A Case of Eosinophilic Fasciitis in a 72-Year-Old Man

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Eosinophilic fasciitis (EF) is a rare disorder of unknown etiology that resembles systemic scleroderma. EF is characterized by the rapid onset of inflammation and thickening of the deep fascia.[1] Several scleroderma-like conditions (eg, scleredema, scleromyxedema) are also rare entities that have clinical presentations similar to EF. This article reports the case of a man who presented with erythema, edema, skin induration, and pruritus of the upper trunk and abdomen, which ultimately was diagnosed as EF. A review of the subtle clinical and pathologic differences among EF and other similar entities is also provided.

CASE PRESENTATION

History

A 72-year-old white man presented to his primary care physician (PCP) with a 3-week history of erythema, edema, progressive pruritus, and skin induration of the upper back, forearms, and trunk with sparing of his hands and lower body. The patient's past medical history was notable for type 2 diabetes mellitus, hyperlipidemia, hypertension, systolic heart failure, inferior myocardial infarction, quadruple coronary bypass surgery, and dual chamber implantable cardioverter defibrillator. His medications included glipizide, metformin, aspirin, simvastatin, felodipine, metoprolol, and captopril.

Clinical Evaluation

Physical examination revealed moderate induration with significant erythema and nonpitting edema of the skin of the abdomen and upper trunk (**Figure 1**) as well as pronounced skinfolds at the waist (**Figure 2**). Laboratory evaluation revealed elevations in the erythrocyte sedimentation rate, aldolase levels, and creatinine levels (**Table**), the latter of which prompted discontinuation of metformin. Assays for antitopoisomerase I, anticentromere, and serum antinuclear antibodies were negative. Lyme disease antibodies assessed by enzyme-linked immunosorbent assay were elevated (1.38 [normal, < 0.91 optical density ratio]) but were negative by Western blot. Protein and urine electrophoresis and urinalysis were normal. An occult malignancy was the suspected cause of these skin findings.

Chest radiograph revealed a small density in the right mid lung. Due to renal insufficiency, the patient underwent noncontrast chest computed tomography that revealed a 15 × 13-mm partially calcified nodule but no lymphadenopathy. The nodule was thought to be benign, with a 6-month follow-up assessment revealing no changes. Pulmonary function tests revealed no abnormalities.

A punch skin biopsy of the patient's lower abdomen obtained 3 weeks after initial presentation revealed superficial and deep perivascular infiltrates composed of lymphocytes, histiocytes, and plasma cells. Thickened sclerotic collagen bundles were seen throughout the dermis and the subcutaneous fat. Colloidal iron stain demonstrated minimal mucin deposition in the dermis.

Initial Treatment

The initial work-up failed to reveal an obvious source of malignancy. Due to the lack of a specific diagnosis and the presence of significant pruritus, empiric treatment with prednisone (5 mg/day), hydroxyzine (25 mg every 6 hr), and colchicine (0.6 mg/day) was instituted. On a scheduled follow-up visit 4 weeks after initial presentation, the patient reported the development of severe hyperglycemia, for which prednisone was discontinued. The

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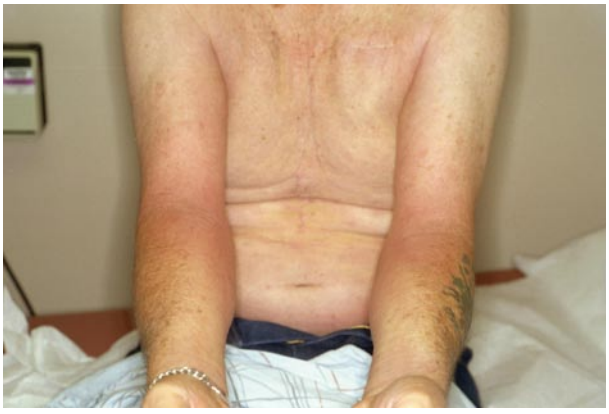

Figure 1. Upper extremities of the case patient show significant erythema and nonpitting edema of the antecubital fossa.

Table. Results of Initial Laboratory Studies for the Case Patient

Study (unit)	Result	Reference Range
Hemoglobin (g/dL)	16	12–16
White blood count (cells/μL)	10,000	4800–10,800
Eosinophils (%)	5.5	0–7
Eosinophils (cells/μL)	550	0–800
Erythrocyte sedimentation rate (mm/hr)	23	0–21
Thyroid-stimulating hormone (μIU/mL)	3.68	0.27–4.20
Creatine kinase (U/L)	49	24–170
Creatinine (mg/dL)	1.4	0.6–1.2
Hemoglobin A_{1c} (%)	7.0	< 7
Aldolase (U/L)	12.8	1.2–7.6

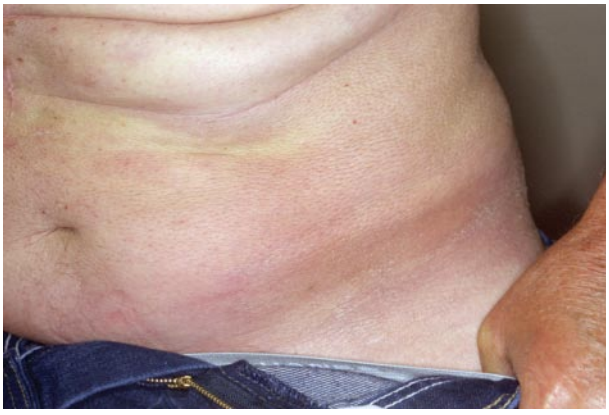

Figure 2. Prominent skin folds at the level of the case patient's waist.

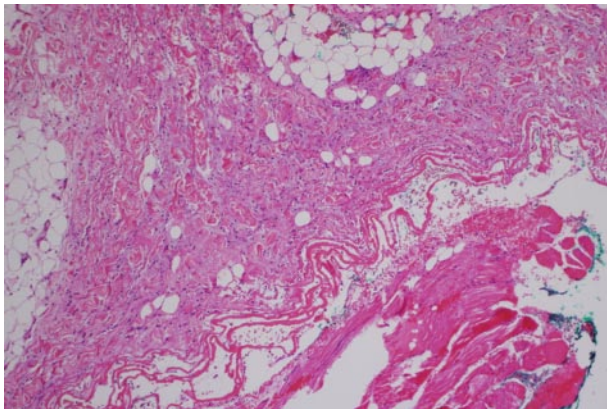

Figure 3. Biopsy specimen showing fibrous septa separating deeply located fat lobules and inflammatory cells involving the fascia and muscle tissue.

dosage of colchicine was increased to 0.6 mg twice/day. The glipizide dosage was increased from 10 mg/day to 10 mg twice daily. By the 2-month follow-up visit, the patient had regained glycemic control, but he also developed flexion contractures of the upper extremities and was scheduled for physical therapy. The equivocal biopsy results and lack of a specific alternative diagnosis prompted referral to a major medical center for a second opinion.

Clinical Course

At referral, the acute presentation and distribution of the patient's skin findings along with the fast progression of the disease suggested EF. Magnetic resonance imaging (MRI) was recommended but not performed due the presence of a pacemaker. An alternative deep incision biopsy including the fascia of the left triceps was obtained. Two weeks after referral, the patient presented to his PCP because he remained symptomatic with erythema and pruritus and had lost nearly 20 lb. Prednisone was resumed at a higher dose (5 mg twice daily). Three weeks following referral, the patient was seen again by his PCP to discuss biopsy results and treatment options. Fascia biopsy revealed dermal sclerosis, prominent fibrosis that separated fat lobules in the deep fascia, and mild to moderate chronic inflammation suggestive of EF. The inflammatory infiltrate consisted of lymphocytes and plasma cells without a significant eosinophilic component (**Figure 3**). A second peripheral blood count revealed 8.4% eosinophils (normal, 0%–7%), with an absolute eosinophil count of 920 cells/μL (normal, 0–800 cells/μL).

Based on the biopsy results, prednisone was optimized to 1 mg/kg daily and, due to worsening hyperglycemia, insulin therapy with neutral protamine Hagedorn insulin was started. Hydroxyzine was increased to 100 mg twice daily as needed. At a follow-up visit with the PCP 2 weeks later, low-dose azathioprine (50 mg/day) was started due to the development of renal insufficiency, and

prednisone was tapered down to 40 mg/day. One month later, the patient presented to his PCP for follow-up. The erythema and edema of his upper extremities had resolved. Flexion contractures of the upper extremities were improved, and his weight loss had ceased. Prednisone was tapered to 5 mg/day. Four weeks later, azathioprine was titrated to 100 mg/day.

The patient returned to his PCP for follow-up 3 months later. Both the pruritus and the flexion contractures had resolved. His glycemic control had improved, glipizide was discontinued, and prednisone 5 mg/day was continued as well as insulin therapy. The last absolute eosinophil count was 10 cells/μL (0.1%). Ten months after his initial presentation, the patient was asymptomatic and had no signs of disease progression.

EOSINOPHILIC FASCIITIS

Shulman[1] first described EF in 1974, and since then approximately 200 cases have been reported.[2] Most patients present around age 40 years, although the disease may present throughout the lifespan.[3] There is no sex predilection, and family history is not a risk factor.[4] Although the etiology of EF remains unknown, drug exposure (L-tryptophan ingestion,[5] trichloroethylene,[6] phytonadione,[7] simvastatin[8]), strenuous physical exertion,[9] and infection with *Borrelia burgdorferi*[2] occasionally have been associated with EF. Because this patient had been taking simvastatin for years, his skin findings were thought to be unrelated. The case patient did not have a previous history of Lyme disease, and, although enzyme-linked immunosorbent assay demonstrated weakly positive titer antibodies, Western blot analysis ruled out this disease.

Clinical Features

Cutaneous involvement in EF is a nearly universal finding. In decreasing order of frequency, early EF demonstrates the rapid onset of nonpitting edema and painful erythematous skin of the upper and lower extremities, hands, trunk, neck, and feet. Raynaud's phenomenon is rare in EF, and the skin of the hands is usually spared.[10] The face is rarely affected in EF. Uncommon features include malaise, weakness, fever, livedo reticularis, pruritus,[11] and weight loss;[11,12] both pruritus and weight loss were present in the case patient. Rarely, pitting edema has been reported.[12] *Groove sign,* an indentation on the skin following the course of the superficial veins, may occasionally be visible when the affected limb is elevated.[2] Another finding not seen in the case patient but described in later stages of EF is "*peau d'orange.*" Once edema resolves, symmetrical induration and "puckering" of the skin becomes apparent, which resembles the texture of an orange peel.[2]

In later stages of EF, flexion contractures develop. Flexion contractures involve the shoulders,[4] elbows, wrists, hands, and knees, leading to limited mobility from thickening and loss of pliability of overlying skin.[4] There may be subsequent subclinical myositis, myalgia, and weakness of the affected limbs. However, flexion contractures are not specific to EF and can be seen in other scleroderma-like conditions.[2] In approximately 25% of EF cases, carpal tunnel syndrome is also present. Thyroiditis may also occur,[9] but hypothyroidism is rare.[13] Aplastic anemia, myeloproliferative disorders, and multiple myeloma,[14] among other conditions, have been reported as systemic manifestations. Some have posited that EF may be a variant of scleroderma.[15] Progression to scleroderma also has been documented.[16]

Histopathology

Histopathologic evaluation of EF initially shows chronic inflammation in the deeper reticular dermis, deep fascia, and lower subcutis. The infiltrate consists of lymphocytes, plasma cells, histiocytes, and eosinophils. The eosinophils degranulate locally, releasing proteins with toxic and fibrogenic properties. These substances lead to thickening of the deep fascia and septa of the subcutis[2] with fibrosis, hyalinization, and deposition of type I collagen,[17] findings which are common to scleromyxedema[18] and scleredema.[19] EF, however, is differentiated by a mononuclear inflammatory infiltrate that extends into the skeletal muscle and fascia,[10] causing myofiber degeneration and focal scarring.[4] Although scleromyxedema may also involve the muscle, eosinophils are not present in the infiltrate.[20] In EF, eosinophils become scarcer as the sclerotic process advances. Tissue eosinophilia is focal and often transitory; however, its absence does not exclude the diagnosis.[4,21] Immunofluorescence shows deposition of IgM at the dermal-epidermal junction; immunoglobulin and complement around deep dermal blood vessels; and IgG and complement in the deep fascia and skeletal muscle.[22]

Laboratory and Imaging Studies

Peripheral eosinophilia (> 7% or > 760 cells/μL), which was seen in the case patient at referral, is not required to diagnose EF. However, its presence may help rule out conditions similar to EF, as eosinophilia is not present in scleromyxedema or scleredema.[23] Eosinophil counts are usually elevated early in EF but may decline over time despite active disease; therefore, levels are not useful in following the progression of the disease.[14] Occasionally, the eosinophil count may be initially normal. In untreated patients, elevated eosinophil counts can last for up to 30 months.[24] Elevated

erythrocyte sedimentation rate and hypergammaglobulinemia (polyclonal increase in IgG) are common,[14] but serum creatinine kinase is normal, and nailfold capillaries are not dilated. Antinuclear antibodies, rheumatoid factor, and, rarely, anti-DNA antibodies may be present.[25] Aldolase may also be elevated and has been hypothesized to correlate with disease activity.[26] Some consider the presence of eosinophilia, hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate to be diagnostic of EF.[12]

MRI is a valuable study for diagnosing EF. It may demonstrate an increased T2 signal in the subcutis and deep fascia as well as enhancement on fat-suppressed T1 images after gadolinium administration.[27] MRI is also useful for monitoring treatment response and as a marker of disease activity.[27] Ultrasound shows marked thickening of the fascia and muscle as well as thickening of the skin and subcutaneous tissues.[12]

Differential Diagnosis

Given the clinical and pathologic similarities among systemic scleroderma, EF, and other scleroderma-like conditions, familiarity with these clinical entities is helpful for establishing the correct diagnosis. The following provides a brief review of these conditions, with a focus on distinguishing them from EF.

Systemic scleroderma. Scleroderma is a connective tissue disease with symmetric thickening of the skin predominantly over the hands and face. It is an uncommon disorder with an estimated prevalence ranging from 7 to 489 cases per million persons.[28] Scleroderma has an unclear etiology, but, unlike EF, family history is a significant risk factor.[29] Scleroderma occurs more commonly in women[29] and is rare in children.[28] It is categorized as either localized or systemic, the latter of which may be confused with EF.

Sclerodermatous skin findings include pruritus and edema in the early stages, followed by sclerodactily, digital ulcers, and pitting at the fingertips. Significant involvement of the hands and presence of Raynaud's phenomenon in more than 90% of cases distinguish this entity from other scleroderma-like conditions.[28] The most commonly affected organs include the gastrointestinal tract, lungs, and kidneys.[30] Cardiac disease is an indicator of poor prognosis.[31]

Clinical manifestations of scleroderma are often sufficient to make the diagnosis, and skin biopsy is usually unnecessary unless other conditions are suspected. Autoantibodies (antitopoisomerase I, anti-RNA polymerase, anticentromere) and nailfold capillary abnormalities are usually present in several forms of scleroderma but not in EF.[32] The acute presentation and the lack of systemic involvement made scleroderma unlikely in the case patient.

Treatment of systemic scleroderma varies depending on the extent of skin involvement, organs affected, and whether reversible inflammation is present. Glucocorticoids should be restricted to patients with active signs of inflammation, especially of the lungs.[33] In severe cases, immunosuppressive agents such as cyclophosphamide[34] and cyclosporine[35] are used but their efficacy data are still limited. Prognosis is poor. Organ involvement and the presence of antitopoisomerase I antibodies increase the mortality risk.[36] Complications related to pulmonary fibrosis and hypertension are among the most common causes of death.[37]

Scleromyxedema. Scleromyxedema, a generalized form of lichen myxedematosus,[38] occurs infrequently, with fewer than 150 reported cases.[39] The disease occurs between age 30 to 50 years and both sexes are affected.[39] Its histopathology is similar to EF. Although the epidermis in scleromyxedema can be normal, it may also be acanthotic or atrophic. Focal deposits of mucin and a chronic inflammatory cell infiltrate may be found in the superficial dermis. The dermis exhibits an overabundance of irregularly arranged collagen bundles and fibroblasts in late-stage disease.[19] In severe cases, mucin may be less evident or absent.[40] Both scleromyxedema and EF affect muscle. Scleromyxedema is characterized by vacuolar myopathy with or without fiber necrosis (type II fiber atrophy) and without mucin deposition,[18] whereas EF is characterized by myofiber degeneration and focal scarring.[4]

Thyroid function in scleromyxedema is usually normal, with hyperthyroidism rarely occurring.[41] Muscle enzymes such as aldolase may be normal or elevated,[18] as seen in EF.[11,26] Both scleromyxedema and EF may have systemic involvement. In scleromyxedema, the most common extracutaneous manifestation remains the plasma cell dyscrasia.[42] Scleromyxedema may respond to high-dose intravenous immunoglobulin,[43] interferon alfa,[44] prednisone,[45] extracorporeal photopheresis,[46] isotretinoin,[47] or chemotherapy agents such as melphalan,[48] chlorambucil,[49] and thalidomide,[39] all of which are anecdotal. However, the overall prognosis is poor.[42] Occasional spontaneous resolutions occur. In contrast, patients with EF have a good prognosis and response with treatment.[14]

Scleredema. Scleredema adultorum of Buschke is even less common than scleromyxedema and its incidence is unknown. Scleredema is a rare primary mucinosis that has 4 subtypes.[50] Type 1, the acute variant in children (50%), has a rapid onset after an upper respiratory infection, especially after a streptococcal infection.[51]

It more commonly affects girls and occurs more frequently during winter months. Type 2 is of insidious onset and is unaccompanied by a preceding acute illness or diabetes.[50] Type 3 is usually associated with late-onset uncontrolled diabetes mellitus. Onset is gradual and is most typically seen in obese males. Although type 3 was considered in this diabetic patient, the distribution of the skin lesions and adequate glycemic control at presentation made this diagnosis unlikely. Type 4, the congenital form, was described in an infant with skin lesions from birth and is not associated with infection.[52] All forms of scleredema are characterized by symmetrical nonpitting edema and induration of the neck, face, upper trunk, and upper limbs. Erythema is rare. The skin has a woody consistency and looks waxy, and wrinkling is not seen because the papillary dermis is involved. Systemic manifestations of scleredema are rare but include induration of eyelids and conjunctivae, dysphagia, tongue and parotid gland involvement leading to dysarthria, serosal effusions, and cardiac manifestations.[23]

In scleredema, as in EF, the epidermis is usually unaffected. Increased glycosaminoglycans (hyaluronic acid) thicken the reticular dermis. In early lesions, dermal fenestration occurs due to broadening of collagen fibers. The collagen extends into the subcutis and may contain small quantities of mucin. Only special stains (alcian blue or colloidal iron) may detect mucin deposition. Unfortunately, multiple biopsies are sometimes necessary to demonstrate mucin,[53] since mucopolysaccharide accumulation is not a constant feature. In late stages, fibrosis is the sole finding.

Treatment of scleredema depends on the subtype. Type 1 responds to penicillin if associated with streptococcal infection.[51] It also can be treated with high-dose intravenous corticosteroids,[54] although it may resolve spontaneously within months or years. Types 2 and 3 can be treated with cyclosporine,[55] bath psoralen ultraviolet A,[56] or low-dose methotrexate,[57] but they are usually refractory to therapy and slowly progress.[58] In refractory cases, radiation has been attempted with partial response.[50] Although type 3 was initially suspected in the case patient, his excellent response to treatment further supported the diagnosis of EF. Type 4 responds to physical therapy and whirlpool baths.[52]

Treatment

First-line therapy for EF is corticosteroids. Treatment response is achieved with prednisone 1 mg/kg. A rapid therapeutic response with little disease progression is characteristic.[14] However, some patients improve spontaneously,[14] which complicates evaluation of treatment response. In addition, some patients who previously responded to treatment may relapse. Antitumor necrosis factor monoclonal antibodies,[59] psoralen ultraviolet A photochemotherapy,[60] methotrexate,[4,10] sulfasalazine,[4] antithymocyte globulin,[61] hydroxychloroquine,[14] and cyclosporine[6] have all been tried with varying results in relapsed patients, all of which are anecdotal. In refractory cases, more than 6 months of therapy is necessary to assess clinical response.[11] Ventilatory restriction and perimyositis may occur in treatment refractory patients.[11]

CONCLUSION

EF represents a clinical challenge. The diagnosis of EF is typically delayed as similarities in cutaneous involvement make distinguishing among EF, systemic scleroderma, and scleroderma-like entities difficult. Peripheral eosinophilia may help narrow the differential, and a deep biopsy that includes the fascia is crucial. Early detection and use of glucocorticoids in patients with EF increases the possibility of a favorable outcome. **HP**

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