A case of sarcoidosis associated with chronic eosinophilic pneumonia

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Abstract : A 38-year-old man was hospitalized in our university hospital because of pulmonary opacities with bilateral hilar and mediastinal lymphadenopathy seen on chest radiograph. Eosinophilia was observed in the circulation and bronchoalveolar lavage (BAL) fluid. Histological examination revealed noncaseating epithelioid granulomas and eosinophilic infiltration in the lung. Based on these findings, a diagnosis of sarcoidosis combined with chronic eosinophilic pneumonia was made. The infiltrates on chest radiograph and BAL eosinophilia were promptly reduced with corticosteroid therapy, but only mild reduction was observed in diffuse nodular shadows and hilar and mediastinal lymphadenopathy, and high amounts of lymphocytes in BAL fluid remained. Increased IFN-γ, IL-4 and IL-5 were detected in the BAL fluid, and corticosteroid therapy reduced IL-4 and IL-5 (Th-2 cytokines) but not IFN-γ (Th-1 cytokine). These cytokine levels in BAL fluid were intimately correlated with the clinical course of sarcoidosis and chronic eosinophilic pneumonia. J. Med. Invest. 45 : 131-136, 1998

Key words **:** *sarcoidosis, chronic eosinophilic pneumonia, cytokine, bronchoalveolar lavage*

INTRODUCTION

CD4+ lymphocytes can be subdivided into two distinct populations, Th1 and Th2, defined by the spectrum of cytokines produced by these cells in mice (1, 2) and humans (3). Th1 cells generate interleukin (IL)-2, interferon (IFN)-γ, and promote cellular immunity, whereas Th2 generate IL-4, IL-5, IL-6, and IL-10, and play a role in humoral responses and allergic diseases (4, 5). There is evidence that a balance of different cytokine producers is crucial for an effective immune response and the outcome of infectious, autoimmune, and allergic diseases (6, 7).

In granulomatous diseases including sarcoidosis, there is evidence for a predominant Th1 response. Indeed, lung lymphocytes from sarcoidosis patients produce excessive amounts of IFN-γ and IL-2 (8-11). However, in eosinophilic pneumonia, eosinophils which are known to grow and be activated in the presence of Th2 cytokines are accumulated and activated in the lungs. Both Th1 and Th2 lymphocytes have been suggested to be responsible for the pathogenesis of this disorder (12, 13). Here, we report a patient with sarcoidosis associated with chronic eosinophilic pneumonia (CEP) along with a brief review of relevant literature.

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CASE REPORT

A 38-yr-old man had complained of productive cough since August, 1996. A chest radiograph which was taken for a health check on July 4, 1997, revealed diffuse pulmonary opacities with bil hilar lymphadenopathy. He was admitted to Tokushima University Hospital on Dec. 18, 1997 for further examinations. He denied using any prescription medications, and there was no history of allergic diseases including bronchial asthma.

On admission, a physical examination revealed swelling of several lymph nodes in right (rt) cervical

and bil axillar regions. Leukocyte count, 5100 per μl with 13.0% of eosinophils. Erythrocyte sedimentation rate was within the normal range (2 mm/h), and serum C-reactive protein was slightly elevated (0.39 mg/dl ; normal, <0.3). Slightly increased serum angiotensin-converting enzyme (ACE) (29.6 U/L ; normal, 7.7-29.4) and lysozyme (17.6 μg/ml ; normal, 4.2-11.5) were observed. Arterial blood gas analysis revealed mild hypoxemia (PaO_2 63.8 mmHg) with normal $PaCO_2$ level. Pulmonary function test revealed decreased $FEV_{1.0\%}$ (55.1%) and %DLco (57.7%). Chest radiograph and computed tomographic (CT) scan showed hilar and mediastinal lymphadenopathy, bil diffuse nodularity, and infiltrates with rt lobe predominance (Figure 1a). ^{67}Ga-citrate scintigraphy showed abnormal accumulations in bil supraclavicular regions, parotis, hilar regions, and rt lung. Ophthalmological examination revealed mild uveitis.

Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsies (TBLB) was performed on Dec. 18, 1997. The BAL was performed in the segment of rt B5b with a total volume of 150 ml of sterile 0.9% saline in three 50-ml portions (Table 1).

Table 1. Bronchoalveolar lavage data

	Dec 18, 1997	Feb 25, 1998
BAL bronchus	rt B5b	rt B5b
Recovery rate (%)	88	67
Total cells, $x10^6$	55.0	21.0
AM, $x10^6$ (%)	6.7 (12.1)	2.1 (10.2)
Lymphocytes, $x10^6$ (%)	26.9 (48.9)	18.3 (87.1)
Neutrophils, $x10^6$ (%)	1.3 (2.3)	0.1 (0.7)
Eosinophils, $x10^6$ (%)	20.2 (36.8)	0.4 (2.0)
CD4/CD8	1.0	0.7

AM ; alveolar macrophages

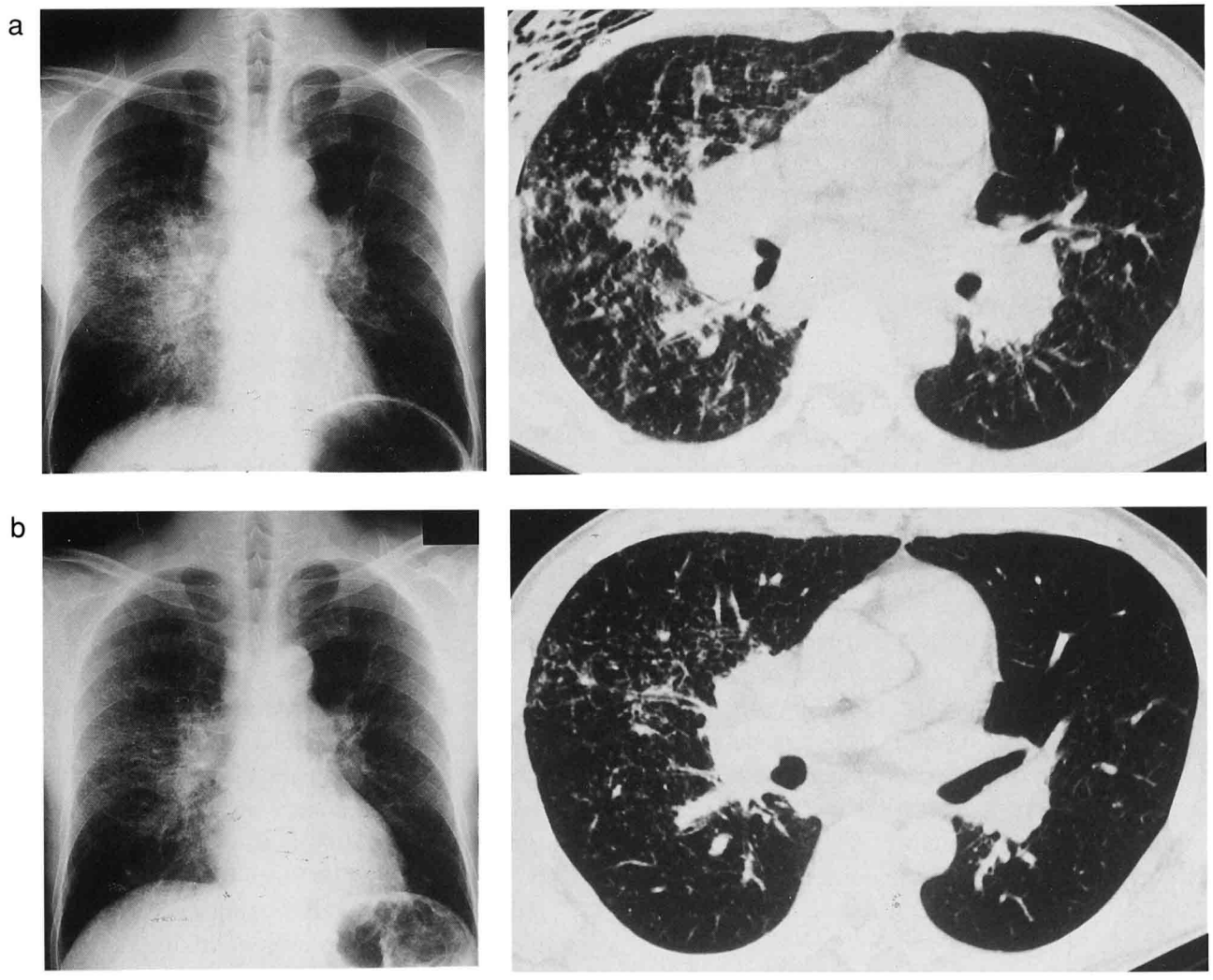

Fig.1. a) A chest radiograph (lt) and chest CT scan (rt) at the time of admission. Hilar and mediastinal lymphadenopathy, bil diffuse nodularity, and infiltrates with rt lobe predominance are seen.
b) A chest radiograph (lt) and chest CT scan (rt) after therapy with corticosteroid. A significant reduction is seen in the infiltrates, but only mild reduction is observed in diffuse nodular shadows and hilar and mediastinal lymphadenopathy.

The number of total cells was, 5.5 x 10^7 and the cell differential revealed increased percentages of lymphocytes and eosinophils. The ratio of CD4 to CD8 was 1.0. Histological examination for TBLB specimen revealed noncaseating epithelioid granulomas and eosinophilic infiltration (Figure 2). Findings of special stains for acid fast, fungal, and parasitic microorganisms were negative.

Based on these findings, a diagnosis of sarcoidosis combined with CEP was made. Therapy was initiated with prednisolone, 30 mg per day, from January13, 1998, and maintained for a week. Then, 2.5mg of prednisolone dosage was reduced every two weeks. The clinical course is summerized in Figure 3. Cough symptoms rapidly decreased following the treatment, and the opacities in the peripheral infiltrates on chest radiograph were also promptly reduced. The swelling of lymph nodes observed in the rt cervical and bil axillar regions gradually decreased. The number of peripheral eosinophils and serum ACE level were reduced. PaO_2 and $FEV_{1.0\%}$ were improved. The BAL, which was performed on Day 42 after corticosteroid therapy had begun, showed a significantly decreased percentage of eosinophils but the high percentage of lymphocytes remained (Table 1). Follow-up chest radiograph and CT scan showed that the infiltrates with rt lobe predominance were significantly decreased, but only mild reduction was observed in hilar and mediastinal lymphadenopathy and diffuse nodular shadows (Figure 1b).

IFN-γ, IL-2, IL-4 and IL-5 in BAL fluid were measured using ELISA as previously described (14) (Table 2). IFN-γ, IL-4, and IL-5 were detected in the BAL fluid obtained before the corticosteroid therapy. After the therapy, IL-4 or IL-5 was not detectable (the detection limit was 20 pg/ml), but IFN-γ was detected at the a

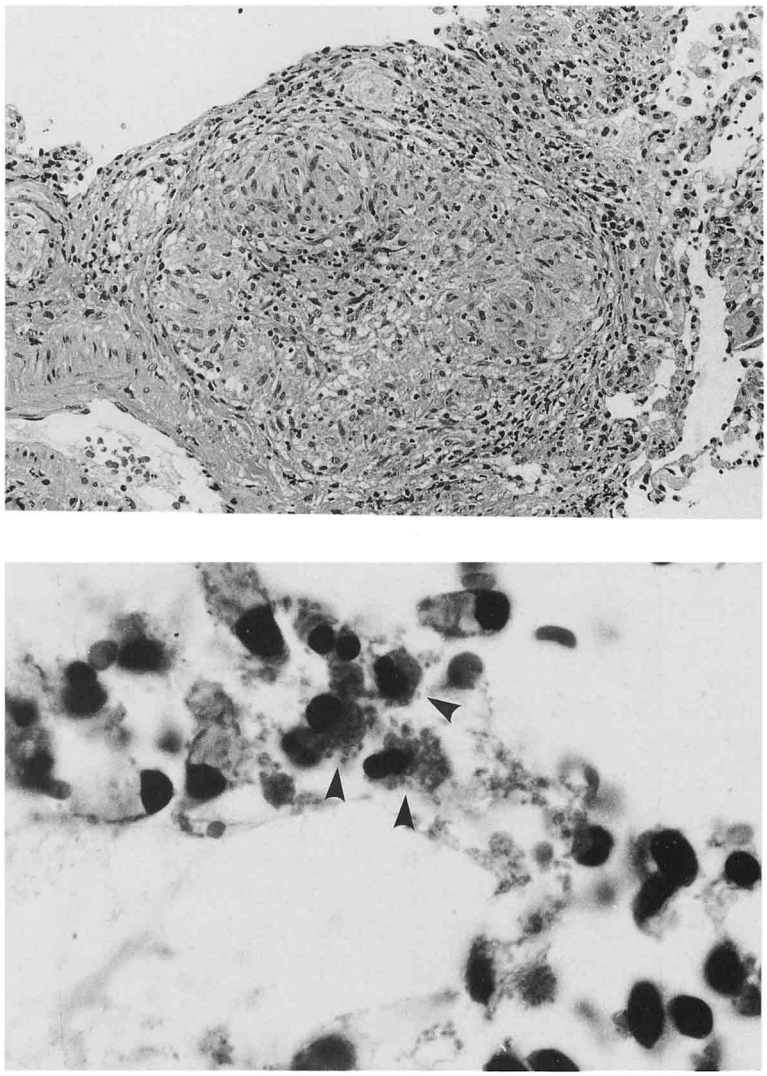

Fig.2. a) A small noncaseating epithelioid granuloma surrounded by mild lymphocytic infiltration (H.E., 66 x).
b) Eosinophilic infiltration (arrow heads) observed in bronchial epithelium (H.E., 250 x).

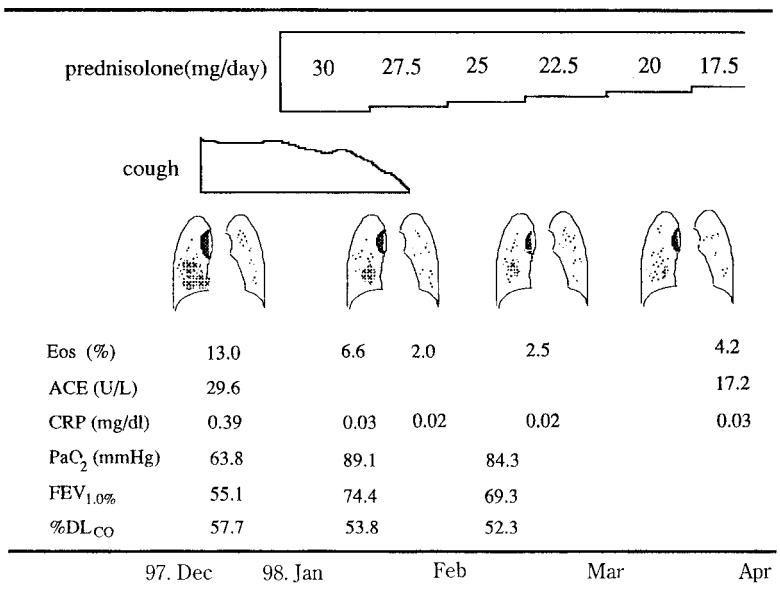

Fig.3. Summary of clinical course

Table 2. Cytokines in bronchoalveolar lavage fluid

Cytokines	Corticosteroid therapy	
	Before	After
interferon-γ	28[a]	27
interleukin-4	49	<20
interleukin-5	179	<20

[a]Data are expressed as pg/ml

similar level as observed before therapy. No IL-2 was detected during the course.

DISCUSSION

Our patient had clinical, roentgenographic and immunological features of sarcoidosis associated with CEP. Chest radiograph and CT scan revealed hilar and mediastinal lymphadenopathy and bil diffuse nodularity. Lung lesions were histologically confirmed to be noncaseating epithelioid granulomas. Ophthalmological examinatoin disclosed uveitis. Serum ACE and lysozyme levels were elevated. These findings were consistent with a diagnosis of sarcoidosis. However, in our patient the infiltrates showed rt lobe predominance on chest radiograph and CT. Moreover, both lymphocytes and eosinophils were increased in the BAL fluid, and eosinophilic infiltration was histologically observed in the TBLB specimen of the lung. From these findings, the disease diagnosed was sarcoidosis associated with CEP.

Davis *et al*. showed that over 5% of BAL eosinophils were observed in 7% of patients with sarcoidosis (15). Allen *et al*. also reported that 6% of patients with sarcoidosis were found to have BAL eosinophilia, but all had relatively modest percentages (less than 8%) of eosinophils (16), indicating that BAL differentials from patients with sarcoidosis rarely include significant numbers of eosinophils. We know of only one report which showed a case diagnosed as CEP concomitant with sarcoidosis ; the case had a prominently increased percentage (94.2%) of BAL eosinophils (17).

Corticosteroid therapy rapidly reduced peripheral pulmonary infiltrates with rt lobe predominance on chest radiograph and the BAL eosinophil percentage. However, diffuse nodularity and hilar and mediastinal lymphadenopathy on chest radiograph and the BAL lymphocyte percentages did not respond well to the therapy. The early response of pulmonary sarcoidosis to corticosteroid has been known to be poorer when compared with that of CEP (18, 19). Therefore, the clinical course in our patient indicated that corticosteroid therapy predominantly reduced lung lesions caused by CEP, and the lesions which did not respond to the therapy might indicate a diagnosis of sarcoidosis.

In this case, increased IFN-γ, IL-4 and IL-5 were detected in the BAL fluid. Corticosteroid therapy reduced IL-4 and IL-5 to undetectable concentrations but not IFN-γ. The activation of Th1-type lymphocytes is known to have an important role in the development of sarcoidosis (20). IFN-γ is suggested to be important in the activation of macrophages, resulting in processing inflammatory cell accumulation, granuloma formation, and fibrogenesis (21, 22). Indeed, in the BAL fluid of active sarcoidosis, only Th1 cytokines can be found, but Th2 cytokines such as IL-4 and IL-5 cannot be detected (12, 20, 23). However, CEP is characterized by the accumulation of eosinophils in the alveolar spaces and the interstitium of the lung. In the BAL fluid from patients with CEP, IL-2, IFN-γ (Th1 cytokine) and IL-5 (Th2 cytokine) can be detected, indicating that both Th1 and Th2 cells may be responsible for the pathogenesis of this disorder (12, 13). IL-5, a cytokine known to induce eosinophil proliferation, differentiation and activation, is important in eosinophilia *in vivo* (24, 25). IL-4 is known to be the master cytokine of the Th2-type immune response (2), and can stimulate eosinophil transmigration to the airway mucosa by enhancing the expression of vascular cell adhesion molecule 1 (25) and the release of eosinophil-survival stimulating activity from bronchial epithelial cells (27). In this case, IL-4 and IL-5 were elevated in the BALF, but neither was detectable after the corticosteroid treatment, correlated with the clinical course of CEP, indicating that the Th2-related cytokines might be responsible for eosinophil infiltration into the lungs.

In this case, radiographical lesions of pulmonary sarcoidosis and IFN-γ levels in the BAL fluid did not respond well to corticosteroid therapy, but serum ACE levels were reduced by the therapy. Serum ACE level is higher in clinically active than in inactive disease. Since ACE is known to be produced by epithelioid cells of granulomas (28), serum ACE reflects the total-body granuloma burden and not just the degree of lung involvement (29, 30). From these observations, corticosteroid therapy

might partially improve granulomatous lesions due to sarcoidosis except in lungs.

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