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.

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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 SpO₂ was 97% under room air on the forth hospital day. The peripheral eosinophil count, which had been 186 cells/mm³ on admission, increased gradually to 1400 cells/mm³ on the seventh hospital day. Although the eosinophilia was prolonged over 1 month, the peripheral eosinophil count decreased to 504 cells/mm³ 2 months after the development of AEP. The peripheral lymphocyte count also increased from 2195 cells/mm³ on admission to 3367 cells/mm³ on the seventh hospital day, and decreased to 2720 cells/mm³ 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.
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. 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. Among these reports, there have been some reports that have proven that cigarette smoking induces AEP by the cigarette smoking challenge test. 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. In the present, the LST for cigarette smoke extract was negative. However, this may be because the LST positive rate is not necessarily high, and may not have been detectable. 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.

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. 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. 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. 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. Furthermore, the cooperation between eotaxin and IL-5 to induce eosinophil accumulation has been reported by several investigators. The expression of eotaxin and IL-5 is up-regulated by IL-4. Chemokines such as RANTES are known to attract not only eosinophils, but also T cells, including memory subtype T cells, Th1, CD8+ T cells and FoxP3+ T cells. Given that the lymphocyte counts in the blood increased in parallel with the eosinophil count with time course in

![Graph showing cytokine levels in BALF and serum](image-url)
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. 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.

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