Eosinophilic Fasciitis Responsive to Cimetidine

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A 53-year-old man with eosinophilic fasciitis had dramatic improvement in his fasciitic symptoms on two occasions after treatment with cimetidine. The observation that H2 histamine blockade is effective therapy in eosinophilic fasciitis lends further support to the concept that this disease is modulated through an altered immune response.

DIFFUSE FASCIITIS WITH EOSINOPHILIA is emerging as a distinct clinicopathologic entity although it is still considered by some physicians to be a variant of progressive systemic sclerosis. Clinical features that distinguish eosinophilic fasciitis from progressive systemic sclerosis include sparing of hands and feet; absence of Raynaud's phenomenon, calcinosis, and visceral involvement; seasonal incidence with preponderance of cases beginning in autumn; frequent onset after physical exercise; acute onset; laboratory findings of elevated erythrocyte sedimentation rate, hypergammaglobulinemia, eosinophilia, and increased serum levels of eosinophilic chemotactic factor; and a dramatic response to corticosteroids, often in low doses (1). Pathologically the disease is characterized by inflammation of the collagen bundles of the deep fascia with a perivascular infiltrate consisting of plasma cells, lymphocytes, and occasional eosinophils.

We report a patient with a clinical and pathologic presentation strongly suggestive of eosinophilic fasciitis whose disease was completely suppressed on two occasions by treatment with cimetidine, an H2 specific histamine receptor antagonist. We briefly discuss the relation between H2 receptors and the immunoregulatory system in an attempt to provide a conceptual framework for this clinical observation.

Case Report

A 53-year-old white man was admitted to Montefiore Hospital for elective evaluation of chronic edema. He had been well until October 1978 when he developed diffuse arthralgias and myalgias while on a business trip to Missouri. A local physician prescribed indomethacin for this condition. Approximately 1 week after commencing indomethacin therapy he developed edema of his legs that progressed to involve his arms and abdomen, but spared his face. He was admitted to Glen Cove Hospital in New York in November 1978. Results of SMA-18, urinanalysis, 24-hour urine protein measurement, liver-spleen scan, renal scan, and lymphangiogram were normal. Mild eosinophila was noted. Sigmoidoscopy was done and stool specimens were examined for ova and parasites; results were negative. The patient was placed on a low-sodium diet and lost 21 kg over the next 3 months. Despite this weight loss, edema persisted involving both upper and lower extremities as well as the abdominal wall, and the patient was admitted to Montefiore Hospital for further evaluation in March 1979.

At this time the patient had no arthralgias or myalgias, Raynaud's phenomenon, dysphagia, dyspnea on exertion, chest pain, constipation, diarrhea, sicca symptoms, fevers, or night sweats. The patient had not had heavy physical exertion. He appeared healthy and had normal vital signs. There was a brawny edema of the abdomen without bulging flanks, shifting dullness, or fluid wave. The abdomen was not tender and no organomegaly was present. Brawny, nontender, nonpitting edema of the lower extremities to the mid-thigh and of the upper extremities to the elbow was noted. Joint motion was not impaired. The patient had no sclerodactyly, calcinosis cutis, or changes of the facial skin. Results of cardiac, pulmonary, and thyroid examinations were normal.

His hematocrit was 42%; leukocyte count was 10 900, with 6% and 12% eosinophils on two consecutive differential counts. The SMA-18, urinanalysis, electrocardiogram, and chest roentgenogram were all normal. Stool examination for ova and parasites was negative. Serum thyroxine, triiodothyronine, and cortisol levels were normal. Latex fixation and antinuclear antibody tests were negative. Serum protein electropheresis was within normal limits. Levels of total hemolytic complement, C4, and C3 were normal and C_1-esterase inhibitor was present. Deep biopsies were done on the left forearm and abdominal wall and both showed marked thickening of the fascia between muscle and fat. There was marked hyalinization of the fascia and infiltration of the fascia by plasma cells, lymphocytes, and rare eosinophils. The inflammatory infiltrate extended between some muscle bundles and around blood vessels; however, there was no evidence of muscle or vascular necrosis (Figure 1). These findings were felt to be consistent with eosinophilic fasciitis and the patient was begun on prednisone, 20 mg/d, which resulted in dramatic diminution of both the edema and induration with complete resolution occurring over several weeks. There was a concomitant disappearance of the peripheral eosinophilia.

The patient was continued on this dose of prednisone therapy for approximately 1 year, after which he developed postprandial epigastric pain. Previous attempts to reduce the prednisone dose resulted in a return of symptoms. The patient was placed on an intensive regimen of antacids and the prednisone dosage was tapered first to 15 mg/d and then to 10 mg/d. On this lower dose the patient had a recurrence of brawny edema in the lower extremities. Epigastric pain persisted despite continued treatment with antacids. Results of an upper gastrointestinal series were negative. The patient was treated with cimetidine, 400 mg every 6 hours, for a presumptive ulcer. Within a few days after starting cimetidine therapy, the induration of his legs resolved completely. Epigastric pain resolved, and cimetidine therapy was continued. While the patient was on cimetidine therapy, his steroidal dosage was further tapered and eventually discontinued without a recurrence of fasciitis.

Cimetidine therapy was continued for 1 year and the patient was free of both gastrointestinal and musculoskeletal symptoms. The patient received 400 mg every 6 hours for 3 months, followed by 400 mg three times daily for 3 months, and then he was maintained on 400 mg twice daily. At the patient's request cimetidine therapy was discontinued. Three weeks later the patient developed pain in the right lateral calf, which was exacerbated by either motion or weight-bearing. The patient also described claudication in the right foot with minimal ambulation.

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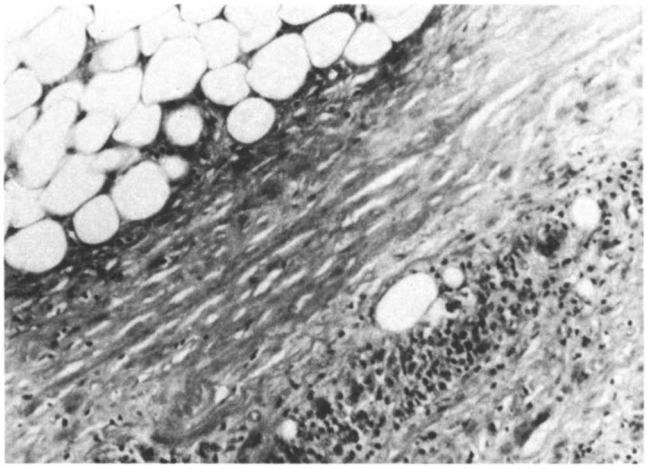

Figure 1. Photomicrograph of subcutaneous tissue and perimysial fascia from the forearm showing marked thickening of the fascia and a perivascular infiltrate of lymphocytes and plasma cells at the myofascial junction.

He was readmitted to Montefiore Hospital for further evaluation.

At this time the patient appeared well and had normal vital signs. There was decreased mobility of the skin over the dorsum of the hands, feet, and right calf with woody induration of the underlying soft tissues. There were no cords in the right calf and Homan's sign was negative. Range of motion at the right ankle was decreased. When the patient was supine, all peripheral pulses were 2+ and symmetric, but when he stood up, the right dorsalis pedis pulse became progressively weaker and the patient had symptoms of claudication. There were no bruits.

His sedimentation rate was 35 mm/h (Westergren); hematocrit, 47%; leukocyte count, 8100 with 61% segmented neutrophils, 37% lymphocytes, and 2% monocytes. No eosinophils were seen. The SMA-18, chest roentgenogram, and electrocardiogram were unchanged from previous examinations.

The patient was thought to be having a recurrence of his eosinophilic fasciitis with secondary mechanical entrapment of the right dorsalis pedis artery. In view of his clinical history, cimetidine therapy, 400 mg every 6 hours, was restarted. On this regimen the patient had a dramatic improvement within 48 hours in both the degree of pain and swelling as well as a normalization of the right dorsalis pedis pulse. All physical findings resolved within 1 week and the patient has remained in complete remission on cimetidine.

Discussion

Our patient with well-documented clinical and histologic features of eosinophilic fasciitis showed a prompt and complete response to cimetidine on two occasions. Cessation of cimetidine therapy resulted in a prompt reappearance of symptoms. These observations suggest that cimetidine exerts a specific therapeutic effect on eosinophilic fasciitis. If corroborated in other patients with this disorder, this effect might provide insight into the pathogenesis of eosinophilic fasciitis.

The cause and pathogenesis of eosinophilic fasciitis remains unclear. It appears unlikely that eosinophils have a primary role in this disease because of the relative paucity of these cells in most biopsy specimens and the occasional absence of peripheral eosinophilia during periods of disease activity, as observed in our patient. More likely, eosinophils are responding to some chemotactic factor by either lymphocytes or mast cells that have been found regularly in the skeletal muscle and fascia from patients with eosinophilic fasciitis. Other clinical features that have been described in some patients with eosinophilic fasciitis support the concept of altered lymphocyte and immunoregulatory function in this disease. These features include humeral suppression of erythropoiesis (2-4), thrombocytopenia (4), and IgA deficiency (1). Conceivably, cimetidine might be acting in our patient through blockade of lymphocyte function rather than on the eosinophil itself.

Several recent studies (5, 6) have shown that a subpopulation of peripheral lymphocytes possess H2 receptors. These cells, when stimulated in vitro with histamine, appear to suppress several types of immune responses including cell-mediated cytotoxicity (7), antibody production induced by pokeweed mitogen (8), migration inhibition factor secretion (9), and lymphocyte proliferation in response to either antigen (6) or mitogens such as phytohemagglutinin or concanavalin A (10-12). Thus, H2 responsiveness represents a functional marker of suppressor T-cell activity. Furthermore, in-vitro studies have established that suppressor T-cell function can be inhibited by the H2 receptor antagonists metiamide (13), burimamide (14), and cimetidine (10, 15).

We emphasize that prednisone still must be regarded as the preferred therapy in uncomplicated eosinophilic fasciitis because of its proven efficacy and safety when used in low doses. Long-term cimetidine therapy has side effects including diarrhea, myalgias, neutropenia, rash, and confusion. In patients who cannot tolerate steroidal therapy or who need doses of steroids that result in unacceptable side effects, cimetidine may represent a valuable adjunct to therapy or, in selected cases, an alternative primary therapy.

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