Eosinophilic Fasciitis in a Pediatric Patient

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Abstract: We report the case of a pediatric patient with eosinophilic fasciitis, who was successfully treated with early high dose corticosteroids and subsequent use of mycophenolate mofetil. We believe that the early institution of corticosteroids helped to suppress the early inflammatory part of the disease and the subsequent use of mycophenolate mofetil maintained this and may have also helped prevent fibrotic skin changes.

Key Words: eosinophilic fasciitis, mycophenolate mofetil, treatment, scleroderma, fibrosis, fasciitis

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The syndrome of diffuse fasciitis with eosinophilia and hypergammaglobulinemia was first recognized by Shulman in 1974[1] and the term eosinophilic fasciitis (EF) was later proposed by Rodnan, based on the prominent eosinophilic component of the inflammatory fascial infiltrate.[2]

EF is a rare scleroderma-like condition which shares some features with deep morphea, hence some investigators have supported the idea of EF consisting a subtype of localized scleroderma.[3,4] Others believe that this is a unique cutaneous reaction to different stimuli, thus a separate entity.[5] This belief is enhanced by the fact that Raynaud phenomenon, sclerodactyly, nailfold capillary changes, and positive antinuclear antibodies, which are common features of scleroderma, are rarely seen in patients with EF.[6] In addition, eosinophilic fasciitis has an inflammatory infiltrate which is primarily in the muscular fascia, while the dermis and epidermis are typically spared (Fig. 1). Systemic involvement is rare.[7]

More than 200 cases of EF have been reported to date. The disease mainly affects adults 20 to 60 years of age[5] with equal occurrence in adult males and females.[8] Whites are more commonly affected than African-Americans and Asians.[5]

Eosinophilic fasciitis rarely occurs in childhood,[6] with only approximately 32 cases of pediatric EF published up to 2008.[9] The childhood form of EF is similar to that in adults.[10] According to Grisanti et al,[11] the clinical manifestations, laboratory parameters, and response to therapy for pediatric EF are generally indistinguishable from the adult cases. However, comparison between adult and childhood EF shows a female preponderance of cases in children (75% vs. 36% in adults). Furthermore, pediatric EF is less frequently associated with arthritis (25% vs. 44% in adults) and haematological complications, such as aplastic anemia and thrombocytopenic purpura, have not been described. With lack of hematological involvement, pediatric EF would seem to have a better prognosis than that in adults.[11] Some children with EF have presented with painless joint contractures, without obvious cutaneous involvement. This may represent an EF phenotype specific to children.[12,13]

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We report here a case of EF in a pediatric patient who was treated with mycophenolate mofetil an agent that has both anti-inflammatory as well as antifibrotic properties, with remarkable improvement in his skin involvement and joint contractures.

CASE REPORT

A 9-year-old boy, usually very active, was noted by his parents to have increased fatigue and to be less interested in playing with his friends over the previous 3 months. He was also noted to have a 5 pound weight loss and a poor appetite. They then noted tightness of his skin and difficulty in bending his elbows. He had no medical history and was taking no medications. Three siblings and his mother and father were all healthy. His initial evaluation revealed woody induration of his skin involving approximately 80% of his total body surface sparing onto his head, neck, and upper chest, and involving even hands and feet. Erythematous changes in the areas involved and peau d'orange changes in the upper arms axillary regions were noted. Using the modified Rodnan skin score, a 51 point scale used for the clinical assessment of skin thickening in systemic sclerosis, the patient's skin score was 38 out of a possible 51. He had severe joint contractures of his ankles, knees, and elbows. There were no symptoms of Raynaud phenomenon, dysphagia, pleurisy, or arthritis. Blood tests revealed a white cell count of 10,600/μL, with an eosinophil count of 22%, a sedimentation rate of 30 mm/h, and a platelet count of 530,000/μL. A serum protein electrophoresis was normal. Antinuclear antibodies were all negative as well as anti-Scl-70 and anticentromere antibodies. A CT of the chest revealed small hilar adenopathy. An MRI of the lower extremities with gadolinium revealed abnormal enhancement of the fascia on T2 images surrounding the gastrocnemius muscles on both sides suggestive of both thickening and inflammation of the superficial fascia. A skin and deep fascia biopsy was performed of the right gastrocnemius region revealing a mild perivascular and deep skin infiltrate of lymphocytes and plasma cells. The fascia revealed chronic lymphoplasmacytic fasciitis with fibrinoid necrosis, while the muscle biopsy was unremarkable other than the fascial inflammation. There were no signs of septal or lobular panniculitis, vasculitis, or myositis.

He was diagnosed with eosinophilic fasciitis and was placed on prednisone 20 mg twice a day for approximately 4 months which was subsequently changed over to monthly 2 g methylprednisolone intravenous pulses over 2 days to avert further Cushingoid changes from prolonged use of oral corticosteroids. Mycophenolate mofetil was then initiated and was slowly increased to a dosage of 900 mg twice a day. The methylprednisolone pulses were slowly tapered over the next 6 months and the Cushingoid changes slowly reversed. A repeat MRI of the lower extremities a year later did not reveal any changes suggestive of fasciitis. The patient continued on the same dose of mycophenolate mofetil without the use of corticosteroids for another year since there was continued skin improvement and a remarkable increase in the range of motion of his ankles, knees and elbows. Two years after the initiation of mycophenolate mofetil, the modified Rodnan skin score was 6 out of a possible 51 and the patient only had 12% of the total body surface involved, the area between the elbows and wrists and between the knees and the ankles on both sides. Through continued physical therapy over the 2 years he was able to run and play sports with very minimal difficulty.

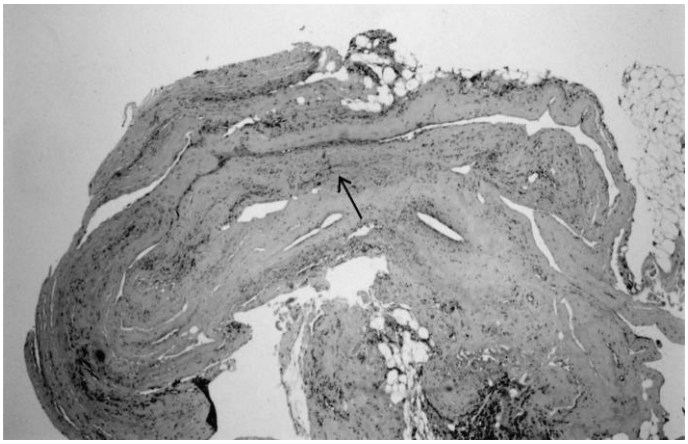

FIGURE 1. Fibrinoid necrosis and lymphocytic infiltration of the fascia (arrow) (H and E 40).

Over the 2 years, he did not develop any side effects from the mycophenolate mofetil and his growth landmarks were all normal.

DISCUSSION

We present a pediatric patient with EF who was successfully treated with mycophenolate mofetil and has achieved a remarkable outcome leading to very minimal if any disability related to his disease.

In the majority of reported cases, systemic corticosteroids have been used as the initial treatment, since this is considered the mainstay of treatment. The response to prednisone alone has been variable. Grisanti et al, in their review of 17 pediatric cases and report of a new one, stated that the majority showed a prompt initial response to prednisone, though, in some cases, joint contractures and skin lesions persisted or recurred.[11] Although definitive treatment cannot be determined, they suggest it is reasonable to initiate prednisone at a dose of 2 mg/kg per day and taper it slowly, as soon as the laboratory values normalize (erythrocyte sedimentation rate, eosinophils, and gamma globulins). They also consider early physical therapy for its value limiting contractures and thus maintaining mobility. Upon worsening of skin lesions or recurrence during prednisone tapering, they suggest the use of D-Penicillamine (125 mg per day) with satisfactory results. This is in accordance with other reports where D-Penicillamine was used to treat pediatric EF.[14–16]

Corticosteroids are usually initiated at a high dose[10,11,17,18] though a dramatic clinical response has been reported at a low dose (0.5 mg/kg), as well.[19] Pulsed steroids (methylprednisolone, 1 g/d for 3 days every 4 weeks) have also been used successfully in an 11-year-old female patient.[13] Clinical response to corticosteroids usually happens within a few weeks to months. Early treatment with systemic corticosteroids has been reported to decrease the duration and development of the disease.[8]

Clinical response is usually defined as softening of the indurated skin, correction of laboratory values, and resolution of joint contractures.[6,20] Aldolase levels have been proposed by some investigators as a disease activity marker believed to be related to the elevated eosinophil count.[21,22] This could be particularly reasonable in children with EF, given the common muscle involvement in childhood cases, though not the case in the patient we presented. The degree of eosinophilia does not correlate with disease severity and laboratory results are not helpful in following disease activity.[20] MRI has been proposed as a useful tool for diagnosis and following the effectiveness of treatment.[23]

The outcome of children with EF treated with systemic corticosteroids is favorable, in the majority of cases. However, variable outcomes have been published as well. According to Farrington et al, 14 out of 21 children with EF were left with a residual scleroderma-like cutaneous fibrosis. Young age (7 years old) and extensive initial disease (involvement of at least 3 extremities) were claimed to be positive risk factors, whereas sex, laboratory results, and type of treatment were not predictive of the development of fibrosis.[24] A 3-year-old female child reported by Williams et al, was left with chronic linear scleroderma lesions after initial dramatic response to prednisone[25] and a 10-year-old boy reported by Balat et al had a poor response to steroids and progressed to linear scleroderma.[3]

On the other hand, spontaneous remission seems to be common. Of 5 untreated patients, 4 had spontaneous improvement of their disease, with resolution in 2 of them.[20] This was also observed in 2 cases, one a 12 and other a 14-year-old, who recovered after the treatment with aspirin and physical therapy alone.[26,27]

Hydroxychloroquine has been said to help in controlling the disease as an adjunct to treatment with corticosteroids.[28] Although this seems to relieve the pain and improve the laboratory profile, induration and stiffness may persist in some cases.[29]

Methotrexate has been used in juvenile EF in combination with low dose corticosteroids and a clinical response was documented.[9,12] It is of note that methotrexate led to a clinical improvement when it was used for the treatment of persistent, progressive, or relapsing disease when steroids alone were not sufficient.[30,31]

Increased histamine levels have been documented in some patients with EF.[32] The involvement of mast cells in the pathogenesis of EF has also been proposed by some investigators.[33] This has led some investigators to try the use of antihistamine medications—both H1 and H2 antagonists—in patients with EF.[34–41]

Although there are not enough data regarding the use of phototherapy or photochemotherapy in juvenile EF, it has been used successfully in generalized morphea of childhood.[42] The combination of UVA with a psoralen for the treatment of EF, the so-called PUVA, has also been published.[43,44]

Since their introduction, tumor necrosis factor alpha antagonists have shown efficacy in many inflammatory and autoimmune conditions including various inflammatory dermatoses such as eosinophilic fasciitis which are refractory to conventional treatment.[45–47] Rituximab, a monoclonal antibody against B lymphocytes that express CD20 has also been used for the treatment of refractory EF and the investigators observed remarkable short-term results.[48]

In the case presented, we describe a pediatric patient with EF who is the first reported case of treatment with mycophenolate mofetil after the use of high-dose corticosteroids. Early high dose use of corticosteroids appears to improve clinical outcome.[49] Mycophenolate mofetil, an inosine monophosphate degydrogenase inhibitor that inhibits the proliferative response of T and B lymphocytes and has a potential antifibrotic effect may be used for its anti-inflammatory and steroid sparing properties as well as to decrease tissue fibrosis.[50]

CONCLUSION

Pediatric EF is considered clinically similar to the adult form of the disease with some differences such as female preponderance, less arthritic manifestations and no hematological complications, which possibly determine a better prognosis than that in adults. It is of note that some patients, particularly those very young and with extensive disease, have an increased chance of developing residual fibrosis despite initial good response to therapy. It is also of particular interest that in some cases clinical remission can occur spontaneously in 3 to 5 years even without treatment.

Along with early introduction of physical therapy, which is crucial for the maintenance of mobility, high-dose corticosteroids

are the mainstay of treatment for eosinophilic fasciitis, with the majority of patients showing a favorable response. Due to its inhibitory effects on the proliferative response of T and B lymphocytes and the potential antifibrotic effect of mycophenolate mofetil, it should be considered in the treatment of refractory eosinophilic fasciitis.

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