T – pulmicort turbuhaler; Pulmicort S – pulmicort suspension; Eo – eosinophil % in peripheral blood.

To control eosinophilic pneumonia, 5 different dosages of inhaled steroids were tried, chosen to avoid adverse effects due to long-term systemic administration of steroids. The controller (ICS) became a single use of steroid inhalation therapy, but several months later, the recurrence of eosinophilic pneumonia symptoms often appear. However systemic treatment using predonine can easily control the disease, and the laboratory data and clinical symptoms showed improvement.

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Discussion

General (non-specific) inflammation parameters are listed in Table 1.

ESR, CRP, and percentage eosinophils were found to be increased in the peripheral blood of the patient. Spirometry showed a forced pattern typical of eosinophilic pneumonia, as shown by an extreme decrease in %FVC. Decreased %FVC may be attributed to an increased accumulation of inflammatory cells, which differs from obstructive dysfunction of bronchial asthma.

Before steroid therapy, eosinophils increased in both BALF (65%) and peripheral blood (33%). An increased expression of HLADR was seen in CD4-positive T-lymphocytes in BALF (62.8%) as compared to that in peripheral blood (6.4%). The expression of CD25 was also found to be increased in CD4-positive T-lymphocytes in BALF (25.5%) compared to peripheral blood (15.5%). The expression of CD25 in CD8-positive T-lymphocytes was almost equal in BALF and peripheral blood. Even in the active phase of bronchial asthma, HLADRCD4/CD4 and CD25CD4/CD4 increased by several percent (1); however, in eosinophilic pneumonia, they increased by at least 10 percent, showing the extremely high levels of inflammation in eosinophilic pneumonia.

In peripheral blood, soluble interleukin 2 receptor concentration (3963 IU/ml) on admission decreased to 1553 IU/ml in remission phase and then increased again to 2504 IU/ml in recurrent phase. In BALF, the concentration of soluble interleukin 2 receptor was below 250 IU/ml during the active phase. Similarly, the concentration of ECP decreased from 206.6 mcg/ml in the active phase to 26.4 mcg/ml in the remission phase and then increased again to 139.1 mcg/ml during the recurrent phase in peripheral blood. The concentration of ECP in BALF was 20.4 mcg/ml. The concentration of interleukin 5 increased to 16.9 pg/ml only in BALF. The concentration of interleukin 5 in peripheral blood was under 7.8 pg/ml.

It is obvious that the T-lymphocyte activation parameters (CD4HLADR/CD4 (%), CD4CD25/CD4 (%) and IL5), also considered as eosinophil-associated activation parameters, increased in BALF more than in peripheral blood. The concentrations of soluble interleukin 2 receptor and ECP in peripheral blood during the active phase were higher than that in BALF (Figure 3). The low values given by volume unit such as ECP and soluble interleukin 2 receptor could not be evaluated due to dilution of normal saline using BALF. On the other hand, the concentration of soluble interleukin 2 receptor increases during malignant diseases [5] and decreases during eosinophil-related diseases. The concentrations of both soluble interleukin 2 receptor and ECP [6] in peripheral blood are reflective of eosinophilic pneumonia. The real results of ECP, IL-5, and soluble interleukin 2 receptor in peripheral tissue should be higher. Eosinophil-related activation parameters are activated in the peripheral airway in chronic eosinophilic pneumonia. By accidental inhalation, antigens that are smaller than asthmatic antigens reach peripheral airways and may cause chronic eosinophilic pneumonia.

Pulmonary function in eosinophilic pneumonia

In this study, %FVC is recognized as a parameter for eosinophilic pneumonia. In fact, change in %FVC was observed along with clinical symptoms like a rise in temperature, chest pain, and respiratory distress, change in percentage of eosinophil in peripheral blood and altered BSR. Sveinsson et al. [7] previously reported that FEV1 and %FVC are decreased in eosinophilic pneumonia. In this study, it was observed that %FVC had a relationship with other clinical and laboratory parameters but not with FEV1%. As compared to other parameters, %FVC offers various advantages in prediction of chronic eosinophilia. The procedure to determine %FVC is non-invasive, quick, less expensive, and less laborious. This is the first study in which %FVC was used as a parameter for predicting eosinophilic pneumonia and in which the disease recurrences were managed using ICS treatments.

Inhaled steroid in eosinophilic pneumonia

Our results show that activated T-cells and eosinophilic inflammation existed mainly in peripheral airways rather than in peripheral blood. We considered that inhaled steroid is useful [8] for treating peripheral airway inflammation in chronic eosinophilic pneumonia. But other group considered inhaled steroids not effective [8]. Chan et al. [9] reported a patient who underwent treatment with systemic corticosteroids followed by inhaled steroids and who remained in remission for 2 years. We tried 5 kinds of inhaled steroids during the active and the remission phases of eosinophilic pneumonia to avoid the adverse effects associated with systemic administration of steroids, but we could not achieve sufficient efficacy using inhaled steroids. A roentgen photograph (Figure 1) showed a borderless, cloudy, and wandering shadow-like appearance of the peripheral lung area. Pulmonary function of eosinophilic pneumonia showed a restrictive pattern. Single use of ICSs could not control the persistence of remission. Three reasons may have contributed to the lack of response. Firstly, the particle size of the inhaled steroid was large and hence could not reach the inflammation region and peripheral lung area, whereas Qval (Beclomethasone, pMDI) releases super-small aerosol (diameter 1.1 μm). The second reason could be the weak anti-inflammatory effect of inhaled steroids themselves. As seen in the roentgen image, the bronchus might be closed by the accumulation of inflammatory cells. Inhaled steroids with smaller particle size [10] and strong anti-inflammatory effects are needed for the treatment of eosinophilic pneumonia.

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Conclusions

Our T-cell activation parameter data (HLADRCD4/CD4 percentages and CD25CD4/CD4 percentages) and eosinophil activation parameter data (IL-5) showed higher levels in BALF than in peripheral blood. The values were higher during the active phase than during the remission phase in the peripheral blood.

The principal inflammation region of eosinophilic pneumonia is considered to be in the peripheral bronchus and in the alveoli. Accordingly, inhaled steroids were considered effective to control eosinophilic pneumonia, but 5 kinds of ICS were not effective to maintain the remission of the disease. Determination of %FVC was useful to predict the recurrence of the disease.

Acknowledgments

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Conflict of interest

None.

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