Respiratory Medicine Case Reports 5 (2012) 16–19

Contents lists available at SciVerse ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

The relationship between the clinical course and cytokine in a patient with cigarette smoking-induced acute eosinophilic pneumonia – A case report

Yuta Kono, Kenji Tsushima*, Koichi Yamaguchi, Seiko Soeda, Akahito Fujiwara, Shinya Sugiyama, Yuki Togashi, Satoshi Kasagi, Yasuhiro Setoguchi

Department of Respiratory Medicine, Tokyo Medical University Hospital, 6-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo, Japan

ARTICLE INFO

Article history:
Received 30 November 2011
Accepted 30 November 2011

Keywords:
Cigarette smoking
Acute eosinphilic pneumonia
RANTES

ABSTRACT

A 19-year-old female was admitted to our hospital because of a sudden onset fever and cough, and she was diagnosed to have acute eosinophilic pneumonia (AEP). The cause was thought to be cigarette smoking, because she had started smoking just before the development of AEP and her condition improved after cigarette smoking cessation, without corticosteroid treatment. The cytokines which are thought to be involved in eosinophilic accumulation in the lungs were analyzed using bronchoalveolar lavage fluid (BALF) and serum. Of the analyzed cytokines, only regulated on activation, normal T cell expressed and secreted (RANTES) increased in the serum after the improvement. RANTES is a unique chemokine which attracts not only eosinophils, but also T cells. Interestingly, in this case, the eosinophil count in the blood increased in parallel with the lymphocyte count after the improvement. These findings are interesting because it may help to understand the pathogenesis of AEP and the role of RANTES.

1. Introduction

Acute eosinophilic pneumonia (AEP) is a disease first described by Allen et al. in 1989, which is characterized by eosinophilic infiltration in the lungs, respiratory distress, a rapid therapeutic response to corticosteroids and the absence of relapse.[1] AEP induced by cigarette smoking was reported recently,[2–6] and it has been reported that there have been many cases of cigarette smoking-induced AEP which showed spontaneous improvement without corticosteroids, following cigarette smoking cessation.[7]

The pathogenic mechanism of AEP is not well understood. However, some cytokines, such as interleukun-5 (IL-5) and eotaxin, are thought to be associated with the eosinophilic infiltration in the lung, and have been evaluated in some reports.[8,9] We herein, present the clinical course and the changes in the level of cytokine expression with the time course in patient with cigarette smoking-induced AEP which showed a spontaneous improvement after the cessation of cigarette smoking.

2. Case report

A 19-year old female was admitted to our hospital because of a sudden onset fever and cough. She had developed the cough, fever and progression of dyspnea two days before admission. Antibiotic treatment prior to hospitalization was not effective for the clinical symptoms. She had started to smoke 20 cigarettes per day two weeks before the admission. She had a history of pollinosis, but no previous history of bronchial asthma. On admission, her temperature was 39.4 °C. Auscultation revealed wheeze in the bilateral lung fields.

An arterial blood gas analysis on room air revealed a pH of 7.434, PaO_2 of 58.1 torr and $PaCO_2$ of 34.2 torr, indicating hypoxemia. A chest radiograph revealed diffuse bilateral infiltrates and pleural effusion in the right lung, as shown in Fig. 1. The patient's peripheral white blood cell (WBC) count was 18,600 cells/mm^3, with 84.4% neutrophils, 11.8% lymphocytes and 1.0% eosinophils. The serum C-reactive protein was 11.5 mg/dl. Her serum immunoglobulins (Ig) were: IgG, 1048 mg/dl; IgA, 166.0 mg/dl; IgM, 199.0; IgE, 196.8 U/ml. Bronchoalveolar lavage fluid (BALF) was obtained from right B^5 area on the third hospital day. The total cell count in the BALF was 98.0 × 10^4/ml, which contained 5.6% neutrophils, 12.0% lymphocytes and 66.6% eosinophils. The CD4/CD8 lymphocytes ratio in the BALF was 1.26. Cultures of the BALF proved negative for bacteria and fungi. A specimen obtained from

* Corresponding author. Tel.: +81 3 3342 6111.
E-mail address: ktsushi@tokyo-med.ac.jp (K. Tsushima).

2213-0071/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmedc.2011.11.008

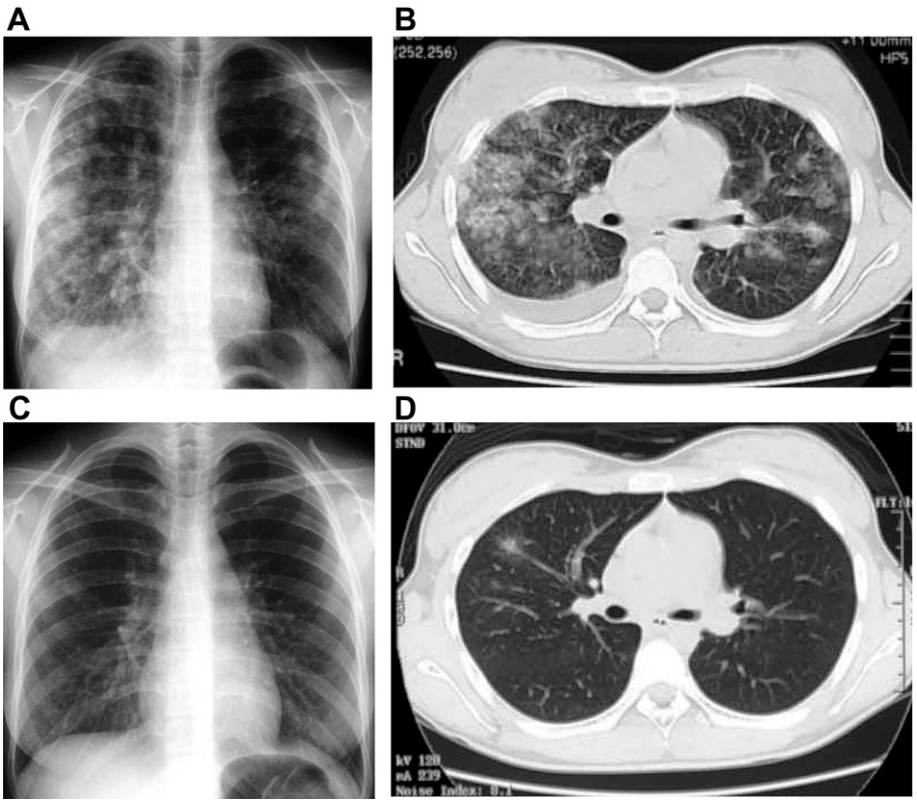

Fig. 1. Chest X-rays and CT scans. A. The chest X-ray on admission showed bilateral ground-glass opacification which was relatively right lung dominant. B. A chest CT on admission showed diffuse ground-glass opacification in the right lung, patchy opacification in the left lung, and a small amount of pleural effusion in the right lung, consist with the opacification on chest X-ray. C. A chest X-ray on the seventh hospital day showed subtle opacification, indicating remarkable improvement. D. A chest CT scan taken on the 12th hospital day showed decreases in the patchy infiltrates.

transbronchial lung biopsy (TBLB) demonstrated eosinophilic infiltration with fibrin exudates into the air space and edematous alveolar walls, indicating eosinophilic pneumonia.

On the fourth hospital day, her chest radiograph and symptoms had remarkably improved without corticosteroid treatment. Her hypoxemia had been gradually improving, and her SpO_2 was 97% under room air on the forth hospital day. The peripheral eosinophil count, which had been 186 cells/mm^3 on admission, increased gradually to 1400 cells/mm^3 on the seventh hospital day. Although the eosinophilia was prolonged over 1 month, the peripheral eosinophil count decreased to 504 cells/mm^3 2 months after the development of AEP. The peripheral lymphocyte count also increased from 2195 cells/mm^3 on admission to 3367 cells/mm^3 on the seventh hospital day, and decreased to 2720 cells/mm^3 2 months after the development of AEP. Therefore, the peripheral eosinophil count appeared to fluctuate in parallel with the peripheral lymphocyte count (Fig. 2).

The patient was discharged on the 13th hospital day. She quit smoking and has not resumed. Three months later, she continued to be asymptomatic. She reported having smoked two kinds of cigarettes. The lymphocyte stimulation tests (LSTs) for the both kinds of cigarette smoke extract were negative.

A cytokine analysis of the serum was performed on admission and on the 13th hospital day, and a cytokine analysis of the BALF was performed on the third hospital day (Fig. 3). The levels of IL-6, IL-5, IL-4, regulated on activation, normal T cell expressed and secreted (RANTES) and eotaxin in the serum on admission were 28.7 pg/ml, 2590 pg/ml, 98.5 pg/ml, 20000 pg/ml and 171 pg/ml, respectively. The cytokine analysis of the serum performed on the 13th hospital day revealed that the levels of IL-6, IL-5, IL-4 and eotaxin had decreased to 1.0 pg/ml, <5.0 pg/ml, 71.9 pg/ml and 104 pg/ml respectively, but that RANTES had increased to 78900 pg/ml. The levels of IL-6, IL-5, IL-4, RANTES and eotaxin in the BALF were 19.4 pg/ml, 883 pg/ml, 6.0 pg/ml, 42.1 pg/ml and 59.3 pg/ml, respectively. The levels of all cytokines in the BALF were lower than those in the serum obtained on admission. In particular, the level of RANTES in the BALF was much lower than that in the serum.

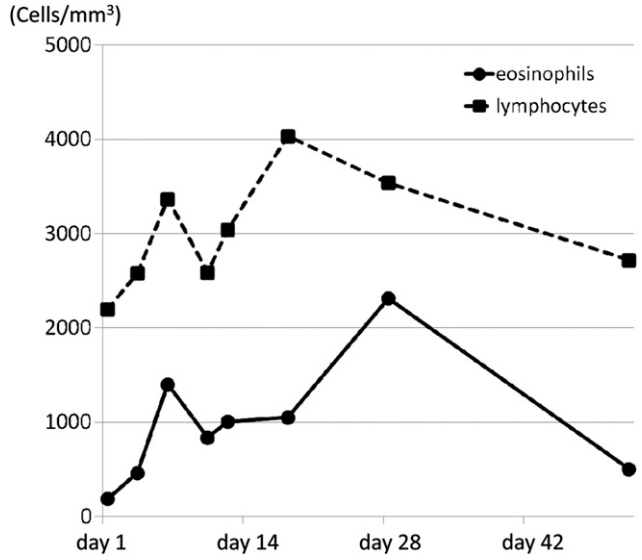

Fig. 2. Serial changes in the number of eosinophils and lymphocytes in the blood. The number of eosinophils increased gradually after the admission, and eosinophilia was prolonged for over 1 month. The number of lymphocytes fluctuated in parallel with the number of eosinophils.

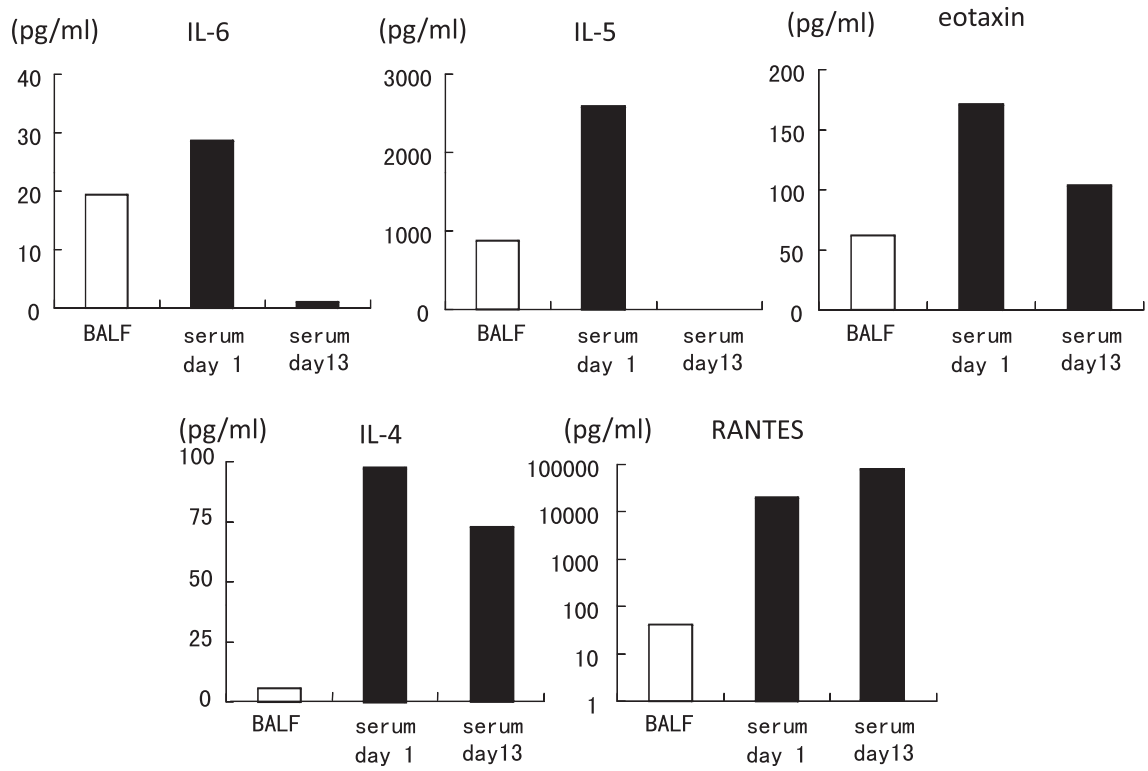

Fig. 3. The result of the cytokine analysis of the BALF and serum. The cytokine analysis of the BALF was performed on the third hospital day. The cytokine analysis of the serum was performed on admission and the 13th hospital day.

3. Discussion

Allen et al. proposed a set of diagnostic criteria for AEP, which is (1) acute febrile illness < 5 day in duration; (2) hypoxemic respiratory failure; (3) diffuse alveolar or mixed alveolar-interstitial chest X-ray infiltrates; (4) BAL eosinophils greater than 25%; (5) an absence of parasitic, fungal, or other infection; (6) prompt and complete response to corticosteroids; and (7) failure to relapse after discontinuation of corticosteroids.[10] This case met most of these diagnostic criteria and was therefore diagnosed as AEP. The cause of the AEP in this case is thought to be cigarette smoking, because the patient had started smoking just before the development of AEP, and showed spontaneous improvement after cigarette smoking cessation without corticosteroid treatment. A few other cases of AEP following cigarette smoking like this case have been reported previously.[2–6] Among these reports, there have been some reports that have proven that cigarette smoking induces AEP by the cigarette smoking challenge test.[2–4] Although the optimal method to prove the association between cigarette smoking and AEP is the cigarette smoking challenge test, she refused to perform the cigarette smoking challenge test. The best reported candidate as an alternative method is LST.[11] In the present, the LST for cigarette smoke extract was negative. However, this may be been because the LST positive rate is not necessarily high, and may not have been detectable.[12,13] Another possible cause is the timing of when the LST was performed, because AEP has been reported to show tolerance for cigarette smoking over time.[3] In the present study, we performed the LST after the AEP had improved. To understand the significance of the LST, and its potential use as an alternative to the cigarette smoking challenge, further investigations will be needed.

The most characteristic feature of AEP is pulmonary eosinophilia. Although the precise mechanism of accumulation in the lungs remains to be elucidated, previous studies indicated that some cytokines are involved in the eosinophil accumulation in the lungs.[14] The cytokines which were reported to be involved in eosinophil accumulation in the lung are IL-3, IL-4, IL-5, IL-8, eotaxin, RANTES and GM-CSF, among others.[14] IL-3, IL-5 and GM-CSF have been recognized as activators of eosinophil function, including migration into the alveoli. IL-5 is reported to be a major factor for in eosinophil accumulation in AEP.[9] Chemokines such as eotaxin, IL-8 and RANTES, have also been found to be eosinophil chemoattractants. The levels of these chemokines in BALF are reported to increase in eosinophilic pneumonia.[15] Furthermore, the cooperation between eotaxin and IL-5 to induce eosinophil accumulation has been reported by several investigators.[16,17] The expression of eotaxin and IL-5 is up-regulated by IL-4.[18,19] We evaluated the changes in the levels of cytokines using serum and BALF in this case. The levels of IL-4, IL-5, IL-6 and eotaxin in serum were high on admission and decreased on the clinical course, thus indicating that these cytokines likely played an important role in the early phase of the condition.

In contrast, the levels of RANTES in the serum increased, thus suggesting that RANTES might play an important role in the convalescent phase. In addition, the level of RANTES in the BALF was much lower than that in the serum, especially compared with the other cytokines. These findings might indicate that RANTES did not play an important role in the eosinophil accumulation in the lung. Interestingly blood eosinophilia was observed after the improvement of the lung involvement in this case. In a previous report, although blood eosinophilia after improvement was reported, the responsible cytokines were not known, because there were no cytokines that increased in parallel with the eosinophils in blood.[8] These findings which were observed in this case suggest that RANTES might be involved in the blood eosinophilia after improvement. RANTES is known to attract not only eosinophils, but also T cells, including memory subtype T cells, Th1, $CD8^+$ T cells and $FoxP3^+$ T cells.[20–23] Given that the lymphocyte counts in the blood increased in parallel with the eosinophil count with time course in

this case, RANTES might induce not only the increase in eosinophils, but also in lymphocytes in the blood after the improvement of AEP. In a previous report, $CD8^{+}CD11b^{-}$ T cells were reported to increase in the BALF after the improvement of AEP and were speculated to be involved in the improvement through their suppressive effect on cell activity.[24] Although the subtype and role of the lymphocytes that increased in this case are not known, there is a possibility that lymphocytes which have the ability to suppress the immune response were attracted by RANTES and were involved in the spontaneous improvement in this case.

To our knowledge, this is a first report which evaluated the expression of cytokines in a case of AEP showing spontaneous improvement. The analysis of the cytokines revealed that RANTES, which is a potent chemoattractant for eosinophils and lymphocytes, increased after the improvement. The precise role of RANTES in AEP is unknown. However, the findings which were observed in this case, including the increased number of eosinophils, lymphocytes and the level of RANTES in the convalescent phase, prompted us to suggest that RANTES might induce an increase in eosinophils and lymphocytes in the convalescent phase, and may be associated with the spontaneous improvement in AEP. Further investigations of the role of RANTES may contribute to the understanding of the pathogenesis of AEP.

Conflict of interest

We have no conflicts of interest to disclose.

References

1. Allen JN, Pacht ER, Gadek JE, et al. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. *N Engl J Med* 1989;**321**:569–74.
2. Shintani H, Fujimura M, Yasui M, et al. Acute eosinophilic pneumonia caused by cigarette smoking. *Intern Med* 2000;**39**:66–8.
3. Shintani H, Fujimura M, Ishiura Y, et al. A case of cigarette smoking-induced acute eosinophilic pneumonia showing tolerance. *Chest* 2000;**117**:277–9.
4. Watanabe K, Fujimura M, Kasahara K, et al. Acute eosinophilic pneumonia following cigarette smoking: a case report including cigarette-smoking challenge test. *Intern Med* 2002;**41**:1016–20.
5. Shiota Y, Kawai T, Matsumoto H, et al. Acute eosinophilic pneumonia following cigarette smoking. *Intern Med* 2000;**39**:pp830–833.
6. Al-Saieg N, Moammar O, Kartan R. Flavored cigar smoking induces acute eosinophilic pneumonia. *Chest* 2007;**131**:1234–7.
7. Ida M, Nakano Y, Inui N, et al. Alterations in smoking habits are associated with acute eosinophilic pneumonia. *Chest* 2008;**133**:1174–80.
8. Okubo Y, Horie S, Hachiya T, et al. Predominant implication of IL-5 in acute eosinophilic pneumonia: comparison with chronic eosinophilic pneumonia. *Int Arch Allergy Immunol* 1998;**116**:76–80.
9. Nakahara Y, Hayashi S, Fukuno Y, et al. Increased interleukin-5 levels in bronchoalveolar lavage fluid is a major factor for eosinophil accumulation in acute eosinophilic pneumonia. *Respiration* 2001;**68**:389–95.
10. Allen JN, Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med* 1994;**150**:1423–38.
11. Matsui S, Yamashita N, Maruyama M, et al. Acute eosinophilic pneumonia induced by cigarette smoking: positive lympocyte stimulataion test of cigarette extract. *Nihon Kokyuki Gakkai Zasshi* 2000;**38**:807–11.
12. Saito M, Yagi M, Uno K, et al. Comparative study of the usefulness of the drug-induced lymphocyte stimulation test and the leukocyte migration test in drug allergies. *Biol Pharm Bull* 2008;**31**:299–304.
13. Matsuno O, Okubo T, Hiroshige S, et al. Drug-induced lymphocyte stimulation test is not useful for the diagnosis of drug-induced pneumonia. *Tohoku J Exp Med* 2007;**212**:49–53.
14. Lampinen M, Carlson M, Hakansson LD, et al. Cytokine-regulated accumulation of eosinophils in inflammatory disease. *Allergy* 2004;**59**:793–805.
15. Katho S, Matsumoto N, Fukushima K, et al. Elevated chemokine level in bronchoalveolar lavage fluid of patients with eosinophilic pneumonia. *J Allergy Clin Immunol* 2000;**106**:730–6.
16. Collins PD, Marleau S, Griffiths-Johnson DA, et al. Cooperation between interleukin-5 and the chemokine eotaxin to induce eosinophil accumulation in vivo. *J Exp Med* 1995;**182**:1169–74.
17. Mould AW, Matthaei KI, Young IG, et al. Relationship between interleukin-5 and eotaxin in regulating blood and tissue eosinophilia in mice. *J Clin Invest* 1997;**99**:1064–71.
18. Teran LM, Mochizuki M, Bartels J, et al. Th1- and Th2-type cytokines regulate the expression and production of eotaxin and RANTES by human lung fibroblasts. *Am J Respir Cell Mol Biol* 1999;**20**:777–86.
19. Kopf M, Le Gros G, Bachmann M, et al. Disruption of the murine IL-4 gene blocks Th2 cytokine responses. *Nature* 1993;**362**:245–8.
20. Schall TJ, Bacon K, Toy KJ, et al. Selective attraction of monocytes and T lymphocytes of the memory phenotype by cytokine RANTES. *Nature* 1990;**347**:669–71.
21. Sallusto F, Lanzavecchia A, Mackay CR. Chemokines and chemokine receptors in T-cell priming and Th1/Th2-mediated responses. *Immunol Today* 1998;**19**:568–74.
22. Fukada K, Sobao Y, Tomiyama H, et al. Functional expression of the chemokine receptor CCR5 on virus epitope-specific memory and effector CD8+ T cells. *J Immunol* 2002;**168**:2225–32.
23. Senug G King, Roland J Piniecki, Harm Hogenesch, et al. Identification of chemokine network that recruits $FOXP3^{+}$ regulatory T cells into chronically inflamed intestine. *Gastroenterology* 2007;**132**:966–81.
24. Taniguchi H, Kadota J, Fujii T, et al. Activation of lymphocytes and increased interleukin-5 levels in bronchoalveolar lavage fluid in acute eosinophilic pneumonia. *Eur Respir J* 1999;**13**:217–20.