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Eosinophilic Fasciitis Induced by Fire Ant Bites

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ABSTRACT

Purpose: To describe a case of eosinophilic fasciitis likely related to proximate fire ant bites and review the literature to summarize the etiology and clinical, laboratory, histopathological, and therapeutic aspects of eosinophilic fasciitis.

Methods: Report of a case of eosinophilic fasciitis and review of the English language literature using a Medline search from 1950 to January 2007.

Results: We describe the case of a New Orleans woman who developed eosinophilic fasciitis after fire ant bites post-Hurricane Katrina. A careful literature review confirms an association of eosinophilic fasciitis with unaccustomed vigorous exercise, arthropod bites, and borreliosis, among other etiologic agents.

Conclusions: Eosinophilic fasciitis, a rare disorder with unclear pathogenic mechanisms, has been associated with arthropod bites and borreliosis. Fire ant bites should be added to the list of etiologic agents for this disorder.

INTRODUCTION

Eosinophilic fasciitis (EF) is a rare scleroderma-like disorder first described by Shulman in 1984.[1] The diagnostic histopathologic findings are thickening and inflammation of the fascia, which in later stages may become sclerosed.[2] The skin changes are associated with early initial peripheral eosinophilia, polyclonal hypergammaglobulinemia, and elevated erythrocyte sedimentation rate, but these findings are usually transient and may not be present at the time of initial consultation. EF may be triggered by unaccustomed vigorous exercise,[3] drugs such as statins,[4,5] heparin,[6] borreliosis,[7–10] arthropod bites, bone marrow transplantation,[11] and/or trauma. An association of EF has also been reported with common variable immunodeficiency,[12] psoriasis,[13] and IgA nephropathy.[14] We report a case of EF, confirmed by biopsy, which is likely secondary to fire ant bites.

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CASE REPORT

A 79-year-old woman, while barefoot in her backyard in New Orleans cleaning up debris shortly after Hurricane Katrina, suffered numerous fire ant bites to the right dorsal foot and ankle. One week later, she noted swelling of her right leg extending from above the ankle to a few inches below her knee. The ant bites occurred in the right ankle and dorsal foot, and the lower extremity induration was above the ankle and proximal to the site of the bites. The swelling in her right leg was associated with induration and thickening of the skin. She underwent further evaluation, including a venous Doppler, which was negative for venous thrombosis. Her erythrocyte sedimentation rate was 4 mm/h; C-reactive protein, 0.5 mg/dL; creatine phosphokinase, normal at 62 μ/L; and complete blood count normal without eosinophils noted on the peripheral smear. For an episode of bronchitis, she was given several courses of the antibiotics clarithromycin and doxycycline. The bronchitis resolved, but the redness and swelling in her right lower extremity did not improve. She then saw a vascular physician who wrapped her leg but did not do any further studies. A dermatologist performed a punch biopsy of the skin from above the right ankle, which revealed dermal edema with chronic inflammation including eosinophils. There was also evidence of thickening of the septa between subcutaneous lobules of fat (Figure 1). Based on the clinical features and biopsy results, a diagnosis of EF was made. The patient presented to a rheumatologist at that time. She was placed on 30 mg of prednisone, which was tapered to 10 mg over the next month. She was then evaluated at Ochsner Medical Center's Department of Rheumatology. A magnetic resonance image (MRI) of the lower extremity, done 8 months into the illness to help determine the activity of EF, revealed only skin and soft tissue edema involving the distal two-thirds of the right leg below the knee, compatible with venous insufficiency; the inflammatory changes had

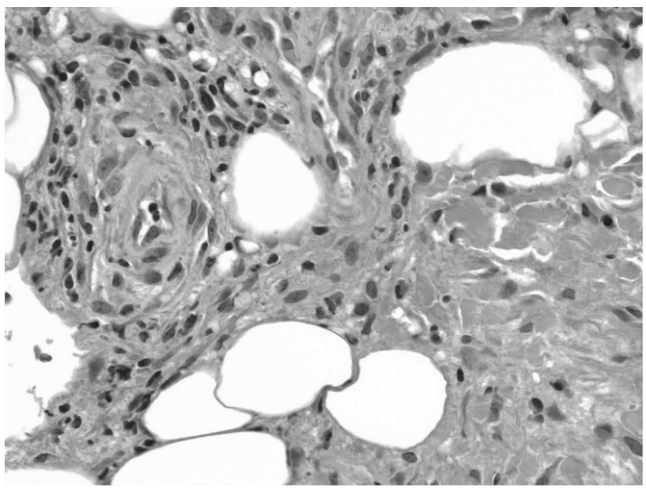

Figure 1. Histopathology of skin biopsy showing thickening and scarring of septa between lobules of fat (Hematoxylin-eosin stain).

resolved. The prednisone was tapered and eventually stopped over the next 4 months. The swelling in her leg improved over the next 4 months except for mild residual venous stasis dermatitis and edema. Recent follow-up 1 year after the last dose of prednisone showed complete resolution of all swelling, with mild residual post-inflammatory hyperpigmentation. The patient was asymptomatic. Her erythrocyte sedimentation rate was 15 mm/h; C-reactive protein, <0.3 mg/dL; and complete blood count normal without evidence of blood dyscrasia, and antineutrophil cytoplasmic antibody remained negative. The patient was felt to be in complete remission.

DISCUSSION

Fire Ant Envenomation

Imported fire ants are aggressive, venomous ants that sting with little provocation and are difficult to avoid in endemic areas. The habitat of fire ants extends from the southeast United States to Virginia and west to California.[15] In most cases, fire ant bites and their medical consequences occur in healthy persons who, during routine activities such as walking, golfing, or simply sitting on the ground, may have disturbed the ground-nesting, mound-building ants.[16] The number of indoor fire ant sting attacks is increasing in the United States, and frail elderly people and infants are at risk.[17–19]

The venom of imported fire ants is approximately 95% water-insoluble alkaloids by volume, and the remaining 5% is an aqueous solution of proteins. The venom alkaloids cause the sterile pustule but are not allergenic. Ninety-nine percent of the alkaloid component of fire ant venom is made up of 2,6-disubstituted piperidines that have hemolytic, antibacterial, insecticidal, and cytotoxic properties.[20,21]

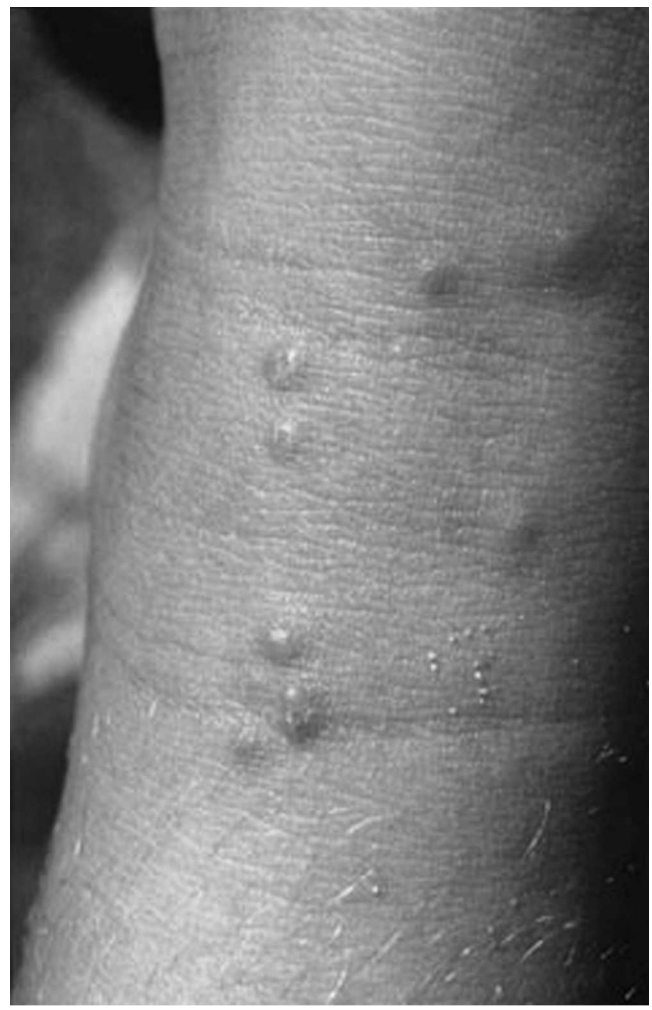

Figure 2. A sterile pustule caused by fire ant bite.

Venom alkaloids do not generate IgE antibody responses and, thus, do not appear to be responsible for allergic reactions to imported fire ant stings. The proteins identified in the venom include a phospholipase, a hyaluronidase, and a third protein that has not been fully characterized but appears to be the enzyme N-acetyl-beta-glucosaminidase.[22,23] The allergenic portion of the venom is the protein component, which may account for the anaphylaxis and delayed phase reaction that can be seen with fire ant bites.

Different patterns of dermal reactivity to fire ant stings have been described. Patients may have immediate wheal and flare reactions, which are prominent by 20 minutes and resolve in 2 hours. A sterile pustule (Figure 2) may develop by 24 hours and usually resolves in a week. Some patients may develop late phase reactions that are IgE-mediated and are characterized by erythema and edema, as well as fibrin deposition and infiltration by eosinophils, neutrophils, and lymphocytes on histology.[24] However, lesions that persist for several months have not been previously described.

Eosinophilic Fasciitis

The skin changes in EF evolve through 3 stages. The majority of patients start with an edematous phase that may include pitting edema of the extremities. In the second stage, this changes to a *peau d'orange* appearance of the skin. The last stage is that of induration with tight skin. There is an acute or subacute development of induration of the skin and subcutaneous tissues of the forearms, flank, and upper legs. The hands and face are usually spared; Raynaud phenomenon is usually absent, an important/critical distinguishing feature from scleroderma. An important dermatologic sign for the diagnosis is called the valley signal or the groove sign, which can be observed during extension and abduction of the arms and corresponds to the linear depression following the vascular path of the area involved.[25]

Extracutaneous manifestations of EF may include arthralgias, arthritis,[26] contractures, and carpal tunnel syndrome.[27] Internal organs are generally not involved in the fibrotic process,[26] though there have been a few reports of involvement of the lungs, esophagus, myocardium, kidney, colon, and brain.[27–30] EF may be associated with low-grade myositis.[2,31] In one study, electromyograms were abnormal in 11 of 15 patients.[26] An association between EF and hematologic disorders, including aplastic anemia,[32,33] thrombocytopenic purpura,[32,34] myeloid leukemia,[35] myeloproliferative disorder,[35] Hodgkin's disease,[36] preleukemia,[37] pancytopenia,[38] multiple myeloma,[39] and polycythemia rubra vera,[40] has been reported. The prognosis for EF when it is associated with hematologic disorders is poor.

Laboratory tests may indicate hypergammaglobulinemia, peripheral eosinophilia, and an elevated erythrocyte sedimentation rate, but these results are not mandatory for the diagnosis as they are often transiently present. Currently, EF can be diagnosed definitively by full thickness (ie, epidermis to muscle) biopsy. Early in the course of the disease, the deep fascia and lower subcutis are edematous and infiltrated with lymphocytes, plasma cells, histiocytes, and eosinophils. As the illness progresses, these structures, and eventually the dermis, become collagenized, thickened, and sclerotic.[2] Infiltrating eosinophils degranulate locally, resulting in release and tissue accumulation of highly cationic granule proteins with potent toxic and fibrogenic properties.[41] The mechanisms responsible for eosinophilia and the excessive deposition of extracellular matrix components in the affected fascia of patients with EF are not known. Elevated levels of serum TGF-β and interleukin-5 have been observed in EF, and these levels improved after immunosuppressive therapy.[42] EF patients have shown increased synthesis of both type 1 and type 2 cytokines.[43] High levels of Th2 (IL-5 and IL-10) cytokines may explain eosinophilia and excess immune globulin production.[43] Primed T lymphocyte clones in the presence of their specific antigens are capable of producing a local or systemic eosinophil response.[44] Once activated and attracted into the inflamed tissue, eosinophils may also be able to perpetuate local inflammatory responses and, consequently, the disease. In this context, eosinophil extracts can induce fibroblast proliferation.[41,45] The hypothesis of an autoimmune origin for EF is supported by the successive detection of elevated immune globulin and circulating immune complexes in patients with active EF,[46] the occurrence of EF in chronic graft-versus-host disease,[47] and the association of EF with other autoimmune disorders such as thyroiditis and Sjögren's syndrome.[28,48]

Until recently, imaging has played little, if any, role in the diagnosis of EF. MRI findings in EF are characteristic and consist of fascial thickening, hyperintense signal within the fascia on fluid-sensitive sequences, and fascial enhancement after intravenous contrast administration.[49,50] These changes are directly proportional to disease activity and response to treatment.[49] MRI scans provide a useful aid for diagnosis and a marker for disease activity and response to treatment.[49]

Differential diagnosis should include systemic sclerosis (characterized by thickened skin), Raynaud's phenomenon (internal organ involvement including the lung and kidney), and nephrogenic systemic fibrosis (characterized by thickening and hardening of skin seen in patients with preexisting renal failure associated with the administration of MRI contrast agents). Eosinophilia-myalgia syndrome may have some pathologic features of EF but is related to ingestion of dietary supplement L-tryptophan and is associated with significant myalgias. Also included in the differential diagnosis is scleredema, characterized by firm, indurated skin on the posterior and lateral portion of the neck and upper back and typically associated with monoclonal gammopathy,[51] and eosinophilic cellulitis, in which the dermis is infiltrated by eosinophils and the skin is edematous and not bound down.

Prednisone, in a divided daily dose of 40 to 60 mg, is the initial treatment of choice for EF. Other pharmacologic agents that have been tried include D-penicillamine,[52] chloroquine,[35,52] azathioprine,[52] cimetidine,[53] cyclosporine,[54,55] antithymocyte globulin,[56] methotrexate,[57] extracorporeal or bath photochemotherapy,[58] ibuprofen,[59] and antihistamines.[60] One third of patients show spontaneous remissions with a protracted course.[26] Physical therapy should be recommended for all patients with skin induration to prevent or lessen joint contractures.

Several etiologic agents have been described to cause EF, including arthropod bites and borreliosis. There have been no previous case reports of fire ant bite-induced EF. We conclude that there is some evidence that increased Th2 stimulation may have a role in the development of EF. It has been observed that IgE has a multifunctional role in the pathogenesis of allergic inflammation. Aside from its involvement in IgE-mediated degranulation of mast cells and basophils, IgE is also involved in the activation of macrophages/monocytes and stimulation of Th2 cells.[61,62] The ant bite-induced IgE response may have a similar pathogenesis leading to EF, as seen in our patient.

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