Dapsone Treatment for Eosinophilic Fasciitis

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REPORT OF A CASE

A previously healthy 38-year-old woman was seen regarding severe skin stiffness and thickening. Previous findings are summarized.

The patient originally saw her primary care practitioner with a 3-month history of limb aches, ankle swelling, and malaise. She was taking no medication. Findings showed an increased serum C-reactive protein level (80 mg/L [to convert to nanomoles per liter, multiply by 9.524]), mild anemia (hemoglobin level, 11.3 g/dL [to convert to grams per liter, multiply by 10.0]), elevated plasma viscosity (1.74 mPa·s), eosinophilia (eosinophil count, 2.92 × 10^3/µL [to convert to value × 10^9/L, multiply by 10^6]), and low serum ferritin and folate levels. A gastroenterologic consultation to investigate suspected malabsorption excluded celiac disease, parasitic infection of the bowel, and a gastrointestinal or gynecological malignant neoplasm. Computed tomography of the abdomen showed only a thickened proximal jejunal loop. Because of persisting eosinophilia (eosinophil count, 4.77 × 10^3/µL and 6.97 × 10^3/µL on 2 further occasions), hypereosinophilic syndrome was considered. The jejunal abnormalities were presumed to represent eosinophilic enteritis, but this condition was excluded histologically.

Because of increasing symmetrical arthralgias, the patient was seen in the rheumatology department. Generalized tightening and tautness of the skin, restricted joint movement (particularly the elbow and metacarpophalangeal [MCP] joints), and a positive prayer sign (inability to oppose the palms of the hands) were documented. A negative result for rheumatoid factor and normal autoimmune screening findings and complement levels made scleroderma spectrum disorders unlikely. A polyclonal increase in γ-globulins (mainly IgG) was found.

In the dermatology department, the stiff induration and predominantly distal limb distribution of skin tethering, together with significant blood eosinophilia, were viewed as highly suggestive of eosinophilic fasciitis (EF). A deep incisional biopsy to the fascia, from the right forearm, supported this diagnosis. Septae between fat lobules were thickened by fibrosis, and a mononuclear infiltrate including numerous eosinophils was seen. Overlying skin appeared normal. Treatment with oral prednisolone was started, initially at 40 mg/d. After 2 weeks, some symptomatic improvement and a reduction of skin edema were apparent, so the prednisolone dose was reduced to 30 mg/d. At review some weeks later, however, there had been little, if any, further improvement.

THERAPEUTIC CHALLENGE

After a gap in attendance, there was still marked skin tightness and severe restriction of flexion and extension at the wrist and MCP joints, with clawing of the hands (flexion deformity of about 30° at the MCP joints and inability to make a closed fist) (Figure 1). In addition, the patient was increasingly intolerant of oral corticosteroids, describing indigestion (despite ranitidine hydrochloride prophylaxis), bloating, and marked weight gain. She was desperate to reduce corticosteroid treatment quickly but unhappy about the possible adverse effects of many immunosuppressive agents and concerned that other relatively safe treatments (cimetidine, hydroxy-
Dapsone was introduced as a corticosteroid-sparing agent, initially at 50 mg/d but increased to 100 mg/d within 2 weeks because of the rapid improvement reported by the patient. Prednisolone was subsequently reduced from 30 to 20 mg/d and then tapered by approximately 5 mg/wk. At 2 months, the daily prednisolone dose was 10 mg and the dapsone dose was 150 mg.

Five months after dapsone treatment was started, the dramatic clinical improvement had been maintained. The patient was able to make a fist with both hands, and extension of fingers was essentially complete (Figure 2). The dapsone dose remained at 150 mg/d, with prednisolone at just 5 mg/d. The eosinophilia and inflammatory markers had normalized. Three months later, she had a normal prayer sign; she experienced an occasional mild residual ache in her lower legs but had normal function. She is scheduled to discontinue prednisolone altogether soon.

Eosinophilic fasciitis (also known as diffuse fasciitis with eosinophilia or Shulman syndrome) is a rare connective tissue disorder characterized by swelling, thickening, and induration of the skin. Limitation of movement is usual and can rapidly progress to joint contractures as a result of fascial inflammation and fibrosis. Histologically, thickening of the fascia and subcutis occurs, with a chronic infiltrate containing eosinophils. Laboratory findings include eosinophilia of up to 30%, hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate. Eosinophilic fasciitis is one of many eosinophilic disorders that a dermatologist may see. Some of these appear localized to the skin or have limited additional features; however, overlap of features and occasional reports of concurrent or sequential different eosinophilic disorders has led to the concept of an “expanding spectrum of multisystem disease associated with eosinophilia,” making diagnosis difficult.

Other disorders in which tissue eosinophilia may occur with fibrosis include eosinophilia-myalgia syndrome, retroperitoneal fibrosis, sclerosing colonopathy, and systemic sclerosis. The mechanism of this association is uncertain, but eosinophil granule products, such as eosinophil-derived neurotoxin (which is mitogenic for fibroblasts), may contribute to the development of fibrosis. Fibroblasts in patients with EF produce more collagen than those of the adjacent epidermis and also produce a connective tissue growth factor. Alternatively, fibroblast-derived cytokines, such as eotaxin and RANTES (regulated on activation, normal T cell expressed and secreted), are chemoattractant for eosinophils and affect eosinophil function, causing increased production of reactive oxygen species.

Although spontaneous recovery is possible in EF, and some patients have a treatable underlying cause, more frequently signs and symptoms persist and require active therapy. Most patients respond to corticosteroids, but no single treatment works reliably; other options may be limited by poor response, adverse effects, or contraindications. Cyclosporine, methotrexate, cimetidine, hydroxychloroquine, chloroquine, penicillamine, azathioprine, griseofulvin, ketotifen, and both psoralen–UV-A and extracorporeal photochemotherapy have all been used, most with limited evidence. Physiotherapy and other rehabilitation may also be useful.
Dapsone is an aromatic amine, also known as 4,4’-diaminodiphenylsulfone. In dermatology, it is mainly used in neoplastic dermatoses but can be effective in disorders in which eosinophils are prominent, including granuloma faciale, eosinophilic cellulitis (Wells syndrome), various small-vessel vasculitides with eosinophilia, and bullous pemphigoid. To our knowledge, this is the first formal report of dapsone as a successful treatment for EF. We found only 1 reference to dapsone for this condition in the literature; it simply postulated dapsone as a potentially useful agent but did not provide any details of experience of its use. In our patient, the rapidity and degree of clinical response were dramatic and clearly temporally related to the introduction of dapsone.

Dapsone may work in eosinophil-mediated inflammation via various mechanisms. Although its better-known anti-inflammatory actions involve several effects on neutrophils (eg, reduced chemotactic attraction, inhibition of neutrophil myeloperoxidase, reduced secretion of reactive oxygen species, and reduced generation of 5-lipoxygenase and other lysosomal enzymes), it also has a significant effect on eosinophil function. The most obvious is the inhibitory effect of dapsone on eosinophil peroxidase (EPO); EPO is more sensitive to inhibition by dapsone than the neutrophil myeloperoxidase. This inhibition leads to decreased production of toxic hypochlorous acid and reactive oxygen species. Furthermore, this inhibition also decreases the effect of EPO on mast cells, decreasing release of histamine and other inflammatory mediators. The eosinophil also affects mast cells by secretion of stem cell factor and, in turn, is stimulated by mast cell production of various eosinophil chemoattractants (such as interleukin 5 and eotaxin) and other proinflammatory cytokines that influence eosinophil activation. Interleukin 5 is also a highly potent enhancer of immunoglobulin-induced degranulation of eosinophils.

Although more sophisticated and targeted therapies, such as cytokine inhibitors and biological agents, may be used in the future for treatment of eosinophilic disorders, this report suggests that dapsone should be considered as a relatively safe and effective option for EF. As with any treatment, potential complications can arise, but its use, monitoring, and adverse effect profile are already well established in dermatology. Like other drugs used for EF, it is likely that it will not work in all cases, but it is an additional and familiar option to consider for this difficult condition.

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