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Eosinophilic Fasciitis Treated with Tocilizumab: Demonstration of Efficacy after Withdrawal and Re-Challenge in a Patient

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Abstract

A 41-year-old man presented with clinical features of eosinophilic fasciitis (EF) confirmed on biopsy. The patient responded to high-dose prednisone but subsequent steroid sparing medication including methotrexate, hydroxychloroquine, etanercept, golimumab and rituximab failed to deliver steroid sparing response. Tocilizumab provided rapid and sustained improvement in the patient's symptoms and signs. Withdrawal of tocilizumab resulted in a flare of the clinical manifestations of EF; retreatment provided rapid recovery. Tocilizumab appears to have a therapeutic benefit in treatment resistant EF.

Keywords

Eosinophilic fasciitis, Tocilizumab, Therapy, Interleukin-6

Introduction

Eosinophilic Fasciitis (EF) is a rare connective tissue disease that is characterized by inflammation and thickening of skin to deep fascia layers in distal arms and legs [1]. This causes skin induration with classic peau d'orange appearance and if left untreated, fibrosis and joint contractures may occur [2]. Diagnosis is usually confirmed with deep full-thickness skin biopsy including fascia demonstrating characteristic lymphocytic and eosinophilic infiltrate with thickened collagen bundles in the fascia. Hypergammaglobulinemia and eosinophilia are usually observed early in the course of disease but are not required for diagnosis [3]. Diagnostic criteria have been proposed and include the above physical and biopsy findings as the major criteria. Muscle weakness or increased aldolase levels and hyperintense fascia on MR T2-weighted images have been suggested as minor criteria [4].

The incidence of EF is uncertain. It occurs most commonly in middle-aged individuals with peak incidence between 40 and 50 years of age. There is no particular racial, ethnic or gender predisposition [3]. The etiology of EF is unknown. Familial cases have been reported although no specific HLA phenotype is associated with the disease [5-8]. There are also reports of EF associated with Mycoplasma and Borrelia infections and as a paraneoplastic phenomenon [9-13]. Other anecdotal disease associations have been reported [3,14,15].

The immunologic pathways leading to inflammation and fibrosis are not fully defined at this time. Interferon gamma, Il-5, Il-10 are increased in the peripheral blood mononuclear cells and are associated with the eosinophilia and hypergammaglobulinemia [16]. Matrix metalloproteinase 13 is also increased in the serum of individuals with EF [17].

Whereas some cases treated early with corticosteroids have a relatively benign course, most studies suggest that additional steroid sparing agents are required. Therapy has included other immunosuppressive agents such as methotrexate and azathioprine or immunomodulatory medications such as hydroxychloroquine [15]. Anti-TNF biologic disease modifying drugs have been reported as helpful in case reports and small series [18]. Recently, a case of an EF patient treated successfully with tocilizumab has been described [19].

Case Report

A 41-year-old white male presented with symmetric forearm and calf pain and arthralgia of gradual onset. There had been no unusual or prolonged exertion prior to the onset of complaints. The patient had never ingested L-tryptophan or other supplements. He had no symptoms of Raynaud's phenomenon or other connective tissue diseases. He had no symptoms of myalgia or neuralgia nor did he have cardiopulmonary or cognitive complaints. There was a crescendo course of his symptoms over six months, prior to being seen. On physical examination, the skin of forearms and calves was taut and indurated. There was no erythema. Classic peau d'orange changes were not observed. There was no evidence of arthritis, morphea or capillary dilatation or dropout on nailbed capillaroscopy.

Initial blood work demonstrated eosinophilia and hypergammaglobulinemia. Erythrocyte sedimentation rate and C-reactive protein were elevated at 30 mm/hr and at 1.9 mg/

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dL respectively. Creatine kinase, anti-nuclear antibodies, anti-SCL 70, anticentromere antibodies, rheumatoid factor and anti-cyclic citrullinated peptide antibodies were normal. HLA typing demonstrated A2, 32; B 44; DR 103, 4; DQ 5, 7.

Full thickness skin biopsy including fascia was performed and demonstrated a chronic inflammatory process involving the dermis and fascia. Inflammatory infiltrates consisted of lymphocytes, plasma cells and macrophages. No eosinophils were noted. CD3 positive T lymphocytes (CD4 and CD8 in approximately equal quantity) and CD68 positive macrophages were noted with rare small foci of CD20 positive B cells. The inflammatory infiltrate extended to the underlying musculature including perimysium and endomysium. No evidence of vasculitis was demonstrated. Acid phosphatase histochemical stains revealed minimal myonecrosis. The findings were suggestive of eosinophilic fasciitis.

The patient began prednisone 40 mg daily after the biopsy was performed. There was improvement of symptoms and findings of skin tightening parallel with a decrease in the acute phase reactants. Methotrexate was added as a steroid sparing medication four months after beginning prednisone therapy. The maximum dose of methotrexate was 30 mg per week administered subcutaneously. Four months after starting the methotrexate, the prednisone was slowly tapered to 25 mg daily. Further reductions in prednisone were not tolerated due to resurgence of symptoms.

Etanercept 50 mg subcutaneously per week was added to the combination of prednisone and methotrexate eight months after starting prednisone. The patient experienced ongoing injection site reactions and lack of efficacy after a five-month trial. Etanercept was abandoned and golimumab 50 mg every four weeks was initiated for an additional four months, with the same outcome. Golimumab was discontinued. Subsequently, two infusions of rituximab 1000 milligrams each did not produce any improvement after four months. Hydroxychloroquine 400 mg daily was added 20 months after starting prednisone but discontinued after eight months because of gastrointestinal intolerance and lack of efficacy.

Tocilizumab 4 mg per kilogram (total: 620 mg) by monthly intravenous infusion was started 28 months after starting prednisone therapy. The patient demonstrated clinical improvement as evidenced subjectively by less pain and swelling of the forearm and calf regions. Objectively, the skin was less thickened and tense on palpation. The clinical improvement was achieved within three months even with concomitant reduction of prednisone to 5 mg daily. Clinical improvement was maintained at six months with reduction of prednisone to 2.5 mg per day.

Intercurrent gastrointestinal complaints unrelated to medication required withholding of the tocilizumab after 18 months of therapy. Within six weeks, there was recrudescence of the pain in forearm and calf regions with clinical findings of increased skin induration and thickness. The prednisone dose was increased to 20 mg daily to provide relief. Tocilizumab 800 mg IV was restarted after a gap of three months. Within a month of the tocilizumab infusion there was subjective improvement of symptoms. The patient was able to reduce the prednisone to 2.5 mg daily two months after restarting tocilizumab. The patient remains subjectively stable with no recrudescence of skin thickening six months after the restart of tocilizumab.

Discussion

Many individuals with EF will respond to relatively low doses of prednisone and maintain long-term remissions on therapy [14]. However most patients will require steroid sparing medications to induce initial remission or prevent relapses. Methotrexate is often sufficient [20]. Hydroxychloroquine is a relatively benign therapy which has also demonstrated some anecdotal benefit in EF [14,21]. A number of other therapeutic interventions used as steroid sparing agents have been reported with some anecdotal efficacy. These include azathioprine [22], sulfasalazine [23], rituximab [24], intravenous gamma globulins [25], anti-thymocyte globulin [26], cyclosporine [26], mycophenolate [27], psoralen ultraviolet A photo chemotherapy [28] and allogenic bone marrow transplantation [29].

More recently anti-TNF therapies including infliximab have been reported to be of benefit [18]. Antibody production and eosinophil responses are stimulated by Th2 lymphocytes through the production of mediators including Il-4, 5, 6, 10. Il-6 may stimulate the production of Il-10 [30]. Eosinophil degranulation and the release of transforming growth factor beta and other catatonic proteins may trigger fibroblast activation. Il-6 production by fibroblasts is enhanced by TGF-beta. Interleukin-6 stimulates collagen production and is implicated in fibrosis [31]. Inhibition of Il-6 would theoretically interfere with the activity of lymphocytes in stimulating antibody production and eosinophil responses as well as fibrosis. An Il-6 inhibitor such as tocilizumab would therefore be a rational therapy given the current state of knowledge of the immunopathology of EF.

Tocilizumab is a monoclonal antihuman IL-6 receptor antibody. It is chimeric with mouse antihuman IL-6 receptor grafted onto human IgG1. The mechanism of action is to prevent binding of Il-6 to its membrane and cellular bound receptors. Tocilizumab has been evaluated by randomized double-blind placebo controlled trials and is an approved therapy for rheumatoid arthritis in both the United States and Canada. The medication is immunosuppressive and there are risks of infection but it is otherwise generally well tolerated [32].

The course of EF is variable. Spontaneous remissions can occur [14,15]. Improvement in a given patient may be attributable to a combination of the natural history of the disease waxing and waning as well as medications. The patient described in this case report as well as the individual described by Espinoza et al. [19] demonstrated significant improvement soon after the introduction of tocilizumab therapy. Prolonged improvements in symptoms and signs were maintained while on the tocilizumab therapy. In this case report, the patient had the tocilizumab discontinued for a period of three months as he underwent further investigations. The symptoms and signs quickly recrudesced off tocilizumab. After the tocilizumab was reintroduced the patient improved rapidly to his previous baseline. The flare of the patient's symptoms off therapy and control again with the reintroduction of therapy is additional evidence that tocilizumab may be useful as a steroid sparing medication in cases of EF resistant to other therapies.

EF is a rare disease and large scale studies using the model of placebo-controlled double-blind interventions are not practical. Further case studies and series of the outcome of EF with various medical interventions will help to determine if Il-6 is a key cytokine in the disease and to determine optimal management strategies.

Ethical Statement

The contents of the case report were reviewed and approved by the CIADS Research IRB.

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