

CASE REPORT

Chronic eosinophilic pneumonia progressing to lung fibrosis

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Chronic eosinophilic pneumonia progressing to lung fibrosis. K. Yoshida, N. Shijubo, H. Koba, Y. Mori, M. Satoh, T. Morikawa, S. Abe. ©ERS Journals Ltd 1994.

ABSTRACT: A 65 year old Japanese man was hospitalized with fever. Opacities distributed mainly in the subpleural regions were found on chest computed tomographic scan (CT), and these promptly cleared with corticosteroid therapy.

Four years later, he presented with severe eosinophilia. Both chest X-ray and high resolution CT scan showed ground-glass opacities and honeycombing, suggesting lung fibrosis. A lung biopsy demonstrated intra-alveolar eosinophil infiltration, interstitial thickening with eosinophil infiltration, and a widely-distributed desquamative interstitial pneumonia-like reaction. With corticosteroid therapy, the ground-glass opacities decreased with a corresponding clinical improvement, although lung honeycombing and blood eosinophilia remained.

In this case, circulating intercellular adhesion molecule-1 and circulating and bronchoalveolar lavage fluid eosinophil granule proteins were felt to be more effective markers for evaluating disease activity than the blood eosinophil number.

Eur Respir J., 1994, 7, 1541-1544.

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Keywords: Chronic eosinophilic pneumonia, circulating intercellular adhesion molecule-1, desquamative interstitial pneumonia, eosinophilic cationic protein, lung fibrosis, major basic protein.

Received: September 7 1993

Accepted after revision March 16 1994

Idiopathic chronic eosinophilic pneumonia (CEP) is a rare disorder, characterized by systemic and pulmonary manifestations, blood eosinophilia, fluffy peripheral opacities on chest X-ray, and a prompt response to corticosteroid therapy [1-3]. Histological studies of CEP show an intra-alveolar exudate of eosinophils, histiocytes and occasionally amorphous material, and eosinophilic interstitial infiltration [1, 3-5]. Although focal areas of interstitial fibrosis are occasionally found in CEP, the alveolar septa are usually intact and interstitial fibrosis is minimal [4-6]. We report on a case of CEP progressing to lung fibrosis.

Case report

A 65 year old Japanese man, who had been a sailor until 60 yrs of age, was hospitalized in September 1989 with fever. He had not received any drugs for the past 2 yrs, and he had smoked one pack of cigarettes daily for 50 years. The leucocyte count was $12.3 \times 10^9/l^{-1}$ with 3% eosinophils. Chest X-ray showed infiltrative opacities and chest computed tomographic (CT) scan (10 mm thick slices) demonstrated opacities distributed mainly in the subpleural regions (fig. 1). Corticosteroid therapy (dexamethasone, 4 mg daily) was prescribed, from September 9, 1989, and the opacities promptly decreased. Corticosteroid therapy was progressively reduced and stopped on October 3, 1989, and the patient remained asymptomatic.

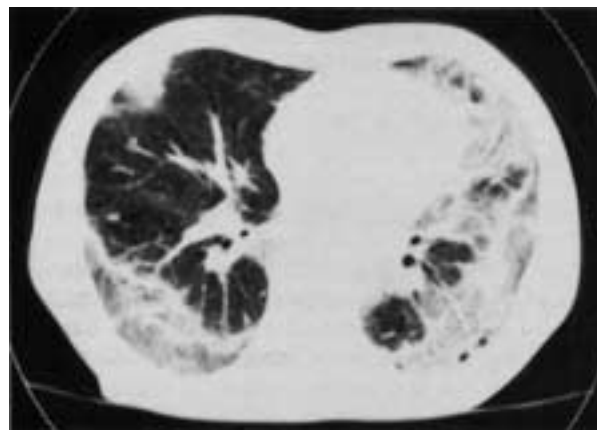


Fig. 1. - Chest computed tomographic scan (CT) (10 mm thick slices) on first admission, showing opacities distributed mainly in the subpleural regions in bilateral lungs.

The patient was referred to us again in February 1993, complaining of fever, productive cough, and dyspnoea on exertion of 3 months duration. He had received no new drugs since October 1989. On admission he had intermittent fever (37.6-38.4°C). Fine crackles were present but no wheezes or cardiac murmurs were heard. The patient had finger clubbing, physical examination was otherwise normal. Chest X-ray showed reticulo-nodular opacities in both lung fields, and high resolution CT (1.5 mm thick slices) showed ground-glass opacities and honeycombing (fig. 2).

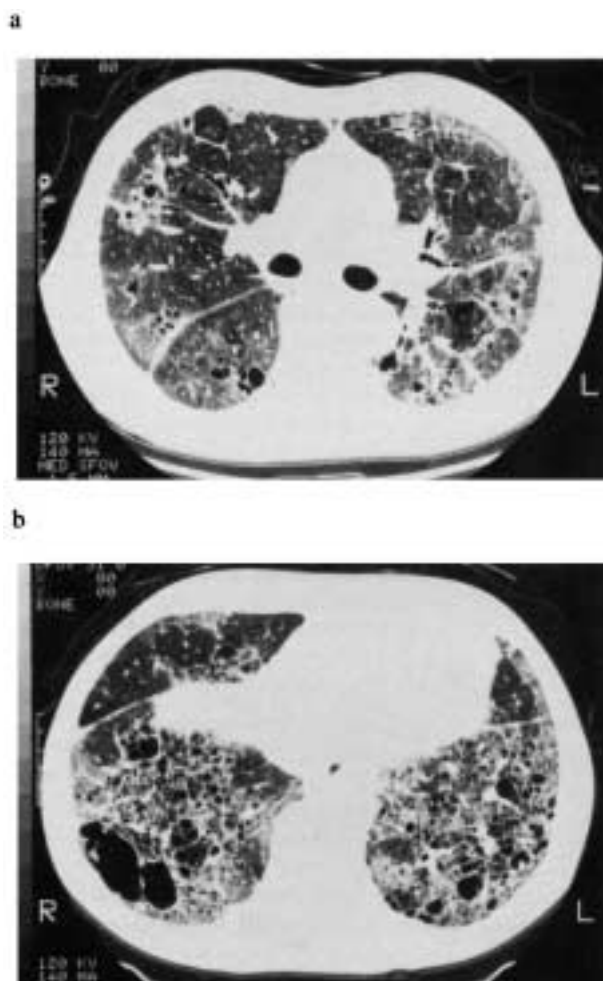


Fig. 2. – High resolution computed tomographic scan (CT) (1.5 mm thick slices) of the chest on second admission showing: a) ground-glass opacities; and b) honeycombing.

Laboratory data were remarkable for leucocyte count $17.4 \times 10^9 \cdot l^{-1}$ with 57% eosinophils; erythrocyte sedimentation rate (ESR) $58 \text{ mm} \cdot \text{h}^{-1}$; C-reactive protein (CRP) $6.59 \text{ mg} \cdot \text{dl}^{-1}$; and lactate dehydrogenase (LDH) $679 \text{ IU} \cdot \text{ml}^{-1}$ (normal range $190\text{--}440 \text{ IU} \cdot \text{ml}^{-1}$). Serum immunoglobulin levels were: immunoglobulin G (IgG) $22.18 \text{ mg} \cdot \text{ml}^{-1}$; immunoglobulin A (IgA) $3.45 \text{ mg} \cdot \text{ml}^{-1}$; immunoglobulin M (IgM) $0.83 \text{ mg} \cdot \text{ml}^{-1}$; and immunoglobulin E (IgE) $8.8 \text{ IU} \cdot \text{ml}^{-1}$. Antinuclear antibody titre was $\times 80$ with a speckled pattern: anti-deoxyribonucleic acid (DNA), anti-extractable nuclear antigen (ENA), anti-ribonucleoprotein, and anti-Sm antibodies were negative. Concentrations of soluble intercellular adhesion molecule-1 (ICAM-1) ($656 \text{ ng} \cdot \text{ml}^{-1}$), major basic protein (MBP) ($2,834 \text{ ng} \cdot \text{ml}^{-1}$), and eosinophil cationic protein (ECP) ($318 \text{ ng} \cdot \text{ml}^{-1}$) in the circulation were prominently increased (table 1), which were measured as described previously [7–9]. Results of tests for acid-fast bacilli and fungi in sputum, for parasites in stools and for antibodies to *Cryptococcus neoformans*, *Aspergillus fumigatus*, *A. niger*, *Microspora faeni*, *Thermoactinomyces vulgaris*, *T. viridis* and *Alternaria* in serum were negative. Pulmonary function tests showed a decrease in carbon monoxide dif-

fusing capacity: total lung capacity (TLC) 5.38 l (105% pred); vital capacity (VC) 3.42 l (105% pred); forced expiratory volume in one second (FEV_1) 2.59 l (78% pred); diffusing capacity of the lung for carbon monoxide (DLCO) $8.81 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ (40% pred); and DLCO/alveolar volume (VA), $2.01 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \cdot \text{l}^{-1}$. Arterial blood gas analysis showed that arterial oxygen tension (PaO_2) was 8.1 kPa (60.7 mmHg) and arterial carbon dioxide tension (PaCO_2) was 4.4 kPa (33.1 mmHg) whilst breathing room air.

Examination of cardiac and abnormal echogram, abdominal CT scan, gallium scan, fiberoptic gastroscop, and of ophthalmological examinations was normal. Bone marrow aspiration examination showed increased eosinophils, (11.2%). The results of bronchoalveolar lavage (BAL) in right middle lobe were: total cell count $4.5 \times 10^5 \text{ ml}^{-1}$; and differential cell count: alveolar macrophages 42.6%; lymphocytes 7.3%; neutrophils 2.8%; and eosinophils 47.3%. MBP and ECP concentrations in BAL fluid were 12.0 and $2.7 \text{ ng} \cdot \text{ml}^{-1}$, respectively (table 1). Lung biopsy was performed in the posterior segment of the right upper lobe, under thoracoscopy. Histological study revealed intra-alveolar and interstitial infiltration by eosinophils, and widely-distributed features suggesting desquamative interstitial pneumonia (DIP): alveolar septal thickening, hyperplasia of pneumocytes, and an increased number of intra-alveolar macrophages (fig. 3). No evidence of vasculitis was observed. Special staining and culture for acid-fast bacilli and fungi were negative. The patient was administered corticosteroid therapy (prednisolone, 30 mg daily) beginning March 31, 1993, and during the next week his symptoms markedly improved. The ground-glass opacities on CT images were gradually reduced, with

Table 1. – Laboratory data before and after corticosteroids (CS)

	Before CS	After CS
Blood		
WBC $\times 10^9 \cdot l^{-1}$	17.4	19.8
Eosinophil $\times 10^9 \cdot l^{-1}$	9.9	9.1
ESR $\text{mm} \cdot \text{h}^{-1}$	58	9
CRP $\text{mg} \cdot \text{dl}^{-1}$	6.59	<0.25
LDH $\text{IU} \cdot l^{-1}$	679	311
MBP* $\text{ng} \cdot \text{ml}^{-1}$	2,834	1,468
ECP* $\text{ng} \cdot \text{ml}^{-1}$	318	85.9
sICAM-1* $\text{ng} \cdot \text{ml}^{-1}$	656	106
Bronchoalveolar lavage		
TCC $10^5 \cdot \text{ml}^{-1}$	4.5	4.4
Eosinophil %	47.3	10.3
MBP* $\text{ng} \cdot \text{ml}^{-1}$	12	<4.4
ECP* $\text{ng} \cdot \text{ml}^{-1}$	2.7	<2.0

The samples in the circulation and in BAL fluid were obtained at 54 days and 26 days after initiation of corticosteroid therapy, respectively. WBC: white blood cell count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LDH: lactate dehydrogenase; MBP: major basic protein; ECP: eosinophil cationic protein; sICAM-1: soluble intercellular adhesion molecule-1; TCC: total cell count; *: normal levels of circulating MBP, ECP and sICAM-1 were $<600 \text{ ng} \cdot \text{ml}^{-1}$ ($n=54$), $2.2\text{--}16.9 \text{ ng} \cdot \text{ml}^{-1}$ ($n=54$) and $53\text{--}153 \text{ ng} \cdot \text{ml}^{-1}$ ($n=48$), respectively. Levels of MBP and ECP in BAL fluids obtained from six normal controls were $<4.4 \text{ ng} \cdot \text{ml}^{-1}$ and $<2.0 \text{ ng} \cdot \text{ml}^{-1}$, respectively.

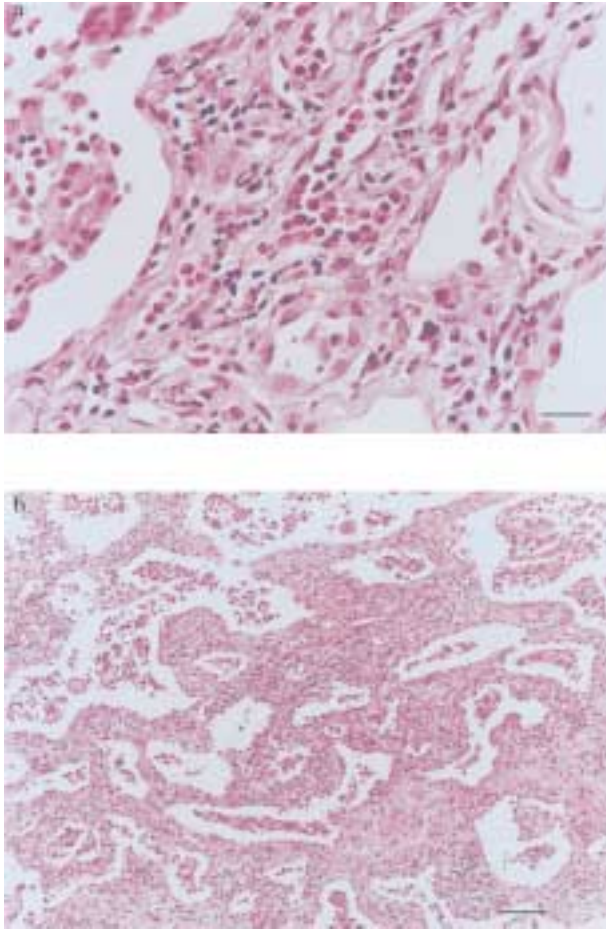


Fig. 3. – Microphotographs from a lung biopsy specimen showing: a) intra-alveolar and interstitial infiltration by eosinophils; and b) widely-distributed features suggesting desquamative interstitial pneumonia: an increased number of intra-alveolar macrophages, hyperplasia of pneumocytes, and interstitial thickening. (Haematoxylin-eosin staining. Bar: a) 100 μm and b) 25 μm .

a corresponding improvement in blood tests (May 24: ESR 9 $\text{mm}\cdot\text{h}^{-1}$; CRP $<0.25 \text{ mg}\cdot\text{dl}^{-1}$; LDH 311 $\text{IU}\cdot\text{ml}^{-1}$; and circulating ICAM-1 106 $\text{ng}\cdot\text{ml}^{-1}$), whilst blood eosinophil count ($9.1\times 10^9\cdot\text{l}^{-1}$) circulating MBP (1,468 $\text{ng}\cdot\text{ml}^{-1}$) and ECP concentrations (85.9 $\text{ng}\cdot\text{ml}^{-1}$) were still high. Eosinophil count (10.3%), MBP ($<4.4 \text{ pg}\cdot\text{ml}^{-1}$) and ECP concentrations ($<2.0 \text{ pg}\cdot\text{ml}^{-1}$) were decreased in BAL fluid (April 26). The dosage of prednisolone was gradually reduced to 10 mg daily in December, 1993. At that time, laboratory tests showed the following: leucocyte count $15.1\times 10^9\cdot\text{l}^{-1}$ with 12% eosinophils; ESR 12 $\text{mm}\cdot\text{h}^{-1}$; CRP 0.30 $\text{mg}\cdot\text{dl}^{-1}$; circulating MBP 752 $\text{ng}\cdot\text{ml}^{-1}$; circulating ECP 38.6 $\text{ng}\cdot\text{ml}^{-1}$; and circulating ICAM-1 98 $\text{ng}\cdot\text{ml}^{-1}$. The ground-glass opacities were greatly reduced on chest CT images, but the honeycombing still remained.

Discussion

The main causes of pulmonary infiltrates with blood eosinophilia are: drug reaction; mycobacterial, fungal and parasitic infections; vasculitides Churg-Strauss

syndrome; inflammatory airway diseases, such as allergic bronchopulmonary aspergillosis; idiopathic CEP; and idiopathic hypereosinophilic syndrome (HES) [6, 10]. Idiopathic CEP is a clinicopathologic entity characterized by systemic and pulmonary manifestations, such as fever, weight loss, cough, dyspnoea, blood eosinophilia, peripheral opacities on chest X-ray, and a prompt response to corticosteroid therapy [1–3]. Idiopathic HES is also a clinical disease entity of unknown aetiology characterized by severe eosinophilia and a range of clinical problems, including cardiovascular, thromboembolic, respiratory, skin and/or nervous system complications [11, 12]. External causes of eosinophilia, such as drug reaction and infections, were ruled out in this patient, and vasculitis was not found histologically. Since blood eosinophilia persisted even after corticosteroid therapy, we considered that the patient might have either CEP or HES. However, whole body examinations including cardiac, neurological, dermatological and ophthalmological examinations were normal, thus ruling out HES.

This case presented an unusual clinical course. In 1989, the patient had opacities distributed mainly in the subpleural regions on chest CT images, and a prompt response to corticosteroid therapy. There was no information on pulmonary eosinophilia, since BAL was not performed. However, the presentation was compatible with CEP without blood eosinophilia, as CARRINGTON *et al.* [1] originally described that some patients with CEP had low eosinophil count in the circulation. In 1993, this case had striking pulmonary and blood eosinophilia and honeycombing on high resolution CT images, suggesting lung fibrosis [13]. In CEP, histological findings are characterized by interstitial and intra-alveolar infiltrates with activated eosinophils in various stages of degranulation [1, 3–6]. It has been reported that the alveolar septa are usually intact and fibrosis is minimal in CEP, despite extensive cellular infiltration [4–6]. There have been very few reports on CEP with lung fibrosis: JEDERLINIC *et al.* [3] reported that one of 19 cases with CEP had linear fibrotic changes on chest X-ray. In our patient, a lung biopsy under thoracoscopy demonstrated intra-alveolar and interstitial infiltration by eosinophils and a widely-distributed DIP-like reaction. A focal DIP-like reaction is usually found in CEP [14], and DIP itself causes only very minor infiltration of eosinophils in the alveolar septa and intra-alveolar spaces [15]. This patient's longstanding repeated episodes of CEP may have much to do with his progression to lung fibrosis. He might have had mild episodes of CEP before the initial presentation in 1989. Persistent stimulation from activated eosinophils could be related to progression to lung fibrosis, since eosinophil granule proteins play an important role during the process of endomyocardial fibrosis in HES [16].

To assess the disease activity, we analysed concentrations of soluble ICAM-1, MBP, and ECP in the circulation, and of MBP and ECP in BAL fluids. Circulating ICAM-1 concentrations seem to reflect a specific mix of production of cytokines, including tumour necrosis factor-alpha and interferon-gamma [17]. Prominently increased concentrations of circulating ICAM-1 are found in

idiopathic pulmonary fibrosis [7], and far advanced tuberculosis [17], and may reflect the disease activity of these disorders. MBP and ECP levels reflect the number of activated (secreted) eosinophils [8, 9, 16, 18, 19]. They appear to be useful markers for understanding and management of eosinophil-associated diseases, since their concentrations in blood or local fluids may, in many cases, uniquely reflect the ongoing disease process [16]. On second admission, the patient had quite high concentrations of soluble ICAM-1, MBP and ECP in serum compared to healthy controls, as well as of MBP and ECP in BAL fluid. After corticosteroid therapy, the concentrations of circulating ICAM-1 and BAL fluid MBP and ECP had decreased to normal limits; and although circulating MBP and ECP concentrations remained high, they had also remarkably decreased, suggesting that activation of eosinophils had been greatly reduced by corticosteroid therapy. We feel that these serum markers have proved to be more useful for evaluating the disease activity than blood eosinophil number in this case.

The response of this patient's blood eosinophilia to therapy was quite sluggish during the period of low dosage corticosteroid therapy, although the therapy was effective for his pulmonary eosinophilia. Circulating eosinophils at 54 days after initiation of therapy were activated, since circulating MBP and ECP concentrations remained elevated. By contrast, BAL MBP and ECP decreased with therapy. In this case, the low dosage of corticosteroid resulted in a distinct decrease of MBP and ECP in the blood and in the lung, a surprising finding that we cannot explain.

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