Allergology International (1999) 48: 79–83

Case Report

Possible eosinophilic pneumonia from *Alternaria*

Shoichiro Taniuchi, Rika Miyazaki, Satoshi Yoshijima and Yohnosuke Kobayashi

Department of Paediatrics, Kansai Medical University, Osaka, Japan

Abstract

We reported a 15-year-old Japanese girl with possible eosinophilic pneumonia (EP) from inhaled Alternaria. She presented with a fever, cough and general fatigue and with a moderate infiltrate in the right lower to middle lung fields on a chest roentgenogram one week previously. On admission, the above infiltrate had disappeared, while a left upper infiltrate had appeared. Eosinophilic pneumonia (EP) was diagnosed by a cytological study of bronchoalveolar lavage fluid and histology of a transbronchial lung biopsy. Skin test to and specific serum IgE antibody against Alternaria were both positive. An inhaled Alternaria challenge test showed both immediate and late phase allergic reactions as evidenced by %FEV1. In addition, Alternaria was significantly detected in all places of the patient's house. Alternaria could be a causative organism of EP and should always be considered one of its etiologic agents.

Key words: *Alternaria*, bronchoprovocation test, eosinophilic pneumonia.

Introduction

Eosinophilic pneumonia (EP) refers to a poorly understood and ill-defined group of disorders that are marked by infiltrations of the lung by eosinophils with or without an excess of these cells in the peripheral blood.[1] *Alternaria* commonly causes bronchial asthma and allergic rhinitis.[2–4] It is also considered to be a causative antigen of hypersensitivity pneumonitis.[5] However, only one case of eosinophilic pneumonia caused by *Alternaria* has been cited in the literature.[6] We report here a case of possible eosinophilic pneumonia from inhaled *Alternaria*.

Correspondence: Dr Shoichiro Taniuchi, Department of Paediatrics, Kansai Medical University, Fumizonocho 10–15, Moriguchi, Osaka 570–8506, Japan.
Email: taniuchi@takii.kmu.ac.jp

Received 8 January 1998. Accepted for publication 28 August 1998.

Clinical summary

A 15-year-old girl was referred to us in mid-August 1994 for further evaluation and treatment of low-grade fever and general fatigue. One month prior to admission the patient gradually developed fever, cough and general fatigue after undertaking regular house-cleaning, which included cleaning the filters of an air conditioner. Pulmonary infiltrates in the right middle and left upper lobes were then found on a chest roentgenogram (Fig. 1, left). The girl was placed on an antibiotic but the symptoms persisted until admission. Personal history was negative for bronchial asthma. Family history disclosed that the patient's mother had suffered from pollen allergy for the previous 10 years. The family had cared for no pet animals or birds. The patient's room was covered with a carpet on Japanese matting (*tatami*). Her wooden house was built 20 years before and did not have any roof leaks.

On admission the patient weighed 47 kg and measured 147 cm. Her pulse was 72 b.p.m., temperature 37.5°C, respiratory rate 16/min and blood pressure 108/68 mmHg. No signs of anemia, jaundice or cyanosis were observed.

Fine crackling rales were audible in the left upper lung field. Pulmonary function tests showed a percentage forced vital capacity (%FVC) of 92.2 and a forced expiratory volume in 1's (FEV1) percentage of 94.8. Leukocyte count was 10 400/ μL with 48% polymorphonuclear cells, 21% eosinophils (an absolute count of 2184/ μL), 26% lymphocytes and 5% monocytes. The erythrocyte sedimentation rate was 73 mm/h, while c-reactive protein (CRP) was 0.5 mg/dL and total serum immunoglobulin E (IgE) level was 267.6 IU/mL. Peripheral lymphocyte subsets were

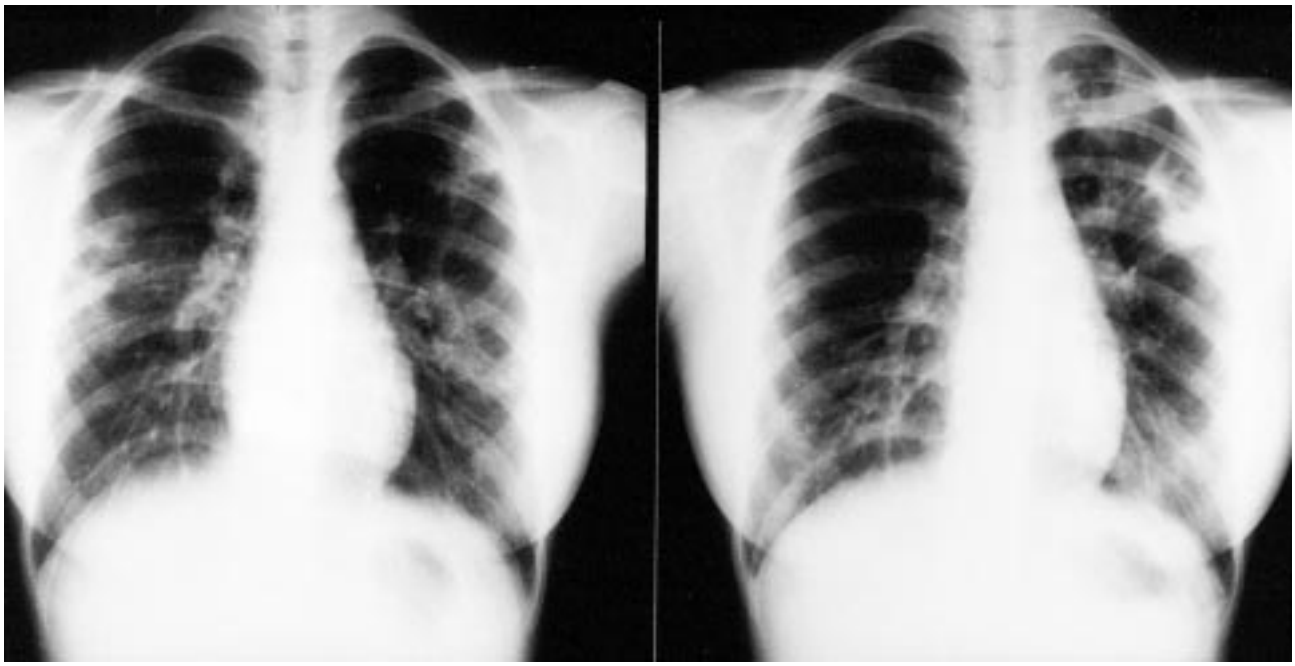

Fig. 1 Chest roentgenogram 2 weeks prior to admission demonstrated small dense infiltrates in the right middle and left upper lobes (left). On admission, a small dense consolidation appeared in the left upper lobe (right).

normal. Stool parasitic ova were negative. Serum mycoplasma pneumonia antibody, antinuclear antibody, antigen-specific IgE antibody against *Candida albicans* and *Aspergillus fumigatus* were negative. A skin test to and specific IgE antibody against *Alternaria* were both positive (Table 1). Precipitating-antibody to *Alternaria kikuchiana* (100 ng/mL) measured by double-immunodiffusion assay was also positive, but that to *Aspergillus fumigatus* (100 ng/mL) was negative.[7]

To confirm the diagnosis of eosinophilic pneumonia, bronchoscopy was performed after informed consent was obtained from the patient and her parents. Bronchoalveolar lavage (BAL) fluid yielded a cell count of 6.6×10^5 /mL, with 47.8% eosinophils, 29.6% macrophages, 20.5% lymphocytes and 1.1% neutrophils. Bronchoalveolar lavage fluid, sputum, urine and blood cultures were sterile. A transbronchial lung biopsy specimen showed severe thickening of the bronchial basement membrane and increased interstitial connective tissue with mild eosinophilic infiltration (Fig. 2). On a chest roentgenogram, a right middle lobe infiltrate had disappeared, whereas a left upper lobe infiltrate had appeared (Fig. 1, right). Computed tomography of the chest showed a dense consolidation in the left upper lobe (Fig. 3).

Nineteen days after admission we carried out an antigen challenge test according to the guidelines of

Table 1. Specific RAST IgE and skin prick test (SPT) against fungal antigens

	RAST	SPT
Alternaria	+*	+**
Aspergillus	–	–
Candida albicans	–	–

* More than score 3; ** more than twice of control solution; RAST, radioallergosorbent test.

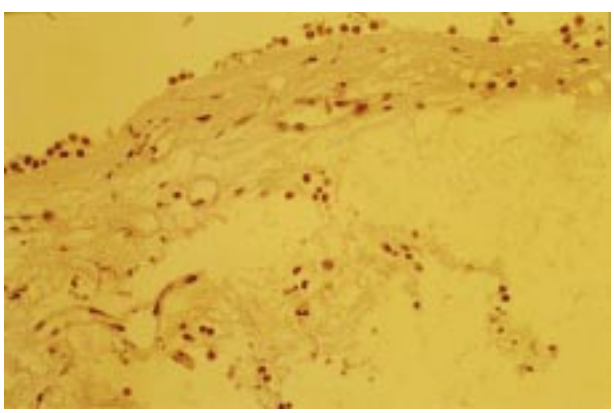

Fig. 2 Histology of a transbronchial lung biopsy specimen showing severe thickening of the bronchial basement membrane and increased interstitial connective tissue with mild eosinophilic infiltration.

Shapiro.[8] Briefly, the antigen was delivered by an ultrasonic nebulizer (Omuron, Tokyo, Japan) with an initial inhalation of $1:10^{10}$ dilution of the *Alternaria kikuchiana* solution (10 mg/mL, Torii Chemical Co. Ltd, Tokyo, Japan) in a dose of 2 mL. Pulmonary functions were measured 10 min after the antigen inhalation. Figure 4 showed changes of %FVC and %FEV1, which decreased from 75.9% to 66.5% and 76% to 61% after the antigen inhalation ($1:10^6$ dilution), respectively, and then returned to initial levels after a salbutamol inhalation. Nine hours after the antigen challenge, %FVC and %FEV1 reduced to 57.5% and 45%, respectively, when moist rales became audible and severe cough appeared. As %FVC and %FEV1 did not recover even after the second salbutamol inhalation, hydrocortisone was given. Twelve hours after the challenge test, %FVC and %FEV1 returned to normal levels.

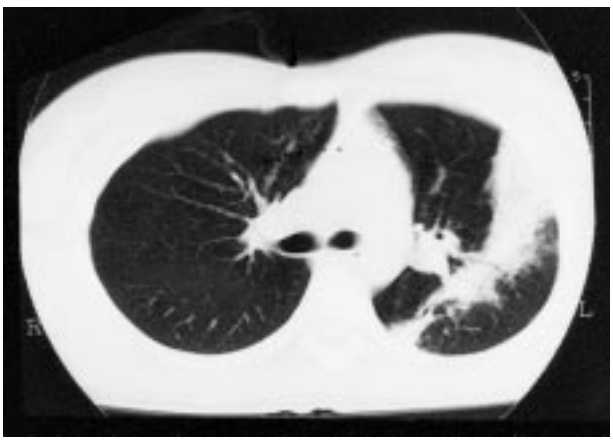

Fig. 3 Computed tomography of the chest on admission showed a dense consolidation in the left lobe.

From the sterile Petri dishes containing Sabouraud's culture medium supplemented with antibiotics, which were exposed for 10 min at several places in the patient's house, *Alternaria* was significantly found in all places (Table 2). No other fungi were detected in these places (Table 2).

Oral corticosteroid therapy was initiated with 1 mg/kg of prednisolone. As both infiltration and eosinophilia disappeared 1 week later, prednisolone was then tapered and withdrawn. To protect the recurrence, beclomethasone inhalation was continued for 6 months and then disodium chromoglycate inhalation therapy was undertaken for 2 years and 6 months. Three years after onset the patient was free of symptoms, although specific IgE antibodies against *Alternaria* still remained positive. No infiltration was seen on chest roentgenograms.

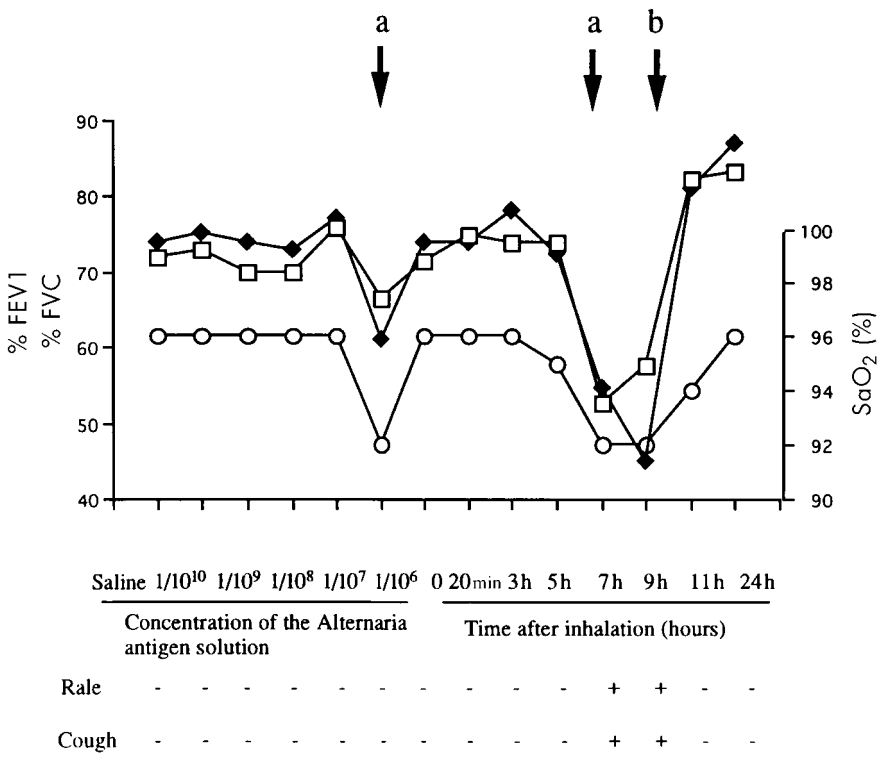

Fig. 4 An antigen challenge test was performed with an initial inhalation dose of 1:100 dilution of the *Alternaria kikuchianas* extract solution (concentration: 10 mg/mL, Torii Chemical Co. Ltd, Tokyo, Japan) used in the prick test. (□), %FVC; (◆), %FEV1; (○), SaO_2. %FEV1 decreased at a concentration of $1:10^6$ of the *Alternaria* antigen solution and then 9 h later it markedly reduced. a, salbutamol inhalation; b, intravenous hydrocortisone (500 mg)

Table 2. Distribution of fungus in the house of the patient by the method of sedimentation on a mycological medium

Location	Fungus type		
At the side of the telephone	*Alternaria* 4*	*Penicillium* 1*	Yeast 8*
In the rest room	*Alternaria* 4*	*Penicillium* 1*	Yeast 8*
On the corridor	*Alternaria* 2*		
On the patient's desk	*Alternaria* 3*		

* numbers of colony

DISCUSSION

We presented a case of possible eosinophilic pneumonia from *Alternaria* of a 15-year-old Japanese girl. The patient was diagnosed as having EP because of her symptoms and BAL findings. However, in the present case we should carefully rule out another disease. Because some patients with hypersensitivity pneumonitis (HP) show BOOP (bronchiolitis obliterans organizing pneumonia) patterns on chest roentogenograms, our case was considered to be a variant of HP.[9] However, BOOP shows the distinct histologic and BAL findings, as opposed to eosinophilic pneumonia, and so it is possible that our case is not a BOOP.[10]

It is difficult to clearly distinguish eosinophilic pneumonia and allergic bronchopulmonary alternariosis (ABPAI) in this case. However, according to diagnostic criteria of allergic bronchopulmonary aspergillosis (ABPA),[11] the present case could hardly be diagnosed ABPAI because of the non-elevated IgE and the lack of an asthma history. Further study is needed in order to establish what constitutes the diagnostic criteria of ABPAI.

The patient demonstrated positive responses in the prick test and specific IgE antibody. Complete response of oral corticosteroid and no relapse of symptoms were observed. Both BAL and sputum were negative for fungal cultures. Therefore, *Alternaria* is unlikely to have caused fungal pneumonia in the present case.

In addition, we excluded a number of etiologic factors that could have produced EP. No drug had been prescribed before the onset and no pathogenic organisms were detected in any sample obtained from our patient. *Aspergillus* was not considered to be a causative agent because both specific IgE and a prick test against *Aspergillus* were negative.

Although the pathogenesis of EP is still unknown, Badesch *et al*. indicate that it may be related to a hypersensitive phenomenon to an inhaled antigen.[12] In our case, the symptoms started after the patient undertook general house-cleaning. Further, *Alternaria* was also significantly found in her house when compared with other fungi. Usually, general house-cleaning is performed every season in Japan. Therefore, it is thought that a large quantity of inhaled *Alternaria* antigen was scattered in the house and provoked eosinophilic pneumonia.

On discharge, we advised the patient to clean up her house and to inhale beclomethasone to prevent the recurrence of EP. In her house a large quantity of *Alternaria* antigen was considered to be constantly present, although inhaled beclomethasone may be considered as being effective in inhibiting the production of cytokines and chemokines such as interleukin (Il)-5 and IL-8 superfamily regulated on activation normal T-expressed and secreted (RANTES).

Greenberger[11] advocated that patients with EP should be divided into four types: (i) acute (less than 5 days' duration); (ii) chronic (insidious onset); (iii) simple (Löffler syndrome); and (iv) tropical (from filariasis). Many cases of simple eosinophilic pneumonia are likely to be due to parasitic infections or medications. Acute EP is characterized by acute respiratory failure with diffuse pulmonary infiltrates. However, patients with chronic eosinophilic pneu-monia (CEP) can present peripheral infiltrates in the distal two-thirds of the lung fields. The present case was classified as CEP because of the persistent symptoms, findings of chest roentgenograms and computed tomographic scans, and a complete response to corticosteroid hormone.

In the antigen bronchoprovocation test the dual airway response was observed as being associated with clinical symptoms such as cough and rale. However, fever, elevated CRP and elevated eosinophils were not observed on the next day of the test. As the patient had a severe cough and showed decreased pulmonary function 9 h after the onset, we prescribed hydrocortisone to treat clinical symptoms. Therefore, the steroid hormone was considered to inhibit Arthus-type allergic reaction.

Bronchial asthma is characterized by eosinophilic infiltration of the bronchi and bronchioles,[13] whereas the features of eosinophilic pneumonia are eosinophilic infiltration in the interstitium and the small air spaces of the lung.[14] In a primate model of allergic bronchopulmonary aspergillosis, Slavin *et al*. reported that the occurence of the characteristic eosinophilic infiltration may need the association of both IgG and IgE antibodies to *aspergillus*.[15] In the present case, the occurrence of the disease may be related to both IgE and IgG antibodies to *Alternaria*, although it is difficult to clearly distinguish

between EP and ABPAI, as already discussed. Further study is needed to elucidate why *Alternaria* causes EP.

Alternaria should be considered to be one of the etiologic agents of eosinophilic pneumonia.

Acknowledgments

A part of this study was supported by the Mami Mizutani Foundation.

References

1 Liebow AA, Carrington CB. The eosinophilic pneumonias. *Medicine* 1969; 48: 251–85.
2 Cantani A, Businco E, Maglio A. Alternaria allergy: a three-year controlled study in children treated with immunotherapy. *Allergol. Immunopathol. (Madr)* 1988; 16: 1–4.
3 Schultze-Werninghaus G, Levy J, Bergmann EM *et al.* Clinical significance of airborne Alternaria tenuis-spores: seasonal symptoms, positive skin and bronchial challenge tests with Alternaria in subjects with asthma and rhinitis. *Experientia* 1987; 51: 153–6.
4 Horner WE, Helbling A, Salvaggio JE *et al.* Fungal allergens. *Clin. Microbiol. Rev.* 1995; 8: 161–79.
5 Schlueter DP, Fink JN, Hensley GT. Wood-pulp workers' disease: a hypersensitivity pneumonitis caused by Alternaria. *Ann. Intern. Med.* 1972; 77: 907–14.
6 Ogawa H, Fujimura M, Amaike S *et al.* Eosinophilic pneumonia caused by Alternaria alternata. *Allergy* 1997; 52: 1005–8.
7 Ouchterlony O, Nilsson LA. Immunodiffusion and immunoelectrophoresis. In: Weir DM, Herzenberg LA, Blackwell C, (eds). *Handbook of Experimental Immunology*, Vol. 1: Immunochemistry. Oxford: Blackwell Science, 1986; 32. 1–32.50.
8 Shapiro GG. Bronchoprovocation in children. *Pediatrician* 1991; 18: 269–79.
9 Epler GR, Colby TV, McLoud TC *et al.* Bronchiolitis obliterans organizing pneumonia. *N. Engl. J. Med.* 1985; 17: 152–8.
10 Izumi T, Kitaichi M, Nishimura K *et al.* Bronchiolitis obliterans organizing pneumonia. Clinical features and differential diagnosis. *Chest* 1992; 102: 715–9.
11 Greenberger PA. Immunologic aspects of lung diseases and cystic fibrosis. *JAMA* 1997; 278: 1924–30.
12 Badesch DB, King TE, Schwarz MI. Acute eosinophilic pneumonia: a hypersensitivity phenomenon? *Am. Rev. Respir. Dis.* 1989; 139: 249–52.
13 Dunnil MS. The pathology of asthma with special reference to changes in the bronchial mucosa. *J. Clin. Immunol.* 1960; 13: 27–33.
14 Carrington CB, Addington WW, Goff AM *et al.* Chronic eosinophilic pneumonia. *N. Engl. J. Med.* 1969; 280: 787–98.
15 Slavin RG, Fisher VW, Levine EA *et al.* A primate model of allergic bronchopulmonary aspergillosis. *Int. Arch. Allergy Appl. Immunol.* 1978; 56: 325–33.