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Adenovirus Serotype 14 Pneumonia at a Basic Military Training Site in the United States, Spring 2007: A Case Series

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ABSTRACT Adenovirus, a frequent cause of mild respiratory disease in military trainees, can result in severe manifestations when outbreaks are caused by novel viral strains for which there is little pre-existing immunity. Twenty-five basic military trainees (BMTs) were hospitalized with adenovirus pneumonia from April 1, 2007 through June 21, 2007. Clinical findings for 9 of these patients with PCR-confirmed adenovirus serotype 14 were studied retrospectively. The clinical picture was characterized by cough (88.9%) and sputum production (77.8%). All trainees were febrile. Laboratory results showed 88.9% had normal white blood cell (WBC) counts, 66.7% with high monocytes, and 55.6% with low lymphocytes on differential. All had lobar pneumonia radiographically. One patient required the intensive care unit (ICU) and later expired. In conclusion, among hospitalized patients with the combination of fever, productive cough, normal WBC, a differential showing high monocytes and low lymphocytes in an immunocompetent young adult with lobar pneumonia warrants a high level of suspicion for adenovirus 14 pneumonia.

INTRODUCTION

Adenoviruses (Ads) were first isolated in 1953 from human adenoids.[1] There are several serotypes that have been associated with a variety of diseases in humans. Among adults, adenovirus subgroup B (serotypes 3, 7, and 21), subgroup C (serotypes 1, 2, and 5) and subgroup E (serotype 4) are a common cause of respiratory tract infection, but not serious disease in the United States[9] and have been a frequent cause of outbreaks among U.S. military training populations. Crowding[2] and numerous stressors[3,4] facilitate transmission of respiratory pathogens and exacerbate the clinical manifestations in military training sites. In the early 1960s, live oral vaccines were developed and fielded against adenovirus types 4 and 7.[20] Vaccine production was halted in 1996 and reserves were given to U.S. military training populations until exhausted in 1999.[7] In the U.S., before the development and employment of Ads vaccine in military, adenoviruses infected approximately 10% of trainees undergoing initial military training[5,6] and were associated with 90% of the pneumonia cases among those infected recruits.

Occasionally, outbreaks of adenovirus have been described with more severe manifestations, particularly when these outbreaks are caused by novel viral strains for which there is little pre-existing immunity.[8,17,21,24,25] Beginning in March 2007, the febrile respiratory illness (FRI) rates in the basic trainees began rising at Lackland Air Force Base (LAFB) in San Antonio, Texas. Trainees presented with a wide spectrum of mild to severe respiratory illness. Initial epidemiologic surveillance and clinical cultures identified adenovirus as the cause of more than 90% of the FRI. Further molecular testing characterized the strain as adenovirus subspecies B2 serotype 14 (Ad14). First isolated in 1955 among military recruits in the Netherlands, it has frequently been a cause of respiratory illness in Eurasia. Ad14 had not been associated with an outbreak among U.S. military recruits before the spring of 2007 and was only recently introduced to the United States in 2006.[7] Ad14 has only rarely been associated with severe disease, making this report of several hospitalized cases a concern.[23]

A previous report[10] described the epidemiology of the outbreak among basic military trainees (BMTs) for this same period of time. This article focuses on the clinical features of the confirmed Ad14 pneumonias hospitalized at the training site.

METHODS

Study Population

LAFB is the training facility for the United States Air Force (USAF) new recruits. At this base, there are roughly 35,000 Air Force (AF) recruits that are processed annually with training lasting 6.5 weeks (in November 2008, training was expanded to 8.5 weeks). From April 1, 2007 through June 21, 2007, 7,537 new recruits began training. BMTs are placed in flights, each consisting of 45–55 trainees and are housed in a bay dormitory. There are on average 8 flights per squadron and a total of 7 squadrons. The total population at this military site varies each week because of new graduates and arrivals, but usually averages around 4,000 trainees on base at any given time. BMTs receive their primary medical care at Reid Clinic and inpatient medical care at Wilford Hall Medical Center (WHMC), which are both located on LAFB.

Cases were defined as a trainee admitted to WHMC during the time period from April 1, 2007 through June 21, 2007 with

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a diagnosis of radiographic-confirmed pneumonia and laboratory evidence of adenovirus by culture of pharyngeal swab or nasal aspirate and serotype 14 by polymerase chain reaction (PCR) on the same specimen. Case series data were extracted from the written WHMC inpatient medical record and by using the data stored electronically in the Composite Health Care System (CHCS) and the Integrated Clinical Database (ICDB). The weekly Population Health Support Division disease nonbattle injury ICD-9 codes were also used to identify cases.

Laboratory results confirming Ad14 came from the Armed Forces Institute of Operational Health (AFIOH), Brooks City-Base, TX and/or Naval Health Research Center (NHRC) in San Diego, CA. The Ad14 PCR initially used by the NHRC lab and later by AFIOH was developed by NHRC after the discovery of several species B2 adenoviruses (Ad11 and Ad16) in respiratory samples from Egypt, which necessitated the development of serotype-discriminatory tests.[26]

Throat swab specimens were obtained from BMTs who met the FRI case definition (documented temperature greater than or equal to 100.5° and cough or sore throat)[11] and were sent to the NHRC and/or AFIOH for analysis. These specimens were analyzed through culture-based testing and PCR. The case investigation data set contains patient demographics, clinical features on admission to the hospital, and details of radiographic and laboratory specimens that were collected.

Data Analysis

Data were entered into an Excel database (Microsoft, Redmond, WA) and imported into SPSS version 10.0 (SPSS, Chicago, IL). SPSS was used to generate descriptive statistical analyses to interpret clinical features for the case definition of Ad14 pneumonia at LAFB.

RESULTS

A total of 57 BMTs presented to the WHMC or Reid Trainee Health Clinic with pneumonia from April 1, 2007 through June 21, 2007. Of the 57 patients, 25 were admitted to WHMC, 4 of these to the Medical Intensive Care Unit (MICU), with the remaining 32 followed as outpatients. Viral culture was performed on 31 patients (15 inpatients, 2 MICU patients, and 14 outpatients.). Of those, 24 were adenovirus positive (15 inpatients, 2 MICU patients, and 7 outpatients) and the remaining 7 outpatients were adenovirus negative. Viral cultures were not performed on 26 patients (6 inpatients, 2 MICU patients, and 18 outpatients). Subtyping was performed on only 9 of the adenovirus-positive patients and all were adenovirus-14-PCR positive. Sixteen (64%) of the trainees hospitalized with pneumonia during that time were excluded from the study either because Ad14 confirmatory laboratories were not performed on positive cultures or they had a negative adenovirus culture result. Of the 9 cases, one patient had a co-infection with one additional adenovirus subtype (type 4) and one patient had a positive bacterial sputum culture with *Haemophilus influenzae* (H. flu). Blood cultures did not reveal bacterial growth.

Among the 9 cases of Ad14 pneumonias, 8 were males (88.8%) and one was female. A total of 88.8% were between the ages of 19 and 24 years old. One fatal case occurred, making the fatality rate 11.1%. The only fatal case was that of the female. Five (55.6%) of the cases occurred in the month of May. During the 6-week training course, week 5 was when 5 (55.6%) of the trainees presented with symptoms of Ad14 pneumonia. The median hospital length of stay (LOS) was 5 days, with an interquartile range (IQR) of 7.5 days. Excluding the one ICU case, the hospital average LOS was 4.88 days with standard deviation of 3.41.

Clinical Features

Prevalence of symptoms shown in Table I demonstrates that the majority of cases had cough (88.9%), sputum (77.8%), chills (55.6%), and dyspnea (55.6%). Of the remaining symptoms observed, only 44.4% had sore throat and nausea; 33.3% had diarrhea, runny nose, malaise, and headache, and 11.1% had vomiting.

All of the cases had temperatures greater than 100.4° at hospital admission and 66.7% had an abnormal lung exam. The abnormal lung exam findings of the cases included the following: two had rhonchi, five had decreased breath sounds, one had rales, and one had wheezing.

Laboratory Findings

Laboratory findings show the initial blood count results on the 9 Ad14 pneumonia cases. The WBC count (normal range, 4.5–11) was normal in 88.9% of the patients. Whereas, the percentage of neutrophils (normal range, 34–66) and the percentage of monocytes (normal range, 0–5.2) were high in most of the cases (77.8% and 66.7%, respectively), 55.6% of the patients had a low lymphocyte percentage (normal range, 23–43). Thrombocytopenia (total platelet normal range, 150–400) was documented in 22.2% of the patients on presentation. Creatinine and hemoglobin were normal in 88.9% of the patients. Individual laboratory results are shown in Table II.

Chest radiographic findings are summarized as follows: All 9 cases had pneumonia, shown radiographically by either

TABLE I. Prevalence (%) of Symptoms on Admission to Hospital, Ad 14 Pneumonia Patients, at a U.S. Military Site, April 1, 2007–June 21, 2007

Symptoms	Prevalence (%)
Cough	88.9
Sputum	77.8
Chills	55.6
Dyspnea	55.6
Nausea	44.4
Sore Throat	44.4
Malaise[a]	33.3
Lethargy	33.3
Headache	33.3
Diarrhea	33.3
Vomiting	11.1

[a]Malaise was reported on 8 of the 9 patients.

TABLE II. Individual Laboratory Values on Admission to Hospital, Ad 14 Pneumonia Patients, April 1, 2007–June 21, 2007

Cases	Hemoglobin (g/dL) Normal Range (12–16)	Platelets (10^3) Normal Range (150–400)	White Blood Cell (10^3) Normal range (4.5–11)	Neutrophils (%) Normal Range (34–66)	Lymphocytes (%) Normal Range (23–43)	Monocyte (%) Normal Range (0–5.2)	Creatinine (mg/dL) Normal Range (0.7–1.5)
1	14.7	141	5	66.7	23.1	9.4	1
2	12.5	200	7.8	74.7	12.5	12.6	0.9
3	13.6	339	5.6	74.5	12.3	13.1	0.9
4	12.9	243	10.8	79.6	6.1	13.9	1.2
5	14.1	175	7.7	85.9	7.3	6.7	0.9
6	14.1	325	8.7	88.2	7.6	3.8	1.2
7	14	339	7.1	69.3	25.3	4.9	1.2
8	10.6	59	5.7	64.5	33.9	4	2
9	13.5	160	3.2	61.4	26.5	11.4	1

Findings on chest radiographs and chest CT scans.

chest radiograph or chest CT scan on admission. Air-space consolidation was the prominent feature. Bilateral lobar pneumonia was seen in one of the cases (11.1%), which had features consistent with acute respiratory distress syndrome (ARDS). Pleural effusion and focal pneumothorax were absent in our series at initial presentation. With time, pleural effusion developed in 3 patients (33.3%) and pneumothorax in one (11.1%). The anatomic location of lobar involvement varied widely: 3 (33.3%) patients had left lower lobe, 2 (22.2%) had left upper lobe, one (11.1%) had lingula (by CT), 3 (33.3%) had right lower lobe, 2 (22.2%) had right upper lobe, and 3 (33.3%) had right middle lobe involvement. Multilobar consolidation was seen in 2 patients (22.2%). Chest CT scan was performed on 3 (33.3%) patients for the following reasons: normal chest X-ray on admission but clinical suspicion of pneumonia, to evaluate progression of lung disease or pleural effusion after thoracentesis.

Clinical Course

Of the 9 patients with Ad14 pneumonia, one was admitted to ICU care because of respiratory distress. Mechanical ventilatory support with positive end-expiratory pressure was required. This patient developed ARDS and later died. About 3 weeks before her Ad14 infection, she had also tested positive for mononucleosis, which was believed to be a contributing factor to the severity of her pneumonia because of her immunocompromised state. One of the pneumonia admissions was also diagnosed with rhabdomyolysis but did not require ICU admission. The 2 cases where a co-infection was present with either adenovirus serotype 4 or H. flu did not require ICU admission and had benign hospital courses.

All patients were treated with empiric antibiotics but the patient who later expired was the only one treated with the antiviral agent cidofovir. All but one of the 9 patients recovered without sequelae. Clinical resolution and fitness for discharge from the hospital required symptomatic improvement, which included being afebrile for at least 24 hours and radiographic evidence of stability or improvement in lung consolidation.

DISCUSSION

Although previous studies have described the clinical features of patients with laboratory-confirmed adenovirus pneumonia,[13] to the best of our knowledge, the clinical features of Ad14 pneumonia have not been described until early 2008.[17] This is likely because of the fact that Ad14 pneumonia, up until recently, was an infrequent occurrence or strain typing was not previously performed in these situations.

The clinical symptoms on presentation of Ad14 pneumonia are similar to those found in cases of "atypical pneumonia," usually caused by other respiratory viruses, as well as *Mycoplasma*, *Chlamydia*, or *Legionella*.[16] However, for those patients presenting with a respiratory syndrome that is more severe than the usual viral acute respiratory disease, especially with productive cough and lobar consolidation, unusual or novel strains of adenovirus should be considered.

The laboratory findings in these cases were consistent with a viral pneumonia with the total WBC being normal or low. However, the majority of our patients had a higher percentage of monocytes and a lower percentage of lymphocytes than is normally seen in viral pneumonia.[18]

Viral pneumonia typically is represented radiologically as poorly defined nodules and patchy areas of peribronchial ground glass opacity and air-space consolidation.

In the literature, frequent radiographic findings of adenovirus pneumonia, especially in children, consist of diffuse bilateral bronchopneumonia and severe overinflation.[14] However, adenovirus pneumonia in children can mimic bacterial pneumonia on chest X-ray, as was shown in a study by Han et al. where 19 out of 21 patients showed lobar or segmental air-space consolidation.[12]

In adults with adenovirus pneumonia, mainly in immunocompromised patients, chest radiographs usually show bilateral or unilateral parenchymal opacities.[13,15] Despite the reputation of respiratory viruses for causing diffuse interstitial infiltrates, adenovirus pneumonia can present with radiographic evidence of lobar consolidation, as was demonstrated with multiple cases in a mental health care center.[9] Also, in a case report in 1981 of an 18-year-old student with confirmed adenovirus 7, his chest radiograph confirmed a right upper

lobe lobar pneumonia that radiographically mimicked a bacterial lobar pneumonitis.[19]

Of note, 3 patients had a normal lung exam at the time of admission despite having an abnormal chest X-ray. All of our cases had lobar pneumonia with 2 of the cases having multilobar or bilateral lobar involvement, again unusual for viral pneumonia but can be seen in cases of severe adenovirus pneumonia and primary influenza pneumonia.

The severity of the pneumonia seen in a young, healthy population presents some concern. In an outbreak of adenovirus 4 acute respiratory diseases resulting from a lapse in vaccination that occurred in basic trainees at Fort Jackson, South Carolina in 1995, no significant complications or sequelae were reported.[20] Out of 116 patients with confirmed adenovirus 7 or 3 during a large epidemic of respiratory illness at the Navy Recruit Training Command in Great Lakes, Illinois in September–October 1997 in unimmunized basic trainees, none had a diagnosis of pneumonia.[21] With adenoviral respiratory infection, immunocompromised patients are more likely to develop pneumonia and acute respiratory distress syndrome than immunocompetent patients,[13] although serious morbidity and mortality from adenovirus infections did occur in previously healthy young adults during the preadenovirus vaccine era.[22] Life threatening Ads pneumonia is distinctly unusual in healthy adults.[9]

None of the trainees developed their pneumonia before the third week of training, implying that the infection was acquired at LAFB and not before arrival. The majority of the BMTs became ill during week 5 of training. During week 4, BMTs are out in the field where they experience a more strenuous environment, sleeping in tents and training for longer hours.

CONCLUSIONS

In 2007, adenovirus strain 14 established itself as an important health hazard among the BMTs at LAFB. It is unclear at this time whether this was an isolated occurrence or the beginning of an ongoing health issue. Once present in a population, control of the disease follows classic preventive initiatives. These include hand washing and appropriate respiratory precautions as the first line of defense. Early recognition of the clinical presentation of Ad14 pneumonia and appropriate therapy to include rest and supportive care are the keys in combating this newly emerging infection in our military training sites. A reliable, rapid diagnostic test, based on nasopharyngeal aspirates, is of great importance in the future management of this disease.

Our clinical findings suggest that among adult hospitalized patients with a combination of fever, cough, productive sputum, normal WBC with a differential showing high monocytes, low lymphocytes, and a lobar pneumonia on chest X-ray, it warrants a high level of suspicion for Ad14 pneumonia.

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