Eosinophilic Fasciitis in Siblings

To the Editor:

Eosinophilic fasciitis (EF) is an uncommon disorder with no documented prevalence and with unknown etiology. We describe a case of siblings with EF and identical HLA types, suggesting a genetic predisposition. The reporting of unique cases such as these is important in furthering our knowledge of rare conditions.

Patient 1 presented at 14 years of age with a 3-month history of upper limb joint stiffness and swelling after prolonged physical exertion with associated general malaise and weight loss. On examination she had skin thickening with digital sparing and venous guttering predominantly of her upper limbs. Decreased range of movement of her wrists and metacarpophalangeal joints was noted. Total white blood cell count (WCC) was normal with an eosinophilia of 1.38×10^9/l (normal 0.04–0.44 $\times 10^9$/l), an elevated serum immunoglobulin G (IgG) of 29.4 g/l (normal 5–13 g/l), and erythrocyte sedimentation rate (ESR) 42 mm/h. C-reactive protein (CRP) and creatinine kinase (CK) levels were within normal limits. A biopsy demonstrated a diffuse inflammatory cell infiltrate in the fascia, with eosinophils, lymphocytes, and plasma cells. She responded well to prednisolone and is maintained on oral methotrexate.

Patient 2, the younger brother and only sibling of Patient 1, also presented at age 14 years with a 3-week history of skin thickening on his upper limbs, with venous guttering and digital sparing. Total WCC and eosinophils were within normal limits, as were CRP, ESR, and CK levels. Serum IgG was elevated at 22.8 g/l. A clinical diagnosis of EF was made and he responded to oral prednisolone and methotrexate. There was a nonspecific inflammatory infiltrate on full-thickness biopsy. Subsequent magnetic resonance imaging (MRI) was normal; however, treatment had been ongoing for several months at the time of imaging.

Cutaneous manifestations are generally the primary symptoms of EF and include painful swelling, edema, and induration; while any part of the body may be affected, limb involvement is most common, with characteristic sparing of the hands. The groove sign is seen because of sparing of the epidermis and superficial dermis, with relative immobility of the connective tissue around deep veins. Joint contractures, inflammatory arthritis, and muscle weakness have been reported[1].

While both ultrasound and MRI are useful, the diagnosis of EF is primarily clinical; an early and often transient peripheral eosinophilia is present in 63% of patients, elevated ESR in 29%, and hypergammaglobulinemia in 35%[1]. An inflammatory infiltrate of eosinophils, mast cells, histiocytes, and lymphocytes is classically seen on full-thickness biopsy, with variable sclerosis of the deep fascia, but eosinophilia on histopathological examination is not required for the diagnosis[1]. The role of steroid treatment is well recognized and other therapeutic options include methotrexate, hydroxychloroquine, cyclosporine, mycophenolate mofetil, mast cell stabilizers, extracorporeal photochemotherapy, and infliximab[2].

The etiology of EF is not known. It has been documented after episodes of intense exercise, localized trauma, and infection. Syndromes similar to EF have been described after exposure to toxic oil and l-tryptophan[3,4].

Up to 10% of cases of EF precede or occur concomitant to hematological malignancy[5]. It has also been reported in association with breast and prostate cancer and postallogeneic bone marrow transplantation, suggesting an immune-mediated basis for disease[6]. The molecular pathogenesis of EF is poorly understood and the roles of interleukin 5, transforming growth factor-ß, CD40 ligand, and mast cells have been implicated, but no definite conclusions have been reached[7,8].

The possibility of a genetic role in the development of EF is controversial. We have described siblings with EF and identical HLA profiles. A 1988 review did not demonstrate a significant difference between HLA profiles compared to controls but there was a trend toward a higher percentage of patients with HLA-A2, AW33, B27, DR1, and DRW9[1]. Reports of family members with EF include a case of siblings with EF and identical HLA profiles, a case of a father and son with no available HLA typing, and cases with possible inciting agents such as toxic oil and breast cancer[3,6,9,10]. When comparing our patients to reported literature of familial cases, all patients were HLA-A2-positive (Table 1).

EF remains poorly understood. This report suggests that family members with similar HLA typing are at increased risk, with a possible link to HLA-A2. It is likely that a second environmental factor contributes to the timing of disease onset. The low disease prevalence makes it difficult to do the case-control studies needed to confirm a correlation with HLA.

Table 1. HLA typing of eosinophilic fasciitis in familial cases.

	HLA-A	HLA-B	HLA-C	HLA-DR
Sibling pair				
Case 1	A2	B7/27	Cw 7/1	DRB1-0103, DRB3-01
Case 2	A2	B7/27	Cw 7/1	DRB1-0103, DRB3-01
Thomson 1989[9]				
Sibling 1	A2/A11	B7/B35	Cw4	DR2/3
Sibling 2	A2/A11	B7/B35	Cw4	DR2/3

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