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Original Article

Outbreak of Febrile Respiratory Illness Caused by Adenovirus at a South Korean Military Training Facility: Clinical and Radiological Characteristics of Adenovirus Pneumonia

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SUMMARY: Adenovirus often causes respiratory disease outbreaks in military training soldiers. Compared with adenovirus pneumonia in young military adults, symptoms arising from febrile respiratory illness (FRI) caused by adenovirus have not been previously evaluated in Korean soldiers. We conducted an event-based outbreak investigation involving 712 male soldiers aged 19 to 21 years from March 14 to 30, 2012 to evaluate the epidemiological and clinical characteristics of patients with pneumonia and FRI caused by adenovirus. We described the laboratory and radiological characteristics of patients with adenovirus pneumonia. Among these, 407 cases of FRI and 15 cases of pneumonia were identified through active surveillance (attack rate of FRI, 57.16%; attack rate of pneumonia, 2.11%). Fire training and march training may present environmental risk factors for adenovirus-associated outbreaks. Most symptoms were mild. The most frequent symptom in patients with pneumonia and FRI was cough. Patients with pneumonia were associated with an increased incidence of dizziness (crude odds ratio [cOR], 9.65; 95% confidence interval [CI], 2.38–37.15) and a decreased incidence of rhinorrhea (cOR, 0.15; 95% CI, 0.04–0.53) during adenovirus-associated outbreaks. Differential leukocyte count revealed high monocytes, low lymphocytes, and low eosinophils, and chest computed tomography revealed a consolidation pattern and right lobar pneumonia. These findings warrant a high level of suspicion for adenovirus pneumonia.

INTRODUCTION

Young healthy adults serving in the military are often at an increased risk of respiratory infections (1). Training stressors (2) and crowding (3) facilitate the transmission of respiratory pathogens. Adenovirus has long been a causative agent of upper respiratory infections and pneumonia among military trainees and occasionally among deployed troops (4,5). In a survey of respiratory viral infections conducted at a military training facility in South Korea between February 2006 and May 2006, the most common virus identified by throat swabs was adenovirus (122/160, 76.3%) (6). This survey was conducted to identify the etiological agent in febrile patients; however, it failed to identify the epidemiological characteristics of an adenovirus-associated outbreak. In addition, there were no clinical, laboratory, and radiological characteristics of fatal cases of pneumonia that occurred in mid-March of 2012, following an outbreak of febrile respiratory illness (FRI) caused by adenovirus at a South Korean military training facility. All patients were young, previously healthy soldiers. Although several studies have described the clinical features of adenovirus infection among military personnel (7–13), few studies have compared the clinical characteristics of pneumonic and non-pneumonic adenovirus cases or evaluated the risk factors associated with military training courses. Furthermore, few reports have provided detailed descriptions of the radiological features of adenovirus infections by means such as thin-section computed tomography (CT) (7,9).

Therefore, the present study aimed to describe in detail the clinical characteristics and radiological features of thin-section CT findings in patients with adenovirus infections occurring at a military training facility, describe the epidemiological characteristics of the outbreak, and analyze the association between the training course and incidence of adenovirus infection.

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MATERIALS AND METHODS

Outbreak investigation: The soldier training squadron of the 6th division (STS6D) is the training facility for new recruits of the South Korean Army. STS6D is

located in Cheorwon-gun, South Korea. STS6D recruits annually undergo training lasting for 5 weeks. From March 2 to April 6, 2012, a total of 712 training soldiers and training support soldiers were enrolled in the study population; these included 565 new recruits who began the training program, which consisted of 2 companies (A, $n = 297$; B, $n = 268$) and 147 training support soldiers. Acute FRI was defined as an STS6D soldier with a fever of $\geq 38°C$ or higher and/or cough or shortness of breath. Pneumonia was defined as an FRI case with radiological evidence of pneumonia confirmed by military doctors. All the pneumonia cases were inpatients, whereas other FRI cases were outpatients. The military training staff daily monitored the body temperature of the 712 soldiers from March 18 to 30, 2012, and any simple FRI cases were treated by military doctors of the medical department of STS6D. However, patients with pneumonia were treated by military doctors of the Armed Forces Il Dong Hospital.

The epidemiological investigation was conducted by 3 military doctors, namely 2 preventive medicine specialists and 1 infectious medicine specialist of the Armed Forces Medical Command, from March 22 to 23, 2012. During the epidemiological investigation, we surveyed symptoms and identified 161 FRI cases and index cases by case definition and onset days, analyzed the association between different types of military training courses with the onset of FRI, and estimated the attack rate among 161 patients with FRI and pneumonia.

Laboratory confirmation: Nasopharyngeal swab specimens ($n = 36$) were collected at the emergency department or wards when the 36 patients with FRI belonging to the same division visited the emergency department or when symptoms developed in the remaining patients with FRI who came into contact with them. Reverse transcription-polymerase chain reaction (RT-PCR) analysis of influenza A was performed in a tertiary military hospital in South Korea. Nasopharyngeal swab specimens ($n = 11$) were collected from patients with pneumonia and FRI by a military doctor and were subjected to PCR analysis for adenovirus, influenza A virus, influenza B virus, metapneumovirus, parainfluenza virus, rhinovirus, coronavirus, respiratory syncytial virus, bocavirus, and enterovirus by the Green Cross Co. (Yongin-si, Korea). Nucleic acids were extracted using NucliSENS easyMAG (bioMerieux, Marcy l'Etoile, France). Complementary DNA (cDNA) was synthesized using random hexamers. Each cDNA preparation was subjected to multiplex PCR using Seeplex RV12 (Seegene, Seoul, Korea), which uses novel dual-priming oligonucleotides as PCR primers (14).

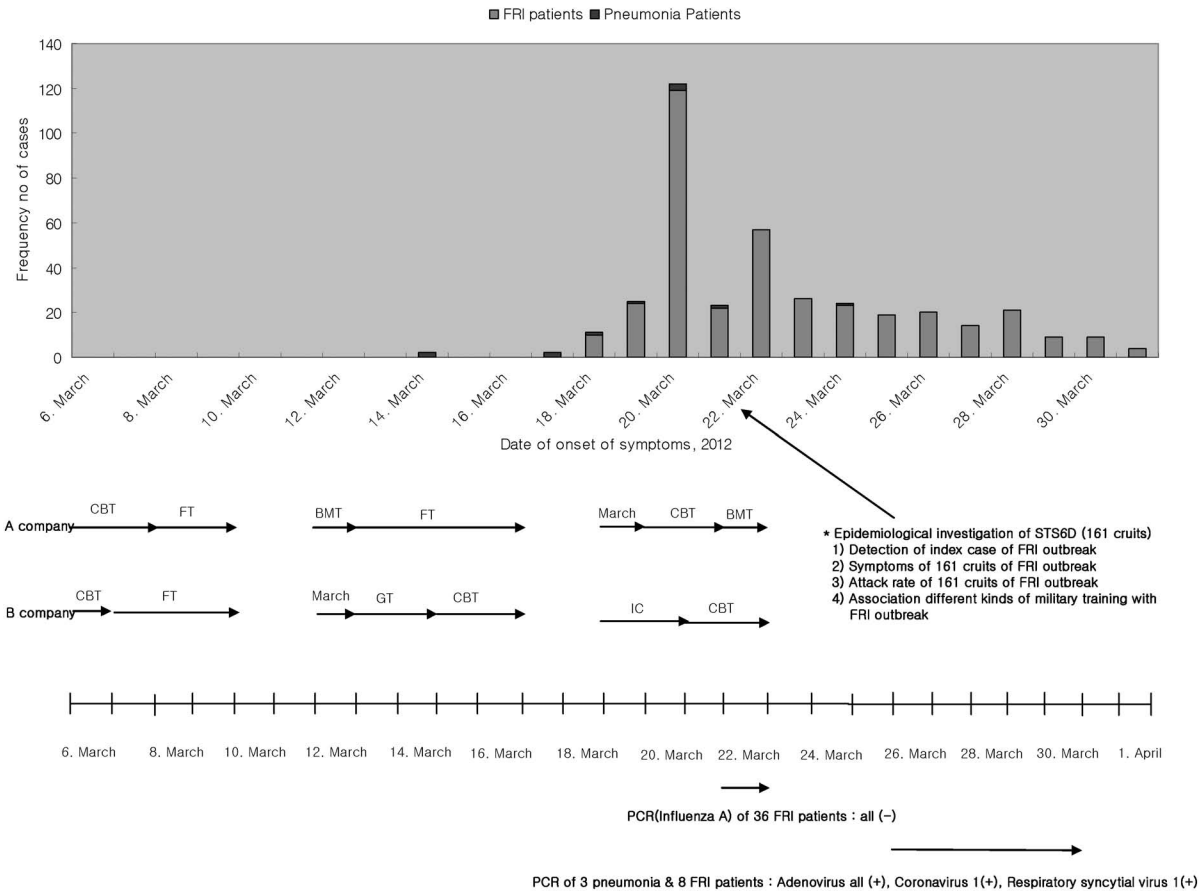
Review of clinical and laboratory characteristics: To analyze the clinical features, the initial symptoms such as fever, cough, sputum, rhinorrhea, sore throat, myalgia, headache, dizziness, nausea, vomiting, and diarrhea were recorded. In addition, the progression of patient symptoms during treatments was reviewed. The laboratory data included results of hematological analysis of the leukocyte count, erythrocyte count, hemoglobin level, hematocrit level, platelet count, neutrophil count, eosinophil count, basophil count, monocyte count, and lymphocyte count and biochemical analysis of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels. Pneumonia severity was assessed using the Pneumonia Severity Index (PSI) risk class and CURB score (15–18).

Review of chest thin-section CT: Thin-section CT images were obtained from 15 and 11 patients. All thin-section CT images were reviewed by experienced chest radiologists using a picture archiving and communication systems (PACS) viewer. Chest radiographs were analyzed for the presence of nodular opacity; consolidation or interstitial patterns; distribution of findings including the right, left, upper, middle, and lower lung zones; and the presence or absence of pleural effusion. The sites were described by the name and number of the involved lung segments. Presence of other abnormalities such as pleural effusion was also considered.

RESULTS

Outbreak investigation: In March 2012, a total of 712 basic military trainees participated in basic training at a South Korean military training facility. Among these, 407 FRI and 15 pneumonia cases were identified through active surveillance (attack rate of FRI, 57.16%; attack rate of pneumonia, 2.11%). In addition, 3 (20%) of 15 patients with pneumonia and 8 (1.97%) of 407 patients with FRI were randomly selected and tested for the presence of adenovirus and other respiratory viruses by PCR. The results showed that, of 11 samples, all were positive for adenovirus, 1 for coronavirus, and 1 for respiratory syncytial virus) (Fig. 1). The FRI rates increased in mid-March, peaked between March 20 and 22 (with a smaller peak on March 20), and resolved by April 1. The outbreak involved 2 military companies. The first 2 patients with pneumonia developed symptoms on March 14, when company A had just completed fire training (FT) and march training, while company B was conducting FT. At the peak of the outbreak (March 20), company B had just completed FT and march training, while company A had completed individual combat training. Of the samples tested from March 22 to 23, none was positive for influenza A or B by PCR at the Army Armed Forces Capital Hospital. On March 26, nasopharyngeal swab specimens ($n = 4$) were randomly collected from FRI cases by military doctors at the Army Armed Forces Capital Hospital. In addition, on March 27, nasopharyngeal swab specimens ($n = 7$) from 3 patients with pneumonia and 4 patients with FRI were collected by military doctors at the Armed Forces Il Dong Hospital. On March 27, these samples were transferred to the Green Cross Co. for identification of the causative organisms of the FRI outbreak. After 4 days, all samples of FRI ($n = 11$) were confirmed to be positive for adenovirus by PCR. In addition, 1 case each of coronavirus and respiratory syncytial virus was detected among the 8 samples of FRI cases.

Clinical and laboratory characteristics of patients: In the 11 patients with pneumonia who visited the emergency department of the military hospital, the mean interval between symptom onset and emergency room visit was 4.6 ± 2.6 days (range, 1–10 days). In addition, the average length of hospitalization was 11.1 ± 2.6



Explain of military training and association military training with FRI patients (March 22, 2012)

	Contents of military training	Rank of training physically toughness[1)]	Rank of contact between them by sharing the rifles[1)]	Rank of spread with dust and sand in training[1)]	No. of FRI patients[2)]
March	Walking with full military uniform during 4 h (daytime) & 8 h (night time)	1	2	2	11
Individual combat (IC)	Passing through terrain obstacle & the general simulated combat training (total training time, 29 h)	2	3	3	
Fire training (FT)	At the daytime, 10 shots in standing shooting position and also 10 shots in prone shooting position. At the night time, 15 shots in prone shooting position (total training time, 46 h)	3	1	1	91
Grenade training (GT)	The theory and practice of hand grenades throwing (4 h), throwing 5 grenades for practice (2 h) and throwing 3 grenades for combat (2 h)	4		4	
Based military training (BMT)	Military manners, step of march and basic positions in manual exercise (total training time, 27 h)	5	4	5	
Computer based training (CBT)	Collective learning of indoor of training room for military security (2 h) and training of mobilization preparation (2 h)	6		6	11

[1)]: Rank of training physically toughness and contact between them by sharing the rifles and spread with dust and sand was evaluated by military training staff, and grenade training and computer based training had been doing without the rifles.
[2)]: No. of febrile respiratory illness (FRI) patients was frequency which 161 soildiers of FRI and pneumonia inpatients answered for the cause of FRI outbreak (March 22, 2012).

Fig. 1. Epidemic curve of febrile respiratory illness patients (probable case by adenovirus) with laboratory-confirmed cases of adenovirus and military training schedule.

days (range, 6–14 days). The clinical symptoms of all patients (FRI and pneumonia) are summarized in Table 1. Cough was the most common symptom in all patients. In general, dizziness and miscellaneous symptoms were significantly more frequent in the pneumonia group than in the FRI group (crude odds ratio [cOR], 9.65; 95% confidence interval [CI], 2.38–39.15). Otherwise, rhinorrhea was significantly less frequent in the pneumonia group than in the FRI group (cOR, 0.15; 95% CI, 0.04–0.53).

The laboratory data of the 11 patients with pneumonia are summarized in Table 2. None of the patients had

Table 1. Symptoms of patients with FRI and pneumonia during the military outbreak of FRI

Symptom	No. (%) of pneumonia patients n = 11	No. (%) of FRI patients n = 161	P[1]	cOR[2] (95% CI)
Fever	11 (100)	132 (82)	0.260	
Cough	11 (100)	143 (88.8)	0.507	
Sputum	10 (90.9)	117 (72.7)	0.329	3.76 (0.47–30.24)
Rhinorrhea	**4 (36.4)**	**128 (79.5)**	**0.004**	**0.15 (0.04–0.53)**
Sore throat	5 (45.5)	77 (47.8)	0.873	0.91 (0.27–3.10)
Myalgia	2 (18.2)	43 (26.7)	0.789	0.61 (0.13–2.94)
Headache	7 (63.6)	78 (48.4)	0.507	1.86 (0.52–6.61)
Dizziness	**4 (36.4)**	**9 (5.6)**	**0.002**	**9.65 (2.38–39.15)**
Nausea	0 (0)	21 (13)	0.422	
Vomiting	0 (0)	10 (6.2)	0.853	
Diarrhea	0 (0)	14 (8.7)	0.652	
Miscellaneous	**4 (36.4)**	**9 (5.6)**	**0.002**	**9.65 (2.38–39.15)**
Dyspnea & Chest discomfort	1 (9.1)	13 (8.1)	0.652	1.14 (0.14–9.60)

Data are presented as no. (%), unless otherwise stated, and statistically significant result is indicated in bold letters about P-value and cOR.
[1]: P values were calculated using the χ^2 test.
[2]: Number of pneumonia patients by adenovirus for febrile respiratory illness (FRI) patients.
cOR, crude odds ratio; CI, confidence interval.

Table 2. Laboratory findings of pneumonia patients during the military outbreak of FRI

Laboratory finding	Value[1] (median, range)	No. (%) of abnormal patients[2]
Leukocyte (k/μL)	6.12 ± 2.49 (6.20, 2.60–9.80)	3/11 (27.3)
Erythrocyte (m/μL)	4.78 ± 0.42 (4.63, 4.19–5.49)	1/11 (9.1)
Hemoglobin (g/dL)	14.24 ± 0.91 (14.10, 13.00–15.90)	0/11 (0)
Hematocrit (%)	41.65 ± 2.70 (40.90, 39–46)	0/11 (0)
Platelet (k/μL)	178.73 ± 40.15 (184, 105–265)	2/11 (18.2)
Neutrophil (/μL)	66.91 ± 12.01 (70.80, 43.40–82.70)	4/11 (36.4)
Eosinophil (/μL)	1.73 ± 3.77 (0.10, 0–12.30)	9/11 (81.8)
Basophil (/μL)	0.35 ± 0.29 (0.30, 0–0.90)	0/11 (0)
Monocyte (/μL)	8.00 ± 2.37 (8.30, 3–12.10)	6/11 (54.5)
Lymphocyte (/μL)	23.42 ± 9.34 (22.40, 8.70–34.00)	5/11 (45.5)
Alkaline phosphatase (IU/L)	200.43 ± 39.69 (211, 135–253)	7/7 (100)
Aspartate aminotransferase (IU/L)	49.00 ± 23.21 (43, 21–95)	8/11 (72.7)
Alanine aminotransferase (IU/L)	35.00 ± 18.76 (25, 21–72)	3/11 (27.3)
Creatine kinase (IU/L)	195.67 ± 61.13 (191, 137–259)	2/3 (66.7)
Erythrocyte sedimentation rate (mm/h)	30.71 ± 18.76 (31, 5–64)	5/7 (71.4)
C-reactive protein (mg/dL)	4.60 ± 2.81 (3.94, 0.84–11.06)	10/11 (90.9)
Lactate dehydrogenase (mg/dL)	464.67 ± 106.61 (427, 382–585)	3/3 (100)

[1]: Data are mean ± standard deviation.
[2]: Data are no. of abnormal patients/no. of total patients.

leukocytosis. Eight (72.7%) had leukocyte counts within normal limits, whereas 3 (27.3%) had leukocytopenia. In addition, thrombocytopenia, neutrophilia, monocytosis, lymphocytopenia, eosinophilosis, and eosinopenia were present in 2 (18.2%), 4 (36.4%), 6 (54.5%), 5 (45.5%), 1 (9.1%), and 8 (72.7%) patients, respectively. No abnormality was detected in the hemoglobin level, hematocrit level, platelet count, and basophil count. The ALP, AST, and ALT levels were abnormal in 7 (100%) of 7 patients, 8 (72.7%) of 11 patients, and 3 (27.3%) of 11 patients, respectively. CK was elevated in 2 (66.7%) of 3 patients. ESR was elevated in 5 (71.4%) of 7 patients. CRP was elevated in 10 (90.9%) of 11 patients, and LDH was elevated in 3 (100%) of 3 patients.

Thin-section CT findings and severity of patients with pneumonia: Thin-section CT images were obtained from 11 (73.3%) of 15 patients. Of these 11 patients, 1 (9.1%) had a finding of ground-glass opacity (GGO), 2 (18.2%) had a diffuse or bronchopneumonia type pattern, and 9 (81.8%) had a consolidation pattern (Table 3). Regarding segmental lung involvement, 6 (54.6%) had a lesion of the right lower lobe, 4 (36.4%) had a lesion of the right middle lobe, 3 (27.3%) had a lesion of the right upper lobe, 3 (27.3%) had a lesion of the left lower lobe, 3 (27.3%) had a lesion of both lobes, and 1 (9.1%) had unilateral pleural effusion. In addition, the severity of 11 patients with pneumonia was assessed by the PSI and CURB score. Of the 11 patients, 9 (81.8%) had a PSI of I and 2 (18.2%) had a PSI of II. Regarding

Table 3. Thin-section CT images and severity of pneumonia patients during the military outbreak of FRI

Case no.	CT image			Severity	
	Pattern	Affected segment[1)]	Other findings	PSI risk class[2)]	CURB scores[3)]
1	Consolidation	RLL		I	1
2	Consolidation	RLL, LLL, Both Lobe		I	1
3	Consolidation	RUL, RML		I	0
4	Diffuse or Bronchopneumonia	Both Lobe		I	0
5	Consolidation	LLL		I	0
6	Consolidation	RUL, RML, RLL	Unilateral pleural effusion	II	1
7	Consolidation & Ground-glass opacity	RLL		I	0
8	Consolidation	RLL		I	0
9	Consolidation	RUL, RML		I	0
10	Consolidation	RML, LLL		I	1
11	Diffuse or Bronchopneumonia	RLL		II	0

[1)]: RLL, right lower lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe.
[2)]: Pneumonia Severity Iindex risk class.
[3)]: Confusion, urea nitrogen, respiratory rate, and blood pressure score.

the CURB score of 11 patients with pneumonia, 7 (63.6%) had a CURB score of 0 and 4 (36.4%) had a CURB score of 1.

DISCUSSION

The surveillance data in the present study demonstrated that Korean military personnel were susceptible to adenovirus infections during military training. We isolated adenoviruses from randomly selected patients during an acute FRI outbreak in the military and from all 11 inpatient pneumonia cases. Adenovirus is a common and important pathogen causing acute respiratory disease (ARD) outbreaks in Korean military soldiers. Epidemics of adenovirus-associated ARD have been widely reported among recruits at the US Department of Defense (DoD) training centers (1,19,20). The most common symptoms of adenovirus infections in the present cases were fever and cough, which are in accordance with previous reports (9,20,21).

Past studies in the United States reported that adenovirus epidemics were associated with preventive interventions such as adenovirus vaccines and hand washing (8,22). However, the association of adenovirus epidemics with the types and difficulties of military training has remained uncertain in previous studies. In the present study, the frequency of FRI and pneumonia cases was separately studied on the basis of the types of military training. On March 14, 2012, 2 recruits from the same company were diagnosed with pneumonia 1 week before the mass fever spread throughout the military facility during FT and march training. Through a case from the Korean Army, we deduced that FT and march exercises were physically demanding and could increase the number of patients with adenovirus infections or worsen their symptoms. Many of them were exposed to dust and sand at the FT facility. In addition, we found that most patients with pneumonia displayed symptoms directly after completing march training. In the questionnaire, 91 (56.5%) of 161 patients replied that the incidence of FRI sharply increased directly after FT and 11 (6.8%) replied that the number increased after computer-based training and march training. FT and march training are considered as the most physically demanding components of training. During these training exercises, the soldiers are in close contact with one another, share equipment such as rifles, and are exposed to dust and sand carried by wind. Our analysis revealed that march training and FT were statistically associated with the onset of pneumonia and FRI, respectively. In addition, according to a former study, rifles were most commonly observed in the military environment. Therefore, FT may be a risk factor for the spread of adenovirus and a cause of FRI in the army (23). However, further studies are required to clarify these associations (Fig. 1). In addition, a study by Christakis and Fowler reported that the progression of an epidemic in a group of friends occurred 13.9 days (95% CI, 9.9–16.6) before that in a randomly chosen group (i.e., the population as a whole) based on clinical diagnoses (24). In the present study of Korean military recruits, we identified a large scale of patients (approximately 407), resulting from only 2 recruits with pneumonia, which led us to conclude that a small number of patients with illness can lead to mass infection, which is in accordance with the results reported by Christakis and Fowler (24). The only difference between the 2 sets of results was the estimation of the lead time, which heavily depends on the causative strain, group characteristics, relation between the infected group and the whole population, and the rate of contact. Although the study of Christakis and Fowler (24) found that a small prevalence of viral infection may occur 2 weeks before a large-scale outbreak, we observed a 1-week period between the 2 events. Comparison of the patients with FRI and pneumonia caused by adenovirus revealed that more patients with pneumonia experienced episodes of dizziness. On the other hand, more patients with FRI experienced rhinorrhea. Although there was no statistical correlation, sputum, headache, dyspnea, and chest discomfort were observed more often in patients with pneumonia than in those with FRI, suggesting that adenovirus pneumonia causes more systemic symptoms such as dizziness. In general, the laboratory findings of the present cases were consistent with those of a previous study of adenovirus pneumonia. Although the total

leukocyte count was normal or low, the majority of our patients had a higher percentage of monocytes and a lower percentage of lymphocytes than that normally seen in viral pneumonia (21,25). However, the majority of our patients had a lower overall percentage of eosinophils. These findings seem to be related to stress from training and acute viral infection (26). In addition, the lab results of this study revealed an overall increase in serum ALP (100%), AST (72.7%), CK (66.7%), ESR (71.4%), CRP (90.9%), and LDH (100%) levels, except for ALT (27.3%) levels. This is similar to the conclusions of a community-based outbreak study in the Oregon State and a study on an adenovirus-associated outbreak among handicapped children at a care facility (27). Thin-section CT images of 11 patients with pneumonia revealed that 2 had diffuse bronchopneumonia, 1 had GGO, and the rest showed consolidation patterns. Although viral pneumonia is typically represented radiologically as poorly defined nodules and patchy areas of peribronchial GGO and air-space consolidation, other studies on adenovirus pneumonia in soldiers and children revealed lobar consolidation patterns, as seen in the present study (21,28–30). However, we were able to detect more specific segments of lung infiltration than previous studies, indicating right lower lobe involvement (54.6%). Both the PSI and CURB score of patients with pneumonia who were assumed to be infected by adenovirus were low, and no patient died or developed acute respiratory distress syndrome; therefore, we concluded that adenovirus pneumonia has a relatively low fatality rate. In addition, there were no significant differences in the PSI and CURB score among the different categories of CT features.

The present study has several limitations. First, although there were 407 FRI cases and 15 pneumonia cases among the 422 cases, only 11 tested positive for adenovirus. Therefore, it was difficult to confirm the results of comparison of pneumonia and FRI cases by the presence of adenovirus. However, it may be possible that the outbreak was not caused by adenovirus but was caused by other viruses such as coronavirus or respiratory syncytial virus, which were also identified in 1 case during this outbreak. Here, all 11 samples were positive for adenovirus, which is a known causative pathogen of FRI outbreaks in a military setting. The clinical features and natural courses of the outbreak were also very similar to those of previously reported outbreaks in military camps (21,27). For example, in 2006, when any specific outbreaks of adenovirus were reported in South Korea, the majority of military recruits (76.4%) were positive for adenovirus (6). In addition, among the randomly selected patients with FRI and pneumonia, none was infected by influenza, and adenovirus was the cause of the large-scale fever. Considering all these data, it is clear that adenovirus was at the center of the present epidemic of FRI and pneumonia. Second, in contrast to other studies, it was difficult to define, differentiate, and characterize adenovirus serotypes 4, 7, 11a, and 14 (6–13) because the Korean military and private inspection institutions do not maintain data regarding adenovirus subtypes. Finally, this study was based on an epidemiological investigation of 1 outbreak following a military training schedule, which limits the generalizability of our findings to other settings. In conclusion, large prospective multicenter studies are required to confirm our findings regarding adenovirus outbreaks in the military.

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Conflict of interest None to declare.

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