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Eosinophilic fasciitis: a case series with an emphasis on therapy and induction of remission

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Abstract

Eosinophilic fasciitis is an uncommon connective tissue disorder that affects patients of all ages, resulting in significant morbidity. Systemic corticosteroids can induce remission of disease. However, there is no universally accepted treatment ladder for eosinophilic fasciitis. This case series evaluates treatment efficacy in patients with eosinophilic fasciitis seen at Wake Forest University Department of Dermatology outpatient clinics. Patient charts were screened using ICD-9 diagnosis code 710.9 (unspecified diffuse connective tissue disease) to identify patients with eosinophilic fasciitis (n=10) seen at our institution. Patients were treated for an average 24 months with a combination of methotrexate and prednisone therapy, unless one or both were contraindicated, with each medication tapered conservatively to prevent disease flares. Alternate treatments included mycophenolate mofetil with prednisone, azathioprine with prednisone, prednisone monotherapy, and methotrexate monotherapy. Disease remission off therapy and on low-dose therapy was 66 and 70%, respectively. Our first-line therapy of concomitant methotrexate and prednisone is well-tolerated and effective for managing patients with eosinophilic fasciitis. Our study was limited to cases seen at a single academic institution.

Keywords: connective tissue diseases, corticosteroids, dermatology, drug therapy, eosinophilic fasciitis, immunosuppressive agents, methotrexate, prednisone.

Citation

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Introduction

Eosinophilic fasciitis (Shulman's syndrome), first described by Lawrence Shulman in 1974, is an autoimmune connective tissue disorder with significant morbidity. Symptoms often develop rapidly, symmetrically affecting limbs, commonly sparing hands, feet, and face.[1,2] Patients can have myalgias, edema, weakness, and fatigue. Subsequently, patients transition to a 'cellulitic-like' picture, followed by progression to a fibrotic clinical manifestation.[1–3] Patients often demonstrate the classic 'groove-sign' with linear depressions along underlying veins within indurated skin.[1,2]

Eosinophilic fasciitis is diagnosed using clinical appearance, characteristic histology, and other laboratory findings. Patients often present with an elevated erythrocyte sedimentation rate, hypergammaglobulinemia, and transient peripheral eosinophilia.[1–3] Biopsy results of affected areas include hyalinized and thickened fascial layers with an infiltrate of plasma cells, eosinophils, and lymphocytes. Eosinophils may be absent in the biopsy. Diagnosis is confirmed with magnetic resonance imaging (MRI) signal abnormalities and contrast enhancement of superficial, and/or deep fasciae.[1–2] Currently, no validated diagnostic eosinophilic fasciitis criteria exist, though diagnostic algorithms have been proposed.[4]

Multiple triggers of eosinophilic fasciitis have been postulated. Up to 28% of eosinophilic fasciitis patients have a history of extreme physical activity days to weeks prior to presentation.[5–7] Historically, eosinophilic fasciitis was reported to develop after consumption of contaminated L-tryptophan (eosinophilia–myalgia syndrome), or other chemicals. However, these associations are not established. A similar syndrome occurs in European patients exposed to *Borrelia*.[2,6]

Eosinophilic fasciitis is considered to be on a continuum with morphea.[5,8] Studies show localized morphea can develop in 28–65% of eosinophilic fasciitis patients.[3,5,9–11] Coexisting eosinophilic fasciitis and morphea lesions both respond to treatment for eosinophilic fasciitis. However, the

presence of morphea correlates with higher risk of resistant disease.[5,10–12] Furthermore, patients with morphea can have increased morbidity due to increased risk of residual disease damage.[8,12]

Eosinophilic fasciitis typically has a good response to systemic corticosteroids tapered slowly over a period of months to years.[1,9] However, there is higher risk of disease reoccurrence once prednisone is discontinued.[5] Methotrexate can be used concomitantly with prednisone or as second-line monotherapy.[5,7–11] Additionally, some suggest dual treatment with methotrexate and prednisone should be considered mainstay therapy for patients with morphea-like lesions, as these patients often have decreased response to systemic corticosteroid monotherapy.[10] Alternative treatments described in the literature include methotrexate, hydroxychloroquine, azathioprine, cyclosporine, PUVA (psoralen ultraviolet A), infliximab, and other immunosuppressive agents.[5,13–18] However, there is no universally accepted treatment ladder for eosinophilic fasciitis. This study provides an evidence-based approach for treatment of eosinophilic fasciitis.

Methods

After Institutional Review Board Approval (Wake Forest University School of Medicine, Winston Salem, North Carolina, USA), all patient charts from January 1, 1990 to January 1, 2010 were screened with ICD-9 code 710.9 (unspecified diffuse connective tissue disease). A waiver of consent was approved for this retrospective review. Patients with histological or MRI-confirmed eosinophilic fasciitis were included in this study. Exclusion criteria included: a primarily clinical diagnosis, not meeting two required clinic visits, or a different histological diagnosis. Of 134 initial cases, 10 met inclusion criteria.

The mean patient age was 52.4 (SD 18.3) years at presentation. Six females and four males with active disease upon initial visit were included. Patients were followed an average 24 months (range 7–44 months) and for at least 2 clinic visits. Patients off treatment over 5 years without clinic visits were contacted by phone to determine if their disease remained in remission.

Patient age, sex, previous therapy and response to previous therapy, current therapy and response to current therapy, and complications from treatment were recorded. Response to therapy was characterized as: (1) 'none' if the patient had no resolution, (2) 'partial' if the patient experienced some resolution but still had any degree of refractory disease activity, (3) 'complete remission' if the patient had no physical findings or symptoms of the disease, and (4) 'complete remission off therapy' (Table 1).

Methotrexate and prednisone combination regimen was started for all patients, unless contraindicated. Three patients unable to take methotrexate were prescribed alternative treatments. Patients were educated regarding medication side effects and encouraged to read brochures about oral prednisone. Medication side effects were monitored during clinical and laboratory follow-up.

Results

In this study, ten patients were continued on treatment for an average 23.2 months (range 7–44 months). Sixty percent (6 of 10) of patients received a different form of therapy than our standard dual-treatment regimen of methotrexate and prednisone prior to presenting to clinic. The most common initial therapy was prednisone monotherapy (66%, 4 of 6). No patients previously received the combination of methotrexate and prednisone.

Of six patients who tried and failed previous therapies, 66% (4 of 6) were treated with methotrexate and prednisone. Three of the four patients (75%) achieved complete remission on dual therapy. One of the four (25%) achieved only partial response to methotrexate–prednisone therapy. However, this patient had a complicated treatment course due to history of malignancy. Two of six patients who failed previous treatment had alternate treatment regimens. One patient received azathioprine and prednisone, due to cost concerns, and achieved partial disease resolution. Another patient, previously treated with prednisone alone, achieved complete remission with methotrexate monotherapy.

Of four patients who were treatment naïve, 50% (2 of 4) received our standard methotrexate and prednisone dual-therapy. One patient achieved full remission. The second patient was lost to follow-up but was documented improving based on the last clinic note. Two patients received alternative regimens. One patient requested a treatment that permitted alcohol consumption and achieved complete remission with mycophenolate mofetil and prednisone. Another patient received prednisone monotherapy and also achieved complete remission.

The average maximum dose for six patients who received methotrexate-prednisone combination therapy was 15 mg of methotrexate weekly and 25 mg of prednisone daily. Both medications were tapered by 2.5 mg every 4–6 weeks once the disease stabilized.

Discussion

Eosinophilic fasciitis is a rare connective tissue disorder with no universally accepted treatment protocol. Current literature advocates for a course of corticosteroids alone or in combination with other immunosuppressive agents.[1,3] Methotrexate is increasingly used as second-line therapy or combined with prednisone, especially in patients with concomitant morphea lesions.[5,7–11]

In our series, 7 of 10 patients were able to achieve complete remission, with all 10 patients experiencing at least partial resolution of their disease. The majority of patients (6 of 10) received our first-line treatment regimen of dual

Table 1. Eosinophilic fasciitis patient characteristics.

Subject	Age	M/F	Age of disease onset	MRI, biopsy or both	Previous therapies	Response to previous therapy	Most recent therapy	Duration of current therapy	Response to current therapy	Side effects
1	79	F	77	Biopsy	Prednisone	None	Methotrexate	7 months	Complete remission	None
2[a]	88	F	81	Both	None	No previous treatment	Prednisone	21 months	Complete remission	None
3	52	M	49	Biopsy	None	No previous treatment	Prednisone and mycophenolate mofetil	25 months	Complete remission	None
4	66	F	57	Biopsy	Prednisone and leflunomide	Partial resolution	Prednisone and azathioprine	17 months	Partial resolution	None
5	54	F	42	Biopsy	None	No previous treatment	Prednisone and methotrexate	44 months	Complete remission	None
6	64	M	55	Biopsy	Topical corticosteroid	No resolution	Prednisone and methotrexate	40 months	Complete remission	None
7	45	M	39	Both	Prednisone	Partial resolution	Prednisone and methotrexate	15 months	Complete remission	Fatigue
8	59	F	53	Biopsy	Prednisone	Partial resolution	Prednisone and methotrexate	11 months	Complete remission	None
9	58	F	54	Biopsy	Prednisone	Partial resolution	Prednisone and methotrexate	14 months	Partial resolution	Anemia leukopenia previous malignancy
10	22	M	17	Biopsy	None	No previous treatment	Prednisone and methotrexate	38 months	Partial resolution	Nausea

[a]Patient deceased.
F, female; M, male; MRI, magnetic resonance imaging.

methotrexate and prednisone therapy. Four of six patients achieved complete remission and two partial remission. Our treatment protocol consisted of simultaneous prednisone and methotrexate therapy, with an approximate dose of 25 mg per day and 15 mg per week, respectively, depending on patient age and overall renal function. As patients achieved stable disease control, the prednisone was tapered, usually at a rate of a 2.5 mg decrease every 4–6 weeks, followed by a taper of the methotrexate by 2.5 mg every 4–6 weeks. The goal was for the patients to have both medications tapered off while remaining in remission; however, if a patient experienced a disease flare while tapering, the dose was stabilized or increased if needed.

Other studies show methotrexate and prednisone combination therapy to be an effective regimen. A retrospective study of 63 patients reported increased complete remission rates (64%) on corticosteroid and methotrexate combination therapy compared to alternative treatment options.[7] Conversely, an open label, single-arm study of 12 eosinophilic fasciitis patients showed no significant difference (p=0.97) in clinical outcomes of 8 patients administered high-dose intravenous (IV) methotrexate (4 mg/kg/month) with concomitant systemic steroids compared to 4 patients treated with high-dose IV methotrexate alone. Eleven of twelve patients (91.7%) had significantly improved skin induration scores. However, the median durometer score (a measure of skin hardness) did not improve.[18]

One series of 34 patients with eosinophilic fasciitis found higher percentage (94%) of complete remission on oral prednisone alone or intravenous methylprednisolone pulses followed by oral prednisone. In addition, 18% of patients who received methotrexate after failing oral prednisone therapy went into complete disease remission. However, systemic corticosteroids alone often result in short-term symptoms improvement with a higher risk of rebound disease flares.[10]

There is limited evidence of eosinophilic fasciitis responding favorably to other immunosuppressive agents. In one series, one patient achieved complete remission with infliximab (TNF-α inhibitor) and a prednisone taper, while two patients experienced sustained improvement after a combination of infliximab, prednisone, and methotrexate.[16] Complete remission was reported on cyclosporine monotherapy and also with dapsone and prednisolone combination therapy.[14,17] A recent study found 9 of 16 patients underwent remission after methotrexate was added to their treatment regimen of prednisone, prednisone with azathioprine, or prednisone and hydroxychloroquine. However, patients were subsequently tapered off prednisone while on methotrexate and a 70% relapse rate occurred once methotrexate was discontinued.[5]

Limitations of this study include the retrospective nature of chart review. In addition, patients were limited to those seen at a single academic institution. Future studies are needed to further characterize best practice for the management of eosinophilic fasciitis.

This retrospective case series evaluates the efficacy of our standard dual-treatment regimen of methotrexate and oral prednisone for eosinophilic fasciitis. Alternate therapy regimens included methotrexate monotherapy, prednisone monotherapy, mycophenolate mofetil and prednisone dual therapy, and prednisone combined with azathioprine. Concomitant use of methotrexate and oral prednisone is an efficacious and well-tolerated treatment for eosinophilic fasciitis.

Contributions: All authors had full access to all data in this study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors are also responsible for study concept and design, acquisition, analysis, or interpretation of data, and initial drafting and revision of the manuscript.

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