Bilateral Lower Extremity Inflammatory Lymphedema in Air Force Basic Trainees
Clinical and Epidemiologic Study of a New Disease Entity

Kevin A. Fajardo, MD, MPH, MTMH; Patrick Keller, MD, MPH; Todd Kobayashi, MD; Chad M. Hivnor, MD; Bryant J. Webber, MD, MPH; Susan P. Federinko, MD, MPH; Juste Tchandja, PhD

IMPORTANCE This observational study characterizes a new clinical condition identified in 55 military trainees.

OBJECTIVE To determine the incidence and underlying cause of bilateral lower extremity inflammatory lymphedema in Air Force basic trainees.

DESIGN, SETTING, AND PARTICIPANTS An observational study was conducted at Lackland Air Force Base in San Antonio, Texas. Participants included 14 243 Air Force basic trainees who entered training between September 2011 and January 2012 and the 55 trainees (0.4%) who developed bilateral lower extremity inflammatory lymphedema that occurred during the 8½-week basic training course. Two modifiable risk factors were evaluated: vaccine reaction and newly issued military footwear (combat boots and boot socks).

INTERVENTIONS During November 2011, all new trainees wore only white socks and running shoes rather than the issued military footwear. During December 2011 and January 2012, the scheduled administration of tetanus/diphtheria/acellular pertussis and meningococcal vaccines, respectively, was delayed by 1 week for all new trainees. A full medical record review was conducted for every confirmed case of bilateral lower extremity inflammatory lymphedema.

MAIN OUTCOMES AND MEASURES Identification of incident cases, symptom onset, antimicrobial treatment, immunization reaction, laboratory studies, specialty referral, and biopsy.

RESULTS Fifty-four of the 55 incident cases (98%) of bilateral lower extremity inflammatory lymphedema occurred during the first 120 hours of training. Alterations in the timing of the military footwear used and selected vaccine administration had no effect on the incidence of new cases. Two participants (4%) experienced symptom onset before receipt of the vaccines. Oral antimicrobial medications were not found to speed symptom resolution compared with conservative treatment measures (P = .34). One incident case was diagnosed as leukocytoclastic vasculitis by tissue examination.

CONCLUSIONS AND RELEVANCE Multiple training-related risk factors were ruled out as sources of bilateral lower extremity inflammatory lymphedema. Cases are likely secondary to prolonged standing with resultant gravity-dependent venous congestion and inflammatory vasculitis. The potential roles of undiagnosed venous reflux disease and the military physical training environment in these cases remain to be elucidated.

Published online January 21, 2015.

Copyright 2015 American Medical Association. All rights reserved.
In August 2011, we noted that 4 male trainees had been admitted for inpatient care to the Wilford Hall Ambulatory Surgical Center at Lackland Air Force Base (AFB) in Texas with bilateral lower extremity cellulitis. The subsequent evaluation revealed that all 4 patients were in their first week of basic training, having arrived on base in good health only 3 days before hospitalization. All patients described an almost identical clinical course of symptom onset, noted by an initial sensation of ankle and foot discomfort while standing at attention, which rapidly progressed to severe pain and swelling.

Each patient presented with grade 2+ pitting edema of the medial and lateral aspects of both ankles and dorsum of the feet, with varying levels of erythema. Pain was consistently reported in the tissues overlying the lateral and medial malleoli, and the affected skin was warm. None of the patients reported pruritus, and no disruption of the epidermis was noted. Although distal motor and sensory functions remained intact, the range of motion of the ankle joints was significantly reduced secondary to pain. All patients denied recent cough, sore throat, fever, nausea, vomiting, or diarrhea. Their medical history was negative for any noteworthy chronic medical problems.

Laboratory studies performed on all 4 patients included a complete blood cell (CBC) count and a comprehensive metabolic panel (CMP). Two patients had elevated white blood cell counts ranging from 10,300 to 13,100/μL (to convert to ×10⁹/L, multiply by 0.001), which normalized within 2 days of admission. No anemia or thrombocytopenia was noted. The results of all CMP panels were within the reference ranges.

Each patient initially received intravenous antibiotics; the therapy was transitioned to corresponding oral formulations prior to discharge. Hospital stays ranged from 2 to 3 days, with almost complete symptom resolution noted on follow-up at day 4 after discharge. No recurrence was reported for any of the patients throughout the remainder of basic training (8½ weeks).

Although cellulitis was a diagnostic consideration, the bilateral distribution and timing of symptom onset argued against this diagnosis. We conducted a retrospective medical records review of the previous 12 months and found that similar cases had been periodically diagnosed in the basic trainee population. Some were diagnosed as cellulitis and others as contact dermatitis related to newly issued socks. This cluster of cases brought attention to the condition. From September 15, 2011, through January 31, 2012, the preventive medicine staff at Lackland AFB conducted a prospective observational investigation in an attempt to identify the true incidence and cause of this condition.

Methods

Description of Training
The Lackland AFB institutional review board approved this observational study. Full informed consent was given orally by all patients, and no financial reimbursement was offered or given during the study.

Air Force basic training occurs at Lackland AFB. The 8½-week training program processes approximately 800 new trainees per week, with almost 38,000 trainees graduating each year (G. Palmer, MA, oral communication, September 20, 2011). There are always approximately 5600 basic trainees present on base. Trainees are housed in 6 different training squadrons, which are further divided into 14 to 16 flights. Male and female trainees are housed in separate specific flights, but female trainees are represented in each training squadron.

New basic trainees arrive on base on Tuesday or Wednesday of their first week of training, known as “processing week” or week zero. The first few days of basic training are spent primarily standing in line as they move through the various departments on base, including military pay, uniform issue, the barber, and the medical clinic. Physical training during this time is limited to rudimentary marching instruction; regular physical fitness training does not start until week 1.

Prospective Case Identification
The triage nurses assigned to the trainee health clinic identified all possible incident cases between September 2011 and January 2012. The name, squadron number, and week of training of any individual who developed bilateral foot/ankle swelling or pain were noted, and the preventive medicine staff was contacted to confirm whether these patients represented new cases based on clinical signs and symptoms. A trainee was considered to have a confirmed case if he or she experienced the onset of painful, bilateral foot and/or ankle swelling and erythema at any time during the 8½ weeks of basic training.

Combat Boots/Green Sock Wear
During the processing week, all basic trainees are issued white athletic socks, green boot socks, sage green combat boots, and running shoes. To examine the potential causative role of newly issued footwear and socks, basewide guidance was issued to all training squadron commanders. During November 2011, all basic trainees were directed to wear only their issued white athletic socks and running shoes throughout the processing week. All patients with the incident cases of bilateral lower extremity inflammatory lymphedema identified during this period were asked about their footwear practices to ensure that this policy was followed. The routine combat boot and sock wear policies resumed on December 1, 2011.

Infection
The medical records of all incident cases identified between September 2011 and January 2012 were reviewed. Cases were stratified based on whether antimicrobial medications were given as part of the treatment. The speed of symptom resolution based on clinical encounter notes and acute and convalescent photographs was measured in days for both groups and compared to assess the effectiveness of antimicrobial therapy.

Immunization Reaction
All basic trainees receive 4 immunizations during the processing week: tetanus/diphtheria/acellular pertussis (Tdap) vaccine booster, meningococcal vaccine, influenza vaccine (sea-
sonally), and adenovirus vaccine. The adenovirus vaccine is administered during the processing week for male trainees and at week 1 for female trainees (following confirmation of a negative pregnancy test). Starting in September 2011, the immunization records of all incident cases were retrieved and examined. The date of symptom onset was compared with the date of immunization to establish a temporal relationship.

The role of each vaccine as a potentiating cause of the incident cases was investigated. During December 2011, administration of the Tdap vaccine was delayed by 1 week for all trainees scheduled for their processing week vaccinations. During January 2012, the Tdap vaccine was returned to the processing week vaccination schedule and the meningococcal vaccine was delayed by 1 week. The adenovirus vaccine was planned to be delayed during March 2012 and the influenza vaccine during April 2012. A 1-week delay was chosen because all 4 trainees who had been hospitalized developed symptoms within 48 hours of arriving on base. This test would not alter the vaccinations that the trainees received, only the week of training in which the vaccines were administered.

Specialty Referrals
The medical records review of incident cases identified any patients subsequently referred for specialty evaluation. All biopsy specimens were examined by at least 2 staff dermatopathologists (T.K. and C.M.H.) to ensure that an interpretive consensus was reached.

Statistical Analysis
The mean time to the resolution of symptoms between patients who received conservative treatment and those who received antibiotics was compared using a 2-sided t test, with P < .05 considered statistically significant. Statistical analyses were performed using OpenEpi, version 3.03 (OpenEpi Development Team) software.

Results
Incident Case Finding
From September 2011 to January 2012, a total of 14 243 trainees (11 492 male and 2751 female) entered basic training at Lackland AFB. Fifty-five trainees developed bilateral lower extremity inflammatory lymphedema, yielding an attack rate of 0.4%. The clinical presentation was similar in all cases: painful, grade 1+ to 2+ pitting edema and erythema of the medial and lateral aspects of the ankles and dorsum of the feet, with no disruption of the superficial epidermal layers. The toes usually were not involved, but pretibial edema was often noted. All patients with incident cases reported no pruritus, and evidence of chronicity, including hyperpigmentation of the affected tissues, was absent.

Incident cases were diagnosed in all 6 training squadrons. Cases were diagnosed in every month of the observation period: 7 in September 2011, 5 in October, 15 in November, 14 in December, and 14 in January 2012 (Figure 1).

Fifty-four of the 55 incident cases (98%) experienced symptom onset during the processing week (1 patient [2%] noted symptom onset during the sixth week of training). All 55 patients denied experiencing similar symptoms in the past. Furthermore, no recurrence of the symptoms was reported in any incident case for the duration of their time in basic training.

Only 3 of the 55 incident cases (5%) were female trainees, and all 3 were from different training squadrons. There were 2751 female trainees (19%) in the basic trainee population during the observation period.

Combat Boots/Green Sock Wear
During November 2011, all processing-week basic trainees wore only newly issued white socks and running shoes. This intervention had no effect on the incidence of new cases, with 15 (27%) confirmed during this time (Figure 1). All affected trainees reported following the sock and footwear guidance exactly, which was corroborated by their drill instructors.

Infection
The medical records review of all incident cases revealed that 22 of the 55 confirmed cases (40%) were treated with conservative measures only (no systemic antimicrobial or corticosteroid medications). All 22 patients reported no fever, nausea, vomiting, diarrhea, upper respiratory symptoms, or general malaise and described almost complete resolution of the symptoms in a mean of 5.5 days.

The other 33 patients (60%) received oral antimicrobial therapy for a presumptive infectious process. Of the 30 patients with available symptom resolution data, the mean time to resolution was 5.7 days, which was statistically comparable to the time in the group that received conservative treatment (P = .34).

One patient developed severe ankle, foot, and pretibial edema and erythema (Figure 2A). With only supportive treatment measures, significant improvement in the edema, erythema, and pain was noted 3 days later (Figure 2B). No laboratory studies were performed on this patient.
Immunization Reaction

Through the beginning of December 2011, a total of 27 incident cases (49%) of bilateral lower extremity inflammatory lymphedema had been diagnosed. The immunization records review revealed that all 27 patients received the full complement of processing-week immunizations 24 to 48 hours before symptom onset.

The delayed administration of the Tdap and meningococcal vaccines during December 2011 and January 2012, respectively, failed to change the incidence patterns of new cases. Fourteen incident cases (25%) were diagnosed in both December and January (Figure 1). Furthermore, 2 cases (4%) diagnosed during January were confirmed to have experienced symptom onset before the administration of any vaccinations. Because of this finding, the delayed administration of the adenovirus and influenza vaccinations was not conducted as originally planned.

The patient with the last incident case, diagnosed in January 2012, reported symptom onset during the week 6 field training exercise. The patient described rapidly progressive, bilateral lower extremity pain and swelling while serving as a sentry, which involved standing for 5 to 6 hours with minimal walking.

Laboratory Studies

Fifteen of the 55 incident cases (27%) underwent additional laboratory studies, including CBC counts and CMPs. Seven of the 15 patients (47%) had acute leukocytosis, with white blood cell counts ranging from 10,900/μL to 14,300/μL. Three of these 7 patients (43%) had CBC counts performed again 2 days later. None of these 7 patients received antibiotics, but all experienced normalization of the white blood cell count. Results of the CMP studies were unremarkable in all 15 patients.

Nine of these 15 patients (60%) had erythrocyte sedimentation rates measured, and the results were elevated in 4 individuals (range, 45-90 mm/h). Elevated C-reactive protein levels were noted in all 4 patients as well, with a range from 5.7 to 14.3 mg/dL (to convert to millimoles per liter, multiply by 9.524).

Serum complement studies were performed on 2 trainees. The total complement (CH50) as well as C3 and C4 levels were within the reference ranges for both patients (54 U/mL, 118.5 mg/dL, and 34.3 mg/dL, respectively, in patient 1; and 49 U/mL, 90.5 mg/dL, and 26.6 mg/dL in patient 2) (to convert C3 and C4 to grams per liter, multiply by 0.001). In addition, C1q and C3d levels were determined in patient 2; the results were low (<1.2 mg/dL) and within the reference range (8 arbitrary units/mL), respectively.

Specialty Referrals

Patients 1, 2, and 3 were referred to the Wilford Hall Ambulatory Surgical Center Dermatology Clinic for further evaluation and underwent small punch biopsies of the affected tissues. Examination of the biopsy specimen of patient 1 showed subtle vasculitic changes characterized by endothelial cell damage, subtle fibrin deposition, occasional karyorrhectic debris near or within the vessel walls, and extravasated red blood cells. In light of the patient’s clinical history, these histologic changes were concerning for a vasculopathic process that was possibly immune complex mediated involving the cutaneous vessels, with secondary reactive and edematous changes of the dermis and subcutis.
The biopsy specimen of patient 2 demonstrated nonspecific histologic changes, showing only reactive dermal changes, including edema and scant interstitial inflammatory cells. No vasculitis or vasculopathic process was identified in the sections examined, although it was noted that, given the degree of symptoms, the small biopsy sample may have missed the primary pathologic process.

The biopsy specimen of patient 3 demonstrated lower dermal edema with a mixed inflammatory infiltrate of lymphocytes, neutrophils, and eosinophils with focal nuclear dust (leukocytoclasia). No definitive vascular wall fibrin deposition was seen. The initial histologic findings were suggestive of early leukocytoclastic vasculitis. Direct immunofluorescence staining showed deposition of C3 within the walls of superficial dermal vessels. The staining detected no IgG, IgA, IgM, or fibrin.

**Discussion**

In a relatively short time of concentrated identification of cases, we demonstrated that cases of bilateral lower extremity inflammatory lymphedema are more common in Air Force basic trainees than previously thought. Although there have been anecdotal reports of similar cases seen during basic training in the past, a total of 55 incident cases were identified in just 4½ months.

Our investigation eliminated multiple potential training-related causes. First, given the timing of the symptom onset, there was a remote possibility that these cases were the result of an irritant in the issued socks and/or combat boots. However, there was little direct clinical evidence to support this theory, with the primary symptoms being edema and erythema rather than a disruption of the superficial epidermal layers. The subsequent alteration in the timing of the combat boots and green sock wear protocol definitively eliminated this possibility. Despite wearing only white athletic socks and running shoes during November 2011, trainees experienced a similar condition with the same timing of symptom onset at a rate 3 times as high as in October (Figure 1).

Infection was a possible underlying cause given the clinical presentation and severity of the symptoms. However, this supposition proved highly unlikely owing to the lack of risk factors for cellulitis at the time of symptom onset, the bilateral presentation of the cases, the speed of symptom resolution without antibiotic therapy, and the fact that 54 of the 55 cases (98%) became symptomatic during the processing week of basic training.

The immunization reaction hypothesis was also a promising possible cause of bilateral lower extremity inflammatory lymphedema given that most cases became symptomatic 24 to 48 hours after vaccination. There is evidence to support this supposition, citing the role of vaccines in cases of extensive limb swelling secondary to type III (Arthus) hypersensitivity reactions. Unfortunately, the limited laboratory studies conducted in the present study supported only a generalized inflammatory response with elevated erythrocyte sedimentation rate and C-reactive protein levels. Multiple complement studies were done on 2 of our patients, but most of the test results were normal. The medical records review of all 55 cases found no reports of localized vaccine injection site reactions, as is most common in instances of vaccine-related Arthus reactions. Although it is possible that minor injection site reactions were occurring but were not mentioned because of the rapidly progressive symptoms of bilateral lower extremity inflammatory lymphedema, this finding was surprising. However, immunizations were eventually ruled out as a cause of the lymphedema after confirmation that 2 cases became symptomatic before any vaccines were administered.

Other potential conditions were considered improbable given the documented symptoms and demographics of the incident cases. For example, the diagnosis of acute lipodermatosclerosis was doubtful given that most cases occurred in male trainees (95% of all cases), affected tissues generally included the dorsum of the feet yet spared the toes, no patients had a history of venous insufficiency or lower extremity edema, and no cases recurred or progressed following the acute illness. Histologic changes of acute lipoedematosclerosis were also not detected. The clinical presentation, course of disease, and histologic changes were not consistent with eosinophilic cellulitis, allergic contact dermatitis, or stasis dermatitis.

We hypothesize that prolonged standing during the first 3 to 4 days of training results in gravity-dependent venous congestion and subsequent lower extremity tissue inflammation and, in some cases, small vessel vasculitis (possibly immune complex mediated), subsequently leading to worsening edema, inflammation, and pain. Although the diagnosis of leukocytoclastic vasculitis was histologically confirmed in only one case, the striking similarities in clinical presentation and timing of symptom onset support a similar pathologic process in the other 54 patients. It is unclear whether preexisting, yet undiagnosed, venous reflux disease is a contributing factor, although this seems unlikely given that all patients were young and otherwise healthy military recruits. Consequently, our clinical and epidemiologic findings support the hypothesis that these cases represent a distinct clinical entity.

Targeted preventive interventions can be implemented in an attempt to mitigate additional cases of bilateral lower extremity inflammatory lymphedema. For example, the use of compression stockings, even if only during the first few days of basic training, as well as alterations to the processing week training schedule to allow for more walking and/or marching activities may prove to be effective at reducing the extent of gravity-dependent lower extremity venous congestion and vasculitis in this population.

This study should be interpreted in light of its limitations. First, although we were able to alter the timing of certain risk factors, such as the boot/sock wear and vaccination dates, our interventions were applied to all trainees (ie, without a control group and randomization), making our study observational. Second, although demographic and risk factor information was collected from medical record reviews, resulting in incomplete data sets. Third, although we confirmed all 55 incident cases, we did not act as the primary care managers for these trainees. Therefore, we had almost no involvement in
treatment decisions or referrals to specialists. Finally, specialists were consulted for only 3 patients, and only 1 of these patients received a diagnosis of leukocytoclastic vasculitis.

Conclusions

We report a series of 55 Air Force basic trainees with bilateral lower extremity inflammatory lymphedema that was most likely caused by prolonged standing, venous congestion, and subsequent vascular inflammation. Although the investigation did not definitely identify the cause of the lymphedema, our findings ruled out many potential causes and detected a previously undescribed, yet potentially preventable, disorder. In the short term, these results will reduce the number of affected trainees who receive unnecessary antibiotic therapy while facilitating a more rapid return to training. Our Department of Defense sister services may also benefit from our findings since similar cases may be occurring at other basic training facilities. A formal prospective study should be conducted to investigate this condition more fully, with emphasis on the potential roles of undiagnosed venous reflux disease and the military physical training environment.

A Quick Review of the Cutaneous Findings of the Deadly Scourge Ebola Virus

Brian J. Simmons, BS; Robert D. Griffith, MD; Leyre A. Falto-Aizpurua, MD; Keyvan Nouri, MD

Ebola virus, a hemorrhagic fever virus belonging to the family Filoviridae, is one of the newest and most deadly pathogens. Ebola was first identified in Africa in 1976 and has a mortality rate approaching 90%. The virus has had sporadic outbreaks since then; however, one of the biggest epidemics of Ebola started in 2013 and has once again stricken Africa. It has engulfed multiple nations and crossed the Atlantic, leading to the first case of Ebola in the United States. Thus, it is important to review the cutaneous findings of Ebola because they can provide diagnostic pointers during early outbreaks.²

The virus is spread from human to human via direct contact with bodily fluids. It has an incubation period of 2 to 21 days, with an average onset of symptoms within 8 to 10 days.³,⁴ Findings are divided into 3 phases, with phase 1 presenting as a general flu-like syndrome with malaise, myalgia, arthralgia, and headaches. During phase 2, visceral symptoms, including abdominal pain, nausea, and watery diarrhea, develop concurrently with a nonpruritic maculopapular eruption with fine scale. Additional cutaneous hemorrhagic findings that develop during this time frame include petechiae, ecchymosis, gingival bleeding, and oropharyngeal bleeding ulcerations.⁵

The maculopapular eruption of Ebola virus can mimic the presentation of measles, with pinpoint dark-red papules developing around the hair roots, the buttocks, and extremities, then spreading in a centripetal manner leading to diffuse erythema around day 8. In phase 3 the erythema clears in patients who survive, with subsequent desquamation. Mucosal findings can develop as well, ranging from cold sore-like lesions to glossitis and pharyngitis.⁶

Although the cutaneous findings of Ebola virus are not life threatening or specific, it is important for clinicians to keep this viral syndrome in their differential when thinking of viral or hematologic causes for these cutaneous findings. This is especially true owing to the ease of international travel and globalization that can act as efficient delivery systems for pathogens.

NOTABLE NOTES

A Quick Review of the Cutaneous Findings of the Deadly Scourge Ebola Virus

Ebola virus, a hemorrhagic fever virus belonging to the family Filoviridae, is one of the newest and most deadly pathogens. Ebola was first identified in Africa in 1976 and has a mortality rate approaching 90%.¹ The virus has had sporadic outbreaks since then; however, one of the biggest epidemics of Ebola started in 2013 and has once again stricken Africa. It has engulfed multiple nations and crossed the Atlantic, leading to the first case of Ebola in the United States. Thus, it is important to review the cutaneous findings of Ebola because they can provide diagnostic pointers during early outbreaks.²

The virus is spread from human to human via direct contact with bodily fluids. It has an incubation period of 2 to 21 days, with an average onset of symptoms within 8 to 10 days.¹³ Findings are divided into 3 phases, with phase 1 presenting as a general flu-like syndrome with malaise, myalgia, arthralgia, and headaches. During phase 2, visceral symptoms, including abdominal pain, nausea, and watery diarrhea, develop concurrently with a nonpruritic maculopapular eruption with fine scale. Additional cutaneous hemorrhagic findings that develop during this time frame include petechiae, ecchymosis, gingival bleeding, and oropharyngeal bleeding ulcerations.¹

The maculopapular eruption of Ebola virus can mimic the presentation of measles, with pinpoint dark-red papules developing around the hair roots, the buttocks, and extremities, then spreading in a centripetal manner leading to diffuse erythema around day 8. In phase 3 the erythema clears in patients who survive, with subsequent desquamation. Mucosal findings can develop as well, ranging from cold sore-like lesions to glossitis and pharyngitis.³

Although the cutaneous findings of Ebola virus are not life threatening or specific, it is important for clinicians to keep this viral syndrome in their differential when thinking of viral or hematologic causes for these cutaneous findings. This is especially true owing to the ease of international travel and globalization that can act as efficient delivery systems for pathogens.