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CASE REPORT

Histopathology of bilateral lower extremity inflammatory lymphedema in military basic trainees: A leukocytoclastic vasculitis of the deep vascular plexus

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Bilateral lower extremity inflammatory lymphedema (BLEIL) is a recently described condition that presents with exquisite tenderness, erythema and edema of the lower leg, ankle and dorsal foot resembling an acute cellulitis. It was first reported in healthy, young adult military basic trainees with a normal body mass index during the first 72 hours of arrival to basic training. It occurs while standing at attention for many hours, and shows rapid resolution with elevation and rest. We report an additional case of BLEIL and describe the histopathology of this case and 2 of the previously reported cases. All 3 biopsies showed a deep perivascular infiltrate of neutrophils with karyorrhectic debris and prominent red blood cell extravasation. One of the 3 cases was positive for complement by direct immunofluorescence. We postulate this condition represents a deep leukocytoclastic vasculitis with secondary reactive lymphedematous changes.

KEYWORDS

leukocytoclastic vasculitis, lymphedema, military, prolonged standing, trainees

1 | CASE REPORT

An 18-year-old, previously healthy military basic trainee with a body mass index (BMI) of 20, was admitted for intravenous antibiotics with a presumptive diagnosis of bilateral lower extremity cellulitis. Two days prior to admission, he arrived at military basic training at Joint Base San Antonio-Lackland in Texas completely asymptomatic. On the second day of training while learning to march, he noticed tenderness and swelling of his ankles which rapidly progressed over 22 hours. He had not started fitness training, but spent the majority of his time standing at attention for numerous hours with his knees fully extended and feet together. He had minimal movement other than a slight shuffling gait to advance 1 foot while waiting in lines to inprocess the military. He was not taking medications nor had received his inprocessing military vaccinations. He denied any trauma or infection to the affected area or a history of similar episodes. All military recruits are encouraged to be physically active prior to basic training and he ran cross country for 6 years prior to entering the Air Force.

In the acute care clinic, he had a fever to 39 C, a blood pressure of 92/49 and was noted to have 2+ pitting edema with erythema

from the ankles to the mid-calves which were exquisitely tender to light touch. Ankle flexion and extension exacerbated his pain and his peripheral pulses remained intact. Twelve hours after admission there was a significant decrease in erythema with rest and elevation (Figure 1).

Magnetic resonance imaging revealed extensive diffuse soft tissue edema in the bilateral lower extremities, most prominent at the medial and lateral malleoli. Inflammatory markers were elevated with an erythrocyte sedimentation rate of 41 and a c-reactive protein of 18.2. His white blood count was increased at 16 400/ μ L with 79% neutrophils. Blood and tissue aerobic and anaerobic cultures were negative. A complete metabolic panel to include lactate, creatine kinase, thyroid studies, antinuclear antibodies, rickettsial titers, human immunodeficiency virus, ferritin and antinuclear cytoplasmic antibodies were all normal.

The patient was admitted for cellulitis with a concern of necrotizing fasciitis given the rapidity of the development of symptoms and extreme pain, erythema and edema. However, the bilateral distribution argued against a bacterial infection. Empiric antibiotics that included vancomycin, piperacillin-tazobactam, clindamycin and

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FIGURE 1 Unilateral erythema and edema. Photograph taken 12 hours after elevation.

doxycycline were started pending further evaluation. A 4 mm punch biopsy was obtained from his left lower medial leg (Figure 2) approximately 36 hours after onset of the symptoms. Histological examination showed a dense infiltrate centered in the lower reticular dermis surrounding the eccrine ducts and the deep vascular plexus. The infiltrate was composed of a mixture of lymphocytes, histiocytes and abundant neutrophils with extravasated erythrocytes. Neutrophilic infiltration of a medium-sized arteriole with karyorrhectic debris was identified. No definitive fibrin deposition was noted. Although the patient had been started on intravenous antibiotics, these were discontinued after dermatology consultation. Within 36 hours of admission with rest, compression and elevation of his legs, his pain, swelling and erythema had almost completely resolved.

2 | DISCUSSION

We report another patient with bilateral lower extremity inflammatory lymphedema (BLEIL) and further characterize the histopathology of this entity. We reviewed the punch biopsy from the current patient and were able to retrieve 2 other biopsies from the study by Fajardo et al.¹ Review of the slides from the 3 patients revealed very similar histopathology showing a deep dermal neutrophilic infiltrate surrounding the deep vascular plexus with karyorrhexis suggesting an early deep leukocytoclastic vasculitis (LCV). Patient 1, 19 years old with a BMI of 20.8, showed a sparse superficial and deep perivascular

infiltrate with abundant extravasation of erythrocytes. Neutrophilic infiltration of small vessels with karyorrhectic debris and a fibrin plug is noted in one of the small arterioles (Figure 3). This trainee was the only patient to have a direct immunofluorescence (DIF) ordered which revealed complement in the superficial dermal vessel walls without staining for fibrin, IgG, IgA or IgM.¹ Patient 3, 24 years with a BMI of 19.8, showed similar findings (Figure 4) to the other 2 patients. Although unavailable for review, the histopathology of the other case in the article by Fajardo et al.¹ reported dermal reactive changes to include edema and scant inflammatory cells without evidence of a vasculopathic process in the sections examined. The authors mentioned that the small biopsy sample may have missed the primary disease process.¹

Lack of a definitive diagnosis of a vasculitis from 4 of the previously described trainees with BLEIL, may also be related to timing of the biopsy. Ideally, biopsy specimens of suspected cutaneous vasculitis should be obtained from an established purpuric lesion more than 72 hours old.² Histopathology of vasculitic lesions less than 24 hours old are likely to have some infiltration of neutrophils with karyorrhexis but often do not show vessel wall expansion or fibrin deposition.² The biopsy in our case report patient was obtained 36 hours after symptom onset with findings suggestive of an early deep dermal LCV. In addition, the significant dermal edema noted clinically suggests secondary lymphedema. In normal homeostatic conditions, 90% of the blood plasma that enters the interstitial space on the arterial side of the capillary returns to the venules with the remaining 10% returning to the venous system through the lymphatic system.³ Disruption of this process can result in altered phlebolympathic drainage allowing circulating immune complexes, antigens and foreign material to accumulate in the interstitial space triggering cutaneous inflammation.³

Although many types of vasculitis are exacerbated by prolonged standing or activity,⁴ the pathophysiology of the sudden development in previously healthy young adults is not completely understood. Prolonged standing with the knees fully extended and minimal movement for hours may induce a temporary calf pump failure of the venous and lymphatic systems resulting in acute stasis with deposition of immune complexes, ultimately leading to a deep dermal vasculitis.

Other conditions with altered phlebolympathic drainage include golfer's vasculitis (GV), leukocytoclastic vasculitis induced by prolonged exercise and Hypergammaglobulinemic purpura of Waldenstrom (HPW). GV most commonly presents with blotchy erythema prior to the development of a purpuric rash on the legs after prolonged exercise, most commonly 18 holes of golf or prolonged walking, and almost exclusively in hot weather.^{4,5} BLEIL was noted to occur in the winter months from September, 2011 through January, 2012 in the study by Fajardo et al.¹ Both conditions occur in healthy adults, although the mean age is 68 years in GV. A prominent clinical finding in BLEIL was that all patients presented with 1 to 2+ pitting edema of the ankle and dorsal foot. However, only 3 of the 17 patients with GV noticed mild to moderate ankle swelling with the rash often sparing the skin compressed by the sock. Another striking feature of BLEIL is exquisite foot and ankle tenderness which is quite different from GV with 35% denying symptoms. Both reported

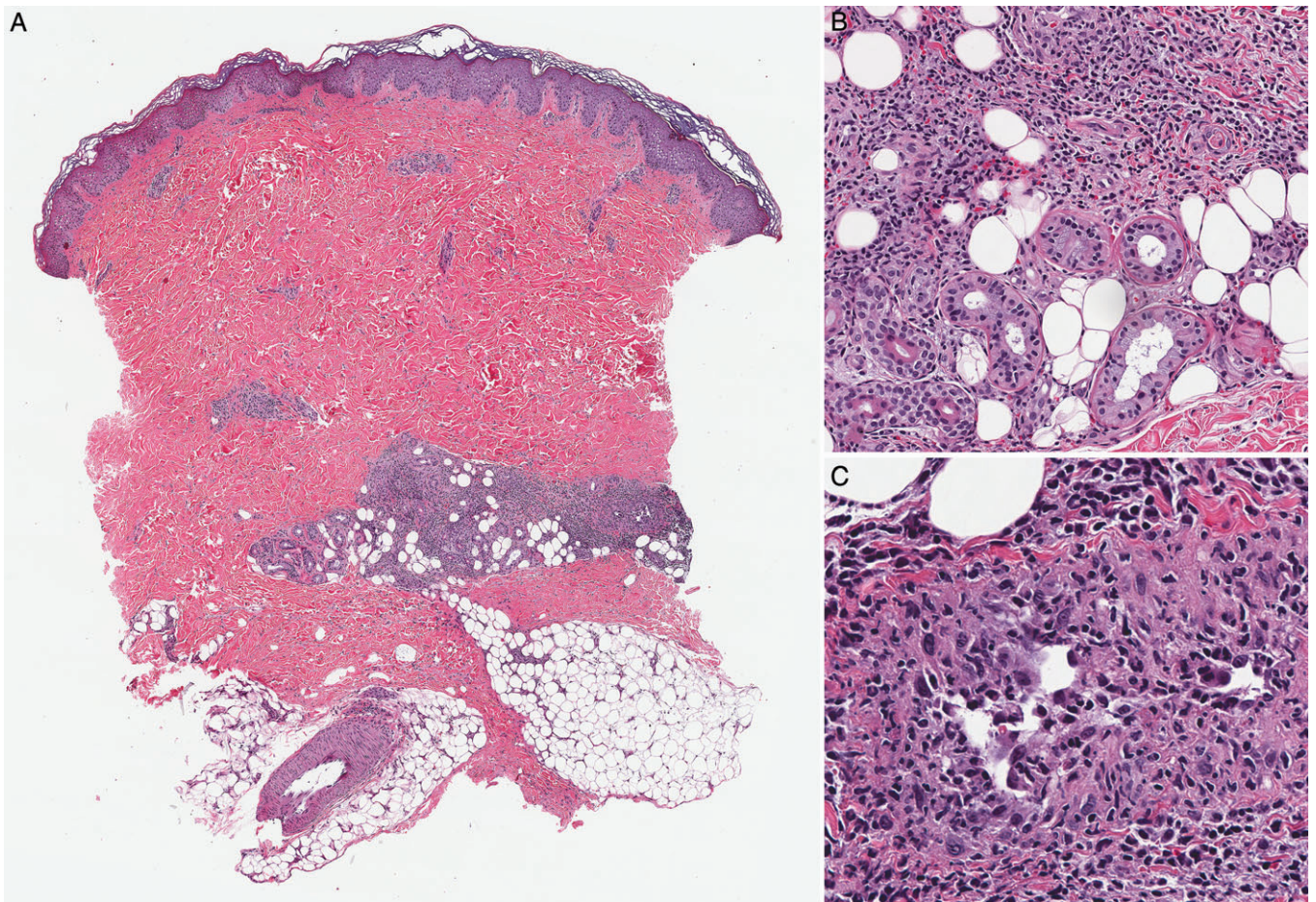


FIGURE 2 Case patient. A, Dense infiltrate centered in the lower reticular dermis surrounding the eccrine ducts and the deep vascular plexus (H&E, original magnification $\times 20$). B, Infiltrate composed of a mixture of lymphocytes, histiocytes and abundant neutrophils. Extravasated erythrocytes are also seen (H&E, original magnification $\times 100$). C, Neutrophilic infiltration of a medium-sized arteriole with karyorrhectic debris. (H&E, original magnification $\times 200$).

spontaneous resolution usually over 3 to 4 days. Histologic findings in 4 of the 6 patients biopsied with GV were similar to BLEIL with evidence suggesting an early LCV without fibrinoid necrosis.

Exercised-induced purpura (EIP) in young, healthy adults without a history of an underlying chronic venous disorder (similar to the

population with BLEIL), has been reported to occur immediately after excessive or major muscular activity.^{6,7} This condition is probably underreported and few publications exist examining this condition, possibly because it often arises during vacations and fades spontaneously prior to medical examination.⁶ It appears most commonly in

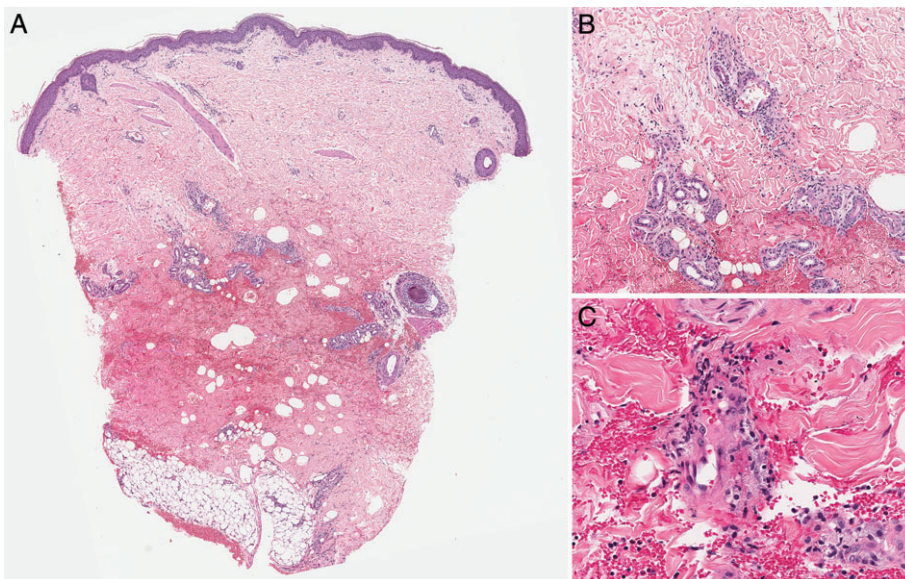


FIGURE 3 Patient 1, A, Sparse superficial and deep perivascular infiltrate with abundant extravasation of erythrocytes (H&E, original magnification $\times 20$). B, Perivascular and peri-eccrine inflammation. (H&E, original magnification $\times 100$). C, Neutrophilic infiltration of small vessels with karyorrhectic debris. A fibrin plug is noted in one of the small arterioles. Direct immunofluorescence of this specimen revealed C3 within the walls of the superficial dermal vessels but was negative for IgG, IgA, IgM and fibrin. (H&E, original magnification $\times 200$).

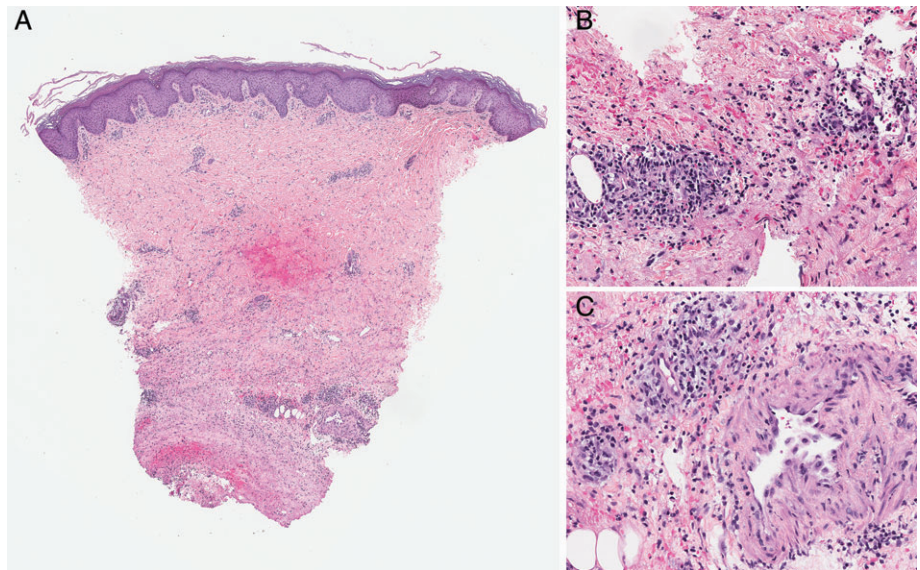


FIGURE 4 Patient 3. A, Moderately dense superficial and deep dermal infiltrate (H&E, original magnification $\times 20$). B, Dense neutrophilic infiltrate with karyorrhectic debris (H&E, original magnification $\times 100$). C, Mostly smaller caliber vessels affected by neutrophilic inflammation. Some infiltration of a larger arteriole (H&E, original magnification $\times 200$).

marathon runners or after long walks and occurs almost exclusively in hot conditions. EIP presents with erythematous urticarial or purpuric plaques on the lower leg sparing the skin covered by the socks. In contrast to BLEIL, frequent relapses of EIP occur with similar exercise. The histopathology of this entity was described as an LCV.⁷ All specimens showed a mild to severe leukocytoclasia with vessel wall invasion by granulocytes and mononuclear cells, and variable positivity for exocytosis of erythrocytes, some with C3c, C1q and IgM deposits but no fibrin deposition.⁷ The depth of the infiltrate of these specimens predominantly involved the superficial dermis but some specimens extended to vessels in the subcutaneous fat. Prominent erythrocyte extravasation has been noted on biopsies of both BLEIL and EIP. Although exercise typically increases venous return, overload of the venous system may induce exhaustion of the calf muscular pump leading to venous stasis with pooling of circulating immune complexes and antigens with complement activation resulting in a cutaneous vasculitis,⁶ similar to the proposed etiology of BLEIL.

Hypergammaglobulinemic purpura of Waldenström is another disease entity triggered by increased hydrostatic forces in the legs caused by prolonged standing or exercise during activities such as walking, running or dancing.⁸ Episodes tend to be recurrent and may be more frequent in summer months like EIP or GV. HPW typically occurs in young to middle-aged women and is associated with a polyclonal hypergammaglobulinemia. It has been noted in patients as a secondary manifestation of connective tissue diseases such as Sjögren's Syndrome and lupus erythematosus and multiple other diseases.⁸ It is clinically different, however, in that the eruption presents as petechiae and purpura on the lower extremities rather than a cellulitic-like process and has been documented to occur on the abdomen and arms unlike BLEIL. It also tends to be recurrent and is associated with a hypergammaglobulinemia. The vasculitis involves the superficial dermal vessels, not the deep vessels, but may show both LCV or lymphocytic perivasculitis with extravasated red blood cells and siderophages. Circulating immune complexes of IgG, IgA and IgM have been documented.

Since the original publication, awareness of BLEIL has increased among the Air Force basic trainee health care providers leading to earlier identification and rapid implementation of the appropriate treatment of rest and lower extremity elevation. Further information to better characterize this process such as optimally timed additional biopsies with DIF, and serum complement levels including C1q binding assays and C3d would be beneficial. In addition, prospective studies are needed on interventions to decrease the risk of BLEIL such as increased physical activity during the first 3 days, breaks to allow the movement of ankles and hips, stepping in place or the use of compression stockings.

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