Exercise-Induced Vasculitis Associated With Autoimmune Disease

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The estimated time to complete this activity is 1 hour.

GOAL

To understand exercise-induced vasculitis (EIV) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Recognize the signs and symptoms of EIV.
2. Identify diseases that may be associated with EIV.
3. Interpret the pathophysiology of EIV.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and generalists.

CME Test and Instructions on page 316.

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Exercised-induced vasculitis (EIV) is an underreported and frequently misdiagnosed condition that occurs on the lower extremities shortly after exercise. Most reported cases have presented in healthy-appearing individuals, but some cases have been linked to other disease processes. A case report is presented of recurring EIV in a 65-year-old woman with a history of dermatitis herpetiformis; chronic, mildly elevated liver transaminases of unknown cause; microscopic colitis; celiac disease; multiple miscarriages; and heart block who was found to have autoimmune hepatitis upon workup of her rash. Both EIV and autoimmune hepatitis were misdiagnosed over

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many years by several clinicians in various specialties. Her family history was remarkable for 2 sisters with systemic lupus erythematosus and similar recurring exercise-induced rashes of the lower extremities, suggesting a familial link for this condition. Clinicians should recognize EIV and consider the possibility that this disorder may be the presenting sign of subclinical connective-tissue diseases.

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Exercise-induced vasculitis (EIV)(also referred to as exercise-induced purpura, golfer's vasculitis, jogger's petechiae) is an unusual condition characterized by recurrent intermittent palpable purpura occurring on the lower extremities within a few hours of exercise, frequently in warmer weather conditions.[1-11] There is striking sparing of areas of compression, such as under the sock, and pruritus may be present. The rash may persist for approximately one week before spontaneously resolving. Biopsy of the rash reveals changes typical of leukocytoclastic vasculitis and direct immunofluorescence may show C3 deposition in the capillary endothelial cells and IgM in the capillary walls.[2] Most cases occur sporadically in healthy-appearing individuals,[1-8] though cases of EIV have been reported in individuals with teratoma,[9] hypergammaglobulinemia,[10] and Sjögren syndrome.[11] Exercise-induced vasculitis is frequently misdiagnosed and is not mentioned in most major textbooks.[1]

Herein is a case report of long-standing EIV in a patient with an autoimmune diathesis, multiple miscarriages, and mildly elevated liver transaminases. Her rash and liver abnormalities were misdiagnosed by several clinicians in internal medicine, dermatology, rheumatology, and immunology over 23 years. Her 2 sisters also had a history of similar recurring exercise-induced rashes and both were diagnosed with systemic lupus erythematosus. This case highlights the clinical features of EIV and the potential association of this condition with other disease processes.

Case Report

A 65-year-old white woman with a 37-year history of diet-controlled dermatitis herpetiformis, microscopic colitis, celiac disease, multiple miscarriages, and second-degree heart block controlled by a pacemaker presented with a rash of 2 days' duration that had recurrently developed on the distal lower extremities above the sock line over 23 years with physical exertion, primarily in warm (>30°C) weather. The rash was mildly pruritic and would typically persist for 4 to 6 days before spontaneous remission. It had been previously diagnosed as urticaria, contact dermatitis, eczema, dry skin, and stasis dermatitis. She also was known to have chronic, mildly elevated liver transaminases that were thought to be attributable to dapsone she had once taken for dermatitis herpetiformis. Her family history was remarkable for 2 sisters with anticardiolipin antibody–positive systemic lupus erythematosus who had reported episodic purpuric rashes occurring under similar circumstances.

Physical examination revealed a slightly palpable, purpuric exanthema on the lower extremities bilaterally, with striking sparing of skin below the sock line (Figure 1). A biopsy specimen of the

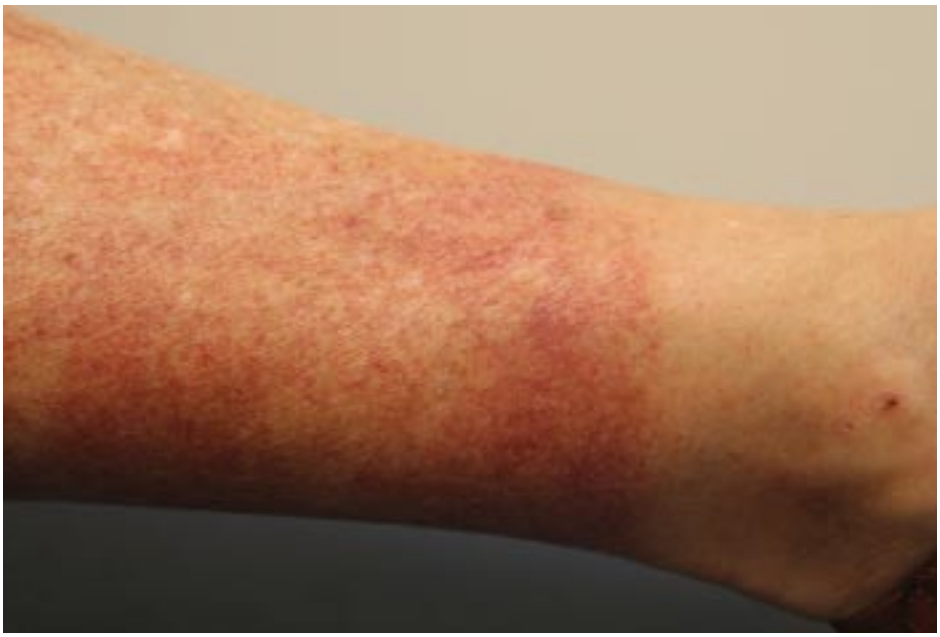

Figure 1. Purpuric eruption on the lower leg above the sock line.

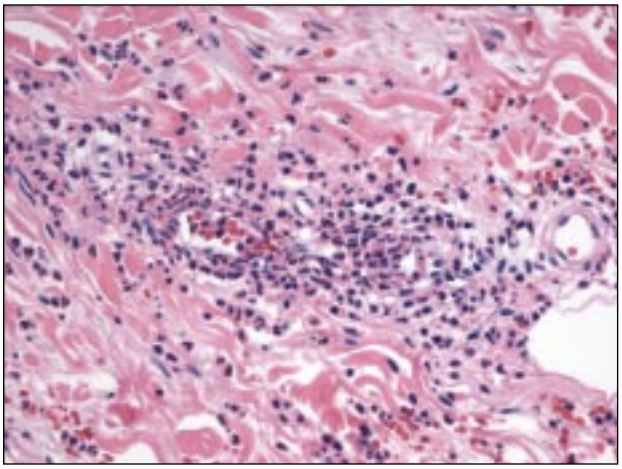

Figure 2. Histopathology of a biopsy specimen taken 36 hours after eruption of the rash showed changes consistent with leukocytoclastic vasculitis (H&E, original magnification ×40).

lesion showed changes consistent with leukocytoclastic vasculitis (Figure 2). A workup to evaluate for vasculitis was initiated. Routine laboratory studies confirmed mildly elevated liver transaminases. IgG anticardiolipin antibody levels were substantially elevated at 86 GPL U (IgG phospholipid units)/mL (reference, <10 GPL U/mL) and were confirmed elevated 2 months later at more than 100 GPL U/mL. Smooth muscle antibody levels also were elevated, but antinuclear antibodies and other autoimmune markers such as antimyeloperoxidase, antiproteinase 3, rheumatoid factor, SS-A/Ro, SS-B/La, Smith, scleroderma-70, anti–double-stranded DNA, anticentromere, β 2 glycoprotein I antibody, C3, and C4 were within reference range. Bleeding and clotting times were within reference range. Further workup of the abnormal laboratory studies revealed autoimmune hepatitis, which was confirmed by liver biopsy.

Comment

A variety of immunogenic and nonimmunogenic mechanisms have been implicated in the pathogenesis of other forms of typical vasculitis,[12,13] which may include types I through IV hypersensitivity mechanisms, hypercoagulable states, stasis, direct infection of endothelial cells, damage of endothelial cells due to exogenous toxins, and intrinsic endothelial cell dysfunction. The pathophysiology of EIV is unknown but has been studied by Kano and colleagues[11] who reported a patient with Sjögren syndrome with a positive antinuclear antibody titer of 1:1280 in a homogeneous pattern, positive rheumatoid factor, increased λ globulin, and positive SS-A/Ro and SS-B/La antibody titers. In this model, deposition of immune complexes and C3 in postcapillary venules leads to complement activation, mast cell degranulation, release of inflammatory cytokines including tumor necrosis factor α, eosinophil activation, and deposition of eosinophil granule proteins. Subsequent up-regulation of intercellular adhesion molecule 1 and E-selectin on the surface of endothelial cells, possibly due to tumor necrosis factor α, leads to an attraction of neutrophils and memory T cells. Neutrophils then release proteolytic enzymes that contribute to vessel wall damage and the changes typically seen in leukocytoclastic vasculitis.[11-14] Altogether these changes can be described as an exercise-induced type III hypersensitivity vasculitis reaction. The precise mechanism by which exercise might trigger a type III hypersensitivity reaction remains unknown but may occur in part because of tissue anoxia in the postcapillary venule.[1,12]

It is unknown to what degree the findings of Kano et al[11] can be extrapolated to explain EIV in otherwise healthy patients or in patients with conditions other than Sjögren syndrome. It has been proposed that most forms of EIV may result solely from vascular injury after exercise due to a decrease in venous return and a blood stasis effect.[1] It is possible that EIV, as with typical vasculitis, might occur by a variety of mechanisms. In our patient, EIV likely occurred because of a type III hypersensitivity mechanism in a setting of autoantibodies, similar to Kano et al.[11] A link between anticardiolipin antibodies and type III hypersensitivity vasculitis has been previously established.[15]

In this case report, recognition of EIV led to a workup to evaluate for vasculitis, which subsequently revealed autoimmune hepatitis. An association between anticardiolipin antibodies, anti–smooth muscle antibodies, and autoimmune hepatitis has been established.[16]

In our patient and her 2 sisters, long-standing EIV occurred within the context of a concomitant connective-tissue disease and pathogenic autoantibodies, suggesting a familial link to this condition. One other case of familial EIV has been reported.[1] The nature of this familial susceptibility factor to EIV remains unknown.

Conclusion

Exercise-induced vasculitis is an underreported condition that is frequently misdiagnosed. It may occur in healthy patients and in patients with underlying disease processes. There may be a familial component to this condition. Prompt recognition and workup of EIV may lead to early discovery of associated subclinical diseases.

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