BRIEF REPORT

EOSINOPHILIC FASCIITIS IN A PAIR OF SIBLINGS

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Two siblings, a 38-year-old woman and a 33-year-old man, developed eosinophilic fasciitis within a period of 6 months. They were found to have identical HLA–A, B, DR, and DQ antigens, raising the possibility of a genetic influence in the development of this disease. No common environmental factors close to the time of onset were identified; however, the possibility of a common, remote environmental factor cannot be discounted.

Shulman, in 1974 and subsequently (1–3), described and defined the disease entity termed eosinophilic fasciitis (EF). The primary clinical manifestations involve the extremities, with sparing of the hands and feet. There is symmetric, widespread inflammation and sclerosis of the dermis, subcutis, and fascia. Peripheral eosinophilia, hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate (ESR) are the principal laboratory manifestations. The disease usually responds favorably to systemic corticosteroid therapy. It appears to be self-limited, with spontaneous resolution generally occurring after periods of 1 or more years. Several excellent reviews of the clinical and pathologic findings in EF have been published (4–7).

Lynch et al (8) performed HLA typing in 22 patients with EF. They found that 32% had HLA–B7, 27% had Bw35, and 23% had B17; none of these prevalence rates was significantly different from those in controls (25%, 16%, and 8%, respectively).

Previously, there have been no reported cases of siblings with EF. We describe a pair of siblings who presented, within 6 months of each other, with clinical and laboratory evidence of this disease.

CASE REPORTS

Patient 1. Patient 1, a 38-year-old white woman, began participating in an exercise program in November 1985. Shortly thereafter, she noted tenderness and swelling of both lower legs. The tenderness and swelling continued into the spring of 1986, when she noted swelling of both ankles. There was a feeling of intense pressure and throbbing in the lateral area of both lower legs. She took aspirin, which provided no relief. In May, swelling and tenderness of the radial aspect of both forearms developed. It came to involve the entire forearms, the wrists, and the elbows. Paresthesias developed in an ulnar nerve distribution bilaterally. There was no history of Raynaud's phenomenon, dysphagia, heartburn, arthritis, dermatitis, other symptoms suggestive of a systemic rheumatic disease, or any other illness. She took no medications except multivitamins and calcium supplements.

Laboratory studies performed in May 1986 revealed a white blood cell (WBC) count of 18.5 $\times$ 10^9/liter (13% eosinophils) and an ESR of 48 mm/hour. When repeated in August 1986, the WBC count was 14.6 $\times$ 10^9/liter (4% eosinophils) and the ESR was 10

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mm/hour. Tests for quantitative immunoglobulins revealed an IgG level of 15.35 gm/liter, an IgA level of 1.93 gm/liter, and an IgM level of 0.91 gm/liter (upper limits of normal 16.47, 3.70, and 3.09, respectively). Findings of tests for rheumatoid factor and antinuclear antibodies were negative, and results of routine blood chemistry studies, urinalysis, and thyroid function tests were normal. Findings of nerve conduction studies of the ulnar, median, and sural nerves were normal, as were the results of an electromyographic examination of the right first dorsal interosseous of the hand and the right vastus lateralis.

When examined in August 1986, the patient was noted to have mild flexion contractures of both elbows, lack of full supination of both forearms, and decreased flexion and extension of the wrists. The skin of the wrists and forearms was taut, bound down, and indurated. Puckering was seen on the volar aspect of both forearms. No palpable tendon crepitus was noted. The hands and fingers were normal.

The skin of the lower legs appeared tense and shiny. A slightly erythematous, macular rash that blanched on pressure, measuring approximately 10 × 5 cm, was present on each posterior calf. All areas of the calves were taut, indurated, and bound down. The ankles had decreased range of motion, but the feet and toes were normal. The remainder of the physical examination results were normal, with no signs of cardiac, pericardial, pleural, or parenchymal lung disease and no abnormal gastrointestinal findings.

A full-thickness biopsy of the skin, fascia, and muscle from the right leg was performed in September 1986. This showed a mild increase in dermal collagen, local septal thickening in the subcutaneous tissue, and mild perivascular lymphocytic infiltrates in both locations. The pathologist did not comment on the thickness of the fascia. Vasculitis and inflammation of the fascial tissue and muscle were absent. The biopsy result was interpreted as being more consistent with scleroderma than with EF.

The patient's subsequent course, however, was typical of EF. Prednisone, 20 mg/day, was started in early September 1986. Over the following 6 months, she regained almost full range of motion of her elbows, wrists, and ankles, and the skin of her forearms and wrists became much more supple and less indurated. The skin of the legs also showed good improvement in tightness and induration, but less so than the forearms. At this time, the patient is no longer receiving treatment. She had no symptoms or signs of disease in her upper limbs and only minimal induration in her distal calves.

Patient 2. Patient 2, the 33-year-old brother of patient 1, first noticed pain in both calves in April 1986. The pain occurred after arising from bed in the morning or after sitting for any length of time. In May 1986, he underwent surgical release of a right carpal tunnel syndrome because of increasingly severe pain in a median nerve distribution and weakness of the thenar muscles. A similar procedure had been carried out in June 1984, and it had been thought at that time that the syndrome was the result of trauma some years earlier.

During July and August 1986, he noticed pain and stiffness in his shoulders and elbows. He would often awake with one or both elbows "locked" and would have to use the opposite arm to straighten out the stiff joint. Throughout the fall of 1986, he became increasingly fatigued, sedentary, and weak. He noticed thickening of the skin on his forearms and lower legs. By December 1986, he was having 1½ hours of morning stiffness in his shoulders, wrists, hands, hips, knees, and ankles. There was never any joint swelling, heat, or erythema. A trial of aspirin treatment produced no benefit. History included the 2 right carpal tunnel release operations, and peptic ulcer disease in 1983. There was no history of Raynaud's phenomenon, dysphagia, heartburn, or other systemic symptoms.

Physical examination in December 1986 revealed patches of vitiligo on the patient's sternum and shoulders. These had appeared in July 1986. The scar from a recent biopsy was present on his right shoulder. Apart from the pigmentary change, the skin in this area was not notably abnormal. The skin of both forearms was puckered on the volar aspect and was taut, indurated, and bound down. The right wrist had decreased range of motion secondary to previous trauma. The left wrist had relatively normal range of motion. The right elbow had a mild flexion contracture. The hands and fingers were normal. There were no palpable tendon friction rubs. The skin of the lower legs was indurated and bound to underlying tissue. The feet and toes were normal. There were no contractures of any lower limb joints. Other than slightly decreased sensation in the right median nerve distribution, the remainder of the physical examination results were normal, with no signs of cardiac, pulmonary, or gastrointestinal disease.

Laboratory tests performed in December 1986 revealed a WBC count of 12.6 × 10^9/liter with 18% eosinophils. The ESR was 3 mm/hour. IgG, IgA, and IgM levels were 15.56 gm/liter, 1.67 gm/liter, and 1.65 gm/liter, respectively. Rheumatoid factor and antinuclear antibody were negative. Results of routine blood

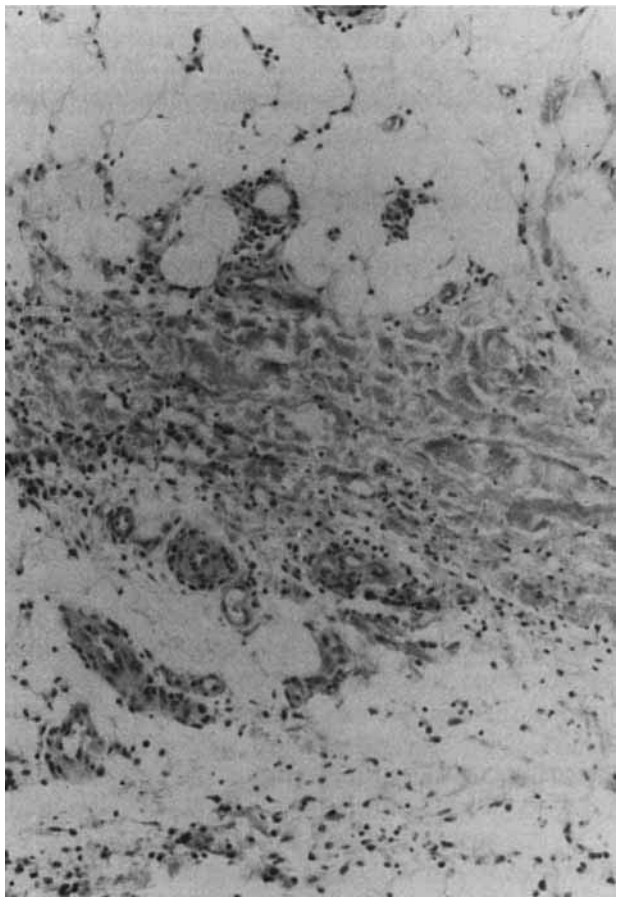

Figure 1. Full-thickness biopsy specimen of subcutaneous fat and fascia from patient 2, showing perivascular and septal inflammation, with thickening and homogenization of the septal collagen (original magnification × 50).

chemistry studies and thyroid function tests were normal.

A full-thickness biopsy of skin, fascia, and muscle from the patient's right deltoid area had been performed shortly before he was seen by us. Despite the absence of induration in this area, the histologic findings were, surprisingly, abnormal. There was marked acute inflammation in the deep fascial tissue. A mixed inflammatory infiltrate of plasma cells, lymphocytes, and smaller proportions of histiocytes and eosinophils was concentrated around small vessels and along the septa, with sparing of the fat lobules. The septa were thickened with fibrosis, edema, and homogenization of the collagen (Figure 1). The vessels also showed thickening of the walls and endothelial cell swelling. The inflammation extended into the connective tissue of the superficial muscle compartment, but there was no involvement of the skin or the upper portion of the subcutaneous tissue, other than mild perivascular infiltrates. These changes were considered typical of EF.

The patient was started on a regimen of prednisone, 30 mg/day. This was maintained for 2 months, at which time slow tapering of the dosage was started. The affected skin of the forearms and lower legs improved with less induration and binding to underlying tissue. The patient continues to take prednisone, 10 mg/day, and still has mild symptoms.

Although this patient and his similarly affected sister both live in the same city, their homes are in different suburban areas, about 5 km apart. Both left the parental home in their late teens to pursue quite different occupations, and they have had almost no contact with each other in recent years.

Family study. The patients' parents are both alive but were not available for study. The mother has hypothyroidism and atrial fibrillation, but is not known to have any evidence of connective tissue disease. The father has osteoarthritis of the knees, but is otherwise in good health.

The patients' 3 other siblings agreed to be studied. All were healthy, with no symptoms or signs to suggest the presence of a rheumatic or connective tissue disease. Typing for HLA–A, B, C, DR, and DQ antigens was carried out on all 5 siblings. The results are presented in Table 1.

Members of the third generation were not studied, but all are reported to be alive and well.

DISCUSSION

The 2 patients described herein appear to be the first reported sibling pair with EF. Both had charac-

Table 1. HLA profiles of 2 siblings with eosinophilic fasciitis and their 3 normal siblings

	HLA loci				
Sibling, year of birth	A	B	C	DR	DQ
Patient 1, 1947	2,11	7(w6),35(w6)	w4	2,3(w52)	w1,w2
Patient 2, 1953	2,11	7(w6),35(w6)	w4	2,3(w52)	w1,w2
Normal sister, 1944	2,11	7(w6),35(w6)	w4	2,3(w52)	w1,w2
Normal brother, 1950	2,3	7(w6)		2	w1
Normal sister, 1955	2,11	7(w6),35(w6)	w4	2,3(w52)	w1,w2

teristic clinical features, and both responded in the expected manner to corticosteroid therapy. The histopathologic findings in patient 1 initially created some confusion since they were reported to be those of scleroderma. Barnes et al (9) have, however, reported the occurrence of dermal sclerosis and minimal fascial inflammation in some cases of EF, and the patient's subsequent course has been entirely in keeping with the latter diagnosis. Of interest was the occurrence of neuropathic symptoms in both patients. Although the presence of an ulnar nerve lesion was not confirmed in patient 1, patient 2 was reported to have a definite carpal tunnel syndrome. Even though this was originally attributed to trauma, its recurrence at the time of onset of his other symptoms may represent part of his disease (10).

The etiology of EF is unknown. Speculation has ranged from the idea that it is a hypersensitivity reaction by the immune system to muscle tissue following exercise-induced damage (2,3), to the notion that it is an autoimmune disease characterized by circulating immune complexes and hypergammaglobulinemia (11). Genetic factors have not received a great deal of attention. The role of HLA antigens was investigated by Lynch et al (8), who concluded that there was no statistically significant association with HLA–A or B antigens. HLA–B17 was found in 23% of patients compared with 8% of controls, but this difference was not statistically significant. Our 2 patients were found to be identical for all HLA specificities tested. The A2 and A11 antigens, which they share, were found to occur with the same frequency as in the control population in Lynch's study. They also share HLA–B7 and B35, which Lynch found to occur in 32% and 27% of patients with EF compared with 25% and 16% of controls, respectively.

We have not found any report of the distribution of class II histocompatibility antigens in EF. Our patients possess HLA–DR2 and DR3, both of which have been associated with systemic lupus erythematosus and other autoimmune diseases (12). They also have HLA–DQw1 and DQw2, which, when present together in Sjögren's syndrome patients, have been shown to accentuate autoantibody production compared with that which occurs with either antigen alone (12).

The implication of the above observations is diluted somewhat by the fact that 2 of the patients' unaffected siblings had an HLA type identical to that of the patients. This clearly indicates that EF is not solely genetic in origin, but it does not exclude the possibility of a hereditary component, as exists in many (or even most) other rheumatic diseases (12).

The close temporal relationship of disease onset in these 2 patients may merely be coincidence, but does suggest the possibility of an environmental trigger. Unaccustomed physical exercise has been implicated as a precipitating cause in several cases (2,3) and may have been a factor in patient 1, but patient 2 was, by his own admission, leading a sedentary life at the time of onset. One could postulate a common environmental factor in these 2 closely related individuals, but they have lived apart their entire adult lives, pursued quite different professional paths, and had very little contact. If environment in any way influenced the development of their disease, its effects must have lain dormant for decades.

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REFERENCES

1. Shulman LE: Diffuse fasciitis with hypergammaglobulinemia and eosinophilia: a new syndrome? (abstract). J Rheumatol 1 (suppl 1):46, 1974
2. Shulman LE: Diffuse fasciitis with eosinophilia: a new syndrome? Trans Assoc Am Physicians 88:70–86, 1975
3. Shulman LE: Diffuse fasciitis with eosinophilia: a new syndrome. Arthritis Rheum 20 (suppl):S205–S215, 1977
4. Sibrack LA, Mazur EM, Hoffman R, Bollet AJ: Eosinophilic fasciitis. Clin Rheum Dis 8:443–454. 1982
5. Michet CJ, Doyle JA, Ginsburg WW: Eosinophilic fasciitis: report of 15 cases. Mayo Clin Proc 56:27–34, 1981
6. Simon DB, Ringel SP, Sufit RL: Clinical spectrum of fascial inflammation. Muscle Nerve 5:525–537, 1982
7. Moutsopoulos HM, Webber BL, Pavlidis NA, Fostiropoulos G, Goules D, Shulman LE: Diffuse fasciitis with eosinophilia: a clinicopathologic study. Am J Med 68: 701–709, 1980
8. Lynch CJ, Rodnan GP, Singh G, Seibold JR: HLA-A and B antigens in eosinophilic fasciitis (letter). J Rheumatol 8:352–353, 1981
9. Barnes L, Rodnan GP, Medsger TA, Short D: Eosinophilic fasciitis: a pathologic study of 20 cases. Am J Pathol 96:493–507, 1979
10. Jones HR, Beetham WP, Silverman ML, Margles SW: Eosinophilic fasciitis and the carpal tunnel syndrome. J Neurol Neurosurg Psychiatry 49:324–327, 1986
11. Seibold JR, Rodnan GP, Medsger TA Jr, Winkelstein A: Circulating immune complexes in eosinophilic fasciitis. Arthritis Rheum 25:1180–1185, 1982
12. Schiffenbauer J, Schwartz BD: The HLA complex and its relationship to rheumatic diseases. Rheum Dis Clin North Am 13:463–485, 1987