Acute Eosinophilic Pneumonia Among US Military Personnel Deployed in or Near Iraq

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Context Acute eosinophilic pneumonia (AEP) is a rare disease of unknown etiology characterized by respiratory failure, radiographic infiltrates, and eosinophilic infiltration of the lung.

Objectives To describe a case series of AEP, illustrate the clinical features of this syndrome, and report the results of an epidemiologic investigation.

Design, Setting, and Participants Epidemiologic investigation of cases of AEP identified both retrospectively and prospectively from March 2003 through March 2004 among US military personnel deployed in or near Iraq. Survivors were offered a follow-up evaluation.

Main Outcome Measure Morbidity and mortality related to AEP.

Results There were 18 cases of AEP identified among 183 000 military personnel deployed in or near Iraq during the study period, yielding an AEP incidence of 9.1 per 100 000 person-years (95% confidence interval, 4.3-13.3). The majority of patients (89%) were men and the median age was 22 (range, 19-47) years. All patients used tobacco, with 78% recently beginning to smoke. All but 1 reported significant exposure to fine airborne sand or dust. Known causes of pulmonary eosinophilia (eg, drug exposures or parasitic disease) were not identified. Epidemiologic investigation revealed no evidence of a common source exposure, temporal or geographic clustering, person-to-person transmission, or an association with recent vaccination. Six patients underwent bronchoalveolar lavage (median eosinophilia of 40.5%). All patients developed peripheral eosinophilia (range, 8%-42%). Mechanical ventilation was required in 67% for a median of 7 (range, 2-16) days. Two soldiers died; the remainder responded to corticosteroids and/or supportive care. Twelve individuals were reevaluated a median of 3 months after diagnosis. At that point, 3 patients reported mild dyspnea and 1 reported wheezing. All patients had finished treatment and had either normal or nearly normal spirometry results. None had recurrent eosinophilia.

Conclusions AEP occurred at an increased rate among this deployed military population and resulted in 2 deaths. Failure to consider AEP in the differential diagnosis of respiratory failure in military personnel can result in missing this syndrome and possibly death. The etiology of AEP remains unclear, but the association with new-onset smoking suggests a possible link.

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EOSINOPHILIC LUNG DISEASES comprise a variety of processes ranging from Churg-Strauss syndrome to drug reactions.[1] Acute eosinophilic pneumonia (AEP) is a recently described syndrome characterized by a febrile illness, diffuse infiltrates on chest radiograph, and pulmonary eosinophilia.[2] Generally, patients with AEP present with respiratory failure requiring mechanical ventilation.[3,4] Clinicians may initially confuse AEP with severe community-acquired pneumonia, acute respiratory distress syndrome (ARDS), or both. It is unclear if less-severe forms of AEP exist.

Histopathologically, lung biopsies in patients with AEP reveal both acute and organizing diffuse alveolar damage with eosinophils filling both the alveolar and interstitial spaces.[5] Peripheral eosinophilia may be noted in AEP; however, it is often absent at the time of presentation, which complicates efforts at diagnosis and case identification and suggests that the initial insult in this disease occurs in the lungs. Although a num-

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Box. Laboratory Evaluation for Patients With Acute Eosinophilic Pneumonia Among Military Personnel Deployed in or Near Iraq

Serologic Evaluation for Infection

Adenovirus group
Bordetella pertussis
Chlamydia spp (*C pneumoniae*, *C psittaci*, and *C trachomatis*)
Coccidioidomycosis
Coxsackie B (1-6)
Coxiella burnetii
Hantavirus
Histoplasma
Influenza A and B
Legionella (serum and urine)
Mycoplasma pneumoniae
Parainfluenza (1, 2, 3)
Respiratory syncytial virus
Rickettsial agents (Rocky Mountain spotted fever group, typhus, Q fever)
Coronavirus
Strongyloides spp
Toxocara spp
Wuchereria spp

Miscellaneous Testing

Antinuclear antibody
Eosinophil cationic protein
Hypersensitivity pneumonitis panel*
Quantitative immunoglobulins
Rheumatoid factor

*Includes antibodies to *Alterneria tenuis*, *Cephalosporium acremonium*, *Candida albicans*, *Micropolyspora faeni*, *Thermoactinomyces sacchari*, *Aspergillus* spp, *Penicillium* spp, *Rhizopus nigricans*, *Geotrichum candidum*, *Fusarium vasinfectum*, and pigeon dropping extract.

ber of agents and infections are associated with pulmonary eosinophilia, the diagnosis of AEP requires the exclusion of known causes of pulmonary eosinophilia.[6] Corticosteroids remain the mainstay of therapy for AEP, and relapses have not been reported.[2-4]

Unfortunately, no prospective studies describe the natural history of this disease and no controlled trials exist to guide clinicians in their use of corticosteroids. Acute eosinophilic pneumonia differs from chronic eosinophilic pneumonia in that many patients with the latter have a preceding history of asthma, a median duration of symptoms prior to diagnosis of approximately 7 months, and rarely progress to respiratory failure.[7]

Acute eosinophilic pneumonia is thought to be a rare disorder and few cases of AEP have been reported in the medical literature. The etiology of AEP is unknown, although prior case series have indicated a potential relationship between tobacco use and AEP.[4,8] Severe pneumonia was previously reported from March through August 2003 among 19 US military personnel who were deployed in support of Operation Iraqi Freedom; 2 of these patients died.[9] Ten of these 19 were diagnosed with AEP; an additional 8 patients were diagnosed through March 2004. This article describes these 18 cases of AEP and the clinical features of this syndrome and reports the results of the epidemiologic investigation of these cases.

METHODS

Case Definition and Identification

We defined cases of AEP based on a modification of criteria proposed by Philit et al.[4] Specifically, patients had to report a febrile illness followed by the development of respiratory symptoms such as cough, dyspnea, or both. Symptoms had to be present for less than 1 month and patients had to have evidence of infiltrates on chest radiograph. Unlike Philit et al,[4] we included individuals who did and did not develop respiratory failure to identify all possible cases of AEP. Patients with evidence of pulmonary eosinophilia based on either bronchoalveolar lavage (BAL) or lung biopsy were classified as definite cases of AEP. Patients who did not undergo BAL or biopsy but who developed peripheral eosinophilia (total eosinophil count, >250 cells $\times 10^3$/mL; percentage of eosinophils, $\geq 10\%$ of differential cell count) in the setting of an acute respiratory illness with new infiltrates were categorized as probable cases of AEP. Patients needing mechanical ventilation were categorized as "severe" cases of AEP. In all instances, known causes of both eosinophilia and acute infection had to be excluded. Laboratory evaluation included complete blood cell count, metabolic profile, C-reactive protein level, and erythrocyte sedimentation rate. In addition, patients underwent evaluation for potential parasitic infection, multiple cultures (sputum, blood, urine, stool) and serologic testing for other acute infectious processes, and serum studies for diseases known to be associated with pulmonary eosinophilia (BOX). Patients were also interviewed about exposures that may result in pulmonary eosinophilia, and vaccine histories were reviewed.

After several cases of AEP were identified in July 2003 based on the criteria outlined above, prospective disease surveillance began both in the US Central Command area of responsibility (which stretches from the Horn of Africa to Central Asia; hereafter referred to as "the theater") and at US military medical treatment facilities. Based on reviews of military medical records, we also conducted a retrospective search for cases back to March 2003.

End Points, Outcomes, and Follow-up Evaluation

The major end point of interest was the clinical characterization of the AEP syndrome. Hence, we collected data regarding patient demographics, symptom prodrome, and severity of illness at presentation. We also recorded information regarding initial chest radiograph appearance and temporal trends in the evolution of peripheral eosinophilia for each case. In addition to therapeutic interventions, we noted whether patients were treated with corticosteroids and their responses to these interventions. Specific management decisions were left to the patients' primary physicians and were not directed by protocol. Need for mechanical venti-

lation, duration of mechanical ventilation, and mortality also served as outcome measures.

All surviving patients with illness onset during 2003 were offered a follow-up evaluation by a pulmonary physician (A.F.S.) and an allergist (W.W.C.) at the Walter Reed Army Medical Center in the fall and winter of 2003. In addition, 1 patient with illness onset in 2004 received a follow-up evaluation. Four individuals were not available for follow-up because they had either returned to the theater or declined evaluation. At these follow-up visits, patients underwent a complete history and physical examination, allergen testing, clinical screening for the presence of atopy, repeat chest radiograph, and pulmonary function testing. We specifically sought evidence for AEP recurrence, development of chronic eosinophilic pneumonia, or evolution of some new collagen vascular disease. Many of the initial laboratory studies and serologic tests were repeated. In addition, eosinophil cationic protein levels were measured. The patients were also reinterviewed using a standardized questionnaire.

Epidemiologic Evaluation

The US Army deployed an investigative team to Germany (July-September 2003) and another to Iraq (August-September 2003) in support of the epidemiologic investigation of severe pneumonia.[9] The Iraq team visited 5 combat support hospitals in Kuwait and Iraq (Baghdad, Tikrit, Balad, and Mosul) and reviewed patient records, laboratory results, and radiographs to identify patients with lower respiratory tract illness. They interviewed clinical staff and patients and attempted to identify common factors among patients (eg, time, place, and symptoms) and whether any unusual exposures or other risk factors may have contributed to these illnesses. Surrogate interviews using a standardized questionnaire were completed by members of the military units of the 2 soldiers who died. The Iraq team queried Iraqi Ministry of Health personnel about pneumonia cases in the local population, specifically searching for reports of AEP. The Germany team deployed to the Landstuhl Regional Medical Center, the US military hospital receiving personnel medically evacuated from the theater. They interviewed patients and designed a laboratory testing protocol.

A standardized questionnaire was used to interview patients and capture demographic, exposure, and clinical data. It was not possible to complete 1 interview because this patient was identified for inclusion in the study after recovering and returning to the theater. A shorter version of the standardized questionnaire (absent the clinical collection tool) was self-administered in Iraq to a convenience sample of 72 members of the respective military units of the 2 soldiers who died (controls). Patients and controls were questioned about the following exposures: use of tobacco products (cigarettes and cigars); dust; sleeping location and duration; petroleum products; bulk ammunition; solvents or other chemicals; medical waste; close contact with the local population or prisoners of war; local sources of water; burning vehicles or buildings; human waste or other refuse; local foods; animals or animal droppings; insects; over-the-counter and prescription medications; insect repellants; and pesticide, fungicide, or herbicide application. Patients were also asked if illicit drugs were available. Smoking status was categorized as nonsmoker, new-onset smoker, or chronic smoker. New-onset smoking was defined as initiation of smoking in the theater (or immediately preceding deployment to the theater) among former nonsmokers or prior smokers (who restarted after at least 1 year of cessation). Patients who smoked cigarettes or cigars on a regular basis (irrespective of quantity) prior to arrival in the theater were classified as chronic smokers.

As this was an epidemiologic investigation performed for express public health reasons and to better define the clinical syndrome, formal institutional review board procedures were not required. Additionally, the study was performed at the direction of the Office of the US Army Surgeon General as part of its responsibility to protect the health of service members. Neither patients nor controls in the case-control study were required to participate.

The crude rate of AEP was calculated by dividing the number of cases by an estimate of the average number of military personnel at risk during the 13-month period. Denominator data were obtained from the US Department of Defense.[10] Comparisons between groups were tested using the Fisher exact test. Statistical analyses were performed using SPSS version 10.0 (SPSS Inc, Chicago, Ill); $P<.05$ represented statistical significance.

Tobacco Product Analyses

Cigarette and cigar samples from the theater were collected and analyzed for several potential environmental agents. Cigarette samples were collected by US Army preventive medicine specialists from local merchants and from the Army and Air Force Exchange Service in Baghdad during late August and early September 2003. Specifically, 15 different brands (2 cartons of each brand) were collected. These products were manufactured in a variety of nations including the United States, France, England, Korea, Jordan, and Iraq. Cigarette control samples (4 cartons, 2 brands) were collected from the Army and Air Force Exchange Service at Aberdeen Proving Ground, Md. In addition, a cigar that was partially smoked by a patient in the theater (in Djibouti) immediately prior to symptom onset was available for testing. Laboratory analyses included the standard US Food and Drug Administration pesticides screen with additional screening for paraquat and diquat; bacterial and fungal colony counts and identification of prevalent species; and special-threat agents (including ricin, strychnine, picrotoxinin, and lobeline). Cigarette filters were similarly analyzed. Supporting analytical laboratories included the US Army Medical Research Institute of

Infectious Diseases, US Department of Agriculture, and the US Food and Drug Administration. Samples were also sent to clinical investigators at Northwestern University Medical School, Chicago, Ill, for analyses of allergic-immunologic cross-reactions with serum samples from the case patients. Serum samples from patients were tested against a variety of fungal agents and an extract made from the tobacco purchased in the theater to evaluate patients for evidence of hypersensitivity pneumonitis.

RESULTS

Clinical Syndrome

During the 13-month period, 18 cases of AEP were diagnosed, with 7 meeting criteria for definitive AEP on the basis of either BAL or lung histology results. The median age of the cohort was 22 (range, 19-47) years and included 2 women. There were 2 deaths, resulting in a case-fatality rate of 11%. One individual died during aeromedical evacuation from Iraq before AEP was diagnosed. The second death occurred in a patient receiving mechanical ventilation during treatment for AEP and was due to the development of nosocomial pneumonia. Respiratory cultures were positive for *Klebsiella pneumoniae*, and the autopsy confirmed the presence of bacterial superinfection.

Symptoms characterized by half of the patients during the epidemiologic interview included shortness of breath, fever/chills, fatigue, and/or cough accompanying the onset of the syndrome (TABLE 1). No patient reported rash; 3 described joint pain. Time in the region before becoming ill varied widely (1 day to 11 months). The time between illness onset and presentation for medical evaluation was a median of 1 day (range, 1-4 days).

Chest radiographs revealed bilateral alveolar infiltrates in 10 patients; infiltrates were unilateral in the remainder. The infiltrates were alveolar in 10 cases and mixed alveolar-interstitial in 8. Pleural effusions were seen in only 1 individual. A typical chest radiograph is displayed in FIGURE 1A. Computed tomography scans obtained on admission to the intensive care unit in 6 of 12 patients demonstrated dense alveolar consolidation and pulmonary edema consistent with acute lung injury or ARDS. The pattern of the injury appeared to follow a bronchovascular distribution. Neither chest radiographs nor computed tomography scans revealed the presence of adenopathy.

The proportion of eosinophils in BAL fluid ranged from 25% to 74% (me-

Table 1. Symptoms Reported by Patients With Definite or Probable Acute Eosinophilic Pneumonia Among Military Personnel Deployed in or Near Iraq, March 2003-March 2004*

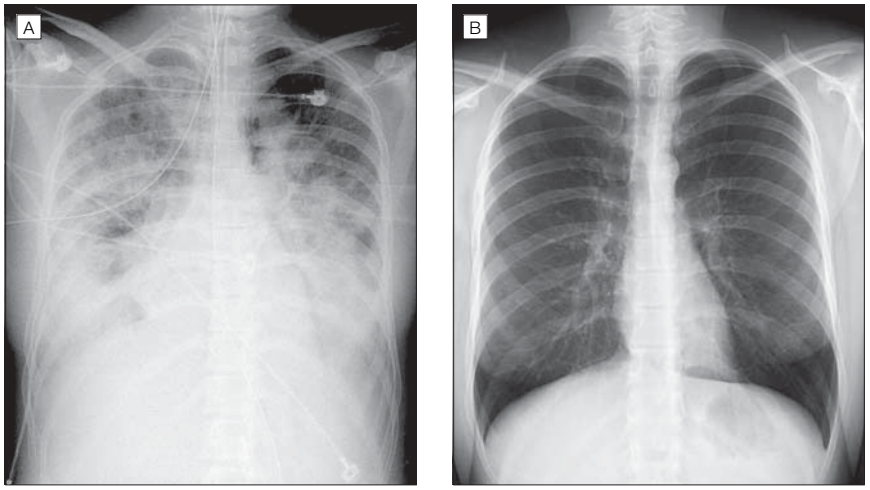
Patient No.	Arrival to Symptom Onset, mo	Symptom Onset to Medical Evaluation, d	Shortness of Breath	Cough	Chest Pain	Fever/ Chills	Fatigue	Other Symptoms
Definite Cases								
1	6	1	+	–	–	–	–	NA
2	2	1	+	+	+	+	+	Joint aches, abdominal pain
4	5	2	+	+	–	+	+	Abdominal pain, decreased appetite, vomiting, confusion
6	6	1	–	–	–	+	+	Profuse sweating, blurry vision
8	11	NA	NA	NA	NA	NA	NA	NA
17	3	1	+	–	–	+	+	Rigors, muscle aches
18 (Deceased)	1	4	NA	NA	NA	NA	NA	NA
Probable Cases								
3	8	NA	NA	NA	NA	NA	NA	NA
5	4	NA	NA	NA	NA	NA	NA	NA
7	10	NA	NA	NA	NA	NA	NA	NA
9	3	4	+	+	+	+	+	Rigors, muscle aches, joint aches, profuse sweating, abdominal pain
10†	1	2	+	+	+	+	–	Joint aches, muscle aches, sore throat, nasal congestion, wheezing, abdominal pain, vomiting, profuse sweating, decreased appetite
11 (Deceased)	1	1	NA	NA	NA	NA	NA	NA
12	1	3	NA	NA	NA	NA	NA	NA
13	2	1	+	+	+	+	+	Muscle aches
14†	2	1	NA	NA	NA	NA	NA	NA
15	3.5	1	+	+	+	+	–	Coughing blood, decreased appetite
16	<1‡	NA	NA	NA	NA	NA	NA	NA

*Arrival to symptom onset indicates months in the theater before symptom onset; NA, patient was not initially queried during epidemiologic interview regarding symptoms.
†Identified retrospectively (all others obtained prospectively).
‡In the theater for 1 day prior to symptom onset.

dian, 40.5%) (TABLE 2). Of the 6 BALs performed, 4 were performed within 24 hours of patient arrival at Landstuhl Regional Medical Center (after evacuation from Iraq), while the remainder were deferred for approximately 96 hours because of the patient's clinical status. On initial evaluation at Landstuhl Regional Medical Center, all patients had normal peripheral eosinophil counts. Despite evidence of pulmonary eosinophilia in the patients who underwent BAL, peripheral eosinophilia did not peak until approximately 3 days after admission. The median peak peripheral eosinophil count measured 20% and 2500 cells × 10^3/mL (Table 2).

Twelve of the 18 patients had severe disease requiring mechanical ventilation (Table 2). Nine of the 12 persons receiving mechanical ventilation required at least 4 days of ventilatory support, while 2 were extubated while in the intensive care unit at Landstuhl Regional Medical Center within 48 hours of arrival from Iraq. Excluding the soldier who died prior to transport out of Iraq, the median duration of mechanical ventilation was 8 days. Among those 12 treated in the intensive care unit and requiring mechanical ventilation, the mean ratio of arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FIO_2) measured 170 (range, 88-232). All patients requiring mechani-

Figure 1. Chest Radiographs From a Patient With Acute Eosinophilic Pneumonia



A, Baseline radiograph showing pronounced diffuse mixed alveolar and interstitial infiltrates consistent with acute lung injury. B, Radiograph taken approximately 3 months later documents resolution.

Table 2. Respiratory Aspects of Patients With Definite or Probable Acute Eosinophilic Pneumonia Among Military Personnel Deployed in or Near Iraq, March 2003-March 2004

	Mechanical Ventilation			BAL			
Patient No.	Required	Duration, d	PaO_2/FIO_2 Ratio	Performed	Eosinophils, %	Initial Peripheral Eosinophil Count, Cells × 10^3/mL	Peak Peripheral Eosinophil Count, Cells × 10^3/mL
Definite Cases							
1	–	NA	NA	+	74	200	1500
2	+	16	126	+	28	200	2500
4	+	8	154	+	25	600	2000
6	+	7	168	+	36	200	1150
8	+	9	192	+	56	200	1000
17	+	10	88	+	45	200	2100
18 (Deceased)	+	2	Unknown*	–	NA	. . .	. . .
Probable Cases							
3	–	NA	NA	–	NA	200	1900
5	–	NA	NA	–	NA	. . .	1000
7	+	12	170	–	NA	300	3200
9	+	2	220	–	NA	300	2600
10	+	5	228	–	NA	200	6600
11 (Deceased)	+	8	156	–	NA	700	3400
12	–	NA	NA	–	NA	. . .	850
13	+	5	232	–	NA	600	4000
14	+	4	208	–	NA	. . .	3100
15	–	NA	NA	–	NA	. . .	1400
16	–	NA	NA	–	NA	300	5000

Abbreviations: BAL, bronchoalveolar lavage; ellipses, data not avilable because initial complete blood cell count was either not obtained or not documented; NA, not applicable; PaO_2, arterial partial pressure of oxygen; FIO_2, fraction of inspired oxygen.
*Due to missing records.

cal ventilation met criteria for ARDS.[11] Three required transient (<12 hours) treatment with vasopressors after air transport from Iraq. Conventional modes of mechanical ventilation were used, with the amount of positive end-expiratory pressure never exceeding 15 mm Hg in any patient. Two patients needed inversion of the inspiratory-expiratory ratio on the ventilator to maintain adequate oxygen levels. Highly aggressive interventions for ARDS, such as prone positioning, high-frequency jet ventilation, and extracorporeal oxygenation were not required. Only 1 patient received paralytic medications, but this was for less than 12 hours. None of the 17 patients arriving at Landstuhl Regional Medical Center progressed to respiratory failure if they were evacuated from Iraq breathing spontaneously.

Serum measures of liver function and renal function were normal on presentation and remained normal in all survivors. None of the survivors progressed to refractory shock, organ failure, or both. The soldier who died of nosocomial pneumonia experienced renal failure and refractory shock, but only after acute respiratory failure and peripheral eosinophilia had begun to resolve.

Patients with severe AEP were uniformly treated with at least 7 days of broad-spectrum intravenous antibiotics. The most commonly used regimen included a combination of imipenem/cilistatin, levofloxacin, and doxycycline. Nonsevere cases were given intravenous antibiotics in some instances if they required hospitalization. For those not needing admission, physicians prescribed oral antibiotics. All but 4 patients received corticosteroids. Patients with severe AEP were given methylprednisolone intravenously. Nonsevere patients were treated with oral prednisone. In all instances, corticosteroids were tapered off over a 4- to 6-week period. Patients given corticosteroids had improvement in their respiratory status within 96 hours. However, clearing of their infiltrates lagged. Among these individuals, time to complete radiographic resolution was longer in those with severe AEP than in those not needing mechanical ventilation (11 vs 4 days). Individuals with unilateral disease on chest radiograph also had more rapid radiographic clearing than those with bilateral disease. However, this likely reflects the fact that no patient with unilateral disease required mechanical ventilation. There was no apparent association between severity of respiratory failure as measured by the Pa_{O_2}/F_{IO_2} ratio and radiographic resolution. The soldier who died prior to aeromedical evacuation did not receive corticosteroids. The 3 other patients not treated with corticosteroids improved with supportive care.

There was no difference between patients receiving mechanical ventilation and those not receiving mechanical ventilation with respect to their symptom prodrome or time in region prior to disease onset. All intubated patients had bilateral infiltrates on chest radiograph, while 3 of 6 less-severely ill patients presented with unilateral infiltrates ($P=.02$). There was no difference in peak peripheral eosinophil counts as a function of need for mechanical ventilation (mean peak eosinophil count, 2877 (SD, 1538) cells $\times 10^3$/mL vs 1942 (SD, 1544) cells $\times 10^3$/mL for patients receiving mechanical ventilation vs those not receiving mechanical ventilation).

Follow-up Evaluation. Twelve of the 16 survivors were seen for follow-up evaluation a median of 3.5 (range, 1-4) months after the initial diagnosis of AEP. At this point, no patient was still being treated with corticosteroids. All individuals had normal chest radiograph results at reevaluation. Three reported residual dyspnea that was self-graded as mild, and 1 reported wheezing. Subsequent pulmonary function testing included both bronchodilator challenge and measurement of carbon monoxide diffusing capacity (DLCO). Spirometry results were normal in all individuals. The mean forced vital capacity (FVC) was 97% (SD, 12%) of predicted (range, 76%-114% of predicted), while the mean forced expiratory volume in one second (FEV_1) was 94% (SD, 11%) of predicted (range, 75%-111% of predicted). No patient had airflow obstruction or a positive bronchodilator response to albuterol inhalation. The FEV_1/FVC ratio varied from 0.77-0.99. The DLCO was mildly reduced (eg, 65%-75% of predicted) in the 3 patients complaining of residual dyspnea. Among those seen for follow-up the mean DLCO was 82% (SD, 9%) of predicted (range, 66%-99% of predicted).

Results of serologic testing for a number of infections and collagen vascular disorders were negative. Allergy testing demonstrated that all patients had at least 1 positive percutaneous skin prick test result using a standard aeroallergen panel of trees, grasses, weeds, molds, and environmental allergen extracts (US Army Centralized Allergy Extract Laboratory, Silver Spring, Md). In addition to this panel, a tobacco leaf extract was also used (Greer Labs, Lenoir, NC). There was no pattern in the antigens resulting in positive skin test results and no patients tested positive to tobacco leaf extract. A tobacco smoke extract was developed using albumin-condensated tobacco smoke, and enzyme-linked immmunosorbent assay testing revealed no evidence of antismoke antibodies in those patients tested (Northwestern University Medical School). The level of eosinophilic cationic protein was normal in all 12 of the survivors seen for follow-up evaluation.

Epidemiologic Evaluation

An average of 183 000 military personnel were in or around Iraq during this time, yielding an AEP incidence of 9.1 per 100 000 person-years (95% confidence interval, 4.3-13.3). Patient demographics reflected the population serving in the theater with a median age of 22 years (range, 19-47 years). Fifteen patients (83%) were in the Army; 2 were in the Navy, and 1 was in the Marine Corps. All but 2 patients were men and were from multiple military specialties ranging from infantry to combat medic. Fourteen (78%) were junior enlisted personnel, 3 were noncommissioned officers, and 1 was an officer. Patients served in both active and

reserve components and were from different military units. Twelve patients were assigned to units in Iraq, 2 in Kuwait, 2 in Djibouti, 1 in Qatar, and 1 in Uzbekistan.

There was no evidence of a common source exposure or person-to-person transmission; cases were not clustered temporally. However, AEP incidence peaked in the summer months, with more than half (55%) of patients becoming ill from June through August (FIGURE 2). The most frequently reported exposures among patients were smoking tobacco (100%), fine airborne sand or dust (94%), convoy operations (76%), and close contact with the local population (71%). Nine of 15 patients reported that illicit drugs were available but only 2 stated they had used them while deployed.

Tobacco smoking was the only exposure that was more common among patients than controls (TABLE 3). All of the patients in the theater reported smoking tobacco and 14 (78%) were new-onset smokers. In contrast, 48 controls (67%) in the theater reported smoking tobacco and only 2 reported that they started during this deployment. Therefore, military personnel who were new-onset smokers had a significantly increased risk ($P<.001$) of AEP compared with controls (odds ratio, 122; 95% confidence interval, 17-1270).

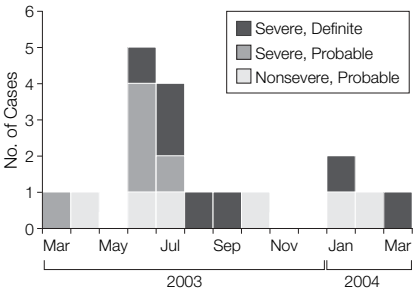
Patients categorized as new-onset smokers began smoking a median duration of 1 month (range, 2 weeks to 2 months) prior to illness onset. Of the 4 chronic smokers, 2 were unique in that their occasional tobacco smoking (prior to arriving in the theater) increased in quantity while in the theater. The quantity of cigarettes smoked among new-onset smokers ranged from 2 to 10 cigarettes per day. No patient reported smoking more than 1 pack of cigarettes per day. Although 2 patients did not smoke cigarettes, they had recently started smoking cigars or cigarillos. Members of the military units of the 2 deceased soldiers reported that one had recently started to smoke and the other was an occasional smoker who had increased his cigarette quantity in the theater.

Patients used a variety of tobacco brands, all of which were manufactured in the United States (and purchased at the Army and Air Force Exchange Service or mailed in packages from family members). Ten of the patients and 32 of the controls also purchased cigarettes from local merchants (eg, street vendors). Analysis of tobacco products obtained from the theater revealed no unusual components, toxins, or pesticide residues.

Specifically, there were no detectable residues of ricin, strychnine, picrotoxinin, lobeline, or paraquat/diquat or other pesticides in any cigarette sample (tobacco, paper, and filters). Mold colonies developed on dilution platings for 3 brands of cigarettes, and in each case the number of colony-forming units per gram of tobacco was low (<100 colony-forming units per gram of tobacco).

The majority of patients (67%) underwent vaccination against both smallpox and anthrax prior to developing AEP. However, 6 patients never received smallpox vaccine. All patients received at least 1 dose of anthrax vaccine; only 1 patient completed the 6-shot series (median number of anthrax doses received was 3). The time between vaccination with either agent and onset of symptoms varied from 3 to 11 months.

Figure 2. Illness Onset of 18 Acute Eosinophilic Pneumonia Cases, March 2003-March 2004



See "Methods" section for definitions of severe, nonsevere, probable, and definite. There were no patients in the "nonsevere, definite" category.

Table 3. Most Frequently Reported Exposures Among Patients With Acute Eosinophilic Pneumonia and Controls

Exposure	No. (%) Patients (n = 18)	No. (%) Controls (n = 72)*
Fine airborne sand or dust†	16 (94)	70 (97)
Convoy operations†	13 (76)	60 (83)
Close contact with the local population†	12 (71)	72 (100)
Smoked tobacco	18 (100)	48 (67)
New onset‡	14 (78)	2 (3)
Chronic	4 (22)	46 (64)
Nonsmoker	0	24 (33)

*Soldiers without acute eosinophilic pneumonia (controls) from the respective military units of the 2 patients who died were self-administered a standardized questionnaire.
†These exposure data were available for 17 patients with acute eosinophilic pneumonia who were administered the standardized questionnaire.
‡New-onset smoking was defined as initiation of smoking in the theater (or immediately preceding deployment to the theater) among former nonsmokers or prior smokers (who restarted after at least 1 year of cessation).

COMMENT

Although AEP is thought to be a rare disorder, we identified 18 cases of AEP among 183 000 military personnel deployed in or near Iraq, with an incidence of 9.1 per 100 000 person-years. Inquiries to the Iraqi health officials did not suggest that AEP was occurring in the local population or that there had been an unusual increase in the incidence of pneumonia of any kind during the study period.

In our case series, 2 patients died, 1 from a nosocomial superinfection and the other from rapidly progressive and refractory respiratory failure. Most often, patients with AEP survive if treated promptly with corticosteroids. The high case-fatality rate we noted underscores the seriousness of this entity and the fact that clinicians should consider AEP in the differential diagnosis of patients presenting with respiratory failure. Additionally, because of the increased incidence of AEP in this population, we recommend that military personnel presenting with unexplained respiratory failure undergo bronchoscopy to exclude AEP and that their clinical syndrome not be assumed to simply represent severe community-acquired pneumonia. For patients needing mechanical ventilation,

their treatment was not complicated by other organ failures. However, their respiratory failure was very severe and necessitated use of high levels of positive end-expiratory pressure and inversion of the inspiratory-expiratory ratio in certain instances.

All patients with AEP were smokers and 14 of 18 began to use tobacco shortly after deployment. Comparison with controls suggests an association between recent-onset smoking and AEP. Previous reports have suggested a link between recent-onset smoking and AEP.[8,12,13] For example, Nakajima et al[12] described several patients in Japan whose AEP was diagnosed soon after the patients began smoking. Similarly, Philit et al[4] completed a large retrospective review of AEP in France and noted that 6 of 8 individuals with AEP who smoked had begun doing so within the 3 months preceding disease onset. Bolstering the hypothesis that there is a nexus between recent tobacco exposure and AEP, Shintani et al[8] reexposed an individual with AEP thought to be related to tobacco. After reexposure, the AEP, which had resolved, returned. Among our patients, 1 had returned to the theater and restarted smoking 14 months after the onset of AEP. To date, AEP has not recurred in any of these patients.

In an animal model of hypersensitivity pneumonitis, which is both distinct from AEP and rare in smokers, nicotine has been shown to alter the expression of certain cytokines in the lung.[14] In turn, the balance between T_H1 and T_H2 lymphocytes shifts and the T_H1 phenotype is suppressed. This change can lead to expression of chemokines that attract eosinophils and might explain biologically any relationship between smoking and AEP. However, given the prevalence of smoking in both the general population and the deployed US military population (approximately 1 in 3 service members) as well as the rarity of AEP, it seems that tobacco alone is unlikely to be either a necessary or sufficient condition for the development of AEP. Service members have easy access to tobacco, with the ability to purchase it from local vendors or the military exchanges. Family members also mail tobacco products to deployed personnel. Efforts are under way to counsel deployed service members against tobacco use, and the military has several tobacco cessation initiatives.

Dust may also play some role in the etiology of the AEP cases we observed, as all but 1 of our patients described significant exposure to fine airborne sand or dust. Small particles in dust can irritate the airway and cause local inflammation that could result in a state leading to the production of cytokines such as interleukin 5, a potent recruiter of eosinophils. Several earlier cases of AEP have been reported arising after dust exposure.[15,16] Recently, Rom et al[17] described a firefighter who developed AEP after being exposed to dust from the collapse of the New York World Trade Center. Bronchoalveolar lavage revealed increased levels of interleukin 5 and stimulated $CD4^+$ cells. Mineralogic analysis of the dust showed high levels of asbestos fibers. Although asbestos was not noted in our cases, other as-yet unidentified particles may have contributed to AEP. Alternatively, recent exposure to tobacco may prime the lung in some way such that a second exposure or injury, eg, in the form of dust, triggers a cascade of events that culminates in AEP.

Other than tobacco use we could not identify epidemiologically a clear toxin or exposure to account for the high incidence of AEP. Our patients represented a variety of occupations and the disease appeared in a variety of locations, both in and outside of Iraq. Onset of illness developed soon after deployment in some patients, while others served in the theater for nearly a year before becoming ill. The list of potential causes of pulmonary eosinophilia is large, and it may be inappropriate to assume that whatever triggered this disease was the same in each patient. Different exposures or combinations of exposures may be responsible for the pulmonary eosinophilia and respiratory failure. Inability to identify another cofactor, however, does not preclude that one exists or that the cofactor might vary from patient to patient.

Eosinophilic lung disease has been reported previously among military personnel.[18] In 1997, 2 soldiers from the National Training Center area at Fort Irwin, Calif, presented with ARDS shortly after beginning training in this hot, desert environment. Despite broad-spectrum antibiotics, the soldiers' respiratory failure did not improve. Bronchoalveolar lavage revealed eosinophilia, and both patients developed a significant peripheral eosinophilia several days later. Notably, both soldiers had recently begun smoking cigarettes. Since March 2004, there have been 4 additional cases of AEP, all severe, among military personnel deployed in or near Iraq. Our findings have prompted heightened surveillance for AEP, and from March 2003 to October 2004 we have identified 3 cases of AEP in military personnel not deployed in or near Iraq (2 in Korea, 1 in Texas).

Many of the clinical features of AEP we noted do not match those previously described. In earlier case series, normalization of the chest radiograph has required nearly 1 month.[3,4] Our patients' radiographs improved more quickly, ranging from 4 to 11 days. This suggests that variability can be expected in the time to radiographic clearing. Alternatively, the rapid clearing might reflect the fact that all patients were expediently evacuated out of the area where they developed their illness, thus ending their exposure to any potential toxin that might have triggered the disease. Rapid radiographic improvement could also reflect that all of our patients were otherwise young and healthy prior to the onset of AEP.

Furthermore, we noted 3 patients who improved without corticosteroids. This has not been reported in previous case series. In fact, initial early proposals for case definitions for AEP required a positive response to corticosteroids. The ability of patients to improve without corticosteroids underscores the possibility that removal from some as-yet unidentified agent or combination of agents may be crucial for the

care of AEP. On the other hand, this observation implies that the AEP we observed may represent a unique syndrome, different from traditional forms of AEP. Finally, AEP has always been thought to result in respiratory failure.[1-4] Many of our patients did not progress to respiratory failure, which underscores that less-severe forms of AEP likely exist. However, most of our patients with less-severe AEP never underwent BAL to confirm the diagnosis, which limits our ability to draw conclusions regarding this possibility.

Our analysis has several important limitations. First, although we specifically conducted prospective surveillance for AEP, this report is technically retrospective, with all the accompanying limitations of this approach, including both case identification and recall bias. Second, as noted above, not all of our patients underwent BAL. However, being conservative and excluding "probable" cases still results in a high incidence of AEP. Third, the selection of the control population for the epidemiologic analysis limits our ability to draw strong inferences regarding potential causes and associations. The controls used in this analysis completed a self-administered questionnaire and represented only 2 military units that were deployed in Iraq. Finally, because patients and controls both used a combination of different tobacco products manufactured in different nations (eg, United States, Iraq), we could not determine if one particular type of tobacco product contributed to AEP. However, the biochemical and microbiological analyses of the cigarettes revealed no differences between those made in the United States and those produced elsewhere.

In summary, we describe a case series of AEP among military personnel deployed in or near Iraq. Patients can present with fulminant respiratory failure or have less-severe forms of the disease, both of which can mimic community-acquired pneumonia. Civilian and military physicians should both consider this diagnosis in military personnel presenting with respiratory complaints during, or after, a recent deployment or training exercise.

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