Eosinophilic Fasciitis. Favorable Response to Treatment With Cyclosporin A

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Introduction: Eosinophilic fasciitis (EF) is a disease of unknown aetiology characterized by cutaneous swelling and indurations. The disease affects predominantly the extremities and usually show an elevation of serum immunoglobulins, and eosinophilia. Objective: Evaluation of the efficacy of cyclosporine A as a therapeutic alternative in patients with EF refractory to steroids. Patients and method: We report 3 patients with clinical, laboratory and pathologic characteristics of EF who did not show a satisfactory response to steroids treatment. All patients disclosed scleroderma-like signs with orange skin, groove sign, and indurations of the affected extremities associated to peripheral eosinophilia and increased creatine-kinase. Epidermis histological findings were normal and intense linfocitary inflammation of the fascia was observed in all patients’ biopsies. All patients were treated for average of 8 months with prednisone 30-50 mg daily with an insufficient clinical response. Results: Patients started on cyclosporine A 5-7 mg/kg/day, showing a fast improvement (2 months). The treatment induces a clinical remission that permits to reduce or even stops the cyclosporine A treatment during follow-up. Conclusions: It seems that cyclosporine A may be an effective therapeutic alternative in patients with EF refractory to steroids. Key words: Eosinophilic fasciitis. Cyclosporine A. Treatment.

Fascitis eosinofílica, respuesta favorable al tratamiento con ciclosporina A

Introducción: La fascitis eosinofílica (FE) es una enfermedad de origen desconocido, caracterizada por induración de la piel, debido a inflamación de las fascias del tejido conjuntivo. Afecta principalmente a las extremidades y se acompaña de elevación de inmunoglobulinas y eosinofilia periférica. Objetivo: Evaluar la eficacia de ciclosporina A en pacientes con FE con resistencia al tratamiento convencional con glucocorticoides. Pacientes y método: Presentamos 3 pacientes con manifestaciones clínicas y serológicas de FE que tuvieron resistencia al tratamiento estándar con glucocorticoides (30 a 50 mg/día, durante un período de hasta 8 meses). Las manifestaciones clínicas principales fueron: induración de la piel de las extremidades y el tronco que se acompañó de eosinofilia periférica y elevación de la creatincinasa. Histológicamente se observó un engrosamiento con intensa inflamación linfocitaria de las fascias. Resultados: Todos los pacientes fueron tratados con ciclosporina A, a dosis de 5 a 7 mg/kg/día con una rápida mejoría clínica (2 meses). El tratamiento condujo, en todos los casos, a una remisión clínica que permitió reducir e incluso retirar la ciclosporina A durante el seguimiento. Conclusiones: La ciclosporina A parece una alternativa terapéutica eficaz en el tratamiento de pacientes con FE resistente a glucocorticoides. Palabras clave: Fascitis eosinofílica. Ciclosporina A. Tratamiento.

Introduction

Eosinophilic fasciitis (EF) is a disease that presents connective tissue fascia inflammation, which secondarily leads to skin induration. Shulman described it for the first time in 1974 in 2 patients who presented skin and soft-tissue thickening, peripheral eosinophilia, and hypergammaglobulinemia.
It is considered an affection of connective tissue related with the specter of scleroderma-like diseases. In spite of several publications on the use of different treatments, there is still no consensus for the treatment of the disease. The objective of this study is to evaluate the therapeutic response to cyclosporine A (CsA) in 3 cases with glucocorticosteroid-resistant EF.

**Patients and Method**

Three patients were referred for EF to our department in a consecutive manner during an 18-month period. They were initially treated with prednisone (PD) at a dose of 30–50 mg for an average of 8 months without clinical response and therefore were included for treatment with CsA.

**Patient 1**

A 42-year old woman with a history of malaise and joint pain in shoulders and wrists, which started 2 months prior and presented progressive thickening and ascending edema of the legs, extending to the abdomen and forearms, accompanied by muscle pain and paresthesia. Faced with a clinical suspicion of EF she was sent to our unit where blood analysis revealed leukocytosis (9200/µL), with eosinophilia (29% eosinophils, 2610 in total), a discrete elevation of antinuclear antibodies (ANA) (1:80) and creatine-kinase (CK) (791; normal, 38–174 U/L). Examination showed conserved muscle strength but the patient had restriction of movement due to flexion contracture of the upper extremities. The skin was hardened on the anterior face of the thorax and abdomen, but predominantly in the proximal regions of the 4 extremities (Figure 1A) and was accompanied by changes in the color with areas of hyper and hypopigmentation in the distal region of both legs. Electromyography of the lower extremities evidenced a sensitive neuropathy but without any signs of myopathy. A profound skin biopsy was carried out which showed, in the deep tissue, thickening and inflammation of the fascia and fatty tissue, with a perivascular infiltration of lymphocytes but without the presence of eosinophils. The epidermis and dermis did not show significant histological changes. A study to determine any possible visceral extension was negative. A diagnosis of EF was established and treatment with prednisone 30 mg/day and gabapentin 600 mg/day was established, with an apparently favorable response, disappearance of the eosinophilia at 2 weeks, although the rigidity and skin hardening kept the patient in functional class III. At 6 months of treatment and due to the poor clinical response it was decided to treat the patient with methylprednisolone (30 mg/kg) pulse therapy, followed by an increase to 50 mg/day in the dose of prednisone. After 8 months without a clinical improvement with steroids, treatment with CsA was started at a dose of 5 mg/kg/day, achieving an adequate clinical response at 2 months (functional class II), which was maintained after 6 months (functional class I). The skin induration on the abdomen disappeared and it was considerably reduced on the extremities (Figure 1B), allowing us to progressively reduce the dose of prednisone to 2.5 mg/day and CsA to 3 mg/kg/day. At 20 months CsA was suspended and only low-dose steroid was maintained.

**Patient 2**

A 50-year-old male presented rapidly progressing edema for 2 months in both legs and progressively evolved to edema of the upper extremities and upper abdomen. The examination showed a flexion contracture of the 4 extremities and circular, morphea-like lesions on the
thorax. Treatment with prednisone (20 mg/day) was begun, with a discreet improvement in the inferior extremities. Blood count showed eosinophilia (23.9%; 1910 total eosinophils), immunologic studies were negative for ANA, DNAn, and Scl-70. A profound biopsy did not show any pathologic changes in the skin, the deep tissue showed an intense lymphocytic inflammatory process with a thickening of the muscle fascia and the adjacent muscle and fatty tissue in a diffuse manner, with no presence of eosinophils (Figure 2). The visceral extension study resulted negative. Based on this data, a diagnosis of EF was established and treatment with prednisone at a dose of 50–70 mg/day was begun. After 7 months and due to the persistence of peripheral eosinophilia, skin induration and a class III function, the decision to start therapy with CsA at a dose of 5 mg/kg/day. The patient presented a rapid clinical response and, after 4 weeks, achieved an evident reduction in the induration of the skin on the legs, abdomen and the anterior face of the thorax, with a correction in the number of eosinophils and with the patient achieving functional class I. During the second month of treatment, the patient presented an increase in blood pressure and a discrete elevation of urea and creatinine, requiring a dose of CsA to 3 mg/kg/day, maintaining clinical remission. Because the patient was obese and hypertensive, the suspension of CsA treatment was agreed upon at 6 months, substituting it for methotrexate 15 mg/week and low-dose deflazacort (3 mg/day); until today the patient has presented 2 episodes of reactivation.

**Patient 3**

A 46-year-old woman, with a history of self-limited monoarthritis of the right 9 months prior came to the outpatient clinic due to the appearance of hard, ascending edema which reached the upper third of both legs and which evolved progressively until it affected both forearms with changes in coloration and areas of hyperpigmentation. The examination showed induration and hyperpigmentation on the skin of the anterior side of the forearms and legs with a flexion contracture of the 4 limbs, leading the patient to functional class II–III. Laboratory tests showed anemia, eosinophilia (23%; 1587 total eosinophils) and slightly elevated CK. A profound biopsy showed discreet lymphocytic inflammation in a perivascular pattern in the superficial skin and intense inflammation of the fascia with perivascular lymphocyte infiltration and the presence of isolated eosinophils. A study of possible visceral extension resulted negative. With the diagnosis of EF, treatment with prednisone 50 mg/day was started, with a rapid progression of the disease, persistence of skin induration, bone and joint contraction and fatigue. Three months later an increase in blood eosinophils was observed with a deterioration of functional class and persistence of skin induration in the lower extremities, justifying the start of treatment with CsA at a dose of 5 mg/kg/day. After 3 months of treatment, a notable improvement with a reduction of skin induration (functional class I) was seen, although changes in the coloration of the skin and a discreet eosinophilia were seen (400 total). The patient is currently in clinical remission with a CsA dose of 3 mg/kg/day and prednisone at 5 mg/day.

**Discussion**

Eosinophilic fasciitis is a rare condition characterized by a subacute inflammatory process of the deep fascial of bone and muscle tissue. The inflammatory process can evolve producing a fascia and adjacent connective tissue thickening, even involving subcutaneous fat and muscle. Its pathogenesis and the relationship it has with scleroderma-associated syndromes is unclear. Fibroblasts from patients with this disease show great activity for the production of collagen and an increased expression of some cytokines has been detected. The progression of EF can be good, even spontaneously resolving itself after 2–3 years of the acute episode. Generally, therapy with steroids is recommended, at a dose of 1 to 2 mg/kg/day; however, in resistant cases, a variety of alternate treatments have been attempted, such as cimetidine, methotrexate, photochemotherapy with ultraviolet light, among others, without achieving, in general, a clear evidence of benefit. The use of CsA in the treatment of scleroderma has been previously described, its apparent benefit is based on in vitro studies in which an increase in the expression of collagenases from skin fibroblasts is demonstrated, resulting in an increase in the rate of fibrotic extracellular matrix turnover and a degradation of collagen. Several diverse and isolated cases or a response to CsA therapy...
have also been published in the past. Different authors communicated 3 cases of EF related to other diseases such as leukemia, aplastic anemia, and myelodysplasic syndrome; the authors prescribed treatment with CsA for the underlying illness and observed noticeable improvement of the EF.\textsuperscript{12-14} In addition, the experience in the use of CsA in patients with an unsatisfactory response to steroids or other drugs has been published. Valencia et al\textsuperscript{15} describe the case of a 58-year-old woman with EF who, after a lack of response to steroid treatment for 7 months, presented evident clinical improvement at 3 weeks after starting treatment with CsA (300 mg/day). In another case, Hayashi et al\textsuperscript{3} weeks after starting treatment with CsA (300 mg/day). For 7 months, presented evident clinical improvement at 3 weeks after starting treatment with CsA (300 mg/day) with EF who, after a lack of response to steroid treatment for 6 weeks of treatment. Finally, Bukiej et al\textsuperscript{16} describe the case of a 50-year-old male who, after 18 years of exposure to trichloroethylene solvent, developed EF. He was initially treated with steroids without clinical improvement and, after therapy with CsA was started at a dose of 3.5 mg/kg/day, showed evident improvement after 6 weeks of treatment. Finally, Bukiej et al\textsuperscript{17} presented the case of a 45-year-old woman with EF of 4 months of progression, resistant to high-dose steroid and cimetidine (1600 mg/day) who, after starting treatment with CsA at 5 mg/kg/day for the first 4 weeks, then reducing the dose by 50%, presented clinical remission at 8 weeks and maintaining stability for the duration of treatment.

In summary, we present 3 cases of steroid-resistant EF that improved rapidly when treated with CsA, with the most evident clinical improvement by the fourth to sixth week of therapy. The clinical response was maintained during follow-up and administration with CsA was even reduced or stopped in some cases, without any considerable side effects. This study supports the isolated data previously published on the efficacy and safety of CsA as a therapeutic alternative in cases of steroid-resistant EF. However, due to the possibility of spontaneous clinical improvement in the course of the disease, larger controlled studies are necessary in order to safely establish the efficacy of CsA in this therapeutic indication.

References