Clinical Characteristics and Factors Influencing the Occurrence of Acute Eosinophilic Pneumonia in Korean Military Personnel

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Acute eosinophilic pneumonia (AEP) is an uncommon inflammatory lung disease, and limited data exist concerning the clinical characteristics and factors that influence its occurrence. We retrospectively reviewed the records of AEP patients treated at Korean military hospitals between January 2007 and December 2013. In total, 333 patients were identified; their median age was 22 years, and all were men. All patients presented with acute respiratory symptoms (cough, sputum, dyspnea, or fever) and had elevated levels of inflammatory markers including median values of 13,185/μL for white blood cell count and 9.51 mg/dL for C-reactive protein. All patients showed diffuse ground glass opacity/consolidation, and most had pleural effusion (n = 265; 80%) or interlobular septal thickening (n = 265; 85%) on chest computed tomography. Most patients had normal body mass index (n = 255; 77%), and only 30 (9%) patients had underlying diseases including rhinitis, asthma, or atopic dermatitis. Most patients had recently changed smoking habits (n = 288; 87%) and were Army personnel (n = 297; 89%).The AEP incidence was higher in the Army group compared to the Navy or Air Force group for every year (*P* = 0.002). Both the number of patients and patients with high illness severity (oxygen requirement, intensive care unit admission, and pneumonia severity score class ≥ III) tended to increase as seasonal temperatures rose. We describe the clinical characteristics of AEP and demonstrate that AEP patients have recently changed smoking habits and work for the Army. There is an increasing tendency in the numbers of patients and those with higher AEP severity with rising seasonal temperatures.

Keywords: Pulmonary Eosinophilia; Clinical Characteristics; Demography; Factors; Army; Seasonal

INTRODUCTION

Acute eosinophilic pneumonia (AEP), first described by Allen et al. in 1989 as a distinct disease entity, is an uncommon inflammatory lung disease (1). AEP presents with acute-onset respiratory symptoms, diffuse radiographic infiltrates, and eosinophilic infiltration into the lungs without a known cause of pulmonary eosinophilia, such as drugs, toxins, or parasite infestations (2-4). The clinical severity of respiratory distress associated with AEP varies from mild to severe; however, most patients with AEP exhibit rapid responses to systemic corticosteroid therapy without sequelae, even in fatal cases (5-8).

Recent studies concerning the clinical features of AEP have suggested that unidentified inhaled antigens could be partly responsible for the inflammatory process (9-14), and recent molecular studies have revealed that several inflammatory cytokines are associated with eosinophil recruitment into the lungs, degranulation, and eosinophil survival (15-19). However, to date, limited data exist concerning the detailed clinical features of AEP and possible factors in its occurrence, limiting insights into its epidemiology or pathophysiology.

In Korean military hospitals, several cases of AEP are diagnosed and managed annually, and an abundance of medical records and demographic data regarding the characteristics and outcomes of AEP patients has accumulated (5,6,20,21). Thus, in this study, we retrospectively investigated the clinico-demographic data of AEP cases managed in Korean military hospitals to evaluate clinical characteristics and associated factors that contribute to the development of, or increased vulnerability to, AEP.

MATERIALS AND METHODS

Study population

We retrospectively reviewed the medical records of consecutive adult patients with newly diagnosed AEP between January 2007 and December 2013 at multiple Korean military hospitals, including The Armed Forces Capital Hospital, The Armed Forces Busan Hospital, The Armed Forces Cheongpyeong Hospital, The Armed Forces Chuncheon Hospital, The Armed Forces

Daegu Hospital, The Armed Forces Daejeon Hospital, The Armed Forces Gangneung Hospital, The Armed Forces Goyang Hospital, The Armed Forces Hampyeong Hospital, The Armed Forces Hongcheon Hospital, The Armed Forces Ildong Hospital, The Armed Forces Seoul Hospital, The Armed Forces Wonju Hospital, The Armed Forces YangJu Hospital, The Naval Marine Medical Center, The Naval Pohang Hospital, and The Air Forces Aerospace Medical Center.

A definitive diagnosis of AEP was based on a modification of the criteria proposed by Philit et al. (2), as reported previously (5): 1) acute onset of febrile respiratory manifestations < 1 month in duration; 2) bilateral diffuse infiltrates on chest radiography; 3) > 25% eosinophils in bronchoalveolar lavage (BAL) or eosinophilic pneumonia on lung biopsy; and 4) absence of known causes of pulmonary eosinophilia, including drugs, toxins and infections. If bronchoscopy with BAL or lung biopsy was not available, a clinical diagnosis of AEP was made when a rapid response to systemic corticosteroid therapy was achieved, in addition to definitive diagnostic criteria 1), 2), and 4). All patients with a definitive and clinical diagnosis of AEP were included in the analysis.

Patient management and data collection

Patients who were clinically suspected of AEP underwent a diagnostic workup consisting of laboratory examinations, chest radiography, computed tomography (CT), and/or flexible bronchoscopy with BAL. Infectious etiologies were investigated using peripheral blood, sputum, tracheal aspirates and BAL fluid using the following techniques: staining and microbiological culture for bacteria and *Mycobacterium tuberculosis*; multiplex polymerase chain reaction for respiratory viruses, including influenza virus, parainfluenza virus, adenovirus and respiratory syncytial virus; and serological testing for atypical pathogens, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and parasites using specific antibody tests. Whether diagnostic tests or interventions were performed was decided by the attending physician.

Most patients diagnosed with AEP were treated with systemic corticosteroid. Before May 2007, the dose or duration of corticosteroid tapering was not standardized, while after May 2007, 2- or 4-week tapering protocols were widely used (5). After the publication of a study in May 2012 showing the non-inferiority of 2-week corticosteroid treatments compared to 4-week corticosteroid treatments in managing AEP patients (5), 2-week tapering protocols became widely applied to AEP patients. An example of the 2-week corticosteroid treatment protocol is as follows: the initial dose of corticosteroid is chosen based on the presence of respiratory failure, defined as a partial pressure of arterial oxygen (PaO$_2$)/fraction of inspired oxygen (FiO$_2$) ratio ≤ 300 and/or tachypnea (respiration rate > 30 breaths/min). Patients with respiratory failure received 60 mg methylprednis-

olone intravenously every 6 hours for 3 days followed by 30 mg oral prednisolone twice daily for 4 days. Patients without respiratory failure received 30 mg oral prednisolone twice daily for 7 days, followed by tapering over 2 weeks. However, when oxygenation was not severely impaired (PaO$_2$/FiO$_2$ ratio > 350) and symptoms were mild, the patient underwent conservative treatment without corticosteroids based on the decision of the attending physician.

The following data were collected retrospectively: demographic characteristics including age, sex, body mass index, underlying diseases, history of recent upper-respiratory infections, smoking habits, and working position in military services. Clinico-radiological findings and laboratory data at initial presentation were collected, and clinical parameters that reflect disease severity, including oxygen requirement rate, intensive care unit (ICU) admission rate, the need for mechanical ventilation, and pneumonia severity index score, were also collected. Annual incidence rates and seasonal variations were also evaluated.

In calculating annual incidence rates, we used the cited population of each military service as a denominator, which is published biennially by The Ministry of National Defense, Korea, in

Table 1. Clinical characteristics of patients with AEP

Characteristics	No. (%) of patients
Patients	333 (100)
Definitive AEP	304 (91)
Clinical AEP	29 (9)
Acute symptoms or signs	
Cough	321 (96)
Sputum	284 (85)
Dyspnea (> MMRC scale II)	257 (77)
Fever	294 (88)
Chest computed tomography findings	
Diffuse ground glass opacity ± consolidation	333 (100)
Interlobular septal thickening	282 (85)
Pleural effusion	265 (80)
Laboratory findings	
White blood cell count, /μL	13,185 (9,700-17,697)
Peripheral eosinophil count, /μL	314 (182-538)
C-reactive protein, mg/dL	9.51 (5.72-14.4)
Eosinophil % in BAL fluid	43 (31-56)
PaO$_2$/FiO$_2$ ratio	276.2 (239.3-329.0)
Oxygen requirement	258 (78)
ICU admission	103 (31)
Mechanical ventilation	8 (2)
PSI classification	
Class I and II	242 (72)
Class III	86 (26)
Class IV	4 (1)
Class V	1 (1)
Diagnostic flexible bronchoscopy	304 (91)
Corticosteroid treatment	306 (92)
Conservative treatment without corticosteroid	27 (8)

PaO$_2$/FiO$_2$ data were missing in 56 cases. Data are presented as medians (interquartile ranges) or numbers (%). AEP, acute eosinophilic pneumonia; BAL, bronchoalveolar lavage; PaO$_2$, partial pressure of arterial oxygen; SpO$_2$, oxygen saturation; ICU, intensive care unit; MMRC, modified medical research council; MV, mechanical ventilation; PSI, pneumonia severity index.

the defense white paper. This was used to calculate annual incidence rates of AEP among the entire military population and within each service. A Poisson-distribution was applied to estimate confidence intervals since most medical events are considered to follow Poisson-distributions, especially rare diseases like AEP. Follow-up data were last obtained on February 1, 2014. All medical records were anonymized or de-identified.

Statistical analysis

Data are presented as medians and interquartile ranges (IQR) for continuous variables and as numbers and percentages for categorical variables. Data were compared using the Kruskal-Wallis test (more than two independent groups) for continuous variables, and a χ^2 or Fisher's exact test for categorical variables. Values of $P < 0.05$ were considered to indicate statistical significance. All statistical analyses were performed using the PASW software (ver. 18.0; SPSS Inc., Chicago, IL, USA).

Ethics statement

The study protocol was designed in accordance with the Declaration of Helsinki and was approved by the institutional review board of the Armed Forces Capital Hospital (AFMC-14-IRB-016) and the Armed Forces Medical Command on behalf of the military hospitals that were involved in the current study. Informed consent was exempted by the board.

RESULTS

Clinical characteristics of patients with AEP

Three hundred and thirty-three patients with AEP were identified in the study period, including 304 (91%) definitive and 29 (9%) clinical AEP patients. Clinical characteristics of study patients are shown in Table 1. All patients had acute respiratory symptoms or signs including cough, sputum, dyspnea, or fever. On initial chest computed tomography scans, all patients had diffuse ground glass opacity with or without consolidation (Fig. 1), 282 (85%) had interlobular septal thickening, and 265 (80%) had pleural effusion. All patients had elevated inflammatory markers, including white blood cell count and C-reactive protein, with median values of 13,185 (IQR, 9,700-17,697)/μL and 9.51 (IQR, 5.72-14.4) mg/dL, respectively, and median peripheral eosinophil counts of 314 (182-538)/μL. The median value of the PaO_2/FiO_2 ratio was 276.2 (IQR, 239.3-329.0), 32% of the patients had severe hypoxemia ($PaO_2/FiO_2 < 250$), and 258 (78%) patients had an oxygen requirement. Of the study patients, 103 (31%) were admitted to the ICU, 8 (2%) required me-
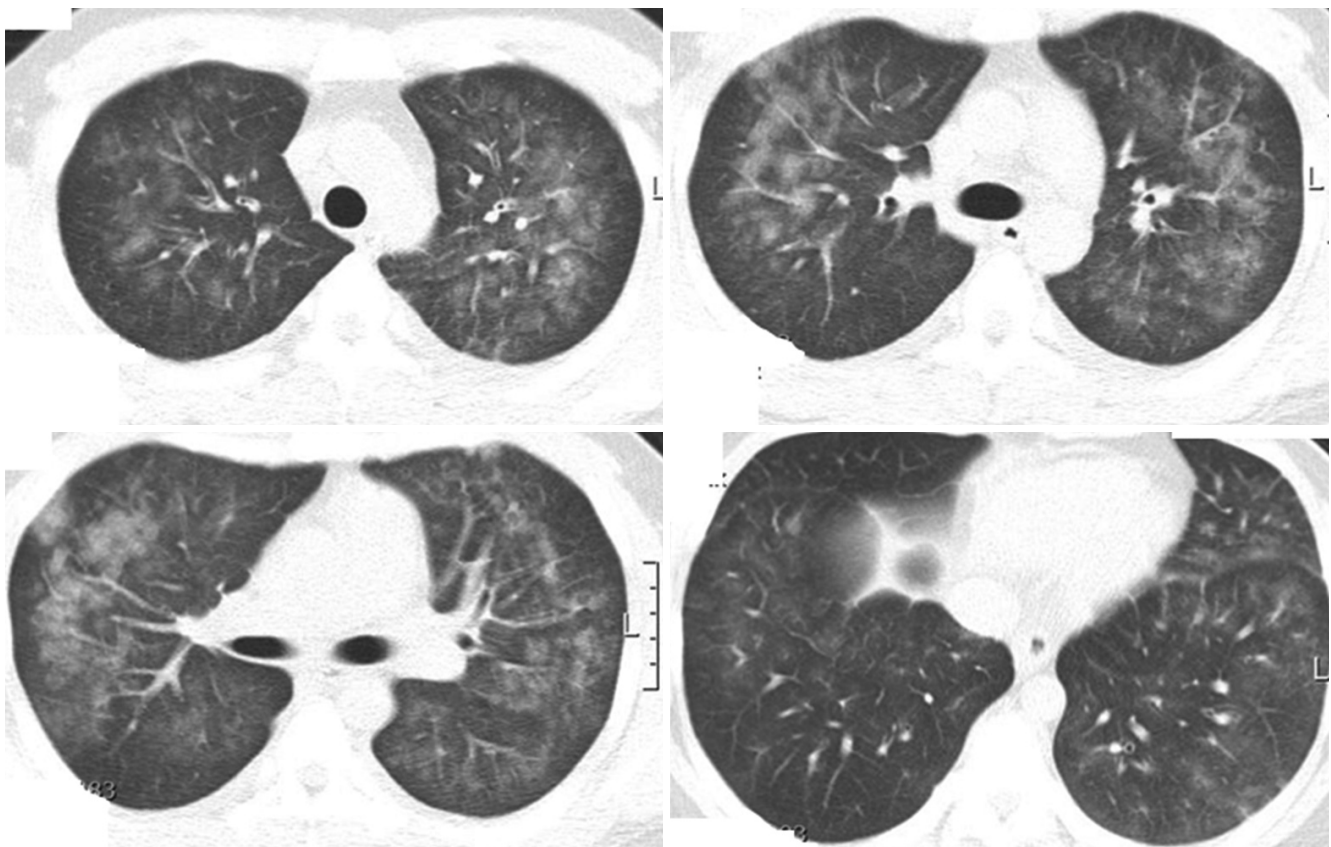

Fig. 1. Typical chest computed tomography findings in patients with acute eosinophilic pneumonia. Diffuse bilateral ground-glass opacity and interlobular septal thickening are seen in both lungs.

Table 2. Demographics of patients with AEP

Characteristics	No. (%) of patients
Age, yr	20 (20-21)
Gender, male	333 (100)
Body mass index, kg/m²	22.9 (21.2-24.6)
> 25	67 (20)
≥ 18.5 and ≤ 25	255 (77)
< 18.5	11 (3)
Smoking	
Current smoker	309 (93)
Recently started smoking	175/333 (53)
Resumed smoking	100/333 (30)
Increased the number of cigarettes	13/333 (4)
No change in smoking habits	21/333 (6)
Ex-smoker	3 (1)
Never smoker	21 (6)
Underlying diseases	30 (9)
Allergic rhinitis	17/333 (5)
Asthma	9/333 (3)
Atopic dermatitis	4/333 (1)
Recent history of inhalation burn	1/333 (1)
Recent history of upper respiratory infections	1/333 (1)
Military services	
Army	297 (89)
Navy	29 (9)
Air force	7 (2)

Data are presented as medians (interquartile ranges) or numbers (%). AEP, acute eosinophilic pneumonia.

Table 3. Annual incidence of AEP occurrence according to military service

Years	Entire forces	Army	Navy	Air force
2013	11.0 (8.6-13.9)	12.6 (9.8-16.3)	8.8 (3.2-19.2)	0.0 (0.0-5.7)
2012	8.1 (6.1-10.8)	9.5 (7.1-12.7)	2.9 (0.4-10.6)	3.1 (0.4-11.1)
2011	6.3 (4.5-8.6)	7.1 (5.1-10.0)	5.9 (1.6-15.1)	0.0 (0.0-5.7)
2010	6.7 (5.0-9.1)	8.3 (6.1-11.2)	1.5 (0.0-8.2)	0.0 (0.0-5.7)
2009	8.7 (6.7-11.4)	10.0 (7.5-13.2)	7.4 (2.4-17.2)	0.0 (0.0-11.1)
2008	7.8 (5.7-10.0)	8.4 (6.0-11.0)	7.4 (2.4-17.2)	3.1 (0.4-11.1)
2007	2.8 (1.7-4.4)	3.5 (2.1-5.5)	0.0 (0.0-5.4)	0.0 (0.0-5.7)

Data are presented as incidence per 100,000 person-year (95% confidence interval). In each year, the incidence of AEP tended to be higher among Army personnel compared to Navy or Air Force personnel, and these differences were statistically significant (P = 0.0021). AEP, acute eosinophilic pneumonia.

Fig. 2. Incidence of AEP according to military service per year.

chanical ventilation support, and approximately one-third of the study patients had more than a pneumonia severity index score (PSI) class II; class III (n = 86; 26%), class IV (n = 4; 1%), and class V (n = 1; 1%). Overall, 306 (92%) AEP patients were treated with systemic corticosteroid and 27 (8%) patients did not receive corticosteroid; all patients survived without sequelae.

Demographics of patients with AEP
The demographics of AEP patients are shown in Table 2. The median age was 22 (IQR, 20-21) years and all patients were male. The median body mass index was 22.9 (IQR, 21.2-24.6 kg/m²); 67 (20%) patients were overweight (> 25 kg/m²) and 11 (3%) patients were underweight (< 18.5 kg/m²). Most patients were current smokers (n = 309; 93%); among these, 175 (53%) patients had recently started smoking, 100 (30%) patients had resumed smoking, and only 24 (7%) patients were ex-smokers or had never smoked. Only 30 (9%) patients had underlying diseases; allergic rhinitis (n = 17; 5%) was the most common, followed by asthma (n = 9; 3%) and atopic dermatitis (n = 4; 1%). One patient with a recent history of inhalation burns and one patient with a recent upper respiratory infection were identified. Most of the patients were in the Army (n = 297; 89%), with 29 (9%) in the Navy and only 7 (2%) in the Air Force.
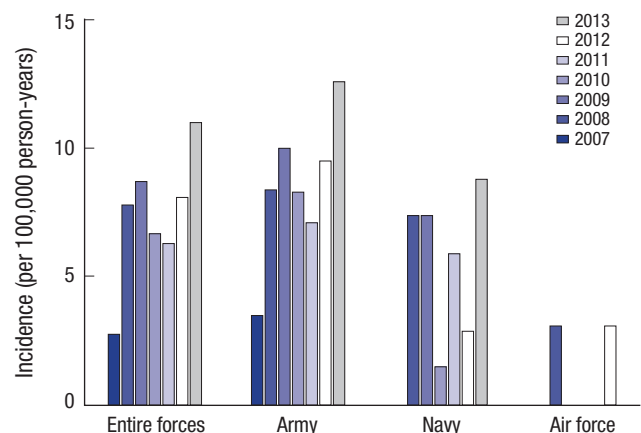
Annual incidences of AEP occurrence according to military service
Because absolute numbers of AEP patients were much lower in the Navy and Air Force than in the Army, as shown by the de-

mographics of study patients, we calculated and compared the annual incidence of AEP occurrence according to military service (Table 3). Among all forces, in 2008 the incidence of AEP abruptly increased compared to 2007, and by 2013 the incidence of AEP was highest at up to 11.0 per 100,000 person-years (95% confidence interval, 8.6-13.9; Fig. 2). Interestingly, in each year, the incidence of AEP tended to be higher among Army personnel compared to Navy or Air Force personnel, and these differences were statistically significant (Kruskal-Wallis, P = 0.002). However, the differences in other clinico-demographic data between the different military services were not statistically significant (data not shown).

Seasonal variation in the occurrence of AEP patients
Since physicians working at military hospitals generally estimate that more cases of AEP are encountered in the summer than in other seasons, we investigated seasonal variations in the occurrence of AEP among all military services to estimate whether occurrence was influenced by season (Table 4). Of all AEP cases, 125 (38%) occurred during the summer, 100 (30%) during the autumn, 58 (17%) during the spring, and only 50 (15%) during the winter. Numbers of AEP patients tended to increase as seasonal temperatures increased (Table 4) and peaked in the summer each year, around August.

Table 4. Numbers of occurrence of AEP patients according to season per year

Years	Spring			Summer			Autumn			Winter			Total
	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	
2013	1	2	8	5	11	9	11	10	3	3	5	2	70
2012	5	2	6	4	1	10	9	6	4	3	1	1	52
2011	3	1	5	6	3	6	2	1	6	2	3	2	40
2010	2	1	2	3	7	7	4	7	3	5	1	2	44
2009	2	3	2	4	9	8	7	5	3	4	6	4	57
2008	3	3	6	2	11	8	2	5	6	3	0	2	51
2007	0	0	1	3	3	5	0	4	2	1	0	0	19
Total	16	12	30	27	45	53	35	38	27	21	16	13	333

Data are presented as numbers of AEP patients.

Fig. 3. Levels of C-reactive protein in patients with AEP according to season.

Table 5. Number of AEP patients with a relatively higher severity of illness according to season

Characteristics	Spring			Summer			Autumn			Winter		
	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb
Oxygen requirement	12	9	23	22	33	44	27	32	20	16	10	10
ICU admission	4	4	9	7	13	18	9	16	7	5	5	6
Mechanical ventilation	0	0	2	0	1	1	1	1	2	0	0	0
PSI class III	5	2	9	8	9	14	9	10	7	4	4	5
PSI class IV	0	0	0	0	3	0	0	1	0	0	0	0
PSI class V	0	0	1	0	0	0	0	0	0	0	0	0

Data are presented as numbers of AEP patients. AEP, acute eosinophilic pneumonia; ICU, intensive care unit; PSI, pneumonia severity index.

We additionally evaluated the number of AEP patients with a relatively high severity of illness according to season (Table 5). The number of severe cases tended to increase as seasonal temperatures rose and peaked around the summer, from late spring to early autumn. The numbers of patients who needed oxygen (n = 99) and ICU admission (n = 38), and had a PSI score of III (n = 31) or IV (n = 3) tended to be higher in summer than in other seasons. None of the patients who needed mechanical ventilation was seen during the winter. One of the most severe cases of AEP (PSI class V) occurred during late spring, in May. However, differences in other clinico-demographic data according to season (spring vs. summer vs. autumn vs. winter) were not statistically significant (data not shown). The initial level of C-reactive protein in AEP patients had a slight tendency to be higher during summer and autumn than during spring and winter (Fig. 3), and median values of C-reactive protein in spring, summer, autumn, and winter were 9.53 (IQR, 5.34-13.1) mg/dL, 9.04 (IQR, 4.90-13.8) mg/dL, 10.10 (IQR, 6.62-16.02) mg/dL, and 7.90 (IQR, 5.96-12.61) mg/dL, respectively; however the differences did not reach statistical significance.

DISCUSSION

In this study, we investigated the clinical characteristics of AEP and evaluated possible demographic factors that may contribute to its development in Korean military personnel. Our data suggest that several environmental factors such as recently chang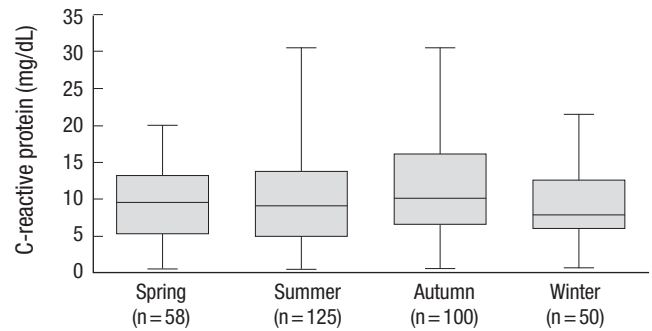ed smoking habits, military service in the Army, and increasing seasonal temperature could be related to the occurrence of AEP. Regarding environmental influences on the development of AEP, previous studies have indicated that inhaled stimulants may trigger the inflammatory processes of AEP (9-12). For example, an observational study that included 33 AEP patients found that altered smoking habits, not only starting to smoke but also restarting smoking and increasing daily smoking doses, were associated with the development of AEP (12). Moreover, Rom et al. presented a case study of a firefighter that developed AEP after exposure to dust from the World Trade Center collapse (10). Similar to these previous studies, the majority of our patients (n = 288; 87%) had recently altered smoking habits and the annual incidence of AEP was highest in the Army, which may be because the Army has more ground services, and outdoor activity in mountainous areas of Korea may increase the likelihood of inhaling unidentified antigens.

Interestingly, in this study we found that the occurrence of AEP was related to seasonal variations. The number of AEP patients tended to increase as seasonal temperatures rose and peaked around summer, which was associated with greater disease severity than the other seasons. Moreover, AEP with relatively high illness severity was more common in the summer than in other seasons, although seasonal differences in the parameters that indicate disease severity did not reach statistical significance. These phenomena could be partly explained by the rise in temperature as the season changes from winter to summer, possibly increasing the likelihood of inhalation of stimulants or unidentified antigens, which in turn may trigger lung

inflammation. One other study has described an association between AEP occurrence and season or climate. When evaluating the clinical features and epidemiology of 18 AEP cases in the United States military personnel deployed in or near Iraq, summer had the highest incidence of AEP (22). However, limited data exist concerning environmental influences on AEP occurrence, and well-designed studies of its occurrence that adjust for other confounding factors have not been performed, mainly due to the rarity of the disease, which limits insight into its epidemiology or pathophysiology.

In our study only a small proportion (n = 11; 3%) of patients had a low body mass index (< 18.5 kg/m^2) and the majority of patients (n = 255; 77%) had a normal body mass index. This body mass index distribution is uncommon in other pulmonary diseases such as tuberculosis and other inflammatory pulmonary diseases. Additionally, only 9% of study patients had underlying allergic diseases. These findings suggest that inflammation in AEP is not a chronic process and that AEP may have different inflammatory processes than known allergic reactions. To date there has not been a comprehensive study of the association of AEP with immunoglobulin E-mediated or allergic reactions. The results of a recent study indicated that immunoglobulin G levels decreased significantly during active disease states and increased during remission, but serum immunoglobulin E levels did not change significantly, suggesting that the pathogenesis of AEP may negatively impact serum immunoglobulin G levels but not immunoglobulin E levels (23). However, accurate data concerning the inflammatory process are limited; thus, further pathophysiological studies along with epidemiological data are needed.

In our study, the incidence of AEP in recent years was similar to previously reported rates. In a study of the characteristics and epidemiology of AEP among the United States military personnel, Shorr et al. (22) reported an AEP incidence of 9.1 per 100,000 person-years (95% confidence interval, 4.3 to 13.3). However, in our current study the annual AEP incidence rate varied from 2.8 per 100,000 person-years in 2007 to 11.0 per 100,000 person-years in 2013. The lower incidence in 2007 compared to other years is likely due to inadequate awareness of AEP in military hospitals in Korea. The peak incidence of AEP in 2013 may be due to improved insight into AEP by military physicians as well as the increased performance of diagnostic flexible bronchoscopies using the BAL procedure in unknown respiratory failure patients. Therefore, more aggressive diagnostic evaluation of patients will facilitate determination of accurate incidence rates, changes in AEP incidence rates, and aid the investigation of its epidemiology.

This study has some limitations. First, there was no matched normal control group to compare to the AEP group since we performed a retrospective case series study. This type of study was chosen since collecting medical data from healthy military personnel is difficult as it is not permitted without definite medical evidence in any of the Korean armed forces. Thus, based on the results of this study, we evaluated only accurate case series data. Second, because our study was conducted at military hospitals only, most patients were previously healthy males with a uniform median age, and thus not representative of the general population. Third, there is a possibility that the incidence or occurrence of AEP might have been underestimated in our study population because some patients might have been treated at a local military hospital or might have improved spontaneously. However, we cautiously estimate that this influence is not significant due to the unique characteristics of the medical system of the Korean military services. According to the military law of Korean military personnel, all soldiers should be treated in military hospitals first if possible. Accordingly, most patients with suspected AEP were likely transferred to a military hospital, including the Armed Forces Capital Hospital, which is the largest tertiary referral military hospital in Korea, where bronchoscopy is available.

In conclusion, in this study we investigated the clinical characteristics of AEP, demonstrated that patients with AEP frequently have recently changed smoking habits and work for the Army, and found an increasing tendency in the numbers of patients and of patients with higher AEP severity with increasing seasonal temperatures. These results highlight the need for future pathophysiological and epidemiological prospective studies to evaluate the impact of external environmental variables on the occurrence and pathophysiology of AEP.

DISCLOSURE

All authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and design of the study: Yoon C, Jhun BW. Data collection and analysis: Yoon C, Kim SJ, Kim K, Lee JE, Jhun BW. Writing the first draft: Yoon C, Jhun BW. Revision of manuscript: Yoon C, Jhun BW. ICMJE criteria for authorship: Yoon C, Kim SJ, Kim K, Lee JE, Jhun BW.

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REFERENCES

1. Allen JN, Pacht ER, Gadek JE, Davis WB. *Acute eosinophilic pneumonia*

as a reversible cause of noninfectious respiratory failure. *N Engl J Med* 1989; 321: 569-74.

2. Philit F, Etienne-Mastroïanni B, Parrot A, Guérin C, Robert D, Cordier JF. *Idiopathic acute eosinophilic pneumonia: a study of 22 patients. Am J Respir Crit Care Med* 2002; 166: 1235-9.

3. Hayakawa H, Sato A, Toyoshima M, Imokawa S, Taniguchi M. *A clinical study of idiopathic eosinophilic pneumonia. Chest* 1994; 105: 1462-6.

4. Daimon T, Johkoh T, Sumikawa H, Honda O, Fujimoto K, Koga T, Arakawa H, Yanagawa M, Inoue A, Mihara N, et al. *Acute eosinophilic pneumonia: thin-section CT findings in 29 patients. Eur J Radiol* 2008; 65: 462-7.

5. Rhee CK, Min KH, Yim NY, Lee JE, Lee NR, Chung MP, Jeon K. *Clinical characteristics and corticosteroid treatment of acute eosinophilic pneumonia. Eur Respir J* 2013; 41: 402-9.

6. Jhun BW, Kim SJ, Kim K, Lee JE. *Clinical implications of initial peripheral eosinophilia in acute eosinophilic pneumonia. Respirology* 2014; 19: 1059-65.

7. Lim SY, Suh GY, Jeon K. *Acute eosinophilic pneumonia presenting as life-threatening hypoxaemia necessitating extracorporeal membrane oxygenation. Int J Tuberc Lung Dis* 2012; 16: 1711-2.

8. Kawayama T, Fujiki R, Morimitsu Y, Rikimaru T, Aizawa H. *Fatal idiopathic acute eosinophilic pneumonia with acute lung injury. Respirology* 2002; 7: 373-5.

9. Imokawa S, Sato A, Hayakawa H, Toyoshima M, Taniguchi M, Chida K. *Possible involvement of an environmental agent in the development of acute eosinophilic pneumonia. Ann Allergy Asthma Immunol* 1996; 76: 419-22.

10. Rom WN, Weiden M, Garcia R, Yie TA, Vathesatogkit P, Tse DB, McGuinness G, Roggli V, Prezant D. *Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. Am J Respir Crit Care Med* 2002; 166: 797-800.

11. Watanabe K, Fujimura M, Kasahara K, Yasui M, Myou S, Kita T, Watanabe A, Nakao S. *Acute eosinophilic pneumonia following cigarette smoking: a case report including cigarette-smoking challenge test. Intern Med* 2002; 41: 1016-20.

12. Uchiyama H, Suda T, Nakamura Y, Shirai M, Gemma H, Shirai T, Toyoshima M, Imokawa S, Yasuda K, Ida M, et al. *Alterations in smoking habits are associated with acute eosinophilic pneumonia. Chest* 2008; 133: 1174-80.

13. Kitahara Y, Matsumoto K, Taooka Y, Moritani C, Nakamura K, Ohashi N, Daido K, Arita K. *Cigarette smoking-induced acute eosinophilic pneumonia showing tolerance in broncho-alveolar lavage findings. Intern Med* 2003; 42: 1016-21.

14. Shiota Y, Kawai T, Matsumoto H, Hiyama J, Tokuda Y, Marukawa M, Ono T, Mashiba H. *Acute eosinophilic pneumonia following cigarette smoking. Intern Med* 2000; 39: 830-3.

15. Katoh S, Matsumoto N, Matsumoto K, Fukushima K, Matsukura S. *Elevated interleukin-18 levels in bronchoalveolar lavage fluid of patients with eosinophilic pneumonia. Allergy* 2004; 59: 850-6.

16. Mato N, Bando M, Kusano A, Hirano T, Nakayama M, Uto T, Nakaya T, Yamasawa H, Sugiyama Y. *Clinical significance of interleukin 33 (IL-33) in patients with eosinophilic pneumonia. Allergol Int* 2013; 62: 45-52.

17. Miyazaki E, Nureki S, Fukami T, Shigenaga T, Ando M, Ito K, Ando H, Sugisaki K, Kumamoto T, Tsuda T. *Elevated levels of thymus- and activation-regulated chemokine in bronchoalveolar lavage fluid from patients with eosinophilic pneumonia. Am J Respir Crit Care Med* 2002; 165: 1125-31.

18. Allen JN, Liao Z, Wewers MD, Altenberger EA, Moore SA, Allen ED. *Detection of IL-5 and IL-1 receptor antagonist in bronchoalveolar lavage fluid in acute eosinophilic pneumonia. J Allergy Clin Immunol* 1996; 97: 1366-74.

19. Okubo Y, Horie S, Hachiya T, Momose T, Tsukadaira A, Takashi S, Suzuki J, Isobe M, Sekiguchi M. *Predominant implication of IL-5 in acute eosinophilic pneumonia: comparison with chronic eosinophilic pneumonia. Int Arch Allergy Immunol* 1998; 116: 76-80.

20. Lee JE, Rhee CK, Lim JH, Lee SM, Shim YS, Lee CT, Lee SW. *Fraction of exhaled nitric oxide in patients with acute eosinophilic pneumonia. Chest* 2012; 141: 1267-72.

21. Jhun BW, Kim SJ, Kim K, Lee JE, Hong DJ. *Clinical implications of correlation between peripheral eosinophil count and serum levels of IL-5 and tryptase in acute eosinophilic pneumonia. Respir Med* 2014; 108: 1655-62.

22. Shorr AF, Scoville SL, Cersovsky SB, Shanks GD, Ockenhouse CF, Smoak BL, Carr WW, Petruccelli BP. *Acute eosinophilic pneumonia among US Military personnel deployed in or near Iraq. JAMA* 2004; 292: 2997-3005.

23. Matsuno O, Takenaka R, Hiroshige S, Ono E, Nishitake T, Ueno T, Miyazaki E, Kumamoto T. *Reduced IgG levels found during acute eosinophilic pneumonia, which normalize during recovery from disease. Respir Med* 2008; 102: 899-903.